HEMO STUDY MANUAL OF OPERATIONS
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1. RECRUITMENT

1.1 How to Select Patients for the HEMO Study and Quotas for Baseline Enrollment

The study coordinator has the primary responsibility for reviewing charts of patients who are on in-center hemodialysis. Patients currently enrolled in other intervention studies are ineligible for screening.

During Months 1 to 18, each clinical center has a quota of 6 B1s (initial Baseline kinetic modelling sessions) per month. During Months 2 to 12, each center should randomize an average of four patients per month. At that point, the randomization goals may be changed depending on the mortality seen in the first year of the study. The randomization targets will be updated in order to be following 900 randomized patients in the study (60 patients per clinical center) by Month 20 on November 30, 1996 (18 months of enrollment plus about two months of Baseline). Subsequently, additional patients will continue to be enrolled in Baseline and randomized to replace previously randomized patients who die or drop out of the study. Replacement of patients who die or drop out will continue until the final year of Follow-Up.

1.2 Recruitment and Information Brochures

Participant and staff brochures have been distributed (English and Spanish versions).

1.3 Before the Patients are Enrolled

The patient ID number will be assigned at the time of chart review by the study coordinator. The general format for assigning IDs will be the center number as the first two digits followed by sequential numbering (e.g., 01001, 01002).

The study coordinator has the primary responsibility for assigning patient IDs and name codes. IDs are assigned at the time of chart review using Log A (see end of this section). Name codes will be four letters long and usually will consist of the first two letters of the first name and of the last name (e.g., John Smith = JOSM). If the name code already exists for another patient, study coordinators may re-use the same name code or use another method. Name codes do not change if a patient's name changes.

The study coordinator should work with the Principal Investigator to set up a Baseline visit for patients who appear to be eligible on the basis of their chart review (Form 1: Screening Form).

1.4 Forms Completion

Screening and enrollment forms should be completed and entered rapidly so recruitment reports are current.

1.5 Monthly Screening Reports

The DCC sends monthly reports indicating the current enrollment status. Please see the end of the study coordinators' chapter (this manual, Section 2) for the format of recruitment-related tables in the monthly report. The unit-by-unit report also appears in protocol Section 5.3.

1.6 Enrollment into Baseline

Before patients can enter Baseline, they must be determined eligible on the basis of all criteria defined in the chart review (Form 1) and they must have signed the Baseline Informed Consent Form (see protocol Section 3). The study coordinator must fax the signature page with the patient's ID and name code also noted to the Data Coordinating Center (DCC). The original informed consent form should be kept in a secure location at the clinical center. The DCC will store informed consent forms away from other study forms in an especially secure manner, since they include patients' names.

For each patient entering Baseline, the physician and the study coordinator should work together to collect the demographic (Form 2) data at or before the first kinetic modelling visit.

1.7 Timetable for Baseline and Follow-Up Enrollment

The DCC will provide weekly reports reflecting the progress of Baseline enrollment in the format shown in the appendix to the study coordinators' chapter (this manual, Section 2).

1.8 Eligibility for Randomization

The detailed schedule of measurements and procedures during the Baseline period is given in protocol Sections 4 and 6. Briefly, there will be complete kinetic modelling using the patient's standard membrane during weeks 1 and 2 to establish patient's volume. During weeks 4-14, kinetic modelling will be done weekly, as necessary, to have the patient reach (on two of three separate occasions) an eKt/V of at least 1.3 estimated by variable volume double pool (VVDP) kinetics. This is one of the inclusion criteria for randomization and the DCC will provide this information to the clinical center via the Eligibility Report Form (described in Form 22).

1.9 Follow-Up Informed Consent Procedures

Once the patient has been determined to be eligible for randomization, he/she will be asked to sign a Follow-Up Informed Consent Form (see protocol Section 3). The staff at the clinical center must fax the signature page, with the patient's ID number and name code also noted, to the DCC at least 24 hours before randomizing the patient.

1.10 Randomization Procedures

If the patient has been deemed eligible for randomization (Form 22) and has signed the Follow-Up Informed Consent Form, then he/she may be randomized. Randomization is done on line with the DCC computer. Details for randomization are given in protocol Section 7.

1.11 Weekly Follow-Up Enrollment Reports

The DCC will provide weekly reports reflecting the cumulative number of randomized
patients. This is shown in Appendix B to the study coordinators' chapter (manual, Section 2).

1.12 HEMO Study Retention Plans

I. The key to good retention is prevention.

A. Patients can be eliminated at any time in baseline, for any reason, as long as it is prior to randomization.

B. A baseline patient who expresses reservations about one of the four HEMO treatment arms should not be randomized.

C. Randomized patients need continued incentives throughout follow-up so they will feel appreciated.

II. It is good to keep people in their randomized treatment arms. The PI should have a sincere discussion with any patient who, in follow-up, expresses reservations about his random treatment assignment.

A. It is great if a person wants to stay on both his Kt/V and flux assignments. If he is willing to do this, his events contribute accurately, in an unbiased fashion, to HEMO primary and secondary outcome analyses.

B. A person willing to stay on his or her Kt/V assignment contributes accurately, in an unbiased fashion, to the Kt/V comparisons regardless of his or her membrane.

C. A person willing to stay on his or her membrane assignment contributes accurately, in an unbiased fashion, to the membrane comparisons regardless of his or her achieved or selected Kt/V level.

D. A patient who will stay on neither his Kt/V nor flux goal remains in the primary analysis plan on his original Kt/V and membrane, since the analysis plan follows the standard randomized trial "intent to treat" plan.

III. Once a patient is randomized, all efforts for follow-up data collection will continue regardless of his or her staying on his or her randomly selected membrane and/or his randomly selected Kt/V goal. See protocol pg. 10004: Loss to complete routine follow-up as a result of patient request is not expected to reduce dialysis data collection (Form 5) or secondary outcome data collection (Hospitalization Forms). However, if a person is unwilling to provide complete data, some data are more critical to the study's success.

A. Priority of data collection

1. Most important: If the patient dies, death Form 17 is needed. If the patient receives a transplant, Form 19 is needed. If the patient switches to peritoneal dialysis or home hemodialysis or transfers to in-center hemodialysis at a facility not in the HEMO Study, Form 19 is needed.
2. Next priority: Hospitalization data.
3. Next priority: Form 5 and Central Biochemistry Lab BUN's for kinetic modelling.
4. Next priority: Central Biochemistry Lab data: Albumins
5. Next priority: Central Biochemistry Lab data: 24-hour urine annually to update residual renal function.
6. Access complication data on Form 6 every 6 months.
7. Collection of data items 1 through 6 provides excellent follow-up for patients who request less than complete routine follow-up. Collection of data and quality of life data is part of the protocol but can be sacrificed temporarily or permanently in the event of patient request.

B. Clinical centers should check periodically with any non-compliant randomized patients to see if they can be brought back into compliance.

1. Check compliance to treatment: Every 6 months or so, if it is possible to do so without unduly upsetting the patient, the PI or the patient's favorite staff member should discuss with the patient the possibility of the patient returning to his random assignments, since this will greatly improve the power of the primary analysis.
2. Check compliance to data collection protocol: Every 6 months or so, if it is possible to do so without unduly upsetting the patient, the PI or the patient's favorite staff member should discuss with the patient the possibility of the patient returning to complete routine follow-up.

C. Randomized patients who are non-compliant to treatment or request less than complete routine follow-up are not "reclassified."

1. The kinetic modelling reports on a patient who elects a membrane or Kt/V goal or time other than that assigned will show an incorrect membrane or Kt/V goal or time on his kinetic modelling compliance reports.
2. The DCC cumulative missing forms reports on a patient who is refusing to provide, for example, Form 48 data, will show missing Form 48's on this patient. (These can be coded as "truly missing" by the center. The missing forms system is not yet in place.)

2. STUDY COORDINATORS

2.1 Introduction

The study coordinator plays an integral role at each clinical center of the HEMO Study. He/she, along with the Principal Investigator, Co-Investigators, and dietitians, keeps the study running smoothly at the clinical center level, with the assistance of the dialysis unit dietitians and technicians.

The study coordinator must work closely with the physician at the clinical center to screen and enroll patients, to make sure patient information is gathered, recorded, entered and verified correctly, and to ensure that the HEMO Study protocol is followed. He/she must coordinate the patients' visits with the physicians, the dialysis unit, and the dietitian. He/she will work closely with the Data Coordinating Center (DCC), helping resolve problems that arise with patient data.

All HEMO study coordinators must attend central training in order to be certified to participate in the HEMO Study. Central training of the study coordinators will help enhance compliance with the protocol and will help in the development of uniform procedures for data acquisition. At the central training session, the study coordinators will learn about the HEMO Study and be certified to complete forms, enter data into the Oracle database, and correct errors. If a study coordinator must leave his/her position at the clinical center, he/she should help train his/her replacement. Any new person who will be entering data must be certified at an abbreviated central training session at the DCC.

Each study coordinator will have a copy of the protocol and the manual of operations. He/she should be familiar with the protocol, all forms contained in the forms manual, and the manual of operations. The study coordinator should make sure any revision pages are inserted. The DCC staff welcomes questions about the protocol or the manual of operations.

Each study coordinator should have a copy of the address directory.

2.2 Patient Instructions during Baseline

Study coordinators assume the primary role of educating the patient during Baseline. The patient education material given in the Patient Education Brochure must be covered.

2.3 How to Randomize a Patient and Initiate Follow-Up

During Baseline, the study coordinator may run the eligibility check program at any time.

When all eligibility issues have been confirmed and a patient's Follow-Up Informed Consent Form has been received and filed, the study coordinator can run the randomization program. The study coordinator has the primary responsibility for getting the randomization assignment.

The study coordinator is responsible for initiating Follow-Up procedures on the dialysis visit held on the first Monday or Tuesday after the patient is randomized. The DCC will provide a Follow-Up appointment schedule that will include the month-long visit windows for each patient's monthly visit.

2.4 Hospitalization Review Procedures

When a patient is hospitalized, the study coordinator should notify the DCC by submitting Form 13 (the Clinical Center Hospitalization Notification Form) within one week of the hospitalization. When the patient is discharged from the hospital, Form 14 (the Clinical Center Hospitalization Review Form) should be completed by the coordinator and Principal Investigator within two weeks of discharge. If a patient is hospitalized before being randomized, it is considered a follow-up hospitalization if the hospital discharge date is greater than the randomization date. However, recall that exclusion criteria (#1 of the Protocol) excludes patients currently in an acute care or chronic care hospital. If a patient dies while in the hospital, Forms 16 and 17 (the Clinical Center Death Notification Form and the Clinical Center Death Review Form) should be submitted (submit Form 16 as soon as the clinical center is aware of the patient's death; submit Form 17 within six weeks of the date of death). Form 16 notifies the DCC of the death and Form 17 describes the causes of death. A Form 16 must also be entered <u>before</u> the Form 14, if a death occurs during a hospitalization that is less than

overnight. If the Form 16 is not entered first, in this case, the database will not accept the Form 14.

Form 8, the Documentation Folder Mailing Form, is to be completed for all deaths; first cardiovascular and first infection hospitalizations; and other hospitalizations as selected by the DCC. Procedures for hospitalization and death forms are more specifically described in Appendix A to this section and on the first page of the individual forms.

2.5 Coding Hospitalizations

Hospitalizations are divided into three categories with respect to access: those that are access related (that is, the sole purpose of the hospitalization is related to the access); those that were access related at the time of admission, but then the participant suffered complications while in the hospital; and those that are unrelated to the vascular access. At the time of each admission, the applicable admitting diagnosis should be selected from the list of possible admitting diagnoses. As many admitting diagnoses as appropriate should be selected. (For example, a patient admitted with chest pain and fever at the time of admission would have two admitting diagnoses.) At the time of discharge, the primary and secondary causes of hospitalization should be selected from the hospitalization cause list by the Principal Investigator. In general, these are more specific diagnoses, such as myocardial infarction, pneumonia, etc.

In addition to the admitting and discharge diagnoses, information regarding the admitting and discharge ICD-9 CM and DRG codes should be entered on Form 41. The study coordinator should obtain this from the medical records department of the institution where the patient is/was hospitalized.

2.6 Coding Deaths

The Principal Investigator will determine the primary and secondary causes of death, selecting from the list of possible causes of death. In general, the cause of the death should not reflect the immediate terminal event but rather the precipitating cause of death. For example, a participant with severe sepsis and untreatable hypotension secondary to sepsis whose heart finally stops beating will have the primary cause of death coded as sepsis, not cardiac arrest, and

the secondary cause of death coded as untreatable hypotension. The Cause of Death Code List is provided as an attachment to Form 17.

2.7 Coding Composite Cardiovascular Events

A cardiovascular endpoint is reached if either a participant is hospitalized for or during a hospitalization has new or worsening angina, a myocardial infarction, new congestive heart failure and arrhythmia, or another cardiac event, excluding pericarditis. The hospital discharge summary should document the cardiovascular endpoint and if it does not, the PI may want to submit other documentation to support that this cardiovascular endpoint has been reached. Form 14 should also reflect that a cardiovascular event hospitalization has been reached.

2.8 Coding Infection Events

An infection hospitalization event has been reached if a participant has been hospitalized for a non-access infection or has a severe non-access infection while hospitalized for another cause. The discharge summary for the hospitalization should reflect that the infection event has occurred and if it does not, the PI may want to submit other documentation to support that this infection endpoint has been reached. Form 14 should also reflect that an infection event has occurred.

2.9 Death and Composite Review Procedures

The Outcome Committee will, throughout the course of the study, review the deaths and events. A discussion of the review and classification procedures can be found in protocol Sections 4 and 11.

2.10 Action Items

An action item is a defined event that requires a specific change in the patient's treatment protocol. The HEMO Study action items are declining serum albumin and undesired weight loss. Every time Form 5 or Form 9 (Central Biochemistry Laboratory Report Form,

which contains albumin levels) is transmitted to the DCC, the DCC will check for defined action items. If an action item is found, the DCC will notify the clinical center. When the study coordinator receives an electronic mail message that a patient has reached an action item, he/she should notify the Study teams including the Principal Investigator so that appropriate response to the action item may be taken as outlined in Section 10 of the protocol. The DCC will notify the clinical center if and when the action item has been resolved.

2.11 Pregnant Patient

During pregnancy and lactation, follow usual medical practice. Later, bring the patient back into the protocol at exactly where she would have been had she not had this "break".

Throughout the pregnancy, continue to fill out forms as usual as much as possible, but if the pregnancy causes you to do the dialysis prescription or flux differently for the well being of the patient, so be it. Likewise, if this necessitates any missing data, again, so be it. This is like giving her a "break" from her randomized group assignments.

2.12 Ordering and Filing Data Forms

The Forms Completion Schedules appear as Appendix A.

The study coordinator is responsible for each clinical center's forms supply. The DCC will try to project forms requirements, and distribute some forms periodically to cut down on photocopying at the clinics.

A HEMO Study file should be established for every patient who enters Baseline. This file should include the patient's Study forms. The dietitian may also have an HEMO dietary file for each patient, or these two files may be combined into one HEMO file.

2.13 Electronic Mail (E-Mail) Files

The study coordinator is primarily responsible for printing, distributing, and filing any e-mail received.

2.14 Logs or Minutes of Staff Meetings

The funded HEMO staff members at each clinical center should meet regularly. The study coordinator should keep a log of when these meetings were held, who attended, and any major issues raised or resolved.

2.15 Weekly and Monthly Reports

The study coordinator should circulate the weekly and monthly reports.

2.16 Site Visits

Each clinical center will be site-visited by NIH and DCC personnel during the study. These visits will enhance the working relationship between the DCC and each clinical center, and provide an opportunity for face-to-face questions and answers on any outstanding problems a clinical center is having with individual patients or with study procedures in general.

At the site visits, the DCC will monitor the clinical center's performance in following the protocol by observing HEMO Study procedures. HEMO Study patient files will be inspected, and a sample of HEMO Study data forms will be checked against original source documents in the patients' medical records.

Throughout the course of the study, each clinical center's performance will be monitored by a series of data quality reports. These include reports of enrollment, number of missing forms, rates of invalid data, data quality, and numbers of missed visits. These reports will routinely be sent to the clinical centers, the Steering Committee, and the NIH Program Office.

The site visits will be scheduled in advance by the Forms/QC Committee Chair and the DCC. It will be held after the data audit.

Each member of the site visit team will receive a “site visit packet” consisting of four parts:

I. Site visit Agenda, which includes names of site visit team and exact location of the site

visit (where a cab would bring the site visitors).

II. Address Directory pages for center.

III. Certification information - who on the staff has been certified in what (data entry,

anthropometry) and when (include staff no longer there).

IV. The DCC Site Visit Report.

The agenda and the DCC Site Visit Report will be provided to the clinic in advance of the site visit.

2.17 Re-Enrollment

Complete Form 12 when you have a patient you wish to re-enroll into Baseline (see below). this form **must** be entered in the database before the DCC can transfer the patient's old data. You also need to notify the DCC that you want to re-enroll a patient so that we can transfer the old data, and you will need to fax the DCC a copy of the original Baseline consent form for the patient, using the re-enroll fax cover sheet to indicate that this consent form is currently acceptable to your IRB. You may also have the patient sign a new baseline consent form, but please indicate that this is a re-enroll patient. You will need DCC assistance to re-enroll the patient. Following transfer of the old data, you can enter the patient's new Forms 1 and 2.

You will complete this form for patents excluded for any reason (with Form 22) during a prior Baseline who will now be re-enrolled. The date request for re-enrollment must be at least three calendar months (e.g., February 22 to May 22 = three calendar months) from the patient's exclusion date. The exclusion date is defined **either** as the day the Form 22 was entered into the database **or** one day after the patient's 14-week Baseline window expires, whichever comes first.

APPENDIX A -- MOP Section 2

FORMS COMPLETION SCHEDULE

BASELINE FORMS

Time	Forms															
	1	**2**	**3**	**4**	**5**	**6**	**9**	**10**	**22**	**29**	**30**	**33**	**34**	**37**	**39**	**48/49**
Prior to enrollment into Baseline	x															
Week 1a		x			x		x	x*		x*	x*		x*			
Week 2a					x		x	x*		x*	x*		x*			
Week 3																
Week 4					x	x	x					x				
Week 5			x		x		x							x	x	x
Week 6					[x]		[x]		(x)							
Week 7					[x]		[x]		(x)							
Week 8					[x]		[x]		(x)							
Week 9					[x]		[x]		(x)							
Week 10					[x]		[x]		(x)							
Week 11					[x]		[x]		(x)							
Week 12					[x]		[x]		(x)							
Week 13					[x]		[x]		(x)							
Week 14					[x]		[x]		(x)							

a test for residual renal function -- suggested in Week 1 or 2 -- urine must be collected between a dialysis session

immediately preceding a modelling session and the modelling session itself

* complete *either* Week 1 *or* Week 2

[ ] if necessary

( ) complete Form 22 as first step for randomization after KM report indicates that delivered eKt/V is at least

1.3 on two of three consecutive kinetic-modelling sessions

APPENDIX A -- MOP Section 2

FORMS COMPLETION SCHEDULE

FOLLOW-UP FORMS

Time	**Forms**												
	3	4	5	6	9	10	29	30	33	34	37	39	48/49
Month 1		x	x		x								
Month 2		x	x		x								
Month 3		x	x		x								
Month 4		x	x	x	x								
Month 5		x	x		x								
Month 6		x	x		x	x							
Month 7		x	x		x								
Month 8		x	x		x								
Month 9		x	x		x								
Month 10		x	x		x								
Month 11		x	x		x								
Month 12	x	x	x	x	x	x	x	x	x	x	x	x	x

-- Measurements are not required during hospitalizations.

-- 24-46 hour urine specimens will be drawn annually IF the most recently computed residual renal clearance exceeds 0.5 ml/min/35 L.

-- Pre- and post-beta-2 microglobulins at Follow-up months 1, 2, 4, and every two months thereafter in the high flux group and 1, 12, 24 and every twelve months thereafter in the low flux group.

* Form 4 is completed every other month. Odd numbered centers will fill out Form 4 in odd numbered months. Even numbered centers will do so in the even numbered months.

APPENDIX A -- MOP Section 2

OTHER FORMS TO BE COMPLETED AS NEEDED

Form 8: Documentation Folder Mailing Form

Complete Form 8 for:

- all deaths
- first cardiovascular hospitalizations
- first infection hospitalizations
- other hospitalizations selected by the DCC (randomly selected)

Form 11: Local Lab Reference Ranges and Methods Form (not available yet)

Form 11 is to be completed upon request of the DCC. Please complete the form for *each dialysis unit.* Report the normal reference range for your lab for each value.

Form 12: Re-Enrollment of a previously Excluded Patient

Complete Form 12 for patients who were excluded for any reason with a Form 22 during a prior Baseline enrollment. The date of request for re-enrollment (question 3 of Form 12) must be three calendar months from the patient's exclusion date on Form 22.

Form 13: Clinical Center Hospitalization Notification Form

Complete Form 13 *within one week* after a patient is hospitalized.

Form 14: Clinical Center Hospitalization Review Form

Complete Form 14 *within two weeks* after the patient is discharged or dies in the hospital. Please see page one of the form for more instructions.

Form 16: Clinical Center Death Notification Form

Complete Form 16 when you learn of a patient's death. Please see the form for more instructions.

Form 17: Clinical Center Death Review Form

Complete Form 17 with the Principal Investigator within six weeks following the date of the patient's death. Please see the form for more instructions.

APPENDIX A -- MOP Section 2

Form 19: Stop Point or Loss to Routine Follow-Up Documentation Form

Complete Form 19 with the Principal Investigator when a participant reaches a stop point as described in Section 10 of the protocol.

Form 21: Annual Follow-Up after Loss to Routine Follow-Up

Complete Form 21 for "lost to routine Follow-Up" randomized participants annually. Also complete the form for non-randomized participants on an annual basis.

Form 22: Eligibility for Randomization or Baseline Dropout Form

Complete Form 22 as soon as the participant drops from Baseline, whether during or at the end of Baseline. Also complete the form when a participant is to be randomized.

Form 35: Supplement Distribution Form

Complete Form 35 when you give a vitamin, mineral, or enteral supplement to a patient.

Form 41: Clinical Center Hospitalization ICD-9 and DRG Form

Complete Form 41 when you complete the other hospitalization forms or when ICD 9 codes are available.

Appendix B -- MOP Section 2

BASELINE SCHEDULE TRACKING SYSTEM

Activity	Pt. #1	Pt. #2	Pt. #3	Pt. #4	Pt. #5
Week 1					
Form 2	2/10/95				
Urine	2/10/95				
2-BUN	2/10/95				
Form 33	2/12/95				
Week 2					
Form 34	2/17/95				
2-BUN	2/17/95				
Week 4					
Anthro.	3/3/95				
3-BUN	3/3/95				
Week 5					
Comorbid.	3/10/95				Checks completed date

Appendix B -- MOP Section 2

BASELINE ACTIVITIES TRACKING SYSTEM

	Week 1	**Week 2**	**Week 3**	**Week 4**	**Week 5**	**Week 6**
Sign Consent	X					
Urine Collection	X					
Kinetics •2 Blood Samples	X	X			X	
•3 Blood Samples				X		
Usual Dialysis	X	X	X			
Monthly Bloods	X					
Appetite Assess.		X				
New Dialysis Prescription				X		
Complete Diet Records					X	
Body Measurement				X		
Quality of Life Questions					X	

Appendix B -- MOP Section 2

KINETIC MODELLING (KM)

SESSIONS: TO-DO LIST

1. Identify patients for KM the day before
2. Prepare/label blood tubes
3. Inform dialysis staff of KM
4. Obtain blood
5. Process blood as per protocol
6. Prepare blood for shipping
7. Complete Form 9 and CBL Form
8. Call courier for pick-up
9. Obtain dialysis flow sheet
10. Complete Form 5
11. Enter Forms 5 and 9 into database

Appendix B -- MOP Section 2

SCHEDULE INSERVICES FOR

- Dialysis unit staff members
- Attending physicians

Describe the study and recruitment - how are we going to do it?

Appendix B -- MOP Section 2

Example Patient Preparation Form for a 2-BUN Session

Patient Name

Dialyzer

Qb = 250

Time: 3:30

(210 minutes)

BUN Measurements

Pre Dialysis

Post Dialysis

Appendix B -- MOP Section 2

Example Patient Preparation Form for a 8-BUN Session

Patient Name
Dialyzer

Qb = 250
Time: 3:30

(210 minutes)

BUN Measurements	**RTD Clock**
Pre Dialysis	
60 Minutes Full Outlet	2:30
60 Minutes Full Inlet	2:30
60 Minutes Slow Inlet	2:30
Post Dialysis Full Outlet	0:00
Post Dialysis Full Inlet	
Post Dialysis (+ 20 sec) Slow Inlet	

APPENDIX C -- **Organization Suggestions for HEMO Study**

- **CHARTS**
- **PHONE LINES**
- **STORAGE SPACE**
- **WORK SPACE**
- **SPECIMEN COLLECTION AND MODELLINGS**
- **BASELINE ACTIVITIES**

APPENDIX D -- MOP Section 2

HEMO Timeline
Revision of May 11, 2001

Close Out visits July 1, 2001 to December 31, 2001

For patients who have had a transplant/are on PD/have moved away:

Annual follow up on Form 21
Mortality follow up on Form 16

For patients in routine follow up:

- If the patient has less than three years of follow up or if patient has missed their annual visit between January 1, 2001, and June 30, 2001, do an extra ANNUAL VISIT data collection with a target date the date of patient annual visit + 6 months. (Approximately 1 or 2 extra visits/month/center)
- If the patient has completed F 36, F 48, F 60, or F 72 annual visit forms (we will look for diet records and especially Form 48/49) during January 1 to June 30, 2001, no extra close out visit is necessary.

Complete:

Form 3	Baseline/Annual Comorbidity Assessment Form
Form 5	Detailed Dialysis Session for a Kinetic Modelling Day
Form 6	Access Related Conditions Form
Form 9	Central Biochemistry Laboratory Mailing Form
Form 10	Local Biochemistry Lab Form
Form 29	Anthropometry Form
Form 30	Diet Diary Assisted Recall Form
Form 33	Diet Prescription and Supplement Documentation Form
Form 34	Appetite Assessment Form
Form 37	The Karnofsky Index (KI) of Functional Ability
Form 39	Index of Physical Impairment
Form 48/49	Quality of Life Assessment

- At End of Study patient is given:

Gift
Personal Results folders: Patient's Kt/V over time

Patient's diet results over time
Any other results of interest

These personal results folders were drafted by the DCC in early June, for your approval. The final results folders will be assembled starting January 2002, using the most recent data.

APPENDIX D -- MOP Section 2

Visits continue until December 31, 2001

Patients should remain on membranes and goals and continue Form 5.

December 2001 visits: Certificate of appreciation (real "end")
Letter to the personal physicians of patients

No visits December 31 to March/April 2002

Find data on any deaths before January 1, 2002
Form 13's for any hospitalizations with admissions before January 1, 2002
Form 14's for hospitalizations with admissions before January 1, 2002 and discharges before February 1, 2002
Obtain data on all 2000 hospitalizations reported in USRDS

March/April 2002

Time to present results to patients in a HEMO Study Results Folder
Can be done as individual visits or group visits (perhaps four groups, depending on KtV/flux)
Study results will also go to the personal physicians of study patients
Study Results folder will contain:
Overall study results, similar to the press release (layman's language)
Implications of results to your group (depending on KtV and flux goal)

Late March 2002

For patients who have had a transplant/are on PD/have moved away:
Final follow up on Form 21

April 17-22, 2002

Study results at spring NKF meetings and in press release

May 1, 2002
For all patients:
Last day to submit a death notification Form 16 for deaths 1/1/02 to 5/1/02:
May 1, 2002

APPENDIX D -- MOP Section 2

FORMS COMPLETION SCHEDULE

CLOSE-OUT FORMS

Time	**Forms**											
	3*	5	6	9	10	29	30	33	34	37	39	48/49
Close-Out	X	X	X	X	X	X	X	X	X	X	X	X

- Complete annual diet records.
- Collect an afterthought sample labelled "close-out".
- All hospitalizations occuring before midnight on December 31, 2001 must have Forms 13 & 14 entered into the database.
- A new form (not yet available) will be used in December, 2001 to collect the final data.

* The Form 3 should be dated from the previous Form 3 visit to the date that the extra close-out Form 3 actually occurs. This may not ba full calendar year.

E-mails dated 6/4/01 have been sent out concerning extra close-out visits. These include patients randomized between 1/1/99 and 6/30/99, 1/1/00 and 6/30/00, and after 1/1/01. Extra close-out visits are also required for patients whose final annual visit was targeted for January-June 2001, but who missed this visit. Windows for form completion are included in the e-mail.

3. MEMBRANES

3.1 Selection of Membranes

Two types of membranes (low and high flux) will be used for the dialyzers required for the study. (In addition, it is required that all dialyzers have a KoA for urea of > 500 ml/min at a dialysate flow rate of 500 ml/min.) The flux requirements depend on the ability of dialyzers to remove (high flux) or not remove (low flux) large molecules by any mechanism, including diffusion, convection, or adsorption. In addition, flux is defined by ultrafiltration. Unsubstituted cellulosic membranes are not permitted because they are considered less biocompatible than the substituted cellulosic or synthetic membranes recommended for the dialyzers to be used in the study.

The criteria for initially allowing a dialyzer to be used in the study are based on the dialyzer KUf and β_2M clearance *at first use*. Once a dialyzer is allowed in the study, its performance with reuse will be monitored for each reuse method. The Membrane/Flux Committee will then determine whether dialyzer - reuse combinations should be prohibited, discouraged, or encouraged based on the mean β_2M clearance over the average number of reuses for each dialyzer - reuse combination.

3.2 Dialyzer Criteria for Initial Inclusion in the Study

The following criteria must be satisfied in order that **any** dialyzer be included in the study:

1. **Not** unsubstituted cellulose (i.e., not cuprophane, cuprammonium rayon, saponified cellulose ester, or regenerated cellulose)

2. Mean *in vitro* KoA urea ≥ 500 ml/min at a dialysate flow rate (Qd) of 500 ml/min

Note: Consistent with the requirement that patients be dialyzed in the shortest possible time, centers using dialyzers with KoA between 500 and 600 ml/min on patients with urea volume > 35 L will be required to use dialysate flow rates of at least 750 ml/min. Mean *in vitro* KoAs must be determined by at least five independent clearance measurements obtained at a specified laboratory; see Section 4.3.3.

In order that a dialyzer can be used in the **low flux arm** of the study, the following criterion must be met for dialyzers at first use:

L1. The average β_2M clearance must be < 10 ml/min.

In order that a dialyzer can be used in the **high flux arm** of the study, the following two criteria must be satisfied:

H1. The average β_2M clearance at first use must be > 20 ml/min, and

H2. Industry *in vitro* KUf ≥ 14 ml/hr/mm Hg or *in vivo* KUf ≥ 14 ml/hr/mm Hg.

Notes: i) An exception to H1 will be made for dialyzers that can be demonstrated to have a mean β_2M clearance > 20 ml/min over the standard lifetime of the dialyzer on a particular reuse technique. Such dialyzers may be used only on the reuse technique satisfying the β_2M clearance criteria.

ii) Dialyzers with average β_2M clearance > 25 ml/min at first use must be used for patients with urea volume ≥ 35 L.

iii) Acceptable methods for determining average β_2M clearance are described below. (β_2M clearances should be adjusted for ultrafiltration.)

The HEMO Membrane/Flux Committee will have the responsibility of determining whether the above criteria are met for individual dialyzers during the course of the study. The criteria for initially allowing dialyzers in the low and high flux arms are based primarily on first use because it is not logistically feasible to test β_2M clearance data after multiple reuses for different reuse techniques for all dialyzers to be included in the study. However, as discussed in Sections 3.1.5 and 3.1.6 below, the Membrane/Flux Committee will periodically review β_2M clearance data for different dialyzer - reuse method combinations based on data from i) regular follow-up of study patients, ii) special studies of the effects of reuse organized by the Membrane/ Flux Committee, and iii) published results of other studies. This Committee will have the option of prohibiting dialyzer - reuse combinations if it becomes clear that these combinations compromise the separation in β_2M clearance between the low and high flux arms.

In addition to determining which dialyzers - reuse combinations should be allowed in the Study, the Membrane/Flux Committee will also provide recommendations to the HEMO Study Executive Committee regarding the distribution of free dialyzers.

The criterion L1 may be established by any of the following means:

L1i: Published data pertaining to the dialyzer in question, or an identical membrane with larger surface area, showing that the mean of at least five independent first use β_2M clearance measurements is < 10 ml/min.

L1ii: Manufacturer-supplied raw data from the dialyzer in question, or an identical membrane with larger surface area, showing that the mean of at least five independent first use β_2M clearance measurements is < 10 ml/min.

L1iii: At least 5 independent first-use β_2M clearance measurements from the MMHD Pilot Study for the dialyzer in question, or an identical membrane with larger surface area, with mean < 10 ml/min.

L1iv: At least 5 independent first-use β_2M clearance measurements from a β_2M clearance study arranged by the Membrane/Flux Committee for the dialyzer in question, or an identical membrane with larger surface area, with mean < 10 ml/min.

The criterion H1 may be established by any of the following means:

H1i: Published data pertaining to the dialyzer in question, or an identical membrane with smaller surface area, showing that the mean of at least five independent first use β_2M clearance measurements is > 20 ml/min.

H1ii: Manufacturer-supplied raw data from the dialyzer in question, or an identical membrane with smaller surface area, showing that the mean of at least five independent first use β_2M clearance measurements is > 20 ml/min.

H1iii: At least 5 independent first-use β_2M clearance measurements from the MMHD Pilot Study for the dialyzer in question, or an identical membrane with smaller surface area, with mean > 20 ml/min.

H1iv: At least 5 independent first-use β_2M clearance measurements from a β_2M clearance study arranged by the Membrane/Flux Committee for the dialyzer in question, or an identical membrane with smaller surface area, with mean > 20 ml/min.

The special studies required by criteria L1iv and H1iv are based on a protocol developed by the Membrane/Flux Committee which includes measurement of β_2M concentrations at a designated central laboratory.

3.3 List of Allowable Dialyzers

A goal of the study is to have dialyzers that reflect the practice of dialysis in the United States, and thus multiple dialyzers will be permitted. A tentative list of available high and low flux dialyzers for the study appears as Table 3.3.1. Dialyzers with tentative estimated in-vitro KoAs between 500 l/min and 600 ml/min at a Qd of 500 ml/min are asterisked. *The list of dialyzers with asterisks will be updated following finalization of the in-vitro KoA study results.*

The division of dialyzers into low and high flux is based on what is currently known about their removal of β_2M according to publications, information from manufacturers, the results of the MMHD Pilot Study, and the results of special β_2M clearance studies arranged by the Membrane/ Flux Committee. As discussed above the behavior of these dialyzers during the trial and across reuse (both technique and reuse number) will be monitored during the Study. Any new dialyzer developed after the trial begins will have to meet the flux criteria before it can be introduced into the study. Clinical Centers wishing to introduce a new dialyzer in the study may be asked to carry out a study of the β_2M clearance of the dialyzer.

3.4 Dialysis Procedure for Double Dialyzers

The following procedure for hemodialysis with two dialyzers (double dialyzers) should be considered as a guideline. **The details of the procedure can and should be altered in accordance with the existing procedures and policies of the individual dialysis units participating in the HEMO Study.** However, the following protocol requirements must be adhered to in all cases:

PROTOCOL REQUIREMENTS:

1. Only series configurations of double dialyzers may be used.

2. Double dialyzer configurations may be used in follow-up for the purpose of improving adherence to the HEMO Study Kt/V goals. Double dialyzer configurations are not permitted during baseline.

3. At the present time, only the following double-dialyzer combinations are approved under the HEMO Study protocol:

   Low Flux Arm: Two F-8 dialyzers in series
   Two CA-210 dialyzers in series

   High Flux Arm: An F-8 followed by an F-80 in series
   A CA-210 followed by a CT-190 in series

   The impact of these double dialyzer configurations on the treatment time required to achieve an eKt/V of 1.45 is summarized by Tables 1-4 below.

The key features of the double dialyzer procedure are the use of the commercially available connecting blood side tubing and bridging dialysate tubing between the dialyzers that must be used to safely accomplish the treatment.

PROCEDURE: (STEPS SPECIFICALLY RELATED TO THE DOUBLE DIALYZER CONFIGURATION ARE HIGHLIGHTED)

1. In all cases, turn on machine and string bloodlines, as done for regular single dialyzer configurations. Using aseptic technique, **establish connection between the venous blood port of the low flux dialyzer and the arterial blood port of the high flux dialyzer (for subjects randomized to High Flux) or the venous blood port of one low flux dialyzer and the arterial blood port of a second low flux dialyzer (for subjects randomized to Low Flux). The connecting piece is available from Hematronics: Part # 505EXT25 (sterile 10 inch female-female locking connector (1-800-633-78770) or Part MPC-850, Series Hookup Adapter. (Molded Products, Harlan, IA 51537, 800-435-8957).**

2. Use **two dialyzer holders on pole approximately 12 inches apart. Place the dialyzers in holder, with arterial ends up.**

3. If formaldehyde or glutaraldehyde is employed in the reuse procedure, the following setup method can be adapted to the existing policy of the individual dialysis units: Test dialysate for correct composition and connect dialysate tubing to the dialyzers. **Tubing with Hansen connectors attached to each end is used as a bridge between the two dialyzers. Connect one side of this bridging tubing to the dialysate port on the venous side of the first dialyzer (always a low flux dialyzer) to the dialysate port of the arterial side of the lower dialyzer (high or low flux dialyzer depending on the randomization assignment).**

4. **Connect the dialysate hoses from the machine as follows: the blue dialysate inflow line from the machine is attached to the venous end of the lower (high flux or second low flux dialyzer) and the red dialysate outflow line is attached to the arterial end of the upper dialyzer (always a low flux dialyzer).** Leave the blood ports capped and establish dialysate flow at least 500 ml/min and make sure that the air is flushed from the dialysate compartment. This step should precede the attachment of the bloodlines and the priming of the bloodside of the **dialyzers**.

5. Using aseptic technique, connect 1 liter of 0.9% normal saline to arterial bloodline.

6. Prime arterial bloodline preferably prior to connecting the line to the arterial blood port of **the first dialyzer. Attach the venous bloodline to the venous blood port of the second (lower) dialyzer. Invert both dialyzers 180 degrees (venous sides up).**

7. Flush **1000 ml** of saline via the arterial bloodline at 150 ml/min

8. When **1000 ml of saline** has been infused, connect the arterial and venous bloodlines together, clamp the saline administration line and replace the saline bag. Recirculate the blood side at $\geq$ 400 ml/min and periodically clamp the venous line below the venous drip chamber to help remove air. Set an ultrafiltration rate for approximately 2 liters/hr. Administer saline as necessary when TMP rises. Rotate **both dialyzers** 180 degrees so that the arterial ends are upright again, halfway through the recirculation procedure.

9. After an appropriate rinse time, test the system for residual germicide, per unit procedure. After an acceptable test, dialysis should be initiated or recirculation should be continued with the blood pump set at 100 ml/min and the UF rate set at 100 ml/hr.

10. If Renalin or heat is the employed in the reuse procedure, the following setup method can be adapted to the existing policy of the dialysis unit: Test dialysate composition.

11. **The arterial side of the dialyzers should be downwards. The arterial bloodline should be connected to the arterial blood port of the lower dialyzer and the venous bloodline should be connected to the venous blood port of the upper dialyzer.** Flush approximately **1000 ml** of saline through the blood side at 150 ml/min. Clamp the saline administration line and replace saline bag.

12. **Attach the bridging dialysate tubing between the dialysate port on the arterial side of the upper dialyzer and the dialysate port on the venous side of the lower dialyzer. Attach the blue dialysate inflow line to the venous dialysate port of the upper dialyzer and the red dialysate outflow line to the arterial dialysate port of the lower dialyzer and then rotate both dialyzers 180 degrees. Establish dialysate flow of at least 500 ml/min.**

13. **When air is cleared from the dialysate side, rotate both dialyzers again so that the arterial ends are again downwards. Connect the arterial and venous bloodlines together and recirculate the bloodside at 500 ml/min. Periodically clamp the venous line below the drip chamber to remove air. Turn the UR rate to 2 liters/hr. About halfway through the recirculation procedure, rotate the dialyzers 180 degrees (arterial sides up).**

14. Test for residual germicide per unit policy. After an acceptable test, dialysis should be initiated or recirculation should be continued with the blood pump set at 100 ml/min and the UF rate set at 100 ml/min.

15. If a new dialyzer is used and it has not been preprocessed, use the same **configuration of bloodlines dialysate inflow, outflow and bridging lines indicated above and prime both dialyzers that have been connected in series** per dialysis unit policy.

16. **Double dialyzers can only be used in series for the HEMO Study**.

17. **The prescription for the double dialyzer is given by the DCC.**

18. **The dialysate tubing and Hansen connectors that serves as a bridge between the two dialyzers should be disinfected or sterilized in the same fashion and with the same frequency** as the dialysate tubing and connectors of the dialysis machine, according to the policy of the dialysis unit.

3.5 Calculation of β_2M Clearance

Beta-2 microglobulin clearance is calculated under a 1-pool variable volume model, in which the post-dialysis volume for distribution of beta-2 microglobulin is assumed to be equal to 1/3 the post-dialysis total urea volume. Our current plans are to assume a 0 net rate for beta-2 generation during dialysis under the assumption that the body is in a steady state.

The equation for the clearance is:

$$Kd = Qf \times 1 + \frac{\log(B2_{post}/B2_{pre})}{\log(V/V + Qf \cdot t)}$$

were Kd represent clearance of beta-2, Qf is the ultrafiltration rate, $B2_{post}$ is the post-dialysis beta-2 concentration, $B2_{pre}$ is the predialysis beta-2 concentration, V is 1/3 the total urea volume, and t is the duration of dialysis.

The Membrane/Flux Committee is in the process of working out the details of an additional adjustment for change in hemoconcentration, which will be incorporated into the above formula.

3.6 Assessment of β_2M Clearance Data by the Membrane/Flux Committee

The DCC will provide the Membrane/Flux Committee with updated β_2M clearance data every two weeks as the study progresses. The β_2M clearances will be summarized as a function of reuse method and reuse number, both overall for the whole study, and separately by Clinical Center and Dialysis Unit. Regression analysis will be used to relate the mean β_2M clearance to reuse number for each reuse technique. The results of the regression analyses will be used to compute the average β_2M clearance over the mean number of reuses each dialyzer - reuse combination is actually used. β_2M clearances will be obtained at the F1, F2, F4, visits, and every 2 months thereafter in the high flux group, and F1, F12, F24 and every twelve months thereafter in the low flux group. Assuming uniform patient accrual, this means that the following numbers of β_2M clearances will have been conducted at the indicated time points:

Number of Months After 1st Patient is Randomized	Number of β_2M clearance Measurements
2	150
4	500
6	900
8	1300
10	1700
12	2150
14	2650
16	3150
18	3650

Thus, by 6 months into follow-up, 900 β_2M clearance measurements will be available. By one year into follow-up, 2150 β_2M clearance measurements (about 145 per Clinical Center) will be available. This extensive data will provide a clear picture of the relationship between β_2M clearance and reuse number for the different types of dialyzer-reuse combinations which are commonly used in the study.

The Membrane/Flux Committee will employ this information to determine whether certain dialyzer - reuse combinations should be prohibited or discouraged (and whether others should be encouraged) in order to assure a good separation in β_2M clearance between the low and high flux arms of the study. Note that while the initial criterion for inclusion of dialyzers into the study is based on β_2M clearance at initial use, the subsequent decisions of the Membrane/Flux Committee based on follow-up clearance data will consider the average β_2M clearance of the mean number of reuses the dialyzer - reuse combinations. As an initial guideline, it is considered desirable that the smallest mean β_2M clearance for a high flux dialyzer - reuse combination be at least 4-fold greater than the greatest mean β_2M clearance for a low flux dialyzer - reuse combination. This guideline will be refined as the β_2M clearance data becomes available.

Restriction of the use of a particular dialyzer - reuse combination by the Membrane/Flux Committee will not imply that dialyzer - reuse combination is in anyway contraindicated for clinical use outside of the HEMO study. The restriction of dialyzer - reuse combinations will be done solely for the scientific objective of clarifying the design of the study to distinguish between the effects of low and high flux membranes.

4. UREA KINETIC MODELLING

4.1 Introduction

4.1.1 Urea and á2 Microglobulin (á2M): Markers for the Kt/V and Flux Interventions

The HEMO Study is an investigation of the impact of removal by dialysis of more than standard levels of small molecules (Kt/V intervention) and large molecules (Flux intervention) on the prognosis of hemodialysis patients. The numbers of different small and large molecular weight molecules that accumulate in the body with potentially toxic effects are far too great to measure and manipulate in dialysis prescriptions. Hence a single small molecule, urea, will be used as a marker for small molecular weight toxins, and a single large molecule, á2 microglobulin (á2M), will serve as a marker large molecular weight toxins.

Urea is the most abundant organic compound to accumulate in the body when the kidneys fail. It is a product of protein breakdown (catabolism) in the body, and constitutes about 90% of waste nitrogen accumulating in the body between dialyses. While not toxic itself (except at very high concentrations), urea is considered to be an excellent marker for toxins associated with protein catabolism and for the effectiveness of dialysis.

The molecular weight of á2M of 11,900 daltons is about 200-fold greater than urea's molecular weight of 60 daltons. á2M is too large to pass through conventional "low flux" membranes in appreciable amounts, which generally are able to remove only an insignificant fraction of substances with molecular weight over about 2,000 daltons. By contrast, some high flux membranes can remove up to 40% of á2M during a dialysis session. The normal kidney excretes and/or catabolizes substances with molecular weights up to 60,000 daltons. In the HEMO Study, the amount of removal of á2M will serve as an indicator of the ability of a membrane to remove such large molecular weight proteins.

During the last 15 years or so, the removal of urea during dialysis has been rigorously quantified using kinetic models that allow dialysis prescriptions to be precisely determined. Hence in the HEMO Study the dialysis prescriptions will be fine-tuned in order that patients in the standard and high Kt/V groups have fixed levels of delivered therapy, with a minimal margin of error. By contrast, the quantification of á2M removal is in its early stages, and is still not

fully understood. Consequently, the dialysis prescriptions will not be fine tuned to achieve precise levels of á2M removal. Rather, dialyzers used in the study will be classified as either low or high flux, with the recognition that there will be a substantial variability in the amount of á2M removed in both flux arms of the study, especially in the high flux arm.

Additional material pertaining to the Flux intervention may be found in Section 2 of the Protocol, and in Section 3 of this Manual. This chapter summarizes the concepts of single- and double-pool urea kinetic modelling that are pertinent to Kt/V intervention of the HEMO Trial and provides a detailed description of the kinetic modelling procedures of the Study.

4.1.2 Content of the Kinetic Modelling Chapter

Sections 4.2 and 4.3 provide a non-technical background to the kinetic modelling concepts underlying the Kt/V intervention. This background is essential for understanding the kinetic modelling procedures used in the Study, and also provides a starting point for gaining a clear understanding of the kinetic modelling material in Sections 2 and 4 of the Protocol.

Sections 4.4 - 4.7 deal with the logistical aspects of kinetic modelling in the Study, including the schedule of modelling sessions, the procedures for blood draws and urine collections, the DCC dialysis prescriptions, and other DCC reports that deal with kinetic modelling.

Sections 4.8 - 4.10 give a non-technical conceptual background to troubleshooting aberrant results from kinetic modelling sessions, and provide guidelines for Clinical Centers in carrying out troubleshooting procedures.

Section 4.11 contains the protocol for the Biostat dialysate sampler, which will be implemented at six of the Clinical Centers.

Section 4.12 provides a detailed, technical description of the equations used in the DCC's kinetic modelling programs.

4.2 Single Pool Kinetic modelling

4.2.1 Urea and the BUN profile during and between dialyses

Urea is the most abundant organic compound to accumulate in the body when the kidneys fail. It is a product of protein breakdown (catabolism) in the body, and constitutes about 90% of waste nitrogen accumulating in body water between dialyses. Its small molecular size, high water solubility, and lack of electrical charge allows it to diffuse easily among body water compartments including both the intracellular and extracellular spaces. These properties also facilitate its diffusion across semipermeable membranes allowing rapid removal during therapeutic hemodialysis. Urea is not considered toxic, except at very high concentrations, but is a marker for accumulated toxins that are known to be associated with protein catabolism and for this reason it is also a marker for the effectiveness of dialysis. Urea concentration, traditionally expressed as blood urea nitrogen (BUN), is routinely measured as part of a pre-dialysis clinical biochemical assessment in most dialysis patients. Depending on the intensity and duration of treatment, 50 to 70% of total body urea is often removed during a single dialysis. This causes the concentration profile to oscillate as shown in Figure 4.1. The rapid fall three times per week is caused by dialysis and the slower rise between treatments is caused by the generation of urea within the patient from protein and amino acid breakdown. In stable patients protein and amino acid breakdown are dictated by dietary protein intake. The rate and pattern of rise is also influenced by the patient's fluid intake and native kidney function, both of which attenuate the rise.

The kinetics of urea nitrogen generation and removal are shown simplistically in Figure 4.2, where the body water compartments are considered as a single large pool (single compartment model) the volume of which is V. Urea is added to the pool mostly from the liver where it is generated as an end-product of protein breakdown. Urea is removed from the pool by two routes, the dialyzer and the patient's native kidneys. A key concept in understanding the removal of urea is the urea clearance, which specifies the volume of blood water which is cleared of urea in a particular period of time. During dialysis treatments, the urea clearance by the dialyzer (denoted by Kd) is usually several orders of magnitude higher than residual native

kidney clearance (usually denoted by Kr), so the latter can be ignored. Between dialyses, even small residual renal clearances play an important and quantitatively significant role in reducing the blood urea concentration (see discussion of residual renal clearance in Section 4.7 below).

The drop in blood urea nitrogen (BUN) during the dialysis session depends on the amount of urea removed and the patient's urea distribution volume. Removal of similar amounts of urea from a large patient and from a small patient will result in small and large decreases, respectively, in the BUN. The amount of urea removed in a single pool model can be understood as the product of the product of the total urea clearance during dialysis and the (geometric) mean urea concentration during the dialysis session.

The relationship between BUN concentration and time during dialysis is curvilinear. This is because although dialyzer clearance Kd remains constant, the rate of urea removal is proportional to the urea concentration seen by the dialyzer. Since the concentration of urea is greater at the beginning than the end of dialysis, the rate of fall in BUN early during dialysis is greater than the rate of fall late in dialysis. The rise in BUN during the interdialytic interval depends on the patient's urea distribution volume (V) and the rate of urea generation (G) as shown in Figure 4.3.

4.2.2 Solute removal during hemodialysis

4.2.2.1 Urea removal, dialyzer clearance, and dialyzer intrinsic clearance (KoA)

Dialyzer clearance (denoted Kd) is an expression of solute removal. The units of clearance are usually given in ml/min, although they also might be in L/hr. Kd is usually calculated by multiplying the blood flow rate (denoted Qb) by the percent reduction in urea concentration across the dialyzer:

$$Kd = Qb \times (Cin - Cout)/Cin.$$

In this expression, Cin represents the urea concentration in the inlet (arterial) line going into the dialyzer, and Cout specifies the urea concentration in the outline line leaving the dialyzer. For example, if the blood flow rate is 400 ml/min, Cin = 50 mg/dl, and Cout = 20 mg/dl, then Kd = 400 (50-20)/50 or 240 ml/min. Although the blood leaving the dialyzer contains 20 mg/dl

urea, we could imagine that 160 ml/min of the blood leaving the dialyzer has an unchanged urea concentration, and 240 ml/min has a zero urea concentration. In other words, 240 ml/min of blood are being completely cleared of urea.

Dialyzer clearance depends on blood and dialysate flows. The effect of blood and dialysate flowing countercurrently (that is, in opposite directions) through the dialyzer is predictable and can be expressed mathematically. As blood and dialysate flows are increased, the clearance increases, but by a smaller amount that the increases in the blood and dialysate flows. For example, if we increase the blood flow from 400 to 500 ml/min, we will usually not obtain a 20% increase in clearance, because the diffusive processes taking place in the dialyzer will not take place rapidly enough to maintain a dialyzer outlet BUN of 20 mg/dl. As we raise the blood flow from 400 to 500 ml/min, the dialyzer outlet BUN may increase from 20 to 24 mg/dl. At the faster blood flow rate the clearance is now:

$$Kd = 500\ (50-24)/50 \quad = \quad 260 \text{ ml/min}$$

Thus, a 100 ml/min increase in the blood flow rate may result in only a 20 ml/min increase in dialyzer clearance. The same is true for dialysate flow rate. Usually, increasing the dialysate flow rate from 500 ml/min to 800 ml/min results in about an 8-15% increase in clearance (depending on the efficiency of the dialyzer and the blood flow rate).

Mathematically, for a given solute and for any given dialyzer, one can extrapolate solute clearance to very high blood and dialysate flow rates until one reaches a theoretical maximum clearance that would be found at infinite blood and dialysate flow rates. This quantity is the intrinsic dialyzer clearance, or KoA, and is proportional to the permeability constant of the membrane (K0) multiplied by the membrane surface area (A). For countercurrent flow, the intrinsic clearance of a dialyzer in the absence of ultrafiltration is:

where Qb is dialyzer blood flow and Qd is dialysate flow. The higher the K0A, the greater the dialyzer clearance for any fixed combination of blood and dialysate flow rates.

In principle, K0A is a constant for each dialyzer and solute. However, as we will see below, we are finding that the effective K0A's of many dialyzers actually increase as the dialysate flow rate is increased.

4.2.2.2 In vivo clearance from in vitro measurements

If one knows the intrinsic dialyzer clearance (K0A), one can, using an appropriate equation, estimate the clearance for that dialyzer at any given set of blood and dialysate flow rates. Conversely, if one knows the clearance at any given blood and dialysate flow rate for a dialyzer, one can derive the intrinsic dialyzer clearance (K0A), working the equation in reverse.

The in vitro clearance tends to overestimate the in vivo clearance for several reasons. Dialyzer clearance data provided by the manufacturer is usually based on in vitro measurements using crystalloid or albumin-containing solutions in the blood compartment. Also, the clearances measured under such laboratory conditions tend to be idealized and don't reflect commonly encountered problems such as loss of active fibers in the dialyzer due to clotting, previous reuse, or entrapment of air in the fibers.

Another problem has to do with the fact that urea is contained only in the water fraction of blood flowing through the dialyzer. Blood is a complex mixture of plasma and red cells, both containing proteins which occupy about 7% and 30% of their volumes respectively but contain no urea. The water content of blood varies with the hematocrit and when the hematocrit is 28-32 vol% it will comprise about 90% of the blood volume flowing through the dialyzer. Plasma water content is about 93% of the plasma volume and is independent of hematocrit. This means that dialyzer whole blood clearance is about 10% higher and plasma clearance is about 7% higher than blood water clearance. Also, there is a certain component of clearance due to ultrafiltration.

In the HEMO Study, the intrinsic dialyzer clearances of all study dialyzers will have been measured by one of the Clinical Centers, using crystalloid solutions in the blood compartment. The equations which are described in the appendix are then used to estimate the true in vivo clearance at any given set of blood and dialysate flow rates. In the equations used, a number of corrections are made for the in vivo situation, including a correction for the fact that urea is

contained only in the blood water fraction. Another correction is made based on the fact that the actual blood flow rate being delivered at high blood flow rates is usually less than that estimated from the rate of pump rotation alone.

4.2.2.3 Comparison of blood-side with dialysate-side methods

Solute removal during dialysis can be estimated either from blood or dialysate side methods. With the blood side method, the amount of solute removed is simply the dialyzer clearance (Kd) multiplied by the (geometric) mean BUN during dialysis. Because the decrease in BUN becomes progressively slower during dialysis, the true average BUN during the dialysis session is slightly less than the standard arithmetic mean (postBUN + preBUN)/2. For example, if the preBUN is 100 mg/dl and the postBUN is 30 mg/dl, the arithmetic mean BUN is 130/2 = 65 mg/dl, and the geometric mean (the average taking into account the curvilinear fall in intradialytic BUN) is 55 mg/dl. If the clearance is 250 ml/min, the amount of solute removed can be calculated after first converting all of the quantities to the same units. 55 mg/dl = 550 mg/L = 0.55 mg/ml. 250 ml/min x 0.55 mg/ml = 137.5 mg/min. Thus, on average, during this dialysis session, blood sided modelling predicts that urea was being removed at 137.5 mg/min. During the first part of the dialysis session, when the BUN was high, the rate of urea removal was higher, and towards the end of the dialysis session it was lower. If the dialysis session length was 180 min, the total urea removal should have been 137.5 x 180 = 24750 mg, or 24.75 g of urea.

Solute removal can also be calculated more directly, by simply collecting all of the dialysate in a large tank and estimating its urea concentration. If the dialysate flow rate was 800 ml/min, and the dialysis session length was 180 min, we can expect to have 144000 ml of "spent" dialysate in the drain tank. If the urea concentration of this was 17 mg/dl, or 0.17 mg/ml, the total urea in the drain tank would be 0.17 x 144000 = 24480, or 24.48 g of urea. As will be discussed further, the amounts of urea estimated from blood and dialysate sided modelling rarely agree to this extent. Almost invariably the amount of urea removal estimated by conventional single-pool blood sided modelling is greater than that obtained by collecting the dialysate. The reasons for this will be discussed later, but briefly, access recirculation, cardiopulmonary

recirculation, and compartment effects conspire to lower the actual intradialytic BUN profile during dialysis. For example, assume that the blood sided estimate of urea recovery is as before, about 24.5 g of urea, but we recover only 20 g in the spent dialysate. The two measurements can be reconciled if we realize that the "average" BUN during dialysis may not have been 55 mg/dl, as previously suggested, but 45 mg/dl. If this is the case, then urea removal by blood sided modelling would be 250 ml/min (Kd) x 180 (t) x 0.45 mg/ml = 20250 mg or 20.25 g, much closer to the dialysate results. The effects of access recirculation, cardiopulmonary recirculation, and compartment effects on the intradialytic BUN profile are discussed below.

4.2.3 Kt/V and its relationship to the pre-dialysis/post-dialysis BUN ratio

The Kt/V is a dimensionless ratio representing fractional urea clearance. K is the dialyzer clearance (in ml/min or L/hr), t is dialysis session length (min or hr), and V is the distribution volume of urea (ml or L):

Kt = L/hr x hr = Liters
V = Liters
Kt/V = Liters/Liters = dimensionless ratio.

To understand the meaning of Kt/V more clearly, it is helpful to consider more carefully the individual terms K, K/V, and Kt. As discussed previously, the dialyzer clearance K (often abbreviated as Kd, as in other sections of this Manual) is the amount of blood water which is cleared of urea in a specified period of time. However, the impact of a particular dialyzer clearance on the urea concentration in the blood depends on the size of the patient, or more precisely on the volume of the distribution of urea (V). A particular dialyzer clearance will reduce the urea concentration only half as fast for a patient with total urea volume of 50 liters as for a patient with urea volume equal to 25 liters. Hence, a more appropriate measure for the rate of dialysis for the patient is K/V, the ratio of the dialyzer clearance to the patient's total urea volume. Under the single pool model, K/V represents the fractional reduction in urea concentration in a short time period during dialysis. Since Kt/V is equal to (K/V) X t, Kt/V can be thought of as the rate of dialysis (K/V) multiplied by the duration of dialysis. Alternatively, Kt/V can be expressed as (K X t)/V, i.e., as the ratio of the total volume of blood water cleared

of urea during dialysis and the patient's total urea volume. For example, when we say that Kt/V = 1.0 we must by definition also mean K X t = V, which means that the total volume of blood cleared during dialysis (K x t) is equal to the total body urea distribution volume (V). Both of these interpretations lead to the concept of Kt/V as the total dose of dialysis.

To understand how the post/pre BUN ratio R is related to Kt/V, one first can consider the hypothetical example in which fluid that flows through a dialyzer is completely cleaned in a single pass. In this hypothetical and very unnatural example, all of the fluid that has passed through the dialyzer is temporarily collected outside of the "body" until dialysis stops. At the end of dialysis, the dialyzed fluid is mixed back with any remaining body fluid that has not yet been dialyzed (Figure 4.4).

The clearance "K" of this ideal dialyzer will be equal to the fluid flow through the device. Because the dialyzed fluid is not routed back to the body until the end of dialysis, the inlet BUN concentration (80 mg/dl in this example) will remain constant throughout dialysis. The outlet BUN concentration will always be zero. The volume of fluid cleared by the dialyzer will be K x t. For example, is the flow through the dialyzer is 10 L/hour, and dialysis lasts 2 hours, K x t will be equal to 20 liters.

When Kt/V = 1.0, Kt will be equal to V, the total body water. If we assume, for example, that V is 40 liters, is K is 10 liters per hour, K x t will be 40 liters when t is 4 hours. At that time, a volume equal to the body water will have passed through the dialyzer. By definition, the total body water will have been completely cleared of waste solutes, and the ratio of post-dialysis BUN to pre-dialysis BUN will be zero. Thus, in this idealized situation, a Kt/V of 1.0 represents a complete dialysis, which is impossible to improve upon.

At Kt/V values less than 1.0, the post/pre BUN ratio will be linearly related to Kt/V. For example, if Kt/V is 0.5, this means that 1/2 of the total V has been cleared through the ideal dialyzer. If V is 40 liters at the outset, by the time that Kt/V = 0.5, 20 liters will have been cleared (BUN = 0 mg/dl) and 20 liters will remain (BUN = 80 mg/dl). On mixing these volumes at the end of dialysis, the post-dialysis BUN will be 40 mg/dl, and the post/pre BUN ratio will be 40/80 = 0.50. Similarly, Kt/V values of 0.25 and 0.75 will result in post/pre ratios of 0.75 and 0.25, respectively.

In actual fact, the fluid returns to the body immediately after passing through the dialyzer. As a result, the inlet BUN does not stay constant, but falls. For this reason, there is less efficiency than in a single pass system. Even after running all 40 liters through our ideal dialyzer, even though the outlet BUN was zero, there will still be some urea left in the tank. Even if we run all 40 liters through a second and a third time, the post-dialysis BUN will still not be zero (Figure 4.5).

The BUN in this dialysis system will decline in an exponential fashion as a function of Kt/V (which can be thought of as the number of "passes" through an ideal dialyzer. The mathematical equation expressing the relationship between Kt/V and R (the post/pre ratio) is:

$$R = e^{-Kt/V}$$

where e is a mathematical constant equal to about 2.72. The equation can be rewritten as:

$$R = 2.72^{-Kt/V}$$

solving the equation for Kt/V, one obtains:

$$Kt/V = - \ln (R)$$

where ln (R) is the natural logarithm of R. If we are interested in a Kt/V = 1.0,

$$\text{then} \quad R = 2.72^{-1.0} = 1/2.72 = 0.37$$

This means that, if the post-dialysis BUN divided by the pre-dialysis BUN is 0.37, the entire volume of the "tank" will have been passed through an ideal dialyzer, and Kt/V = 1.0.

4.2.4 Kt/V vs. R: Correction for urea generation (g) and for ultrafiltration (UF):

In actual fact, there is a small amount of urea generated during dialysis, such that, if you dialyze to a Kt/V of 1.0, the post-dialysis BUN will drop from 100 to only about 40 instead of from 100 to 37, and the R at Kt/V = 1.0 will in reality be 0.40 instead of 0.37. Also, volume contraction during dialysis increases the efficiency of dialysis because it limits the dilution effect of the returning blood.

Based on an analysis of single pool urea kinetic equations, a more reliable (but still approximate) equation expressing the relationship between R and Kt/V is:

$$spKtV = \ln (R - 0.008 \times t) + (4 - 3.5 \times R) \times UF/W$$

where spKtV is the single-pool Kt/V, R is the post/pre BUN ratio, UF is the volume of fluid removed during dialysis in liters, and W is the post-dialysis weight in Kg. If V is known, one can substitute V/0.55 for W and obtain even greater accuracy. A nomogram based on this equation is shown in Figure 4.6. From this nomogram it is apparent that, at a spKtV of 1.0, the post/pre BUN ratio would be about 0.40 (URR = 60%) when no fluid is removed, but may be 0.48 (URR = 52%) when 9% of the post-dialysis weight is removed as fluid during dialysis.

In the HEMO Study, exact urea modelling equations described in the appendix will be used to calculate spKt/V, but the results will, in most cases, be quite similar to those depicted on the nomogram shown in Figure 4.6.

4.2.5 Computation of the urea distribution volume (V)

The curvilinear fall in BUN during dialysis predicted by the single pool model can be transformed into a line when the R (R = postBUN/preBUN) is plotted on a logarithmic scale (ln R) on the y-axis vs. dialysis time (t) on the x-axis. This is because:

$$\ln(R) = -Kt/V$$
$$= -(K/V) \times t$$

The slope of this line will be -K/V. The way a urea kinetic modelling program works is as follows (not exactly in this order, however):

Step 1: One inputs the pre and post BUN, t, and UF
Step 2: The program computes the slope of the fall in BUN, or K/V.
Step 3: One tells the program what the value for K should be
This is usually done by inputting a value for Ki, the intrinsic dialyzer clearance, the blood flow rate, and the dialysate flow rate.
Step 4: The program now has an estimate of K/V and K. V is computed by algebra.

Step 3a: An alternate strategy is for one to input a value for V. This may be based on anthropometric formulae or on the average of previous modeled values for V.

Step 4a: In this case, the program, knowing Kt/V, t, and V, computes an estimated value for K.

Comparing the modeled V (Steps 3, 4) with the anthropometric V or previously modeled values serves as a valuable quality assurance check that the pre and post-dialysis BUN samples are reasonable and consonant with the dialysis treatment that has been delivered.

4.2.6 Use of the modeled urea distribution volume (V) to check the validity of the data

The modeled V can then be compared with predicted or expected V calculated as explained above; the two values should match within 15-20%. If a large discrepancy is observed, an error has occurred. Examples of this type of error include problems with the BUN measurement, erroneous blood or dialysate flow rates, improper recording of time spent on dialysis, recirculation of blood in the access device, or clotting in the dialyzer, each of which reduces the effective clearance. The discrepancy between modeled and expected V becomes a flag that something is wrong that needs attention. This aspect of modelling serves as a quality

assurance tool.

The expected value of V can be obtained by at least two methods. The first method makes use of established anthropometric formulae that describe V in the normal population as a function of height, weight, sex, and age. This method has a large variance but is a useful first approximation. Another more widely used method is to average values for V obtained from previous modelling sessions, excluding those with identifiable errors. The latter is more patient-specific but suffers from the possibility of consistent errors in Kd. To use this method, careful attention must be given to measurement or estimation of Kd, taking into account factors such as reuse, blood and dialysate pump accuracy, and recirculation of dialyzed (venous) blood through the access device. The latter is discussed in more detail below (section 4.2.8).

Another potential source of error in V is the disequilibrium phenomenon. Disequilibrium always reduces the effectiveness of therapeutic dialysis because it reduces the amount of solute removed from the body. The single-compartment equations fail to consider disequilibrium and predict that more solute is removed than reality. The overestimation of solute removal should cause an overestimation of V, because V is the amount removed divided by the change in concentration (-C):

$$V = (\text{amount removed})/-C$$

However, -C is also overestimated by the single compartment model. The errors in the numerator and in the denominator of the above equation are offsetting and in most cases are nearly equivalent. This explains the accuracy of the single pool method for calculating V; the two oppositely directed errors tend to cancel each other. An exactly analogous process can be used to compare modeled Kd with expected Kd. If the clinician has confidence in a value for V, regardless of its source, the modeled value of K/V can be used to calculate Kd. Subsequent comparison of modeled Kd with the expected Kd provides a measure of quality assurance that is analogous to the above comparison of modeled V with expected V.

4.2.7 Computation of urea generation (G) and protein catabolism (PCR)

Most catabolized proteins are broken down to amino acids which are then reincorporated

into other proteins. This is the total protein catabolic rate. Before they are used to resynthesize protein, a small fraction of the amino acids are irreversibly broken down to urea and CO_2. This more complete breakdown of protein is called the net protein catabolic rate. All urea is generated from protein nitrogen but a small percentage of protein nitrogen is converted to other nitrogenous end-products. Urea appearance, therefore, always slightly underestimates net protein catabolism but the underestimation is predictable because the generation rate of non-urea end-products is a function of lean body mass. This means that urea generation can be used to accurately assess net protein catabolism, a useful measure of dietary adequacy and nutritional well being. A linear relationship between urea appearance and protein catabolism was found by Borah, et al., during a careful metabolic balance study in hemodialyzed patients:

$$PCR = 9.35\ G + 11$$

G is the urea generation rate in mg/min. PCR is often normalized to an adjusted body weight. Instead of using the patient's actual body weight a more uniform weight equivalent is obtained by dividing the patient's urea volume (V) by 0.58 liters/kg, the fractional water content of the average adult. This allows comparison of PCR in patients of different size. Although not rigorously proven, this method of normalization is rational because the majority of urea volume is cell water and the body cell mass is the major repository of protein from which urea is derived. In the absence of edema, body water correlates closely with lean body mass. The latter excludes the majority of fat and bone, both of which can be a significant fraction of body mass but generate little urea. When factored by normalized body weight, the normalized protein catabolic rate (PCRn) is expressed:

$$PCRn = 5420\ G/V + 0.17$$

Urea generation is derived from single-pool urea modelling as noted above (section 4.2.1) from the change in urea concentration between dialyses. This approach creates two problems; it ignores the rebound in urea concentration that invariably occurs post-dialysis and it bases the estimate of urea generation on a single interdialysis interval. The first problem can only be addressed by methods that consider urea disequilibrium (see sections 4.2.8, 4.2.9, and 4.3). The second problem can be partially resolved by using two BUN values instead of three to calculate

G. Paradoxically, use of only two BUN values to calculate G results in a value that is more representative of the average G for the preceding week and is less dependent on any single interdialysis interval. Calculation of G using two instead of three BUN values requires a more extensive iterative approach. The calculator or computer uses a Study-and-error approach while calculating the weekly BUN profile in an attempt to arrive at a pre-dialysis BUN one week later that matches the measured pre-dialysis BUN. It does this by repeatedly adjusting G and then recalculating the pre-dialysis BUN until a matching value is obtained (Figure 4.7).

4.2.8. The effect of access recirculation

Figure 4.8 depicts recirculation at the level of the access device. When dialyzer blood flow exceeds flow in the access device, recirculation must occur or the dialyzer arterial pressure will fall and blood flow through the dialyzer will stop. Reflow of blood from the dialyzer venous line to the arterial line relieves the negative pressure build up at the dialyzer blood inlet and allows dialysis to proceed. Mixing of dialyzer venous blood with incoming (afferent) blood in the access device lowers the concentration of solute entering the dialyzer. Although this has no effect on dialyzer clearance, it can markedly reduce the rate of solute removal, because the amount of urea removed by the dialyzer at any given point in time is the clearance multiplied by the incoming urea concentration. If the incoming urea concentration is diluted by 10% due to access recirculation, all other things being equal, the effective dialyzer clearance will be reduced by 10% also.

The fraction of incoming arterial blood that consists of recirculated blood is easily determined from simultaneous measurements of solute concentrations in the arterial line, venous line, and access inlet. The latter can be measured at the arterial port if blood flow is slowed briefly to eliminate the recirculation:

$$AR = 100\ (Cu - Ci)/(Cu - Co)$$

AR is the % access recirculation, Cu is the solute concentration at the access immediately upstream of the vascular access, Ci is dialyzer inlet concentration, and Co is dialyzer outlet concentration.

The ratio of inlet to upstream urea concentration (Ci/Cu) is equal to the ratio of access

clearance to dialyzer clearance. For example, assume that we have a situation where Cu = 100, Ci = 90, and Co = 30. In this case, AR will be 100 x 10/70, or 14%. At any given point in dialysis, Ci/Cu will be 0.9, and access clearance will be only 90% of Kd. Assume that a patient is normally dialyzed to a spKtV of 1.2, and that there is no access recirculation. If 14% access recirculation develops, and if the ratio of the outlet/inlet BUN is about 0.30, there will be an overall 10% reduction in clearance, and the spKt/V will fall to about 1.1. The urea kinetic modelling program will encounter a higher than expected post-dialysis BUN. It will calculate a lower value for K/V. Because the kinetic modelling program still assumes that the same value of K is being delivered, it will compute a value for V that is increased by 10%.

Access recirculation may vary throughout the dialysis, depending on factors that influence peripheral blood flow, such as blood pressure and cardiac output. Thus a single determination or measurement of AR may not be representative of what happened for a given dialysis session. In particular, the amount of AR may increase late in dialysis in some patients due to a fall in access blood flow due to a fall in cardiac output.

4.2.9. Cardiopulmonary recirculation (CPR)

CPR is similar to access recirculation, although this is not apparent on first glance. In general, recirculation during dialysis can be said to exist whenever blood from the dialyzer outlet returns to the dialyzer inlet without first having traversed a bed of urea-rich tissues. Such recirculated blood will not have picked up any urea (or any other waste solutes), and its journey from dialyzer outlet to inlet will have been a fruitless one. Recirculated blood acts to dilute the inlet blood, causing a reduction in the effective clearance and in the amount of solute removal. Whereas with AR the blood journeys from dialyzer outlet to inlet via a short loop pathway represented by the vascular access, with CPR the recirculating pathway is a much longer loop represented by the pathway through the heart and lungs. The CPR loop is that fraction of cleared blood that, after returning from the dialyzer outlet to the heart flows back to the dialyzer instead of to the peripheral tissues.

CPR is not a necessary side-effect of dialysis. CPR only occurs when a dialyzer is being fed from the arterial side of the circulation. When a dialyzer is fed from a central vein, CPR is

by definition zero, because ALL of the blood leaving the dialyzer outlet must traverse the peripheral tissue beds before returning to the dialyzer.

The effect of CPR on dialyzer clearance will be proportional to the A/V gradient that is established during dialysis. If the ratio of arterial to venous urea is 0.93, for example, then a dialyzer attached to the arterial circulation will, at a given point in time, remove only 93% as much urea as one attached to the venous circulation.

Most of the A-V gradient established during dialysis (all of it, initially) is due to cleared blood returning from the dialyzer to the heart. Whenever dialysis is interrupted, the A-V gradient will rapidly diminish, resolving almost completely by 1-2 min after dialysis has been stopped. Because the A-V gradient is typically only about 7% during high efficiency dialysis, the effect on urea removal is small, but the rise in BUN that occurs in an arterial access whenever dialysis is stopped can be a source of confusion when measuring access recirculation. The time constants of rebound due to AR and CPR are discussed more fully in Section 4.3.1.

FIGURE LEGENDS FOR SECTION 4.2

Figure 4.1. Serum urea concentration (BUN) profiles in two patients dialyzed three times weekly. Both receive the same amount of dialysis but patient A has a higher generation rate per liter of urea space which accounts for the higher BUN.

Figure 4.2. Single-compartment model of urea kinetics. The amount of urea found in the body's total water space (V), represented by the rectangular box, is V C where C is urea concentration. Urea enters this space only from the liver where it is generated from protein breakdown. G is the rate of urea generation usually expressed in mg/min. The two exit routes are the patient's native kidneys which are often nonfunctional and the dialyzer which operates intermittently. The rate of removal in mg/min is K.

Figure 4.3. A single BUN profile. The intradialysis curve from C1 to C2 is determined by the dose of dialysis (Kt/V). The intradialysis curve from C2 to C3 is a complex function of the normalized protein catabolic rate (PCRn), residual function, and fluid gain.

Figure 4.4. Relationship between Kt/V and post/pre BUN ratio when dialyzed blood is not returned to the patient until after completion of dialysis. In this case the inlet BUN remains constant. Urea removal is complete when Kt = V, or Kt/V = 1.0.

Figure 4.5. Relationship between Kt/V and post/pre BUN ratio when dialyzed blood is returned to the patient continuously throughout the dialysis session. In this case, even when the entire volume (V) has passed through the ideal dialyzer, there is still 37% of the original amount of urea remaining in the tank; i.e., at Kt/V = 1.0, URR = 63%. The curvilinear relationship between Kt/V and R can be described by equations in the text.

Figure 4.6. Actual relationship between Kt/V and post/pre BUN ratio (or URR) taking into account urea generation and the effects of volume contraction. We now see that a Kt/V of 1.0 can correspond to URR values ranging from 52% (when UF/W = 0.09) to 40% (when UF = 0).

Figure 4.7. Two-BUN method for calculating the urea generation rate (G). In panel A, G is approximated at 9.9 g/min. Using equation 4.3, pre-dialysis and post-dialysis BUN values are calculated for each treatment and the final pre-dialysis value one week later is compared to the measured pre-dialysis BUN. The calculated value is too high, so G is reduced to 7.3 mg/min and

the above process is repeated. The second calculated pre-dialysis BUN is too low as shown in panel B. The computer program systematically adjusts the value of G and repeats the calculations until the pre-dialysis BUN matches the measured value as shown in panel C.

Figure 4.8. Access recirculation. If blood flow through the dialyzer is 500 ml/min and the access can deliver only 400 ml/min either flow will stop as pressure limits are exceeded or the additional 100 ml/min must come from the venous return line.

4.3 Double-Pool Kinetic modelling

In the single pool model, as described above, urea within the body is assumed to occupy a single pool of volume, the urea concentration of which is in equilibrium with the urea concentration of the mixed venous blood. If urea is removed from only a single body pool, there should be no abrupt increase in the BUN (measured at the vascular access site) beyond that occurring in the first 2 minutes due to dissipation of the A-V gradient. There should be a slight increase in BUN over time due to continued generation of urea by the body, but this increase usually amounts to only about 1 mg/dl per hour. In actual fact, a much larger post-dialysis urea rebound normally is observed, especially when a highly efficient dialysis treatment has been given. Although initially this rebound was thought to be perhaps due to enhanced urea generation during the immediate post-dialysis period, it has since become clear that the magnitude of the rebound can only be explained if we reject the notion that urea is effectively removed from a single body space during dialysis. Such observations have led to multicompartment models of urea kinetics. The simplest such model assumes that urea sequestered within cells during dialysis, but that urea in the extracellular space is in rapid equilibrium with the blood. In this extracellular/intracellular model, the intracellular water is poorly dialyzed with respect to the extracellular water. As a result, at the end of dialysis, intracellular urea levels are higher than those in the extracellular space, and rebound occurs due to movement of urea from cells to the extracellular water after dialysis. An alternative model is the regional blood flow model, which assumes that urea is sequestration during dialysis occurs not within cells, but rather within those organs in which the ratio of blood flow to urea content is low (Figure 4.9). This group of organs is made up predominantly of muscle, and receives only 15-20% of the cardiac outflow, whereas it contains up to 80% of the total body urea. With the regional blood flow model, muscle tissue is poorly dialyzed, such that at the end of dialysis muscle urea concentration exceeds that of better perfused organs such as the abdominal viscera. In this model, post-dialysis urea rebound is a result of urea movement from muscle to better perfused organs after dialysis. At the present time there is no compelling reason to chose the extracellular/intracellular or the regional blood flow model. Both models can adequately explain the occurrence of post-dialysis urea rebound.

However, the regional blood flow model predicts that urea rebound should be higher in patients with a large muscle mass and/or in whom muscle perfusion is low. Such patients may include those with low cardiac output and high peripheral vascular resistance, and patients with higher hematocrits.

4.3.1. Post-dialysis urea rebound

The role of post-dialysis urea rebound in dialysis adequacy is quite important. For example, in a single pool model, a urea reduction ratio of 60% (in a patient with no volume change) means that 60% of the urea in the body has been removed during a given dialysis treatment. On the other hand, with a high degree of post-dialysis urea rebound, the BUN may rise substantially during the initial hour after dialysis, due to equilibration of urea between poorly dialyzed and well-dialyzed body compartments. The URR might then rise to 50% 1 hour after dialysis. If one measures only the post-dialysis BUN, then, one can overestimate the amount of urea removed during dialysis (60% vs. 50%). One can estimate an "equilibrated" URR as that which would be observed 1 hour after dialysis, after correction for urea generation during the 1-hour rebound period. In the single-pool model, the URR is closely related to the fractional urea clearance (single-pool Kt/V, or spKt/V). Failure to account for post-dialysis urea rebound will thus also overestimate the "equilibrated" Kt/V. We define here the "equilibrated Kt/V", or eKt/V as the Kt/V based on a URR measured after equilibration, with appropriate corrections for volume contraction and urea generation.

How long does it take for urea in poorly and well-dialyzed body compartments to equilibrate after dialysis? Data from a number of investigators suggest that equilibration is almost always complete by 60 minutes after dialysis. Because it is impractical to ask patients to wait around for 60 min after dialysis, the HEMO pilot centers attempted to fit a curve to the post-dialysis urea rebound profile, to attempt to predict the maximum rebound based on multiple rebound points 2-30 min after dialysis. Urea generated during the equilibration period was subtracted in the analysis. It was found that the curvefit predicted an equilibrated BUN sample that was about 4% higher than the BUN in a sample obtained 30 min after dialysis.

It should be emphasized that there are 3 components to post-dialysis urea rebound when

post-dialysis blood is drawn from the vascular access site. The first, occurring almost immediately after dialysis has ceased and the "dead space" in the dialysis tubing has been cleared, is due to access recirculation. The second, which occurs with an arteriovenous access site only, is due to dissipation of the A-V gradient created in the blood by the dialyzer (cardiopulmonary recirculation effect). This component is largely complete by 2 min after dialysis (Figure 4.10) The third component, which is due to the "compartment" effect, requires 30-60 min to complete.

4.3.1.1 Effect of rebound on Kt/V

In the pilot study, both a single-pool Kt/V (spKt/V) and an equilibrated Kt/V (eKt/V) were calculated. The spKt/V was based on a post-dialysis BUN sample taken 10 sec after slowing the blood pump to 100 ml/min (to compensate for access recirculation). The equilibrated Kt/V (eKt/V) was based on a 30 min post-dialysis BUN sample corrected upwards by 4% to compensate for delayed (30-60 min) rebound. On average, the eKt/V was about 0.2 Kt/V units lower than the spKt/V. In the HEMO protocol, we will be targeting eKt/V levels of 1.0 vs. 1.4. On average, this will translate into single-pool Kt/V levels of 1.2 vs. 1.6. Thus, patients receiving the lower Kt/V amount will still be getting a spKt/V level that is considered to be quite adequate at the present time, and a level that was recommended by a recent NIH consensus committee on dialysis adequacy.

4.3.2. Estimating the post-dialysis rebound and eKt/V

It is intuitively obvious that, if there is a disequilibrium that develops within the body during dialysis, the effects of this disequilibrium will be most pronounced when the rate of dialysis relative to the body water (K/V) is high. Based on a mathematical analysis of the two main multicompartment models of urea kinetics, Daugirdas and Schneditz derived an expression relating the difference in spKt/V and eKt/V (which can be written as a "delta" Kt/V, or -Kt/V), and the efficiency of dialysis, K/V. The equation derived was:

$$-Kt/V = a\,(K/V) - b$$

Where a and b are values that depend on the degree of intracellular/extracellular or organ disequilibrium in the body. Based on their patient data, and based on predictions of cardiac

output, vascular access flow, and flow to muscle and bone, a was assigned a value of 0.6 and b
a value of 0.03. Thus, the equation becomes:

- Kt/V = 0.6 (K/V) - 0.03 (Daugirdas-Schneditz rate equation)

In this equation, the K/V term is defined as the single-pool Kt/V divided by the number
of hours of dialysis (Kt/V divided by t = K/V). Hence, if the spKt/V is 1.2 delivered over 3
hours, K/V will be 0.4, and -Kt/V will be 0.6 x 0.4 - 0.03 = 0.24 - 0.03, or about 0.21. If the
spKt/V is 1.6 delivered over 4 hours, K/V will again be 0.4, and -Kt/V will again be 0.21.
Using this equation, we see that a spKt/V of 1.2 delivered over 3 hours or a spKt/V of 1.6
delivered over 4 hours will result in eKt/V values of about 1.0 and 1.4, respectively. Of course,
the K/V will not always be 0.4. In the HEMO study, the K/V may conceivably range from 0.25
- 0.70 spKt/V units/hr. This would translate into -Kt/V values of 0.12 - 0.39 units.

In the HEMO pilot study, the Daugirdas-Schneditz rate equation was used to compute the
eKt/V, and this was compared with the "true" eKt/V calculated based on a measured 30 min post-
dialysis sample. A very good agreement was found between the two results, especially after
results were averaged for each patient. The HEMO pilot study results suggested that most
patients, on average, have a predictable amount of urea rebound after dialysis, and that this
rebound is primarily determined by the efficiency of dialysis, or K/V. In the HEMO pilot study,
not a single patient was found in whom rebound was consistently very high or very low. It
remains possible that such patients will be encountered in the main HEMO study, but it was
decided that measurement of urea rebound on a regular basis was impractical. It was decided
to measure the actual 30 min post-dialysis serum urea level at F4 and F36. These measurements
will serve to validate the Daugirdas-Schneditz rate equation estimate of -Kt/V.

4.3.2.1. When a venous access is use

The Daugirdas-Schneditz rate equation estimate for -Kt/V is based on total urea rebound
occurring between 20 sec after dialysis (to correct for access recirculation) and 60 min after
dialysis. Close to 30% of this rebound is due resolution of the A-V gradient created during
dialysis due to return of cleared blood to the heart. In patients being dialyzed with a venous
(internal jugular, femoral, subclavian) access, the blood being sampled after dialysis is venous,

and not arterial blood. The spKt/V is really a "venous" spKt/V instead of an "arterial" spKt/V.
The venous spKt/V (Kt/V spven) cannot not be used with the Daugirdas-Schneditz rate equation
without making appropriate adjustments: otherwise the rebound and the -Kt/V will be
overestimated, and the eKt/V will be underestimated. For this reason, it is very important to
inform the Data Coordinating Center whenever a modelling session is being done with a venous
vascular access.

4.3.3. Estimating post-dialysis rebound and eKt/V from the intradialytic BUN profile: the
Smye method

When urea is removed from a single compartment, the amount of urea removed at a given
time is equal to the dialyzer clearance multiplied by the urea concentration. For example, if the
dialyzer clears 200 ml/min (corrected for blood water), and the blood water urea concentration
is 100 mg/dl, or 1 mg/ml, the dialyzer is initially removing about 200 mg/min of urea. Near the
end of dialysis, assume that the BUN is 20 mg/dl, or 0.2 mg/ml. Even though dialyzer clearance
has remained constant, urea removal is only 200 ml/min x 0.2 mg/ml = 40 mg/min. Thus, during
dialysis, the rate of fall in the BUN, initially rapid, tends to level off late in dialysis. In
pharmacokinetics, whenever removal rate is directly proportional to concentration, removal can
be described by a set of equations called "first order" kinetics. The profile of the BUN over time
will be an exponential curve. When plotted on graph paper using a logarithmic scale for BUN
concentration, the exponential curve becomes a straight line with a slope that is approximately
equal to -K/V.

When urea is being sequestered somewhere in the body during dialysis, however, the
initial fall in BUN during dialysis is even more rapid, because urea is initially being removed
from only a portion of the total body water. Late in dialysis, the BUN decrease becomes very
slow, because now urea from sequestered body spaces is entering the "proximal" compartment
to partially offset removal from the "proximal" compartment by dialysis. With urea
sequestration, then, the intradialytic urea profile has an exaggerated "belly" when compared with
the intradialytic urea profile from a patient with minimal urea sequestration during dialysis. The
depth of the "belly" in the curve, or urea "inbound" will be greater when the dialysis efficiency

is high, and also when the degree of urea sequestration is great. The amount of urea "inbound" can be measured by obtaining one or more intradialytic urea samples about 1 hr into dialysis. If one plots all of the BUN values on a logarithmic scale using semi-log paper, the sample obtained 1 hr into dialysis should fall on a line connecting the pre and post-dialysis BUN. If it does not, then some degree of urea inbound is present. The amount of urea inbound is the distance between the actual BUN and the line connecting the pre and post-dialysis BUN values plotted in this way.

Mathematically, the same factors that work to create post-dialysis urea rebound (high dialysis efficiency, and a high degree of organ or intracellular urea sequestration), also work to create a large urea "inbound" (or accelerated early fall in the intradialytic BUN profile). It is not surprising that intradialytic urea "inbound" and post-dialysis urea rebound can be mathematically linked. Using a simplified 2-pool model of urea kinetics, Smye derived an equation to estimate the equilibrated post-dialysis BUN (Ceq) from the pre (C0) and immediate post-dialysis (Ct) BUN values, and from the intradialysis BUN (Cintra):

$$Ceq = C0\ e^{-at}$$
where $a = 1/(t-tintra) \times \ln(Cintra/Ct)$

In this equation, t is the dialysis session length, and tintra is the time into dialysis that the intradialytic specimen is drawn. For example, if the dialysis session length (t) is 180 min, the pre and post BUN values are 100 and 30 mg/dl, respectively, and 60 min (tintra) into dialysis the BUN value is 60:

$$a = 1/(180-60) \times \ln(60/30)$$
$$= 100 \times 0.00833 \times 0.693$$
$$= 0.005774$$

and
$$Ceq = 100 \times \exp(-0.005774 \times 180)$$
$$= 100 \times 0.3536$$
$$= 35.4 \text{ mg/dl}$$

In the HEMO pilot study, the ability of the Smye method to predict Ceq and eKt/V was assessed. The Smye method was found to be generally accurate, although on average, Ceq and eKt/V predicted using the intradialytic BUN sample and the Smye method was no better, and was in fact slightly worse, that the eKt/V predicted using the Daugirdas-Schneditz rate equation. In the full HEMO Study, intradialytic samples will be obtained 60 min into dialysis at F4, F12,

F24, F36, F48, and F60. The purpose of these Smye measurements is to obtain an independent prediction of eKt/V, and to further validate the Daugirdas-Schneditz rate equation. Also, if the amount of post-dialysis urea rebound predicted by the Smye method in a given patient is consistently higher than that predicted by the Daugirdas-Schneditz rate equation, such a patient might belong to a subgroup of patients in whom rebound is aberrant for some reason. If such patients are identified, an attempt will be made to see if they can somehow be characterized. For example, there is preliminary data that anemic patients have less post-dialysis rebound than those treated with erythropoietin. Examination of intradialytic urea inbound may allow us to identify factors that affect urea inbound, and, by assumption, rebound in the HEMO study population.

4.3.3.1. Importance of access and cardiopulmonary recirculation on the Smye estimate of eKt/V

It is important to understand that access recirculation and cardiopulmonary recirculation also depress the intradialytic urea profile, and contribute to urea "inbound". With access recirculation (AR), an AR-effect on inbound will be seen when the intradialytic (60 min) sample is obtained at full blood flow. The urea inbound will be due to the fact that the BUN measured 1 hour into dialysis is lower than expected, due to dilution of the urea in the dialyzer inflow line by recirculated blood. Similarly, with cardiopulmonary recirculation, there will be a rapid drop in the BUN concentration measured at the dialyzer inflow line due to rapid establishment of an A-V gradient during dialysis. Theoretically, the Smye equation, which links inbound to rebound, should work whether or not AR or CPR are present, because in each case, the effect causes both an inbound and a proportionate rebound. However, the intradialytic sample and the post-dialysis sample must be obtained under exactly the same conditions; i.e., they should show the effects of AR and CPR to the same degree. There is one theoretical problem: the Smye method assumes that the factor causing urea inbound is constant throughout the dialysis session. It is known that AR, for example, can be absent 1 hour into dialysis, but be marked at the end of dialysis. Also, the A-V gradient due to CPR can increase in the course of dialysis, due to a falling cardiac output during dialysis.

In the HEMO Study, to effect the Smye technique, we will be obtaining six BUN's during

dialysis. The first sample is the pre-dialysis sample. One hour into dialysis, we will obtain two samples at full blood flow from the dialyzer inflow and outflow line. The outflow line sample will be used to assess dialyzer clearance, and will also be used to quantify the amount of AR present. Another sample will be obtained from the dialyzer inflow line 20 sec after slowing the blood pump to 80 ml/min. Finally, at the end of dialysis, we will obtain a sample at full blood flow, and one after slowing the blood pump to 80 ml/min for 20 sec. In using these samples to derive the Smye estimate, we will concentrate on the intradialytic and post-dialysis samples obtained 20 sec after slowing the blood pump to 80 ml/min. Each of these samples will reflect the actions of CPR and urea sequestration, but should be free of contamination by AR. A comparison of the BUN at the samples obtained at full blood flow and those obtained after 20 sec of slow flow should give us an estimate of AR. In the absence of AR, the BUN values for these sample pairs should be very similar. The Smye method will not work if the intra- or post-dialysis samples are drawn incorrectly. For example, if the intradialysis sample is drawn after 20 sec slow flow, but the post-dialysis sample is drawn after simply stopping the pump, without clearing the dead space volume in the line, the post-sample might be artefactually low due to AR. The line connecting the pre and post-BUN on log-paper will have an unusually steep slope, and the degree of urea "inbound" will be underestimated. The reverse also may happen. If the intradialytic sample is drawn 20 sec after slowing the flow, but the post-dialysis sample is drawn 2 min after slowing the flow, the post-dialysis sample will be drawn after A-V equilibration. The slope of the line connecting the pre and post BUN will be too shallow, and the amount of intradialytic inbound (and rebound) will be overestimated.

4.3.4. Volume estimates

In single-pool urea kinetics, the Kt/V is determined primarily by the urea reduction ratio (URR). The value for t is known, so one can easily compute K/V. The value for V obtained then depends entirely on the value of K that is estimated or measured. All other things being equal, then, if spKt/V is a 12-20% overestimate of the true or eKt/V, one would expect the single-pool volume (V) to be underestimated by the same amount 12-20%. For example, if spKt/V is 1.2, eKt/V is 1.0, and t is 3 hours, and if we assume K to be 200 ml/min= 12 L/hr,

spK/V would be 1.2/3 = 0.3. If spK/V is 0.3 and K is 12, then single pool V would be = 12/0.30
= 40 liters. Now if we repeat these calculations using eKt/V, which was 1.0, we get a value for
"equilibrated" K/V of 0.25, and a value for V of 12/0.25 = 48 liters. Paradoxically, the incorrect,
overestimated spKt/V value of 1.2 give a volume of 40 liters that is much closer to the patients
true urea distribution volume than the 48 liters calculated using the correct eKt/V.

The reason for this apparent paradox is the operation of two counterbalancing errors. In
patients with urea sequestration, post-dialysis BUN will be artefactually low, and Kt/V will be
overestimated. However, urea sequestration will also result in a lowering of the intradialytic
BUN profile during dialysis. Thus, the true effective K is actually substantially lower than the
dialyzer clearance Kd. Thus, we overestimate Kt/V by about 20%, but we also overestimate K
by about the same amount. Dividing the inflated Kt/V by the inflated value for K gives us a
more or less accurate value for V. In contrast, when the "correct" Kt/V, the eKt/V is used, the
inflated value for K results in an inflated value for V. To calculate V correctly using eKt/V, the
equilibrated K, and not the dialyzer K must be used. The quirk in the urea modelling equations
that causes these counterbalancing errors does not work for all levels of Kt/V, but does hold for
Kt/V values in the range of 1.0-1.6.

FIGURE LEGENDS FOR SECTION 4.3

Figure 4.9. Flow-dependent solute disequilibrium. Circulation of blood through the heart and
lungs to peripheral organs and capillary beds is shown as a series of arrows. The concentration
of dialyzable solute in the peripheral compartments is represented by various shades of grey.
Circuits with less flow per volume of tissue lose solute at a lower rate than well-perfused tissues.
The circuit with the highest flow per volume of tissue passes through the access device, the
so-called cardiopulmonary circuit. The inequality of tissue perfusion creates solute gradients
throughout the body which reduce the efficiency of dialysis.

Figure 4.10. The time constants for the 3 types of rebound that can be encountered during
dialysis: Access Recirculation (AR), Cardiopulmonary recirculation (CPR), and Regional Blood
Flow/Compartment effects. The effects of AR are reversed within 10-20 sec, just long enough

for the deadspace in the inlet blood line to be cleared. The effects of CPR begin to reverse within 15-30 sec, and are completely reversed within 1-2 min. The RBF/Compartment effects require 30-60 min to reverse. Accordingly, samples obtained immediately after dialysis will not reflect any of these rebound effects. Samples obtained after 20 sec will reflect AR effects only. Those obtained 2 min after dialysis will reflect rebound due to both AR and CPR, whereas samples obtained 30-60 min after dialysis will account for all 3 rebound effects.

4.4 Logistics of Urea Modelling in the HEMO Full-Scale Study

4.4.1 BUN measurements during kinetic modelling sessions

In the HEMO Study, kinetic modelling sessions will be done weekly during baseline (with the exception of Week 4) and monthly during follow-up. Modelling sessions will require either 2, 3, 6 (troubleshooting), or 7 BUN measurements as follows:

2 BUN Sessions:	1. Pre-dialysis
	2. 15 second (line disconnect) or 20 second (sampling port) post-dialysis inlet slow
3 BUN Sessions:	1. Pre-dialysis
	2. Immediate post-dialysis inlet full
	3. 15 second (line disconnect) or 20 second (sampling port) post-dialysis inlet slow
6 BUN Troubleshooting Session:	1. Pre-dialysis
	2. 1 hour outlet full
	3. 1 hour inlet full
	4. 1 hour inlet slow
	5. immediate post-dialysis inlet full
	6. 15 second (line disconnect) or 20 second (sampling port) post-dialysis inlet slow
7 BUN Sessions:	1. Pre-dialysis
	2. 1 hour outlet full
	3. 1 hour inlet full
	4. 1 hour inlet slow
	5. immediate post-dialysis inlet full
	6. 15 second (line disconnect) or 20 second (sampling port) post-dialysis inlet slow
	7. 30 minute post-dialysis

The 2-BUN sessions will be used for the routine kinetic modelling throughout the study. The results from these sessions will be used to generate and update dialysis prescriptions and for monitoring the levels of eKt/V which are actually delivered. As is done in several currently available kinetic modelling computer programs, in the HEMO Study the DCC will calculate and report to the Clinical Centers the important kinetic parameters under the 1-pool model variable volume model, including single pool Kt/V, the urea reduction ratio (URR), single pool urea volume, and PCR. In addition to this information, the DCC will also use the Daugirdas/Schneditz rate adjustment (see Section 4.3.2 and Chapter 4 of the protocol) to calculate

equilibrated values of these parameters which take into account the expected post-dialysis
rebound in urea concentration.

A 3-BUN kinetic modelling session will be performed in the fourth week of baseline.
This session differs from the routine 2-BUN modelling sessions by requiring an immediate post-
dialysis BUN at full blood flow in addition to the 15 second (line disconnect) or 20 second
(sampling port) post-dialysis BUN at slow flow. The additional post-dialysis BUN will be used
to estimate access recirculation at the end of dialysis.

Special 6-BUN trouble shooting sessions will be required under certain conditions (see
4.4.7 - 4.4.8). The 6-BUN troubleshooting session includes the blood draws of the 3-BUN
sessions plus 1 hour full outlet, 1 hour full inlet, and 1 hour slow inlet samples. The 1 hour
slow inlet sample is obtained 15 seconds (line disconnect) or 20 seconds (sampling port) after
the 1 hour full inlet sample. The 6-BUN sessions will be used to obtain all of the kinetic
parameters calculated in the 2-BUN sessions plus access recirculation at 1 hour into dialysis and
at the end of dialysis.

8-BUN kinetic modelling sessions will be carried out at month 4 and at 3 years follow-up.
The 8-BUN sessions include all of the blood draws in the 6-BUN sessions, plus an immediate
post-dialysis full flow outlet sample and an additional sample 30 minutes post dialysis. The
8-BUN sessions will be used to calculate estimates of recirculation as in 6-BUN sessions, and
will also provide an estimate of equilibrated Kt/V based on the urea rebound that is actually
observed 30 minutes after dialysis. This estimate of equilibrated Kt/V will also be used to
corroborate the Daugirdas rate adjustment approach being used for routine modelling. 7-BUN
sessions will also provide an estimate of equilibrated Kt/V using the Smye technique (see Section
4.3.3). The Smye technique estimates the equilbrated Kt/V based on the amount of decline in
urea in the first hour of dialysis, and will be used to corroborate the estimate of eKt/V based on
the Daugirdas/Schneditz rate adjustment.

See Figures 4.11-4.12 and Tables 4.4.1.1a - 4.4.1.1.b below for concise summaries of the
schedule of kinetic modelling sessions in baseline and follow-up.

During follow-up, it is desirable (but not required) that the dialysis of the kinetic modelling

session and the two preceeding dialyses were held according to the patient's regular weekly
schedule.

4.4.2 Detailed Procedures for Drawing Blood during Kinetic modelling Sessions

At least two blood samples (pre-dialysis and post-dialysis) will be drawn during all modeled dialyses. Kinetic modelling will be done weekly during BASELINE and monthly during FOLLOW-UP. Additional samples will be taken during some of the dialysis treatments as outlined below. To reduce complexity and avoid confusion we urge that you use the same technique for all patients when drawing blood for urea modelling whether or not the patient is part of the HEMO study.

PRE-DIALYSIS SAMPLE

DO draw this blood sample from the cannulation needle before starting dialysis.

DON'T draw from a needle that has been filled with saline as some of this will enter the sample tube and will dilute the BUN level in the sample.

The pre-dialysis sample should be drawn through a dry needle and tubing. If this is not possible and when catheters are used, be sure to remove 3X the fill volume of the needle or catheter and attached tubing before drawing the sample. This will prevent dilution of the sample with saline.

DON'T draw the sample after starting blood flow as saline used to prime the dialyzer will dilute the sample and lower the BUN. Also, within 20 seconds after starting the blood pump the BUN begins to fall rapidly due to cardiopulmonary recirculation.

POST-DIALYSIS SAMPLE

The post-dialysis specimen requires more attention. The goal is to obtain a representative sample of blood entering the access device at the immediate end of dialysis. Care must be taken to avoid recirculation artifacts and rebound artifacts. If blood is recirculating in the access device, the urea concentration in the inlet (arterial) blood line does not reflect the concentration entering the access device but may be MUCH LOWER! Since we cannot be certain that recirculation is absent, we must presume that it is present and take measures to eliminate its diluting effect on the post-dialysis inlet (arterial) sample by slowing the blood pump. When the blood flow rate

is slowed to 80 ml/min, access recirculation stops. Similarly, rebound always occurs, so delays in drawing the sample will result in falsely high concentrations.

Two established methods have been chosen to avoid these sources of error. Both methods require slowing the blood flow to 80 ml/min and maintaining the low flow for 15 or 20 seconds to clear the dead space in the lines of recirculated blood. Timing the sample is of utmost importance. The sample must be drawn within the 20 to 30 second window to avoid the rebound artifact.

(1) Slow-flow, sampling port technique (preferred):

a) Either turn off ultrafiltration completely, or set ultrafiltration rate to 300 ml/hr or less.
b) Insert the Vacutainer needle tip into the sampling port.
c) Slow the blood pump to 80 ml/min.

Next implement either (d) or (d*) (see the notes below for a discussion of the merits of these two approaches):
d) Exactly 20 seconds after slowing the blood pump stop the blood pump completely (i.e., set the blood pump to 0). Then attach the Vacutainer tube and withdraw the blood sample.
d*) Exactly 20 seconds after slowing the blood pump attach the Vacutainer tube and withdraw the blood sample.

(2) Stop-flow, line disconnect technique:

a) Either turn off ultrafiltration completely, or set ultrafiltration rate to 300 ml/hr or less.
b) Slow the blood pump to 80 ml/min.
c) Exactly 15 seconds after slowing the pump, stop the pump.
d) Clamp the tubing on both sides of the connector between the needle line and inlet (arterial) blood tubing and disconnect.
e) Attach a Vacutainer to the needle tubing and withdraw the sample. This should be drawn immediately after stopping the pump and completed within 30 seconds after slowing the pump to 80 ml/min.

DON'TS

1) DON'T wait too long to draw the sample. One should attempt to complete sampling within 30 seconds after slowing the blood pump to 80 ml/min.

2) DON'T slow or stop the blood pump or dialysate flow close to the end of dialysis. This will allow the urea gradients that developed within the patient during dialysis to dissipate (rebound) causing the urea concentration in the post-dialysis sample to be falsely high.

3) DON'T infuse blood or saline (subject to patient safety) if possible during the last 15 minutes of dialysis. This will dilute the post-dialysis sample and reduce the urea concentration.

4) DON'T draw from the dialyzer outlet (venous) line.

NOTES:

The slow-flow sampling port technique is easier to perform than the stop-flow line-disconnect technique, and is the recommended procedure. In addition to these two techniques, the low flow clamp method described at the end of this section may be used by dialysis units possessing the necessary expertise and equipment if granted permission by the HEMO Study Kinetic Modelling Committee.

Comments on whether to stop the blood pump under the sampling port technique:

On analyzing the blood drawing technique at one of the Pilot Centers, it became apparent that the actual blood samples were sometimes drawn more than the prescribed time after slowing the blood pump. This was due in most cases to difficulty in puncturing the line, not having all equipment handy, etc. If option (d*) is used for the slow-flow inlet (arterial) sample under the sampling port technique, it is absolutely essential that the blood draw be started 20 seconds after slowing the pump, and completed by 30 seconds after slowing the pump (i.e., within 10 seconds). Any further delay will result in the sample BUN increasing by up to 5 - 10% due to cardiopulmonary recirculation. This will give a false positive reading for access recirculation, and may lead to unnecessary trouble shooting sessions. The likelihood of this problem may be reduced by completely stopping the blood pump after 20 seconds of slow flow, prior to drawing the blood, as described in option (d). Stopping the blood pump at 20 seconds "freezes" the desired sample in the inlet (arterial) blood

tube. The sample can then be drawn under less time-pressure (within reason). Thus, stopping the pump takes pressure off staff, and should give a more reliable results.

Several members of the Kinetic Modelling Committee feel strongly that stopping the blood pump (option d) is to be preferred over not stopping the pump (option d*). However, when Clinical Centers were polled, some were markedly opposed to stopping the blood pump prior to sampling, primarily on the grounds that this conflicts with local unit policy. Therefore, at the present time either method of sampling (i.e., d or d*) under the sampling port method is allowed on a dialysis-unit basis.

DOUBLE-LUMEN CENTRAL VENOUS CATHETERS: The same method can be used as for peripheral arteriovenous access devices.

MODELLING SESSIONS REQUIRING ADDITIONAL BLOOD SAMPLES

Three BUN measurements:

This will be done at B4 only. The additional blood sample is drawn at the end of dialysis from the inlet (arterial) port while the pump is turning at full blood flow. The sample is taken just before the slow-flow or stop-flow sample described above. The purpose is to screen for access recirculation occurring at the end of dialysis. If there is no access recirculation the urea concentration will be similar to that of the slow-flow or stop-flow sample. If the ratio of high-flow to slow-flow concentration is less than about 0.88, then access recirculation is suspected.

Six BUN measurements:

Three additional samples are taken approximately 1 hr into dialysis. Modeled dialyses requiring six blood samples will be required annually, at F4, and as part of a troubleshooting routine. The latter is required when access recirculation is suspected based on the 3-BUN session at B3 or during follow-up when deviations in single-pool volume are observed in two out of three consecutive sessions.

The three additional samples taken at one hour into dialysis serve 3 purposes:

1) The inlet (arterial) and outlet (venous) samples taken at full blood flow are used to estimated the in vivo dialyzer clearance.

2) The inlet (arterial) sample taken at slow blood flow is compared with the pre-dialysis and post-dialysis samples to estimate post-dialysis urea rebound (eKt/V) using the Smye technique.

3) All three samples are used to calculated access recirculation, using the standard formula.

DRAWING THE 1 HOUR SAMPLES

These three samples should be drawn as close as possible to 1 hour after dialysis, but interpretable results can still be obtained even when the sample is drawn within about 45-90 minutes after starting dialysis. However, it is very important to record (on Form 5) the exact time that the last of the three samples is drawn.

Samples taken at full blood flow:

Always draw these samples first. Draw at full blood flow from the inlet (arterial) and outlet (venous) sampling ports within one minute of each other. It is recommended that the outlet (venous) sample be drawn prior to the inlet (arterial) sample. It is important that the blood flow rate not be reduced during the 10 minute period prior to sampling.

Inlet (arterial) sample taken at slow blood flow:

Draw this sample only AFTER both of the above samples have been drawn. The technique is the same as for drawing the post-dialysis sample (sampling port method): Slow the pump to 80 ml/min for 20 sec, then draw the sample by inserting the Vacutainer needle into the sampling port. It is important to be consistent in the choice of option d or d*. That is, if the blood pump is stopped after 20 seconds slow flow when drawing the postdialysis slow-flow inlet (arterial) sample, then it should also be stopped after 20 seconds when drawing the 1-hour slow flow inlet (arterial) sample. After sampling don't forget to return the blood pump from 80 ml/min to full operating speed.

Eight BUN measurements:

This will be done at F4 and F36 only and will include the above samples plus an additional sample drawn 30 minutes after the end of dialysis. The primary purpose is to obtain a direct measure of post-dialysis urea rebound.

There are two techniques for obtaining the 30-minute post-dialysis sample:

ACCESS NEEDLE METHOD:

Dialyzer blood and saline rinse is returned to the patient in the usual fashion after obtaining the post-dialysis sample. Only one of the two dialysis needles is removed and the other is filled with saline. The patient may get up and walk around, but should not take any fluid. Thirty minutes after stopping dialysis, 10 ml of blood are withdrawn from the line using a syringe. This blood is set aside, and then the thirty minute post-dialysis sample is drawn. The 10 ml may be reinfused or discarded.

ACCESS PUNCTURE METHOD:

With this method, both dialysis needles are removed in the usual fashion. The sample is taken by puncturing the vascular access (not a peripheral vein), using a 25 gauge needle after sterilizing the skin puncture site. Some patients may not accept this method of drawing the sample, and informed consent should reflect use of this method.

Low flow clamp method for drawing the post-dialysis sample

Dialysis units using older models of the Fresenius delivery system or other comparable systems may use this method to insure that no recirculated blood contaminates your sample.
Use of this method requires the permission of the HEMO Study Kinetic Modelling Committee. To use this method you must be able to raise the upper limit of the venous pressure alarm independently of the lower limit. Newer models of most delivery systems tie the upper and lower limits together (create a window) that simplifies pressure monitoring but does not allow this maneuver:

1) Raise the venous pressure upper alarm limit to its maximum (500 mm Hg).
2) Slow the blood pump to 50 ml/min.
3) Within 5 seconds clamp the venous line between the blood pump and the drip chamber.
4) Wait until the alarm sounds and the pump stops.
5) Draw the sample from the inlet (arterial) sample port.

If the alarm limits are not reached within 30 seconds, stop the blood pump and draw the sample as indicated.*

If the alarm sounds within 15 seconds, you may have to release the venous clamp and turn the pump (at 50 ml/min) for a total of 20 seconds.*

* The reason for insisting on at least 15 seconds and not more than 30 seconds for sampling is to adequately clear the tubing of recirculated (venous) blood and to avoid the rebound in urea concentration that begins around 20 to 30 seconds after stopping dialysis. As a practical guide, if your blood tubing (not the pump segment) has an inner diameter of 3/16 inch, it is approximately 0.18 cm2 in cross section. Therefore, one milliliter (cc3) is contained in 5.6 cm of tubing. If the pump is turning at 50 ml/min, it is clearing 281 cm of tubing per minute or approximately 4.7 cm/sec. After 15 seconds, 70 cm (28 inches) of tubing will be cleared. For 1/4 inch tubing, the cross sectional area is approximately 0.32 cm2 and 40 cm or 15 inches will be cleared in 15 seconds. You should measure the distance from the needle to the sampling port to determine the minimum time to wait after stopping the blood pump to draw the postdialysis sample.

4.4.3 Timing of Data Entry and Shipment of Blood Samples

Urea samples drawn in modelling sessions should be shipped to the Central Biochemistry Laboratory (CBL) on the day they are drawn when feasible, and no later than the following working day. The kinetic modelling information on Form 5 should be entered into the data base no later than one work day following the modelling session, although it is recommended that this data be entered on the same day whenever possible. If the Form 5 and the CBL Mailing Form 9 are entered promptly, then a routine kinetic modelling report describing the results of the modelling session will be electronically transmitted to the Clinical Center in the morning within three working days after the shipment of the blood samples. If there are any changes to the DCC dialysis prescription report, this will also be electronically transferred at the same time as the routine kinetic modelling report.

Processing, storage, and shipping instructions are provided in CBL Chapter.

4.4.4 Kinetic Modelling During Baseline

From the standpoint of kinetic modelling, the baseline period has two phases. The first phase is targeted for the first two weeks of baseline, during which two kinetic modelling sessions are done. During this period the patients remain on their usual dialysis prescriptions at the time they entered the study. In particular, they remain on their pre-study dialyzers. Thus the dialyzers used in Weeks 1 and 2 will not always be included in the list of study approved dialyzers. During the second phase, patients will be dialyzed based on prescriptions supplied by the DCC with a target eKt/V of 1.45. During this phase patients must be dialyzed on a study-approved dialyzer. The second phase begins when the Clinical Centers receive the DCC dialysis prescription report following the Week 2 kinetic modelling session.

The purposes of the first phase are to i) characterize the patients' dialysis prescriptions when they enter the study, and ii) to obtain an initial estimate of the patients' total urea volume, which is required by the DCC to calculate dialysis prescriptions in the second phase of baseline. Baseline values for dietary intake will also be obtained while patients remain on their usual prescriptions.

The purposes of the second phase are to i) assess the ability of the patient to achieve

and maintain the high eKt/V goal, ii) improve the estimate of total urea volume to be used by the DCC in calculating dialysis prescriptions after randomization, iii) identify, prior to randomization, problems with delivery of dialysis such as access recirculation, and iv) provide the patient and dialysis unit staff experience with the treatment times and other aspects of the dialysis prescriptions necessary to achieve the high eKt/V goal prior to randomization. A schematic summary of kinetic modelling in baseline is provided in Figure 4.11.

The schedule of kinetic modelling sessions is summarized in Tables 4.4.1.1a and 4.4.1.1b below. In some cases, the target weeks of the baseline kinetic modelling sessions will be thrown off due to sessions with interruptions and hospitalizations. When this happens, the number of weeks into baseline at which the indicated sessions are done may deviate from that indicated in Figure 4.11. To minimize any possible confusion in scheduling in such cases, each kinetic modelling session is also provided a KM Session Number. The KM Sessions numbers BR-1 and BR-2 refer to the two modelling sessions with valid estimates of single pool volume conducted on the patients' routine prescriptions, regardless of the week in baseline these sessions are actually done. (Hopefully, in most cases they will be done in Weeks 1 and 2 of baseline.) The KM Session numbers BP-1, BP-2, BP-3, and so on refer to the baseline modelling sessions conducted with a target eKt/V of 1.45. Finally, F-1, F-2, and so on refer to the monthly follow-up modelling sessions. For sessions with interruption time exceeding 15 minutes, the KM Session Number is followed by an "i".

In both baseline and follow-up, it is required that modelling sessions be postponed if any of the three preceding dialyses were missed, since missed dialyses will disrupt the calculation of key kinetic parameters (particularly PCR and nPCR). In addition, during baseline the kinetic modelling sesion itself and the preceding dialysis session must be held according to the patient's usual weekly dialysis schedule. During follow-up, the kinetic modelling session and the preceding three dialysis sessions must be held according to the patient's usual weekly schedule.

Table 4.4.1.1a
Schedule of Kinetic Modelling Sessions in Baseline

Target Week	Type of Modelling Session	KM Session Number
1	2 BUN BR-1	
2*	2 BUN BR-2	
3	No kinetic modelling	----
4	3 BUN BP-1	
5	2 BUN BP-2	
6 and weekly thereafter	2 BUN BP-3 and so on	

* An extra 5 ml tube for the afterthought specimen should be filled when the pre-dialysis
BUN sample is drawn at either of the first two modelling sessions.

Table 4.4.1.1b
Schedule of Kinetic Modelling Sessions in Follow-up

Target Month	Type of Modelling Session	KM Session Number
1, 2, and 3	2-BUN	F-1, F-2, F-3
4	8-BUN	F-4
5, 6, ..., 35	2-BUN	F-5, F-6, ..., F-35
36	8-BUN	F-36
37, 38, ..., 71	2-BUN	F-37, F-38, ..., F-71

4.4.5 Baseline Weeks 1 and 2

Scheduling of Sessions. During the first two weeks of baseline two 2-BUN kinetic modelling sessions are conducted while patients remain on their usual dialysis prescription. It is recommended that the first of these sessions be held in Week 1 and the other in Week 2, but the protocol permits both modelling sessions to be done in the same week.

Data That Must be in the Data Base Prior to Kinetic Modelling. Form 1 (the screening form) and Form 2 (the demographic form) contain information necessary for analysis of the kinetic modelling results. These two data forms must be completed and entered into the data base prior to entry of data on the Kinetic Modelling Form 5.

The DCC maintains a current list of all dialyzers (and their K0As) being used in all the dialysis units participating in the Study. Because the K0As must be available to the data base in order to analyze of the kinetic modelling results, Clinical Centers with dialysis units introducing new dialyzers should inform the DCC of the new dialyzer at least two weeks prior to entering a patient on this dialyzer into the study.

Data That Must be in the Data Base Prior to Receiving Kinetic Modelling Reports. In order for the DCC to send out kinetic modelling and prescription reports, the following must first take place:

1. The CBL must receive the BUN specimens from the Clinical Center and transmit them to the DCC

2. The Kinetic Modelling Form 5 must be entered and verified in the data base

3. The CBL Mailing Form 9 must be entered and verified in the data base.

Residual Renal Function. Prior to one of the baseline kinetic modelling sessions, a urine specimen of 24- 46 hours must be obtained from any patient producing urine. This urine sample should be collected according to instructions provided by the CBL (see also Section 4.7), and brought by the patient to the modelling session. The urine specimen should be shipped to the CBL if the urine volume is 50 ml or greater.

It is recommended that the urine specimen be collected at the first baseline modelling session whenever possible. This will allow another specimen to be collected prior to the second baseline modelling session should it be determined that the first specimen was not collected properly. Should the residual renal clearance exceed the 1.5 ml/min 35 L exclusion limit, this will also avoid the unnecessary effort of carrying out the second modelling session and other procedures slated for Week 2 for an excluded patient. If a urine specimen cannot be obtained at the first baseline modelling session, then it should be obtained at the next earliest baseline modelling session possible.

In the HEMO study, the eKt/V goals will be based on delivered eKt/V, excluding residual renal function. However, residual renal function will be included in the calculations of the urea generation rate, and PCR. Total eKt/V (including residual renal function) will also be provided in addition to delivered eKt/V on the routine kinetic modelling report.

4.4.6 Baseline Weeks 4 and Later

Assessment of Ability to Reach the High eKt/V Goal. If a substantial number of patients were randomized who are unable to consistently achieve the high eKt/V goal, the average achieved eKt/V in the high Kt/V arm would be reduced, thereby diminishing the separation in achieved eKt/V between the usual and high Kt/V arms. This would imperil the power of the study to demonstrate a possible benefit of the Kt/V intervention. Thus a fundamental objective of the baseline period is to identify patients who are unable to consistently reach the high eKt/V goal so that they can be excluded from randomization.

In order to evaluate the ability of a patient to achieve the high eKt/V goal of 1.4, in the second phase of baseline the DCC will calculate dialysis prescriptions with a target eKt/V of 1.45 and with a dialysis duration of 4 1/2 hours or less. Modelling sessions will be conducted weekly until the delivered eKt/V is demonstrated to exceed 1.30 on two of three successive dialysis sessions. The specification of a target eKt/V slightly higher than 1.4 (i.e., 1.45) and the use of a cutoff for the delivered eKt/V slightly lower than 1.4 (1.3) is necessary due to the measurement variability of eKt/V. (Based on the Pilot Study results, the standard deviation of delivered eKt/V on a fixed dialysis prescription is expected to be about 0.125 Kt/V units.) The constraint that the eKt/V cutoff 1.3 must be met in 4 1/2 hours or less is intended to assure that an eKt/V of 1.4 can be reached in a consistently attainable amount of time during follow-up should the patient be randomized to the high eKt/V arm.

In practice, the ability of a patient to reach the high eKt/V goal within 4 1/2 hours depends on his/her total urea volume and the maximum blood flow tolerated by his/her access. This can be understood by examining the high Kt/V column in Table 9.2 in Chapter 9 of the protocol. This table is reproduced below. The high Kt/V column presents the dialysis duration required to attain the eKt/V goal of 1.4 based on a dialyzer K0A blood and dialysate flow rates of 800, 400 and 500 ml/min (right), and or 850, 450 and 800 ml/min (left). These ranges of K0A, blood and dialysate flow rates are intended to represent typical high efficiency dialysis. As can be seen, at a blood flow of 400 ml/min and a dialysate flow of 500 ml/min it becomes impossible to reach the high eKt/V if total urea volume is greater than about 42 L. If a blood flow of 450 ml/min and a dialysate flow of 800 ml/min are feasible, then patients with total urea volume up to 47 L can be dialyzed at the high eKt/V goal within 4 1/2 hours.

Thus patients with total urea volume greater than 47 L will in most instances not be randomizable. Patients with total urea volume between 42 L and 47 L are in the borderline range, and require an access that can consistently deliver blood flows of at least 400 ml/min as well as a willingness on the part of the patient and the dialysis unit staff to dialyze the patient for over 4 hours. Patients whose total urea volume is greater than 42 L should be

excluded if either the patient or the dialysis unit staff are reluctant to commit to a dialysis duration in excess of 4 hours for all dialysis sessions over a period of up to five years, or if there is any indication that access difficulties will prevent routine attainment of blood flows of 400 ml/min. Caution should also be exercised in recruiting such patients in dialysis units where dialysate flow rates greater than 500 ml/min are not routinely possible.

It should be noted that single pool volume is often overestimated in existing kinetic modelling programs due to several factors, including inflated estimates of dialyzer K0As from industry supplied estimates. Thus, the single pool volumes we calculate on the study-approved dialyzers in the HEMO study may in some cases be smaller on average than previously available single pool volume estimates. In addition, the downward correction of the blood flow of 10% at 400 ml/min leads to an approximate 3 to 5% reduction in the estimated single-pool volume.

Table 9.2 from Protocol

Target Times (Minutes) for Usual and High Equilibrated Kt/V Goals

Volume	Usual Kt/V	High Kt/V
24-26	150	158 - 176
26-28	150	167 - 187
28-30	150 - 151	177 - 198
30-32	150 - 159	187 - 209
32-34	150 - 167	196 - 221
34-36	157 - 175	206 - 232
36-38	163 - 183	216 - 243
38-40	170 - 191	226 - 254
40-42	177 - 199	235 - 265
42-44	184 - 206	245 - 276*
44-46	191 - 214	255 - 288*
46-48	198 - 222	264 - 299*
48-50	205 - 230	274*- 310*
50-52	212 - 238	284* - 321*

* Required time above the upper 4 1/2 dialysis time limit.

Scheduling of Sessions. If the Form 5 and Form 9 data are entered as described in Section 4.4.3, then within three work days after the samples from the second baseline modelling session are shipped the DCC will electronically transfer a prescription report designating alternative dialysis prescriptions for achieving a target eKt/V of 1.45 with dialysis duration no more than 4 1/2 hours. (An example of a prescription report and its interpretation is provided in Section 4.5.3.) After receiving the prescription report, the patient's dialysis prescription should be modified to accord with one of the indicated prescriptions as soon as is possible.

A 3-BUN kinetic modelling session (with KM Number BP-1) is targeted for Week 4 and a 2-

BUN session (with KM Number BP-2) is targeted for Week 5. In order to assure that steady state conditions for urea generation are satisfied, it is desirable that patients be on their new prescriptions for at least two dialyses prior to the Week 4 (BP-1) kinetic modelling session. It is recommended that the Week 5 (BP-2) session be scheduled a full week after the Week 4 modelling session so there will be sufficient time for the patient's dialysis prescription be updated prior to the Week 5 (BP-2) session if necessary. No kinetic modelling is targeted for Week 3.

If an eKt/V of 1.3 or greater is delivered for both the Week 4 (BP-1) and Week 5 (BP-2) modelling sessions, the patient will have satisfied the eligibility criterion demonstrating that he/she is capable of reaching the high Kt/V goal. If the delivered eKt/V of 1.3 is not reached on both of these modelling sessions, then additional 2-BUN modelling sessions must be conducted until the delivered eKt/V exceeds 1.3 on 2 of 3 consecutive sessions. It is advisable that these additional sessions be scheduled at one week intervals in order that there be ample time for the DCC dialysis prescriptions to be updated as necessary between kinetic modelling sessions.

Based on the standard error in eKt/V of 0.125 Kt/V units, it is expected that with the exception of patients who are too large to be randomized or who have chronic delivery errors, at least 89% will reach the 1.3 cutoff within 3 tries, and 95% will reach the 1.3 cutoff within 4 tries. At any time, the Clinical Center staff may conclude that the patient will not be able to reliably achieve the high eKt/V goal, and drop the patient from the study.

4.4.7 Trouble-shooting During Baseline

Unstable Dialysis Sessions. Dialysis sessions with reported total interruption time greater than 15 minutes are classified as unstable sessions, and must be repeated. An interruption is defined as: i) any lowering of the blood flow rate greater than blood flow of 50 ml/min or greater, ii) any time when the dialysate is in bypass, or iii) any time in the middle of dialysis when either the dialysate or blood flow rate is interrupted due to problems with needle placement, clotting, water pressure, or other logistical or mechanical problems. Form 5 should be filled out and blood samples shipped whenever possible even for sessions with

interruptions, since the estimates of Kt/V will normally be valid. The repeat session may be held in the same week as the unstable session. Alternatively, the repeat session may be rescheduled for the following week, in which case the subsequent kinetic modelling schedule for baseline will be pushed back one week.

On the first two attempts (the BP-1 and BP-2 Sessions, usually in Weeks 4 and 5), the results of an unstable dialysis session will not be counted either for or against the eligibility criteria of demonstrating that the high goal can be achieved. On subsequent attempts, an unstable session will be allowed to count if eKt/V is 1.3 or greater.

Modelling sessions with missing or clearly erroneous BUNs must also be repeated.

Troubleshooting Procedures. One of the objectives of the baseline period is to identify access recirculation problems and other errors in the delivery of dialysis so that they can be corrected prior to randomization. These problems will be identified during baseline by the following procedures:

1. Repeating unstable dialysis sessions,

2. Prompt feedback on the routine kinetic modelling reports assessing:

   i) the agreement between the reported Clinical Center dialysis prescription and the DCC prescription report,

   ii) the agreement between prescribed and delivered dialysis time

   iii) the agreement between prescribed and delivered blood flow

   iv) the agreement between modelled single pool volume and anthropometric volume

   v) the agreement between the current session's modelled single pool volume and the previous running mean single pool volume.

3. Determination of post-dialysis access recirculation at the Week 4 kinetic modelling session

In (2iv) the previous running mean single pool volume refers to the average single pool volume of the several preceding modelling sessions. The details on how the running mean is calculated are given in Section 4.5.4. The assessments of single pool volume in (2iii)

and (2iv) are diagnostics for possible errors in the delivery of dialysis or measurement/
sampling errors. Additional details regarding the implications of deviations in the single
pool volume V are described in Section 4.8.

Special 6-BUN trouble-shooting sessions during baseline. The DCC will notify the Clinical
Center on the routine kinetic modelling report that a special 6-BUN trouble shooting kinetic
modelling session is required if either i) the running mean single pool volume exceeds the
anthropometric volume by over 30% after the second baseline kinetic modelling session, or ii)
the estimated recirculation at the end of dialysis at the Week 4 (BP-1) kinetic modelling
session exceeds 20%. At most one trouble shooting session will be required for a single
patient in baseline. The trouble shooting session should be held as rapidly as possible
following notification on the routine kinetic modelling report by the DCC; in most cases it
will replace the next regularly scheduled kinetic modelling session. Trouble-shooting sessions
which are required based on the results of the first two baseline modelling sessions should be
done on the patient's usual dialysis prescription, while trouble shooting sessions required later
in baseline should be done on a rescription from the DCC prescription report. The results of
trouble shooting sessions carried out on a DCC prescription will be counted in the assessment
of whether the eKt/V cutoff is reached in two of three consecutive kinetic modelling sessions.

The troubleshooting session provides an estimate of access recirculation one hour into
dialysis which is more precise than the post-dialysis estimate of recirculation. In addition,
items 44 - 47 regarding needle size and post-dialysis fiber bundle volume are completed on
Form 5.

4.4.8 Kinetic Modelling During Follow-up

During follow-up the objective of the kinetic modelling is to maintain the delivered
eKt/V as close to the randomized assigned eKt/V goals of 1.0 or 1.4 as is possible, and to do
this consistently so that there is minimal variation in eKt/V over time. Essentially all
monitoring of kinetic parameters during follow-up are designed to accomplish this objective.

Scheduling of Sessions. At the time a patient is randomized the DCC will transmit a

prescription report providing a set of alternative dialysis prescriptions for achieving the patients randomized target eKt/V on a dialyzer whose flux matches the patient's randomized flux group. This prescription must be followed for at least three dialysis sessions prior to the first follow-up kinetic modelling session. Kinetic modelling will be done each calander month throughout follow-up. In general, the monthly follow-up modelling sessions can be scheduled to coincide with regular schedule of the dialysis unit. However, if randomization takes place during the first 14 days of a month, an initial follow-up kinetic modelling session should be held later in the same month that the patient is randomized (don't forget the requirement that three dialyses must be done on the follow-up prescription before the modelling session, however.) Subsequently, the regular monthly modelling schedule of the dialysis unit can be used. The first follow-up kinetic modelling session should be held in the calander month after randomization if randomization takes place on or after the 15th day of a month.

If the results of a session indicate that the dialysis prescription needs to be modified, the DCC will also send a revised prescription report. A trouble shooting report detailing possible sources of error in the delivery of dialysis will be transmitted if either i) the single pool volume of the current dialysis session deviates by over 20% from the previous running mean single pool volume, or ii) the weight adjusted running mean of the last four kinetic modelling sessions is over 20% greater than the weight adjusted running mean of the kinetic modelling session 9-12 months previously.

As described in Section 4.4.1, routine monthly kinetic modelling will be based on 2-BUN kinetic modelling sessions. However, additional BUNs will be obtained at 4 months, 1 year, and yearly thereafter in order to estimate access recirculation one year into dialysis and to corroborate the Daugirdas rate adjustment method for estimating eKt/V.

A schematic diagram of the kinetic modelling flow during follow-up is provided in Figure 4.12. All follow-up kinetic modelling sessions and the three preceding dialyses must be held according to the patient's usual weekly dialysis schedule.

Adherence to Dialysis Prescriptions and Target Times. Dialysis prescriptions should be

modified in accordance with the DCC prescription reports as soon as possible after a revised prescription report is electronically transmitted to the Clinical Center. The patient should be maintained on the most recently revised prescription both on kinetic modelling and non-kinetic modelling days. It is essential that the prescription be followed with equal care on both modelling and non-modelling days. This will be monitored by the abbreviated dialysis information form (Form 4). At the end of each month the DCC will transmit the dates of two modelling sessions on non-kinetic modelling days during the past month. The Clinical Center staff will then retrospectively fill out Form 4 based on dialysis records for these two non-modelling days as will as for the kinetic modelling session. The results of Form 4 will be compared between modelling and non-modelling days as the study progresses to identify any dialysis units who are not achieving adherence to the prescriptions on the non-modelling days

Table 4.4.1 below contains an example of a DCC report notifying a Clinical Center of the dialysis sessions to be included on Form 4.

Table 4.4.1
Example Form 4 Assignment Report

Clinical Center: 5 Emory
Month: August, 1995
Date of Report: September 1, 1995

The following patients from your Center had been randomized by July 31, 1995, and thus were in follow-up throughout August, 1995.

050027	050104
050031	050116
050069	050117
050095	050130
050098	050162

For each patient, enter three Form 4's. One should be for the August Kinetic Modelling session. Two more Form 4's should be entered, using the first and second choices if possible:

First choice: Wednesday, August 9, or Thursday, August 10
Second choice: Monday, August 14 or Tuesday, August 15
Third choice: Wednesday, August 23 or Thursday, August 24
Fourth choice: Monday, August 28 or Tuesday, August 29

Note: We will store recommended choices in the database and compare your actual choices to the recommended choices. Please use the first or second choices is possible.

The DCC dialysis prescription report should be followed unless the patient refuses or all prescriptions are incompatible with patient safety. The prescription reports allow the greatest flexibility possible by including a large variety of dialysis prescriptions with the maximum ranges of dialysis time, dialyzer K0A, blood flow, and dialysate flow rates that meet the randomized eKt/V target.

Newly developed access difficulties will sometimes mean that a patient who was able to achieve a blood flow of 400 ml/min at randomization may only be able to achieve blood flows of 200 - 300 ml/min at some later time during follow-up. When this happens, the time required to reach the target eKt/V may exceed 4 1/2 hours. In this case, the longer dialysis time indicated on the prescription report should be used if this is acceptable to the patient and feasible within the dialysis unit. However, if the patient does not accept the increased

dialysis time on the prescription report for the lower blood flow, then dialysis should be conducted on a dialyzer with the maximum available K0A, at the maximum dialysate flow rate, at the highest blood flow that can be achieved, and at the maximum time that is acceptable to the patient. If possible, the access should be corrected according to the guidelines specified in the Protocol.

Unstable Dialysis Sessions. As in Baseline, dialysis sessions with reported total interruption time greater than 15 minutes are classified as unstable sessions, and must be repeated. Form 5 should be filled out and blood samples shipped whenever possible for sessions with interruptions, since the estimates of Kt/V will remain valid. (Failure to include data from modelling sessions with interruptions would lead to a bias in our estimates of the overall average eKt/V throughout follow-up.) The repeat session should be conducted within two weeks, and preferably within one week, of the original unstable session. Dialysis sessions with clearly erroneous BUN measurements also must be repeated.

Troubleshooting Procedures During Follow-up. Kinetic modelling sessions will be monitored throughout follow-up in order to assure that the patients' delivered eKt/V is in close agreement with their randomized target eKt/V of 1.0 or 1.4. As in baseline, trouble shooting procedures include repeating unstable dialysis sessions, immediate feedback on the kinetic modelling report assessing the agreement between the Clinical Center dialysis prescription and the DCC prescription report, deviations in single pool volume, and access recirculation at months 4, 12, 24 and yearly thereafter. See Section 4.8 for a detailed discussion of trouble-shooting concepts.

Machine Calibration. Recommended procedures for calibration of blood and dialysate flow rates for dialysis units participating in the HEMO Study are provided in Sections 4.9 and 4.10. In addition to the recommended routine calibration of flow rates, the trouble shooting procedures will require blood flow calibration if i) the single pool volume from two of three consecutive sessions carried out on the same delivery system exceeds the prior running mean single pool volume by over 20%, or ii) if the DCC determines that the average single pool volumes of patients dialyzed on a particular machine deviate excessively from the mean anthropometric volume.

Special 6-BUN troubleshooting sessions during follow-up. The DCC will notify the Clinical Center on the routine kinetic modelling report that a special 6-BUN troubleshooting kinetic modelling session will be required if the single pool volume from two of three consecutive sessions exceeds the prior running mean single pool volume by over 20%. The trouble-shooting session should be held within one week following notification by the DCC.

4.5 Interpretation of the DCC Reports Related to Kinetic Modelling

4.5.1 Interpreting the DCC Routine Kinetic Modelling Report

The routine kinetic modelling report contains 3 pages. The first page provides a summary of the results of the individual kinetic modelling session. The second page interprets the results of the kinetic modelling session and gives instructions for additional actions. A third page, sent by a companion e-mail message, is a flow sheet with the values of the key kinetic parameters from the current and the previous 5 kinetic modelling sessions.

A sample of page 1 and 2 of the routine kinetic modelling report is provided in Table 4.5.1.1.
The contents are described below:

Page 1, 1st Panel:

This panel identifies the patient, date of session, visit type (Baseline or Follow-up), Week Number (if in Baseline), or Month Number (if in Follow-up), and the day of the Week the session was conducted. In addition, the KM Session Number indicates where the current session falls in the sequence of baseline or follow-up kinetic modelling sessions with valid estimates of single pool volume. The KM Session Numbers are as indicated below:

Kinetic Modelling Session	KM Session Number
Baseline, 1st Session on Usual Prescription (Usually Week 1):	BR-1
Baseline, 2nd Session on Usual Prescription (Usually Week 2):	BR-2
Baseline, 1st Session with Target eKt/V = 1.45 (Usually Week 4):	BP-1
Baseline, 2nd Session with Target eKt/V = 1.45 (Usually Week 5):	BP-2
Baseline, 3rd Session with Target eKt/V = 1.45 (Usually Week 6):	BP-3
Follow-up, Initial Monthly Modelling Session:	F-1
Follow-up, Second Monthly Modelling Session:	F-2

and so on.

The KM Session Number will be followed by an "i" for sessions with interruptions.

Page 1, 2nd Panel:

This panel provides demographic and weight and height information used to compute anthropometric volume, as well as pre- and post-dialysis BUNs and residual renal clearance.
Residual renal clearance is taken to be 0 for patients producing under 50 ml/day of urine, and is estimated from the most recent urine collection otherwise.

Page 1, 3rd Panel:

This panel describes the dialysis prescription. The individual items are:

Target eKt/V — The target eKt/V of this dialysis session. The Target eKt/V is unspecified in the first two weeks of baseline, is equal to 1.45 in Week 4 and later during baseline, and is equal to the randomized eKt/V goal of either 1.4 or 1.0 during follow-up.

Prescribed eKt/V — The level of eKt/V that was reportedly prescribed by the Clinical Center based on the reported prescribed blood and dialysate flow rates, the dialyzer K0A, prescribed dialysis time, and the prior running mean single pool volume. The Clinical Center dialysis prescription will be regarded as inconsistent with the DCC prescription report if the prescribed eKt/V deviates by over .075 Kt/V units from the Target eKt/V.

Target Time — An interval of recommended dialysis times corresponding to "high-efficiency, fast dialysis". The smaller end of the target time interval specifies the expected time required for this patient to reach the Target eKt/V based on a K0A of 800 ml/min with blood and dialysate flows of 450 ml/min and 800 ml/min, respectively. The larger end of the target time window specifies the expected time required for this size patient to reach the Target eKt/V based on a K0A of 800 ml/min, and blood and dialysate flows of 400 ml/min and 500 ml/min, respectively. The target time intervals are guidelines, and deviations from these times will not be regarded as protocol violations.

Prescribed Time — Prescribed duration of dialysis

Actual Time — Actual dialysis duration. The dialysis duration is taken to be the RTD clock time in dialysis units who report to the DCC that they monitor treatment time with the RTD clock, and is calculated from the difference between reported Start and End times in units that to not monitor treatment time with the RTD clock. (This is why sessions with over 15 minutes of interruption time must be repeated.)

Interruptions > 15 min	Indicates whether reported interruption time exceeded 15 minutes. If so, the modelling session is classified as unstable and must be repeated.
Dialyzer	Reported dialyzer.
Dialyzer K0A	In-vitro K0A of the reported dialyzer at the prescribed dialysate flow rate. For study-approved dialyzers, the K0A's are based on special in-vitro studies carried out at the University of Utah for the HEMO study.
Prescribed Blood Flow	Blood Prescribed blood flow rate
Blood Flow, 30 min	Actual blood flow rate at 30 minutes into dialysis (30 min):
Dialysis Flow (Rx)	Prescribed dialysate flow rate
Ultrafiltration Rate	Ultrafiltration rate computed as the weight change divided by the duration of dialysis

Page 1, 4th Panel:

This panel contains the calculated kinetic modelling results. Note that all estimates of volume are expressed in liters, and again as a % of body weight. Individual items are:

Anthropometric volume	Anthropometric estimate of total urea volume calculated from age, gender, weight, and height according to Watson formula.
1-Pool volume (run. mean at last Rx report)	In most cases, the running mean 1-pool volume is defined as the average of the calculated 1-pool volumes from four successive modelling sessions (see Section 4.4.12 for details and exceptions to this definition). This field provides the running mean volume at the time of the last DCC prescription report. This is the volume used in the calculation of the DCC prescription report that was used for the current modelling session.
1-Pool volume (run. mean prior to current session)	The running mean 1-pool volume is as described above, and in more detail in Section 4.4.12. This field provides the running mean immediately prior to the current modelling session. This volume may be up to 5% different from the running mean volume at the last prescription report, since the prescription reports are updated only when the mean volume changes by at least 5%.

1-Pool volume (run. mean including current session)	Estimate of the patient's 1-pool volume based on the current session. If there are no errors in the delivery of dialysis, the kinetically determined 1-pool volume is an estimate of the patient's total volume for the distribution of urea.
% deviation of cur. mean 1-pool vol vs anth. vol	% difference between the first two volume estimates above. Positive % differences of over 30% suggest underdelivery of dialysis, possibly due to access recirculation.

% deviation of cur. session's 1-pool vol vs prior mean	The % difference between the 1-pool volume of the current session and the prior running mean. Positive % differences above 20% suggest either underdelivery of therapy or measurement/sampling errors, while negative % differences greater than 20% suggest overdelivery of therapy or measurement/sampling errors. See the trouble shooting section 4.8 for additional details.
Prescribed Dialyzer clearance	The prescribed dialyzer blood water clearance computed from the dialyzer K0A, the reported blood flow rate at 30 minutes, and the prescribed dialysate flow rate.
Effective Dialyzer clearance	The estimated dialyzer blood water clearance that was actually delivered. Smaller values for the effective than prescribed dialyzer clearance suggest an underdelivery of dialysis.

Estimates of PCR and Amount of Dialysis Actually Delivered

(Note: Single-pool and equilibrated values are provided for each of the following parameters)

PCR (single pool)	Protein catabolic rate computed from the single pool urea generation rate. The single pool PCR has been primarily used in previous studies, but may overestimate the true PCR since it does not take into account post-dialysis rebound.
PCR (equilibrated)	Protein catabolic rate computed from the equilibrated urea generation rate.
nPCR (single pool)	Normalized protein catabolic rate computed from the single pool urea generation rate.
nPCR (equilibrated)	Normalized protein catabolic rate computed from the equilibrated urea generation rate.
TACu (single pool)	Time-averaged urea concentration assuming the single pool model. The TACu was used as the independent variable in the NCDS, but is biased upwards because it does not account for the multi-compartment distribution of urea.

TACu (equilibrated)	Whole-body time averaged concentration of urea calculated based on the pre-dialysis BUN and the equilibrated post-dialysis BUN. This corresponds to the eKt/V calculated based on the Daugirdas/Schneditz rate adjustment.
Urea removal [URR]	The urea reduction ratio. This is the fractional reduction in BUN concentration from the beginning to the end of dialysis. The SRI takes on values between 0 and 1, with 0 in principle representing no removal of urea, and 1 representing total removal of urea by dialysis.
Urea Removal [SRI]	The solute removal index (SRI) corresponding to the equilibrated Kt/V computed using the Daugirdas rate adjustment. The SRI is analogous to the urea reduction ratio, but accounts for estimated post-dialysis urea rebound, ultrafiltration, and urea generation. Like the URR, the SRI takes on values between 0 and 1, with 0 representing no removal of urea, and 1 representing total removal of urea by dialysis.
Total Kt/V (includes Kru) [single pool]	Total single pool Kt/V, including residual renal clearance. The total single pool Kt/V is calculated as (Kd ù t + Kr ù 3360)/V, where Kr represents residual renal clearance in ml/min. Kr is multiplied by 3360 since this represents the number of minutes in 1/3 of a week, so that Kr ù 3360 can be thought of total renal clearance corresponding to the time frame around one of three weekly dialysis sessions.
Total Kt/V (includes Kru) [equilibrated]	Total equilibrated Kt/V, including residual renal function.
Delivered Kt/V (excludes Kru) [single pool]	Single pool Kt/V according to variable-volume single pool model. In the HEMO study, single pool Kt/V is calculated using the variable volume 2-BUN sampling method described in "Prescribing Hemodialysis: A Guide to Kinetic Modelling" by Tom Depner.
Delivered Kt/V (excludes Kru) [equilibrated]	Equilibrated Kt/V (eKt/V) estimated using the Daugirdas rate adjustment.

An expanded version of the routine kinetic modelling report containing information on estimates of eKt/V by the Smye and 30 minute post-dialysis BUNs will be reported for the 7-BUN sessions.

Clinical Centers using the Biostat device will be provided with a separate Biostat kinetic modelling report for sessions at which the Biostat is used.

Page 2

The second page of the routine kinetic modelling report interprets the results of the kinetic modelling session. Text will provide the Clinical Center staff with the following information:

1. Was the dialysis session unstable (defined by interruption time over 15 minutes)? If so, the text indicates that the modelling session should be repeated.

2. If a urine specimen was collected, information on residual renal function is described. In baseline, the text indicates whether the residual renal function inclusion criterion of Kr < 1.5 ml/min/ 35 L was met.

3. Did the Clinical Center dialysis prescription agree with the DCC prescription report? The Clinical Center dialysis prescription will be regarded as in agreement with the prescription report if i) the dialyzer is a study approved dialyzer of the appropriate flux and K0A for urea, and ii) if the prescribed eKt/V is within .075 Kt/V units of the target eKt/V.

4. Did the prescribed dialysis time and blood flow rates agree with the recorded actual dialysis times and blood flows?

5. Did the prescribed and delivered eKt/V agree? This will be assessed by comparing the delivered eKt/V to the target eKt/V and by comparing the current session's single pool volume to the prior running mean. If there was an error in delivered eKt/V, the Clinical Center is informed of the nature of the error. Suggestions of possible sources of the error are provided based on the direction and size of the error, and on any reported discrepancies between prescribed and actual blood flows and dialysis times. If the current single pool volume deviates by over 20% from the prior running mean, the text indicates that the data entered on Form 5 should be reviewed for correctness, and informs the Clinical Center staff that a trouble shooting report has been issued.

6. In Weeks 4 and later during baseline, the text indicates whether the eKt/V cutoff of 1.3 was
reached, and indicates whether additional baseline kinetic modelling sessions will be required
to establish the patient's ability to reach the upper eKt/V goal.

7. At 3 and 7 BUN sessions the text informs the Clinical Center staff if recirculation exceeded
20%.

8. Was the post-dialysis weight over 2 kg deviant from the target weight?

9. Did the prescribed dialysis time deviate by over 20 minutes from the target time interval?
(Deviations of prescribed dialysis time from the target time interval are not regarded as
protocol violations per se so long as the DCC dialysis prescription report is adhered to. The
target time intervals are recommended as guidelines.)

10. The text informs the Clinical Center staff if a special trouble shooting session should be
scheduled. The conditions requiring trouble shooting sessions are specified in Section 4.4.7 -
4.4.8.

A sample of flow sheet of the routine kinetic modelling report is provided by Table 4.5.1.2.
This page contains the values of key kinetic modelling parameters for the current kinetic modelling
session as well as the preceding five sessions. Note that during baseline, as with the sample report
in Table 4.5.1.2, the columns corresponding to several sessions previous will be blank This page can
be used to trace the recent kinetic modelling history of the patient, and may be helpful in identifying
isolated errant modelling sessions or in identifying trends suggesting the development of access
difficulties or other chronic problems with delivery of dialysis.

Table 4.5.1.1
HEMO Study: Standard Kinetic Modelling Report
2-BUN Session

Patient ID:	24	Visit Type:	B
Namecode:	XXXX	Week Number	4
Date of Session:	04/20/94	Day Number:	3
		KM Session Number:	BP-1

Anthropometric and Biochemistry Inputs

Gender	Male	Pre-dialysis BUN	66.0 mg/dL
Age	55 yr	Post-dialysis BUN	17.0 mg/dL
Height (cm)	172 cm	Start Wt	78.8 kg
Height (in)	68 in	End Wt	76.7 kg
Res. Renal Clear. (Kru)	0.0 ml/min	Target Wt	75.0 kg

Dialysis Prescription

Target eKt/V	1.45	Dialyzer	F80B
Prescribed eKt/V	1.42	Dialyzer KoA	876 ml/min
Target Time	200-224 min	Prescribed Blood Flow	456 ml/min
Prescribed Time	200 min	Blood Flow, 30 min	456 ml/min
Actual Time	200 min	Dialysate Flow	850 ml/min
Interruptions > 15 min?	No	Ultrafiltration Rate	10.5 ml/min

Calculated Outputs

Anthropometric volume	40.9 L (53% BW)
1-Pool volume (run. mean at last Rx report)	34.0 L (44% BW)
1-Pool volume (run. mean prior to cur. session)	34.0 L (44% BW)
1-Pool volume (run. mean including cur. session)	35.4 L (46% BW)
1-Pool volume (current session only)	36.8 L (48% BW)
% Dev. of cur. mean 1-pool vol vs anth. vol	-13.5 %
% Dev. of cur. session's 1-pool vol vs prior mean	8.3 %
Prescribed dialyzer clearance	289 ml/min
Effective dialyzer clearance	268 ml/min

	Single Pool	Equilibrated	
PCR	74.2	68.2	g/day
nPCR	1.22	1.12	g/kg/day
TACu	44.1	46.5	mg/dL
Urea removal	0.74 URR	0.70 SRI	
Total Kt/V (includes Kru)	1.57	1.32	
Delivered Kt/V (excludes Kru)	1.57	1.32	

CONGRATULATIONS! The reported dialysis prescription is in agreement with the DCC prescription report.

The delivered eKt/V of 1.32 for this session deviated at least moderately from the target eKt/V of 1.45. However, becuase the running mean volume of 35.4 L including the current session does not differ substantially from the prior running mean of 34.0 L, this deviation is regarded as consistent with measurement error and/or errors in the dialysis prescription. Thus the DCC dialysis prescription report for this patient is unchanged.

The eKt/V cutoff of 1.3 was reached in < 4.5 hr at this modelling session. If the eKt/V cutoff of 1.3 is reached again at the next kinetic modelling session, then the achievement of the 1.4 goal criterion for randomization will have been met.

Table 4.5.1.2

HEMO Study
Routine Kinetic Modelling Report
Kinetic Modelling Flow Sheet

HEMO Study: Kinetic Modelling Flow Sheet

Patient ID:	24	Namecode:	XXXX.		
PARAMETERS					
Session Date	04/20/94	04/13/94	04/11/94	.	.	.
Session	3	3	1	.	.	.
KM Number	BP-1	BR-2	BR-1			
Presc. Trt Time (min)	200	199	196	.	.	.
Actual Trt Time (min)	200	199	196	.	.	.
Dialyzer Code	107	107	107	.	.	.
Dialyzer KoA (ml/min)	876	876	876	.	.	.
Presc Blood Flow(ml/min)	456	440	440	.	.	.
Act. Blood Flow (ml/min)	456	440	440	.	.	.
Dialysate Flow (ml/min)	850	850	850	.	.	.
Prescribed Kd (ml/min)	289	286	287	.	.	.
Pre Weight (Kg)	78.8	78.7	80.3	.	.	.
Post Weight (Kg)	76.7	74.8	76.0	.	.	.
Weight Loss (Kg)	2.1	3.9	4.3	.	.	.
Pre-BUN (mg/dL)	66.0	57.0	67.0	.	.	.
Post-BUN (mg/dL)	17.0	15.0	17.0	.	.	.
ANALYSIS						
Interrup Time > 15?	No	No	No	.	.	.
Volume From S.A.(L)	40.9	40.9	40.9	.	.	.
Mean Vol at Rx (L)	34.0	.	.	.	.	.
Prior Mean Vol (L)	34.0	33.4	.	.	.	.
Current Sess. Vol (L)	36.8	34.7	33.4	.	.	.
New mean Vol (L)	35.4	34.0	33.4	.	.	.
Single Pool nPCR	1.22	1.12	1.06	.	.	.
e(nPCR) (g/Kg/D)	1.12	1.03	1.01	.	.	.
URR	0.74	0.74	0.75	.	.	.
Prescribed sp(Kt/V)	1.70	.	.	.	.	.
Actual sp(Kt/V)	1.57	1.65	1.68	.	.	.
Prescribed e(Kt/V)	1.42	.	.	.	.	.
Target e(Kt/V)	1.45	.	.	.	.	.
Actual e(Kt/V)	1.32	1.38	1.40	.	.	.

Report Prepared: 04/01/95

4.5.2 Interpreting the DCC Troubleshooting Report

The DCC will electronically transmit a troubleshooting report to the Clinical Center whenever the current kinetic modelling session's single pool volume deviates by over 20% from the prior running mean single pool volume. The troubleshooting report will be transmitted at the same time the routine kinetic modelling report is transmitted. A sample troubleshooting report is provided in Table 4.5.2.1.

The troubleshooting report is intended to provide guidance as to the possible sources of error that may have led to a deviation in the current session's single pool volume relative to the prior running mean. The report indicates the sizes of errors in different kinetic parameters (e.g., % access recirculation, errors in blood and dialysate flow rates, errors in dialysis time, etc.) that would be necessary to account for the observed deviation in volume, assuming that all of the error was due to a single parameter. In some cases, this will show that only one or two of the possible sources of error could account for the deviation in volume.

Table 4.5.2.1
HEMO Study
Trouble Shooting Report

Kinetic analysis of the following dialysis session resulted in out of range values indicated an error in the delivery of therapy.

Patient ID:	60	Visit Type:	F
Namecode:	xxxx	Mont Number	4
Date of Session:	07/06/94	Day Number:	3

-------------------Summary of Out of Range Kinetic Parameters-------------------

Prior Mean 1-Pool Volume	32.2 Liters
Current Session's 1-Pool Volume	41.4 Liters
% Deviation	28.6 %
Anthropometric Volume	33.0 Liters
Running Mean 1-Pool Volume	35.4 Liters
% Deviation	7.2 %
Prescribed 1-Pool Kt/V	1.73
Current Session's 1-Pool Kt/V	1.34
% Deviation	-22.3%

A possible error in delivery of dialysis was identified because this session's 1-pool volume was more than 20% greater than the prior mean volume, suggesting an underdelivery of therapy. The error in volume may be due to a combination of errors in dialyzer clearance, treatment time, clearance and BUN sampling/measurement errors. Furthermore, errors in dialyzer clearance may be due to errors in blood flow rate, dialysate flow rate, partial dialyzer clotting and/or access recirculation. In assessing which of these possible errors may account for the reported deviation,
please note the delivered parameter values which would have been required to produce reported volume deviation:

Treatment Parameter	Reported Value	Delivered Value Required to Account for Error*
Dialyzer clearance	264.8 ml/min	205.8 ml/min
Blood Flow Rate	393.8 ml/min	250.0 ml/min
Dialysate Flow Rate	500.0 ml/min	260.0 ml/min
Time of Dialysis	210.0 min	163.2 min
% Recirculation	0 %	27.58 %
Dialyzer Clotting %	0 %	48.20 %

* Assumes all kinetic error due to error in a single treatment parameter. Prescribed Kt/V is calculated based on the running mean volume immediately Prior to this session

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Report Prepared: 03/13/95

4.5.3 The DCC Prescription Report

Interpreting the DCC prescription report. The DCC will electronically transmit the prescription report to the Clinical Center whenever the dialysis prescription needs to be updated. New prescriptions reports are sent i) after the second kinetic modelling session during baseline, ii) when the patient is randomized, and iii) anytime during baseline or follow-up that the running mean single pool volume changes by over 5% from the mean volume used to calculate the preceding prescription report. The 5% change in volume translates into an approximate 5% change in the eKt/V of the dialysis prescriptions. Generally, the prescriptions reports for (i) and (iii) will be transmitted at the same time as the routine kinetic modelling reports within three working days after the previous kinetic modelling session (see Section 4.4.3).

A sample page from a prescription report is provided in Table 4.5.3.1. At the start of the study, the prescription report will be six pages long, with different dialyzers given on different pages. The dialysis prescriptions specify combinations of dialyzer K0As, blood flow rates, dialysate flow rates, and dialysis times which give a prescribed eKt/V equal to the patient's target eKt/V. The K0A's used for the respective dialyzers are those determined from the in-vitro K0A study conducted at the University of Utah. For many dialyzers, the K0A increases at higher dialysate flow rates. The target eKt/V will be 1.45 during baseline after Week 4, and either 1.0 or 1.4 depending on the patients randomized intervention group during follow-up.

To use the report, identify the column corresponding to a dialyzer and dialysate flow rate, and identify the row corresponding to a blood flow rate of interest. Then the dialysis time required to reach the target eKt/V can be found by the designated entry in the interior of the table. For the convenience of the dialysis units, the dialysis times have been rounded to the nearest five minutes.

In baseline, the maximum duration of dialysis is 4 1/2 hours. Hence entries in the table specifying longer dialysis times will be crossed out. During follow-up there is no upper limit to the duration of dialysis, so all dialysis prescriptions are provided, including those with times over 4 1/2 hours.

In order to reduce the frequency that a patient's dialysis time must be changed, the target

time intervals will be modified only at the beginning of follow-up and when the running mean
single pool volume changes by at least 10% from the value corresponding to the current target
time interval.

Specification of dialysate flow rates. Two dialysate flow rates (a "low" and a "high" flow rate)
are provided. These flow rates correspond to the low and high flow rates specified by the
individual dialysis units. Any unit wishing to use a different dialysate flow rate should notify
the DCC at least 2 weeks prior to dialyzing any patient at this flow rate in order to have the
prescription report modified.

Protocol Requirements. One of the dialysis prescriptions contained in the prescription report should be followed unless the patient refuses or all of the prescriptions are inconsistent with patient safety requirements. Note that the range of allowed prescriptions is maximally flexible, including all combinations of blood flow, dialysate flow, dialyzer, and duration of dialysis which result in a prescribed eKt/V equal to the target eKt/V.

Table 4.5.3.1

The Hemodialysis Study
Dialysis Prescription Report

Patient ID:	24		Center/Unit:		Beth Israel/North			
Patient Namecode:	XXXX		Patient Volume for Rx:		36.2			
Target e(Kt/V):	1.0		Patient Volume for Targ. Time:		38.9			
	Baxter CA-150		Baxter CA-170		Baxter CA-210		Althin Altra Nova 200	
Qd	500	800	500	800	500	800	500	800
KoA	526	595	692	773	960	995	637	708
Qb								
100	435	430	430	430	430	430	430	430
150	315	305	305	300	300	300	310	305
200	265	250	250	240	240	235	255	245
250	235	225	225	210	210	205	225	215
300	220	205	205	195	195	185	210	195
350	210	195	195	180	180	170	200	185
400	205	185	190	175	175	165	190	175
450	200	180	180	165	170	155	185	170
500	195	175	180	160	165	150	185	165

Prescriptions indicated in minutes. Rounded to nearest 5 minutes.
Please select a prescription with duration of dialysis within or as close to the target time range of 170 to 190 min as is possible within the constraints of patient safety and dialysis access.

Target Time Guidelines. Target time guidelines for the patients eKt/V goal and total urea volume
are provided in the bottom panel of the report. These guidelines are intended to clarify to
objective stated in the protocol of conducting dialysis in the shortest time possible. DCC dialysis
prescriptions with treatment times which are shorter or longer than those specified by the target
time interval may be used for individual patients for safety or compliance reasons.

4.5.4 How the DCC Dialysis Prescriptions are Calculated (Note: this section is technical
and may be skipped).

In the first two weeks of Baseline, patients will remain on their regular dialysis
prescriptions. During this period, the total urea volume will be estimated at both of two kinetic
modelling sessions, and the mean single pool urea volume m(Vsp) computed. Based on m(Vsp),
a set of dialysis prescriptions designed to achieve the target delivered eKt/V will be calculated
by the following steps:

Step 1: For a given dialyzer KoA, dialysis flow rate (Qd), and blood flow rate
(Qb), calculate the in vitro dialyzer clearance Kd. The formulae used to
compute Kd are provided in Section 4.3.3 of the Protocol; additional
details are provided in Sections 4.2.2 and 4.12 of the Manual of Operations;

Step 2: Given Kd, calculate the prescribed time (tp) based on the Daugirdas rate
adjustment method required to achieve the specified target eKt/V (target
(eKt/V))

$$tp = [target(eKt/V) + (.6 \times Kd/m(Vsp)) - .03] \times m(Vsp)/Kd. \quad (1)$$

The resulting set of parameters (KoA, Qb, Qd, and tp) define a prescription
for achieving the target eKt/V.

Steps 1 and 2 are repeated for a wide range of dialyzer KoAs, dialysate flow rates, and
blood flow rates in order to generate a flexible set of prescriptions as shown in Table 4.5.3.1.
The value of targ(eKt/V) is set at 1.45 after the second modelling session of baseline, and at
either 1.4 or 1.0 during follow-up depending on the patient's randomized intervention. After the

first two weeks of baseline, m(Vsp) is defined as a running mean of up to four preceding volume estimates, with outliers deleted in some cases. Details are provided below.

Self-correction of prescriptions through m(Vsp). An examination of Equation (1) in Step 2 shows that adjustments to the prescription reports as new data is accumulated are determined by changes in the running mean volume m(Vsp). Increases in m(Vsp) lead to increases in the prescribed therapy, while decreases in m(Vsp) lead to reduction in the prescribed therapy.

The self-correcting property of m(Vsp) can be seen by noting that if the dialysis prescription was followed correctly, then:

$$eKt/V - targ(eKt/V) = (Kd \times t - .6 \times Kd) \times \{1/Vsp - 1/m(Vsp)\}, \qquad (2)$$

where eKt/V, Vsp are respectively the equilibrated Kt/V according to the Daugirdas/Schneditz rate adjustment and the single pool volume of the current modelling session, m(Vsp) is the previous running mean single pool volume that was used to determine the prescription of the current session, and targ(eKt/V), t and Kd are as described above. Thus, deviation between the current single pool volume and the prior running mean is mathematically related to the deviation between the delivered and target eKt/V. For example, if the delivered eKt/V is lower than the target eKt/V for a particular modelling session, Equation (2) shows that the single pool volume for this session must be higher than the prior running mean that was used to calculate the prescription this session. By updating the running mean volume to include the current session, the resulting m(Vsp) will usually be increased, this leading to a greater level of prescribed therapy in subsequent dialysis sessions. Conversely, if the delivered eKt/V is higher than the target eKt/V, then the single pool volume will be lower than the prior running mean, and updating the running mean to take into account the current session would result in a reduced level of therapy in subsequent prescriptions.

In order to avoid numerous minor adjustments to the dialysis prescriptions, the prescription report will be revised and transmitted to the Clinical Center only when the updated running mean volume differs by over 5% from the prior running mean used to determine the current prescription report.

Details of Updates to m(Vsp).

In most cases, the running mean volume m(Vsp) is defined as the mean of the preceding 4 nonmissing volume estimates if the coefficient of variation of these estimates is < 10%, and as the mean of all but the most extreme of these volumes if the coefficient of variation is ò 10%. However, in baseline the definition of m(Vsp) is modified to allow rapid upward adjustment of the mean volume if the single pool volumes obtained in Weeks 4 and later should exceed those obtained in the first two weeks of baseline. This modification is done in order to assure that the DCC dialysis prescriptions are consistent with the 1.4 eKt/V goal. In follow-up, a modification to m(Vsp) is made following changes in access in order to give more weight in the calculation to modelling sessions held after the access change.

If k ò 2, define the function tmean(Vsp1, Vsp2, ..., Vspk) to be equal to the mean of the volume estimates Vsp1, Vsp2, ..., Vspk if the coefficient of variation (CV) of the volume estimates is under 10%, and equal to the mean of all but the most extreme volume estimate if the CV is greater than 10%. If k = 1 or 2, tmean is defined simply as the mean of the volume estimates.
Further, define

tmean4 = tmean of last 4 nonmissing Vsp's, including the current session. If fewer than 4 sessions have been conducted, tmean4 represents the tmean of all nonmissing v_sp's.

tmean3 = tmean of last 3 nonmissing Vsp's, including the current session. If fewer than 3 sessions have been conducted, tmean3 represents the tmean of all nonmissing v_sp's.

tmean4s = tmean of last 4 nonmissing Vsp's on study-approved dialyzers, including the current session. If fewer than 4 sessions have been conducted, tmean4 represents the tmean of all nonmissing v_sp's.

tmean3s = tmean of last 3 nonmissing Vsp's on study-approved dialyzers, including the current session. If fewer than 3 sessions have been conducted, tmean3 represents the tmean of all nonmissing Vsp's.

Also define

Vsp_l1 = Previous nonmissing Vsp prior to current session

Vsp_l2 = 2nd previous nonmissing Vsp prior to current session

sameacc = Cumulative number of modelling sessions conducted since last access
change

volnum = Cumulative number of modelling sessions conducted in the study

Based on these definitions, the running mean single pool volume (m(Vsp)) is defined as
follows:

In baseline:

If volnum ó 2 then m(Vsp) = tmean4
If volnum = 3 then m(Vsp) = max(tmean4, .5 ù (mean(Vsp_l1,Vsp_l2) + Vsp))
If volnum = 4 then m(Vsp) = max(tmean4, mean(Vsp_l1,Vsp_l2))
If volnum = 5 then m(Vsp) = max(tmean4, tmean3)
If volnum ò 6 then m(Vsp) = tmean4

In follow-up:

If sameacc = 1 then m(Vsp) = .75 ù tmean4s + .25 ù Vsp
If sameacc = 2 then m(Vsp) = .60 ù tmean4s + .40 ù mean(Vsp,Vsp_l1)
If sameacc = 3 then m(Vsp) = .50 ù tmean4s + .50 ù tmean3s
If sameacc ò 4 then m(Vsp) = tmean4s

4.6 Instructions for Filling Out Form 5

Form 5 should be completed within one working day after each kinetic modelling session.
The data entered on this form is used to determine future dialysis prescriptions, monitor the level
of delivered Kt/V, and to determine the need for trouble shooting procedures. It is therefore
essential that this data form be filled out promptly with the utmost care.

With the exception of Items 10, 20, 22, 23, 24, and 45, all items on Form 5 are required
fields; that is, they must be entered in order for the form to be committed to the data base.

Instructions for Specific Questions:

Instructions for HEMO Study Form 5.
Detailed Dialysis Information for a Kinetic Modelling Day

Question 8a: BUN Measurements:
2 BUNs: Pre + 15 (line disconnect) or 20 (sampling port) sec post inlet slow
3 BUNs: Pre + immediate post inlet full + 15 (line disconnect) or 20 (sampling port) sec
post inlet slow
6 BUNs: Pre + 1 hr outlet full + 1 hr inlet full + 1 hr inlet slow + immediate post inlet
full + 15 (line disconnect) or 20 (sampling port) sec post inlet slow
7 BUNs: Pre + 1 hr outlet full + 1 hr inlet full + 1 hr inlet slow + immediate post inlet

full + 15 (line disconnect) or 20 (sampling port) sec post inlet slow + 30 min post

Question 9: Machine type:

Fresenius	Baxter	Cobe	Althin	Drake Willock
1 = 2008D	5 = 550	7 = Centry 3	9 = System 1000	
2 = 2008E	6 = 1550	8 = Centry 2		
3 = 2008H				
4 = 2008C				

Question 10: If the machine serial number is unknown, the question may be left blank

Question 11: See dialyzer type code list

Question 12: On first use report preprocessing sterilant

Question 13: On first use indicate if bleach was used in the preprocessing procedure

Question 15: Code list for Vascular Access type:

1 = AV graft - forearm
2 = AV graft - upper arm
3 = AV graft - thigh
4 = AV fistula - forearm
5 = AV fistula - upper arm
6 = Temporary venous catheter - internal jugular or subclavian
7 = Temporary venous catheter - femoral
8 = Permacath - internal jugular or subclavian
9 = Permacath - femoral
98 = Other

Question 16: Use of a membrane for the first time will have a reuse # of 0.

Question 33: (Definition of Interruption Time):
Interruption time includes:
1) Any lowering of the blood flow rate greater than 50 ml/min
2) Any time when dialysate was in bypass
3) Any time in the middle of dialysis when either blood or dialysate flow rate was interrupted due to problems with needle placement, clotting, water pressure or other mechanical problems, etc.

Interruption time does not include:
1) Periods when the ultrafiltration rate was lowered, but when blood and dialysate flow rates were maintained.

Questions 34, 35, 36, 39, 40a and 41 DO NOT refer to the HEMO Study prescription report sent by the DCC, but rather to the actual dialysis unit treatment orders.

Question 38: If the blood flow at 30 minutes is not recorded, report the first blood flow recorded after 30 minutes into dialysis.

Question 41: Define any deviation between the dialysis unit prescribed dialysate flow and the

flow actually delivered. Note that answers 1, 2, 3, and 4 assume interruptions in delivered flow,
but answer 5 reflects a stable flow for the entire (to within 15 min.) treatment.

Question 42: Answer 0 if the correct membrane was used, 1-3 if the incorrect membrane was
used due to an error in following the dialysate unit prescription, and 4 if the incorrect membrane
was used because the dialysate unit prescription deviated from the HEMO Study prescription
report.

For Additional Information on Filling Out Form 5, see Section 4.6 of the Manual of
Operations.

4.7 Measurement of residual renal function

Residual kidney function (Kr) is defined as the clearance of urea by the patient's native kidneys. It has a negligible effect during dialysis because treatment duration is relatively short but Kr has a major effect on urea kinetics between dialyses. During the interdialysis interval urea will continue to accumulate but at a slower rate resulting in a lower pre-dialysis BUN in patients who have even a small Kr (1-2 ml/min). It is also possible, although not proven, that the remaining native kidney can eliminate other toxins by secretion and metabolism, functions that are not well duplicated by the dialyzer. Therefore, native kidney function may have an additional beneficial effect that is not reflected in the patient's urea concentration or Kt/V. This means it is doubly important to measure and follow each study patient's Kr. As noted above, because the impact of Kr occurs between rather than during hemodialyses, failure to include a significant Kr (> 1.0 ml/min) in the modelling process causes a significant underestimation of the modeled PCRn and has a negligible effect on modeled Kt/V. The target Kt/V, however, is significantly reduced in patients with residual clearance, so errors will appear in both parameters of dialysis adequacy. Measurement of Kr is simplified by modelling urea kinetics.

To measure the residual renal function (Kr):

Give the patient the urine container provided by the CBL at the dialysis session preceding a kinetic modelling session.

Instruct the patient to:

- ù Keep the container in a cool location, e.g., refrigerator.
- ù Mark the beginning time on the container when he/she voids and to discard the urine. Save all subsequently voided urine in the container for at least 24 hours.
- ù Mark the closing time on the container when he/she voids and to save the voided urine in the container.
- ù Seal the container, keeping it cool until returning it to the dialysis center or to the laboratory at the next dialysis session, which should be a kinetic modelling session.

Dialysis staff should then:

- ù Verify that the urine collection period was contained in the 24-46 hour period immediately preceding the return of the container.
- ù Carry out the kinetic modelling session as indicated in the HEMO protocol, and fill out the information on Form 5.

ù Measure the volume of urine in the container using a graduated cylinder. It the urine volume exceeds 50 ml, send a 5-ml aliquot to the clinical lab for determination of its urine urea nitrogen concentration. Follow processing and shipping instructions in the CBL Chapter of the Manual of Operations.

ù Include the urine volume, the start time and the end time of the urine collection on Form 9.

4.8 Troubleshooting Procedures and Guidelines

Each month every Clinical Center will receive a routine kinetic modelling report. This report will give details of prescribed and delivered therapy, based on an analysis of the BUN samples provided and the information obtained from Form 5. For each monthly modelling session, the Data Coordinating Session will compute a urea distribution volume. The premise is, that the urea distribution volume should be constant in a given patient. However, experience with the HEMO Pilot Study showed that, from time to time, aberrantly high or low values for the urea distribution volume may result. A single aberrantly high or low monthly value for V will be flagged on the routine kinetic report, with suggestions for determining its cause. Aberrant values for V should not be taken lightly, as they more often than not reflect something that has changed with regard to the delivered dialysis therapy. Whenever an aberrant value for V is reported, the Study Coordinator should recheck all of the treatment data submitted for that treatment's Form 5. In addition, the following guidelines may help identify the problem:

4.8.1. Factors resulting in an erroneously high V

An overestimation of V is a common problem in urea modelling. If the prescription has not been changed, the spKt/V will be lower than expected. Because the value for K put into the modelling program is unchanged, the equations predict that a larger than usual patient is being dialyzed. The two reasons leading to an overestimation of V are (1) spKt/V underestimated, and (2) K or t are overestimated.

4.8.1.1 Underestimation of spKt/V

The spKt/V is largely determined by the urea reduction ratio (URR) and secondarily by the amount of ultrafiltrate volume removed relative to the patient weight. The URR can be underestimated due to an error in drawing the pre-dialysis BUN (too low) or the post-dialysis

BUN (too high). The pre-dialysis BUN will be too low if the sample was drawn from saline-filled tubing, or if the pre-dialysis sample was actually drawn after hooking the patient to the dialysis machine or after the start of dialysis. Even one or two minutes after dialysis has begun there will be a substantial decrease in the BUN (due to establishment of the A-V gradient). Similarly, if one waits more than 30 sec after slowing the pump to 80 ml/min, the post-dialysis BUN will have increased due to resolution of the A-V gradient, causing the arterial spKt/V (which is what is being measured) to be underestimated. Drawing the post-dialysis blood from the opposite arm has the same effect and is even worse due to the fact that the blood draining the arm may not be well dialyzed due to organ urea sequestration.

Volume contraction, which can be expressed as the weight change divided by the post-dialysis weight (UF/W) accounts for about 9% of the total spKt/V on average, but this can be as high as 20% in patients with very marked weight changes. Incorrectly keying in the patient's weight change (e.g., putting in no weight change where in fact a large weight change actually occurred) also can result in an underestimation of the true spKt/V.

4.8.1.2. Overestimation of t

In this case, the spKt/V that is measured is actually what is being delivered. V is overestimated because, when calculating V from Kt/V, an erroneously high value of t is put into the equation. This occurs whenever the true dialysis session length is less than that recorded on Form 5. This can be due to interruptions in the treatment, periods during the session when the blood flow rate and/or dialysate flow rate were less than specified by the prescription, or time that the dialysate was in bypass. Also, another common cause is ramping up the blood flow rate slowly at the start of dialysis, reducing the time that the prescribed blood flow was being delivered.

4.8.1.3. Overestimation of clearance K

There are three general reasons why the clearance can be reduced. The first is due to an alteration in the intradialytic BUN profile due to access recirculation. The second is problems with dialyzer performance, and the third is problems in delivering proper blood and/or dialysate flow.

4.8.1.3.1 Access recirculation

Access recirculation results in a high V value only when the blood is drawn properly; i.e., 20 sec after slowing the flow to 80 ml/min. In this case, there is nothing wrong with the dialyzer clearance; the problem is, that the intradialytic BUN profile is being overestimated. The amount of urea removed is the dialyzer clearance multiplied by the mean BUN level during the dialysis session. With AR, the mean BUN level is reduced, often substantially. Hence, although dialyzer clearance may be maintained, the effective dialyzer clearance is actually lower than estimated. Because less urea is removed, the URR (when it is obtained after 20 sec to correct for the AR rebound effect) is reduced, and the program thinks that a large patient is being dialyzed. Clues to AR are a high pre-pump pressure (suggestive of inflow stenosis), or a very high outflow resistance that cannot be related to inappropriate needle size. A useful test advocated by Dr. Gotch is to occlude the access segment between the two needles transiently (and gently) and observe the pre-pump pressure. If the pre-pump pressure becomes more negative, or if the outflow (venous) pressure increases during the period of occlusion, this is functional evidence that AR may be present.

4.8.1.3.2. Overestimation of dialyzer performance (KoA)

The KoA used by the Data Coordinating Center to estimate dialyzer performance is an average value based on that measured in several lots of new dialyzers. The dialyzer performance can be reduced for several reasons.

4.8.1.3.2.1. Decreased fiber bundle volume

It is recommended to pre-process reused dialyzers to obtain a baseline value for fiber bundle volume. This should be consistent with that reported by the manufacturer. With reuse, the fiber bundle volume will drop progressively. Currently the recommendation is to discard the kidney when the FBV drops to 80% of the initial value, as by this time, urea clearance has decreased by >5% of its original value.

4.8.1.3.2.2. Clotting or air in fibers

Improper priming of the dialyzer can result in bubbles of air that persist during a portion of dialysis. Also, introduction of a substantial amount of air into the arterial line that passes on into the inlet (arterial) header can cause air to enter the fibers. Similarly, partial clotting of the fibers

can occur. These problems will not necessarily show up in a reduced fiber bundle volume for the subsequent treatments, as the clots may be dissolved and washed away during the reuse procedure.

4.8.1.3.2.3. Channeling of dialysate

Poor entry of dialysate into the spaces among the hollow fibers can markedly reduce the efficiency of a dialyzer. This may vary from lot to lot or dialyzer to dialyzer.

4.8.1.3.2.4. Manufacturing variance

For some reason, a given lot of dialyzers may not perform as specified. This problem should be suspected if a number of high V values are recorded for patients using the same lot of kidneys.

4.8.1.3.3. Problems with blood and/or dialysate flow

4.8.1.3.3.1. Overestimation of blood flow

Although dialyzer clearance and blood flow are related in a curvilinear fashion, substantial decreases in blood flow have a noticeable effect on clearance. For example, with a high efficiency dialyzer, a fall in blood flow from 400 to 300 ml/min may be associated with a 15-20% fall in urea clearance. Decreases in blood flow of this magnitude can occur with very high pre-pump pressures, with a malfunctioning blood pump, or with use of an incorrect pump segment tubing diameter.

4.8.1.3.3.1.1. Low pre-pump pressure

During dialysis, the rapidly turning blood pump actually establishes a suction or negative pressure in the tubing segment (pre-pump segment) between the inflow needle and the roller pump. This suction causes the tubing under the rollers to flatten (become ovoid in shape). Even when the roller pump totally occludes the tubing segment, and even when the pump rotation is set correctly, each stroke of the pump pushes a lower than usual volume out of the roller segment. The decrease in pump output can become quite remarkable when the negative pressure exceeds -200 mm Hg. Decreases of 50% are possible! When the pressure is -200 mm Hg, the decrease in pump output is in the range of 10%. In the HEMO protocol, all pumps are expected to be calibrated at zero negative pressure. In their modelling equations, the DCC is compensating

for an average expected reduction in pump flow due to negative pressure. However, severe degrees of negative pressure will lower the blood flow rate by much more than predicted by this formula. As a result, the true delivered blood flow can be substantially lower than expected. Less urea is removed than estimated by the UKM program, and the program thinks that a larger than usual patient is being dialyzed.

It is highly recommended to measure the pre-pump pressure whenever possible. One should not be concerned about levels of up to -200 mm Hg, as the effects of such levels of pre-pump pressure are being compensated for by the DCC. Higher levels of pre-pump pressure can occur when an inappropriately small or long needle is used, when the tip of the needle is up against the inside of the access or otherwise improperly placed, when there is stenosis of the access upstream to the needle, or when the access blood flow falls to a low level (i.e., during hypotension).

4.8.1.3.3.1.2. Blood pump output incorrect

Pump output may be lower than on the dial if the rollers are not completely occluding the pump segment, if the rate of rotation of the pump is set improperly, or if the wrong diameter tubing is being used in the roller pump segment. This problem is best avoided by regular calibration of all blood pumps to be used in the HEMO study.

4.8.1.3.3.2 Dialysate problems

These include overestimation of dialysate flow and hooking up the dialyzer incorrectly such that blood and dialysate flow in the same direction along the dialyzer axis (co-current flow) instead of countercurrent flow. It is not uncommon to encounter moderately severe errors in dialysate flow rate. Usually this will affect the clearance by a relatively small amount only. On the other hand, the inadvertent use of 500 ml/min vs. 800 ml/min dialysate flow rate can reduce clearance by 10-15%, especially because clearance with certain dialyzers improves unexpectedly at high dialysate flow rates due to better dispersion of the dialysate among the hollow fibers.

4.8.2 Factors resulting in an erroneously low V

When the prescription has not been changed, this will be reflected by an unusually high apparent spKt/V. Again, the errors can be one of three: (1) The spKt/V has been overestimated,

(2) t has been underestimated, (3) K has been underestimated. An unusually low V is not nearly as common as a high V, simply because it is unusual for dialyzers to perform better than expected, for the blood flow or dialysate flow rate to be higher than expected, or for t to be underestimated. Nevertheless, all of these errors can occur.

4.8.2.1. Overestimation of spKt/V

Again, errors in the URR or in reporting the volume change can lead to an erroneous spKt/V. The URR may be erroneously high. Usually this is due to an erroneously low post-dialysis BUN sample. The most common reasons for overestimation of post-dialysis BUN are: access recirculation when the sample is drawn without clearing the dead space from the arterial line segment between needle and sampling site (2) drawing the blood from the dialyzer outlet line (this causes a huge increase in V!), and (3) dilution of post-dialysis blood by administration of saline or infused blood not too long before sampling.

4.8.2.2. Underestimation of dialysis time

This unusual usually is due to a mistake in data entry or reading the clock time.

4.8.2.3. Overestimation of blood flow rate

This error is most likely to occur when the blood pump rotation rate is too high or when an inappropriately large tubing has been used in the roller pump segment.

4.8.2.4. Overestimation of dialysate flow rate

This can be due to miscalibration of the machine, or more likely, to a failure to reset the dialysate flow rate from a higher level used for a prior patient.

4.8.3. When a troubleshooting report is required

As noted above, whenever there is a single deviation in the patient's V, the information is noted in the routine kinetic modelling report. Whenever the volume deviates in the same direction in any 2 of 3 successive modelling sessions, the DCC will require that an additional modelling session be performed. During this modelling session, special attention is to be paid to the following 3 areas:

1) Access recirculation
2) Provision of adequate blood and dialysate flow rates

3) Fiber bundle volume

Particular care should be taken to assure that the full blood flow and dialysate flow rates are delivered for the entire troubleshooting session length. In the troubleshooting dialysis session, 6 BUN samples are taken. Three samples are taken 1 hour into dialysis to measure access recirculation and dialyzer clearance in vivo. At the end of dialysis, two specimens are taken, one at full blood flow, and the other after 20 sec of slow flow to compensate for access recirculation.

If the blood samples are drawn correctly, the troubleshooting session should accurately identify errors in V due to AR or to an altered dialyzer clearance. Errors in blood and dialysate flow, however, need to be identified by the Clinical Center by appropriate calibration methods.

4.9 Blood pump and dialysate flow calibration

4.9.1 Blood pump calibration protocol

The following is a procedure for calibrated the blood pump that is recommended by the Kinetic Modelling Committee. The procedure is designed to be simple to do, and applicable to all dialysis delivery systems.

Objectives

1. Ensure accuracy of the blood pump meter and the adequacy of dialysis.
2. Test for adequate occlusion of the blood pump segment by the rollers.

Suggested frequency of calibration:

Every 2000 hours or monthly following a calibration error. Whenever the pump behaves suspiciously, e.g., noise, pump stops unexpectedly, consistent modelling errors.

Additional materials:

- Stop watch
- Graduated cylinder, 500 ml or 1000 ml, or a 500 ml volumetric flask
- Screw clamp for tubing
- Water bath set at 37o C or a dialysate reservoir
- New blood tubing, arterial and venous, with proper pump segment diameter.
- Tubing may be reused for calibration if changed monthly and prominently labeled as "not for patient use."

Method:

- Set up the dialysis machine.
- Connect the arterial to the venous line directly, eliminating the dialyzer.

ù Place the arterial inflow and venous outflow ends of the tubing into the water bath or the
dialysate container.
ù Check the blood pump flow meter's zero reading.

Volumetric calibration at low inflow and outflow pressures

ù Raise the flow to precisely 400 ml/min as reported by the RPM meter.
ù Timed collection* (see below)
ù Repeat timed collection* (see below)
ù Decrease flow to 200 ml/min.
ù Timed collection #2* (see below)

Positive pressure test for proper occlusion:

ù Place a clamp on the venous line downstream from the drip chamber and adjust the venous
pressure to 300 mm Hg at a flow of 400 ml/min. This tests the pump's occlusion.

ù Timed collection* (see below)

Tolerance: All volumetric flows should be within 5% of RPM meter reading. If not, the pump
should be recalibrated and flagged for monthly calibration.

*Timed collection: Simultaneously place the dialysate drain line into the graduated cylinder or
into the volumetric flask and start the stop watch. Either record the volume in the graduated
cylinder for precisely one minute or fill the volumetric flask to the mark and record the time.
Calculate flow as volume/time.

Blood Flow Readings (ml/min):

	RPM Meter	Volumetric	%deviation
No occlusion	400		
	400		
	200		
Post-pump clamp	400		

4.10 Dialysate flow calibration protocol

Objective:

To ensure accuracy of the dialysate pump and adequacy of the dialysis prescription.

Suggested frequency of calibration:

Every 2000 hours or monthly following a calibration error. Whenever the pump behaves suspiciously, e.g., noise, pump stops unexpectedly, consistent modelling errors.

Additional materials:

Stop watch
Graduated cylinder, 1000 ml, or a 1-liter volumetric flask.

Method:

During a routine clinical dialysis temporarily discontinue ultrafiltration. Simultaneously place the dialysate drain line into the graduate cylinder or into the volumetric flask and start the stop watch. Either record the volume for precisely one minute or fill the volumetric flask to the mark and record the time. It is important to extend the time for at least one minute because the pulsatile flow produced by many volumetric delivery systems can introduce significant errors if the pulse volume is a significant fraction of the whole collection. Calculate flow as volume/time.
Measure in duplicate.

Repeat for each flow rate used with this dialysis machine. Tolerance: All volumetric flows should be within 5% of the dialysate flowmeter reading. If not, the pump should be serviced, re-checked using the above procedure, and flagged for monthly calibration.

Dialysate Flow Readings (ml/min):

Dialysate Meter	Volumetric Flow	% Deviation

Section 4.11 Procedures for the Use of The Baxter BioStat*1000 Urea Monitor

The Kt/V intervention evaluates whether outcome is improved by higher levels of small solute clearance, while the flux intervention evaluates whether outcome is improved by higher levels of large solute clearance. During the full scale study, equilibrated Kt/V will be monitored using pre-dialysis and post-dialysis BUN in conjunction with the Daugirdas Rate Adjustment Formula.
The purpose of the present study is to provide an independent check of the equilibrated Kt/V levels delivered to the patient using the BioStat*1000 to ensure appropriate separation of the high and low Kt/V arms. The BioStat*1000 is an automated on-line device that performs urea kinetic calculations based on effluent dialysate urea nitrogen concentrations, sampled throughout the treatment. Urea nitrogen concentration is measured in these samples using urease catalyzed breakdown of urea to bicarbonate and ammonium ions coupled with an ion-specific electrode.
Equilibrated Kt/V and other urea kinetic quantities are then calculated from the double exponential concentration-time profile using a built-in algorithm 1,2,3.

Methods

Centers and Patient Selection

Approximately 200 patients drawn equally from five of the participating centers (See appendix for listing) will be monitored on a semi-annual basis using the Baxter BioStat*1000 Urea Monitor. Comparative measurements with the BioStat*1000 will be made at F4, F12, F18, and F24. Due to the staggered nature of patient enrollment, the BioStat*1000 will be used over a period of approximately three calendar years. Only patients originally enrolled in the study will be monitored with the BioStat*1000. No replacement patients will be studied. As approximately 40 of the 60 patients at each of the 5 participating centers will be monitored with the BioStat*1000, patient selection will be left to the discretion of the individual investigator. While patient selection will be affected by geographical location and scheduling considerations, it is suggested that the high and low Kt/V arms be equally represented.

BioStat*1000 Training

A two-and-one-half day training session for the use of the BioStat*1000 will be held in

Minneapolis in late March or early April. One designated operator from each of the five centers will be invited to the training session. In addition to training in the use of the BioStat*1000, training in the use of a software program (UMPC) will be provided. The UMPC software is designed to facilitate record keeping, data analysis, and data import and export between the BioStat*1000 and a personal computer using the touch button memory system.

Devices and supplies

Two BioStat*1000 devices will be provided to each of the participating centers, along with the necessary disposable supplies (membrane caps, fluid packs, Quality Control ampules, etc.) and the UMPC software. This will allow simultaneous monitoring of two treatments, allowing scheduling flexibility. Based on the planned frequency of monitoring, we estimate that, on average, 2 monitored treatments per week will be necessary, requiring approximately one half day per week. The BioStat*1000 and UMPC will be installed and checked out by a Baxter representative prior to the beginning of the study. The BioStat*1000 flow cartridge (the interface between BioStat*1000 and the hemodialysis hardware) will also be installed at this time.

Procedures for BioStat*1000 use

1. Run Quality Control sample (QC)

Allow the BioStat*1000 to run its automatic calibration procedure before analyzing QC
It is only necessary to run QC for first treatment of the day for each BioStat*1000
Run QC sample as described in Operator's Manual

2. Measure dialysate flow rate

For non-Baxter equipment, do a 1 minute collection of dialysate from the drain line into a graduated cylinder. The volume collected in one minute is equal to the flow rate in mL/minute.

For Baxter equipment, enter displayed dialysate inflow from the UFC controller, after it has calibrated.
This flow rate should be measured and entered as the dialysate flow rate input for each treatment.

3. Connect flow cartridge to the saddle of the BioStat*1000

4. Allow the BioStat*1000 to run its automatic calibration procedure at the start of each
treatment

5. Input patient data (Listed below)
Patient ID, Patient Name, UF Goal Dry Weight, Sex, Prescription Time, Treatments/Week,
Session Number, Dialysate Flow rate, Bath Potassium, Residual Renal Function, Dialysate
Type (Acetate or Bicarb).

The inputs may be either entered directly from the BioStat*1000 keypad or entered into the
UMPC program and exported to the BioStat*1000. This data is stored in the memory of the
BioStat*1000 and may be called up and reviewed for accuracy before each treatment.
Treatment specific data such as UF Goal, Session Number, Dialysate flow rate, etc. may need
to be edited for each treatment.

6. Perform Equilibration Sample as described in BioStat*1000 Operators Manual, with
particular attention to:

Dialysate in bypass
Ultrafiltration rate of at least 5 mL/minute
Blood pump at prescribed blood flow rate

7. Start treatment after BioStat*1000 alert (flashing screen, audible alarm) for end of
equilibration sample procedure (Remember to take HD machine out of bypass)

8. The BioStat*1000 will begin to sample automatically
Every 5 minutes for the first 30 minutes
Every 10 minutes for the remainder of the treatment

9. Record any abnormal condition that occurs during treatment on Form 5
Change of blood or dialysate flow rate
Access problems
Hypotensive episodes

10. End of treatment
Edit UF Goal input if it has changed by 0.3 Kg or more
End treatment on the BioStat*1000
Save data
Send data to the printer
Send data to touch button

11. Upload data to UMPC

BioStat*1000 outputs

Treatment Date
Treatment Start Time

Elapsed Time
Rejected Samples
Patient Volume*
Urea Removal
Kt/V Delivered
Total Kt/V

PCR

nPCRw
nPCRv*
SRI Delivered*
Equilibration result*
Whole Body Clearance*
Pearson's r

* Output only available with valid equilibration result

12 Prepare a Treatment Report using the UMPC, and send to Data Coordinating Center.

Equilibration Failure

The purpose of the equilibration sample is to assess the pre-dialysis BUN concentration of the patient. This information allows calculation of additional urea kinetic quantities beyond Kt/V and PCR (See output list above). Deviation from the equilibration procedure may result in an inaccurate equilibration sample, so the BioStat*1000 software contains an algorithm to assess the validity of the equilibration sample result. If the equilibration dependent outputs are missing from the output data for a treatment, it is an indication that the equilibration procedure failed. In this event, it is not necessary to repeat the monitoring, but we suggest that the equilibration procedure be examined in an effort to determine the cause of the failure.

Fit Errors

A Fit Error is defined as any treatment that is unstable to the point that more than four samples are "rejected" because the measured data does not fit the expected exponential trend. The BioStat*1000 software contains a filtering algorithm to assess the agreement of the data with the theoretical exponential decline of urea concentration with hemodialysis. Some typical causes of Fit Errors are listed below.

Change of blood flow during treatment
Access problems that may result in inconsistent blood flow
Unstable dialysate flow
Hypotensive episodes, particularly with the infusion of saline
Clotting dialyzer
Repeated alarms causing stoppage of blood pump

Very low (< 3 mg/dL) dialysate urea concentration

If a Fit Error occurs, the BioStat*1000 results may be invalid. Any treatment complicated by a Fit Error must be repeated.

Contacts with Baxter

Mail printouts weekly to Baxter using SASEs provided.

For hardware problems call 1-800-553-6898.
For clinical and data questions call (612) 337-7362 or 347-4463.
For supplies call [Baxter Healthcare Corporation, Clinical Affairs-number to follow]

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Participating Centers

Centers participating in BioStat*1000 study:

Lankenau Hospital and Medical Research Center, Wynnewood, PA
University of California, Davis, Sacramento, CA
University of Texas Southwestern Medical Center, Dallas, TX
University of Utah, Salt Lake City, UT
Bowman Gray School of Medicine, Winston-Salem, NC
Beth Israel Medical Center, New York, NY

4.12 Kinetic Modelling Equations used in the DCC Modelling Programs (2-BUN Sessions)

This section summarizes the equations used in the DCC kinetic modelling programs for 2-BUN Sessions. In this section the notation has been chosen to match closely with the variable names which are actually used in the DCC programs, and thus in some cases differs from the notation used in the Protocol and in other sections of the manual. In particular, spKt/V is denoted kvt_sp, and the mean single pool volume, which is elsewhere denoted m(Vsp), is represented by mv_sp.

4.12.1 Input Variables

day	day of week of modelling session	1=Mon, .. ,6=Sat
targektv	eKt/V goal	orig rx, baseline 1.45, f/u 1.0 or 1.4
sex	male/female	1 male/2 female
age	age	years
height	height	cm
wt_targ	target weight	kg
wt_pre	pre-dialysis weight	kg
wt_post	post-dialysis weight	kg
amp_left	degree of amputation to left leg	0 - 3
amp_righ	degree of amputation to right leg	0 - 3
newacc	Was access changed since last km session?	0 No/1 Yes
bunpre	pre dialysis BUN (whole blood)	mg/dL
bunpos20	20 sec post dialysis BUN (whole blood)	mg/dL
Tp	prescribed dialysis time	min
Td	actual dialysis time (24 hr clock)	min
interrup	Was interruption time > 15 minutes?	0 No/1 Yes
Qd	dialysate flow rate	ml/min
Qbprep	prescribed blood flow rate	ml/min
Qbrep	blood flow at 30 min	ml/min
dialyzer	type of membrane	integer
studdial	was dialyzer on the study-approved list	0 No/1 Yes
KoA500	KoA at Qd = 500	ml/min
KoA800	KoA at Qd = 800	ml/min
uun	urine urea nitrogen	mg/dL
urine_vol	volume of urine collection	ml

4.12.2 Derived Variables

uft	total ultrafiltration	ml
uf	ultrafiltration rate	ml/min
v_sa	anthropometric volume (Watson formula)	L
C0	bunpre/0.93 (blood water BUN)	mg/dL
Ct	bunpos20/0.93 (blood water BUN)	mg/dL
Qb	30 min blood flow corrected for pre-pump pressure	ml/min
Qbp	Prescribed blood flow corrected for pre-pump pressure	ml/min
KoA	KoA at prescribed Qd	ml/min
Kd	dialyzer clearance computed from Qb, Qd, and KoA	ml/min
Kdp	dialyzer clearance computed from Qbp, Qd, and KoA	ml/min
ktv_sp	Kt/V (1-pool)	none
v_sp	single pool volume (from Kd and Td)	L
g_sp	urea generation rate (1-pool)	mg/min
pcr_sp	PCR (1-pool)	g/d
npcr_sp	PCR (1-pool)	g/kg/d
urr	Urea reduction ratio	
tacu_sp	time averaged BUN, ignoring rebound (formerly tacu)	mg/dL
ktv_tot	total 1-pool Kt/V, including resid renal fun	none
ektv_d	eKt/V by Dau. rate adjustment	none
cinf_d	equilibrated BUN by Dau. rate adj	mg/dL
eg_d	equilibrated g, by Dau. rate adj	mg/min
epcr_d	equilibrated PCR, by Dau. rate adj	g/day
enpcr_d	equilibrated nPCR, by Dau. rate adj	g/kg/day
tacu_d	time averaged BUN, assuming rebound	mg/dL
sri_d1v	solute removal index, by Dau. rate adj, 1 v_sp	proportion
sri_dmv	solute removal index, by Dau. rate adj, m(v_sp)	proportion
Kwb	whole body clearance, by Daugirdas rate adj	ml/min
ektv_tot	total eKt/V, including res. renal function	none
mv_sp	running mean of v_sp, inc current session	L
mv_splag	running mean of v_sp, exc current session	L
mv_splg2	running mean of v_sp, exc last 2 sessions	L
mv_splg3	running mean of v_sp, exc last 3 sessions	L
v_sp_l1	last session's 1-pool volume	L
v_sp_l2	1-pool volume 2 sessions ago	L
sameacc	How many sessions on same access?	integer
volnum	sequence number of km sessions with valid v_sp	L
vsp_rxv	running mean of v_sp, at last rx change (formerly mv_rx)	L
vsp_tv	running mean of v_sp at last target time change	L
Keff	Effective dialyzer clearance (from mv_splag, Qb, Qd, KoA, Td)	ml/min

ktv_rx	prescribed 1-pool Kt/V (from mv_splag, Qbp, Qd, K0A, and Tp)	none
ektv_rx	prescribed eKt/V by Daugirdas rate adj (from mv_splag, Qbp, Qd, K0A, and Tp)	none
ktv_rxa	prescribed 1-pool Kt/V (from vsp_rxv, Qbp, Qd, K0A, and Tp)	none
ektv_rxa	prescribed 1-pool Kt/V (from vsp_rxv, Qbp, Qd, K0A, and Tp)	none
Td_eff	Eff. time, relative to Keff	min
qbeff	Eff. Qb, relative to Keff	ml/min
qdeff	Eff. Qd, relative to Keff	ml/min
KoAeff	Eff. K0A, relative to Keff	ml/min
recireff	Eff. % recirculation, relative to Keff	%
perclot	Eff. % dialyzer clotting, relative to Keff	%
Kr	residual renal clearance	ml/min

4.12.3 Equations used in DCC Programs

4.12.3.1 Expression of BUNs as blood water concentrations

C0 = bunpre/0.93 (3. 1. 1)

Ct = bunpos20/0.93 (3. 1. 2)

4.12.3.2 Small fudges to avoid division by 0 in calculations

if wt_post = wt_pre, then set wt_post = wt_post - .0001 (3. 2. 1)

Qbrep = Qbrep + .0001 (3. 2. 2)

Qd = Qd + .00015 (3. 2. 3)

4.12.3.3 Downward adjustment of blood flow to account for negative pressure

Qb = Qbrep X (1 - max(Qb_set - 200,0) / 2000) (3. 3. 1)

Qbp = Qbprep X (1 - max(Qbp_set - 200,0) / 2000) (3. 3. 2)

4.12.3.4 Ultrafiltration parameters

uft = 1000 (wt_pre - wt_post) (3. 4. 1)

uf = uft/Td (3. 4. 2)

4.12.3.5 Anthropometric volume

Without amputation:

If sex = male,
v_sa = 2.447 - 0.09516 (age) + 0.1074 (height) + 0.3362 (wt_targ) (3. 5. 1)

If sex = female,
v_sa = -2.097 + 0.1069 (height) + 0.2466 (wt_targ) (3. 5. 2)

With amputation:

Step 1:

Set lamp = 0 if amp_left = 0 or 1 (none or transmetatarsal)
= 1 if amp_left = 2 (below knee)
= 2 if amp_left = 3 (above knee)

Set ramp = 0 if amp_righ = 0 or 1 (none or transmetatarsal)
= 1 if amp_righ = 2 (below knee)
= 2 if amp_righ = 3 (above knee)

Step 2:

Set wt_targx = wt_targ X [1 - .05 (lamp + ramp)]

Step 3:

Compute v_sa as in (3.5.1) and (3.5.2) with wt_targ replaced by wt_targx.

Step 4:

Compute the final anthropometic volume for amputees (v_sa(amp)):

Set v_sa(amp) = v_sa X [1 + .05 (lamp + ramp)]

4.12.3.6 Calculation of Dialyzer Blood Water Clearance

4.12.3.6.1 Interpolation to determine K0A at reported Qd

K0A = K0A500 + (K0A800 - K0A500) X (Qd - 500)/300 (3. 6. 1)

4.12.3.6.2 Determination of theoretical blood water dialyzer clearance Kd

Step 1:

Determine whole blood dialyzer clearance Kd1

Step 2:

Adjust whole blood clearance and whole blood flow rate to obtain blood water clerance (Kd2) and
blood wate flow rate (Qe) based on an assumed mean hamatocrit of 35%:

Kd2 = .894 (Kd1) (3. 6. 3)

Qe = .894 (Qb) (3. 6. 4)

Step 3:

Adjust blood water clerance for ultrafiltration to obtain in-vivo blood water Kd:

Kd = (1 - uf/Qe) X Kd2 + uf (3. 6. 5)

4.12.3.6.3 Determination of prescribed dialyzer clearance Kdp

Kdp is calculated using Equations 3.6.1 - 3.6.5, with the prescribed blood flow Qbp substituted
for the recorded 30 minute blood flow Qb

4.12.3.7 Initial Estimate of residual renal clearance (Kr)

Step 1:

Estimate post-dialysis aqueous BUN from previous dialysis (b1):

b1 = (0.86/1.08) X Ct if day = 1 or 2

b1 = (1.00/0.86) X Ct if day = 3 or 4
b1 = (1.08/1.00) X Ct if day = 5 or 6

Step 2:

Determine time between the post BUN of the preceding session and the middle of the urine collection period (midtime) and the time between the post-BUN of the preceding session and the pre BUN of the current session (ttime). The quantities midtime and ttime are computed assuming that the previous dialysis began and ended at the same times as the current dialysis.

Step 3:

Estimate the BUN (in mg/ml) at midtime by linear extrapolation:

mid-BUN = [b1 + (b2 - b1)Xmidtime/ttime]/100, (3. 7. 1)

where b2 is equal to the predialysis aqueous BUN of the current modelling session (C0).

Step 4:

Estimate amount of urea nitrogen excreted per min (urate, in mg/min):

urate = [(uun/100) X urin_vol]/utime, (3. 7. 2)

where utime is the duration of the urine collection (in minutes), uun is the concentration of urea nitrogen in the urine (mg/dL), and urin_vol is the volume of the urine collection (ml).

Step 5:

Compute residual renal clearance (Kr) in ml/min

Kr = urate/mid-BUN (3. 7. 3)

Note: The estimate of Kr is revised using the exact solutions to the 1-pool VV model with the post-dialysis BUN replaced by the equilibrated BUN in Section 4.12.3.15.

4.12.3.8 Computation of v_sp using 2-BUN method

The 2-BUN method described in pages 81-85 of Depner [1991] is used to compute v_sp, ktv_sp, and g_sp based on C0, Ct, Kd, Td, and uf. The method assumes the 1-pool variable volume model, in which:

C(t) X dV/dt + V(t) X dC/dt = g - Kd X C(t), (3. 8. 1)
dV/dt = uf (3. 8. 2)

where C(t) denotes the aqueous concentration of urea in the blood at time t, V(t) denotes the total urea volume at time t, g denotes the urea generation rate, and Kd the in-vivo dialyzer clearance.

We first describe the solution to equations (3.8.1) and (3.8.2) in general, and then indicate how these solutions are used in the DCC programs.

4.12.3.8.1 General solution to the 1-pool variable volume model

Let C1 and C2 denote the blood water BUN concentrations (in mg/ml) at the start and end of the current dialysis session, let V0 denote the total urea volume (in ml) at the beginning of dialysis, and let g denote the urea generation rate (mg/min). The differential equations (3.8.1 - 3.8.2) can be integrated to give the following expression for the urea concentration C(t) as a function of time during the current dialysis:

(3. 8. 3)

The total urea concentration at a time tintr between the first and second dialysis is given by:

(3. 8. 4)

where B denotes the rate of weight gain between dialyses and Vp denotes the total urea volume at the end of the current dialysis session. Equation (3.8.3) can be solved for V0 as:

where t represents the duration of dialysis.

Given V0, Vp is simply

Vp = V0 - uf ù t (3. 8. 6)

4.12.3.8.2 Determination of 1-pool volume (v_sp) in the DCC programs

We next describe how equations (3.8.3 - 3.8.6) are solved iteratively to compute v_sp, g_sp, and ktv_sp in the DCC programs. The iterative solution is based on the premise that in "steady state", the pre-dialysis BUN for the dialysis session exactly one week following the current session should be equal to the pre-dialysis BUN of the current session.

Step 1: Compute pre and post-dialysis blood water BUNs in mg/ml

C1 = C0/100 (pre BUN) (3. 8. 7)

C2 = Ct/100 (post BUN) (3. 8. 8)

Step 2: Estimate rate of change in total urea volume between dialyses by

B = (uf ù t)/(1440 ù Ndays - Td) (3. 8. 9)

where Ndays denotes the number of days since the preceding dialysis. The constant 1440 is the number of minutes in a week.

Step 3: Obtain initial estimate of the urea generation rate g:

g = 1000 ù (v_sa)(C1 - C2)/(1440 ù Ndays) (3. 8. 10)

Step 4: Apply (3.8.5) - (3.8.6) to estimate Vo and Vp based on the inputs:

C1, C2, uf, t = duration of dialysis, Kr, Kd, and g

Step 5: Estimate C2 by applying (3.8.3) based on the inputs:

C1, V0, uf, t = duration of dialysis, Kr, Kd, and g

Step 6: Estimate C3 = pre-dialysis BUN of the next dialysis by (3.8.4) based on the inputs:

C2, Vp, B as calculated in Step 2, tintr = 1440 ù Ndays(2) - t, Kr, Kd, and g,

where Ndays(2) refers to the number of days between the current and the next dialysis

Step 7: Estimate C4 = post-dialysis BUN of the next dialysis by (3.8.3), using C3 in place of C1 and - B/(1440 ù Ndays(2) - t)/t in place of uf.

Step 8: Repeat Steps 6 and 7, and then Step 6 once more to obtain an estimate C1* of the pre-dialysis BUN exactly one week after the current session.

Step 9: Compute the fractional difference between C1* and C1.

FrErr = (C1* - C1)/C1, (3. 8. 11)

and update g by

g = g - FrErr ù g. (3. 8. 12)

Step 10: Repeat Steps 4 - 9 until |FrErr| < 0.001. At this point, set

v_sp = Vp, (3. 8. 13)

4.12.3.8.3 Interruptions > 15 minutes

Set v_sp to missing if total interruption time is 15 minutes or greater

4.12.3.9.1 Update running single pool volume mean based on the nonmissing v_sp's

If k ò 2, define the function tmean(v_sp1, v_sp2, ..., v_spk) to be equal to the mean of the volume estimates v_sp1, v_sp2, ..., v_spk if the coefficient of variation (CV) of the volume estimates is under 10%, and equal to the mean of all but the most extreme volume estimate if the CV is greater than 10%. If k = 1 or 2, tmean is defined simply as the mean of the volume estimates.
Further, define

tmean4 = tmean of last 4 nonmissing v_sp's, including the current session. If fewer than 4 sessions have been conducted, tmean4 represents the tmean of all nonmissing v_sp's.

tmean3 = tmean of last 3 nonmissing v_sp's, including the current session. If fewer than 3 sessions have been conducted, tmean3 represents the tmean of all nonmissing v_sp's.

tmean4s = tmean of last 4 nonmissing v_sp's on study-approved dialyzers, including the current session. If fewer than 4 sessions have been conducted, tmean4 represents the tmean of all nonmissing v_sp's.

tmean3s = tmean of last 3 nonmissing v_sp's on study-approved dialyzers, including the current session. If fewer than 3 sessions have been conducted, tmean3 represents the tmean of all nonmissing v_sp's.

Also define

lag(tmean4)= tmean of the four most recent nonmissing v_sp`s, excluding the current session. If fewer than 4 sessions have been conducted pror to the current session, lag(tmean4) represents the tmean of all previous nonmissing v_sp's.

v_sp_l1 = Previous nonmissing v_sp prior to current session

v_sp_l2 = 2nd previous nonmissing v_sp prior to current session

sameacc = Cumulative number of modelling sessions conducted since last access change

volnum = Cumulative number of modelling sessions conducted in the study

Based on these definitions, the running mean single pool volume (mv_sp) is defined as follows:

In baseline:

If volnum ó 2 then mv_sp = tmean4
If volnum = 3 then mv_sp = max(tmean4, .5 ù (mean(v_sp_l1,v_sp_l2) + v_sp)) if
abs (v_sp - lag(tmean4))/lag(tmean4) < 0.2, and
mv_sp = tmean4 otherwise.
If volnum = 4 then mv_sp = max(tmean4, mean(v_sp,v_sp_l)) if
abs (v_sp - lag(tmean4))/lag(tmean4) < 0.2, and
mv_sp = tmean4 otherwise.
If volnum = 5 then mv_sp = max(tmean4, tmean3) if
abs (v_sp - lag(tmean4))/lag(tmean4) < 0.2, and
mv_sp = tmean4 otherwise.
If volnum ò 6 then mv_sp = tmean4

In follow-up:

If sameacc = 1 then mv_sp = .75 ù tmean4s + .25 ù v_sp
If sameacc = 2 then mv_sp = .60 ù tmean4s + .40 ù mean(v_sp,v_sp_l1)
If sameacc = 3 then mv_sp = .50 ù tmean4s + .50 ù tmean3s
If sameacc ò 4 then mv_sp = tmean4s

4.12.3.9.2 Define previous running mean single pool volumes excluding current session

Set mv_splag = mv_sp from previous sessions with nonmissing v_sp (excluded current session)

Set mv_splg2 = mv_sp from previous sessions with nonmissing v_sp (excluding current and immediately previous session)

Set mv_splg3 = mv_sp from previous sessions with nonmissing v_sp (excluding current and last two modelling sessions)

4.12.3.10 Determination of 1-pool Kt/V, and 1-pool g in the DCC programs

Apply the 2-BUN method outlined in Section 4.12.3.8 to compute the effective dialyzer clearance and urea generation rate g based on the following inputs: current running mean single pool volume (mv_sp), pre- and post-dialysis BUN, weight loss during dialysis, and treatment time.

Let KdEff and g denote the effective dialyzers clearance and urea generation rate when convergence is reached. Then define

$$g\_sp = g, \qquad (3.10.1)$$

$$ktv\_sp = KdEff \times t/mv\_sp \qquad (3.10.2)$$

4.12.3.11 Effective dialyzer clearance

$$Keff = ktv\_sp \times (1000 \times v\_splag)/Td \qquad (3.11.1)$$

4.12.3.12 Equilibrated Kt/V based on Daugirdas/Schneditz rate adjustment

$$ektv\_d = ktv\_sp - (.6)(60)(ktv\_sp)/Td + 0.03 \qquad (3.12.1)$$

4.12.3.13 Whole-body clearance

$$Kwb = ektv\_d \times (1000 \times mv\_sp)/Td \qquad (3.13.1)$$

4.12.3.14 Equilibrated post-dialysis BUN and equilibrated g based on ektv_d

Successively apply equations (3.8.3) and (3.8.4) with Kwb in place of Kd until the predicted pre-dialysis BUN 1 week following the current session converges to the current session's pre-dialysis BUN (convergence within an error of .001). The equilibrated g (denoted eg_d) is defined as the value of g at convergence, and the equilibrated BUN (denoted cinf_d) is defined as the value of the predicted post-dialysis BUN of the current session at convergence.

4.12.3.15.1 Recompute Kr based on the equilibrated post-dialysis BUN and exact solution to the 1-pool VV Model

Successively apply equations (3.8.3) and (3.8.4) with Kwb in place of Kd and with the urea generation rate set at eg_d as determined in 4.12.3.14 in order to obtain the estimated aqueous BUN levels at six equally spaced time points through the interval of the urine collection. Then use the trapezoidal rule to estimate the area under the BUN curve (AUC) througout the urine collection, and compute the mean BUN concentration during the collection as:

conc_ca = AUC/(ur_time), (3. 15. 1)

where ur_time is the duration of the urine collection. Then recompute Kr as

Kr = urate/conc_ca. (3. 15. 2)

The recomputed estimate of Kr differs from the original estimate in Section 4.12.3.7 by taking into account the concave shape of the inter-dialytic BUN curve and post-dialysis rebound.

For reporting purposes and for assessing the residual renal function entrance criterion, residual renal clearance is expressed as a whole blood clearance: 0.93X Kr.

4.12.3.15.2 Update Estimates of single and equilibrated kinetic parameters based on recomputed Kr

Repeat Sections 4.12.3.8 - 4.12.3.14 using the recomputed Kr from Section 4.12.3.15.1.

4.12.3.16 Total 1-pool Kt/V and eKt/V

ktv_tot = [Kd ù Td + 3360 ù Kr]/(1000 ù v_sp) (3. 16. 1)

ektv_tot = [Kwb ù Td + 3360 ù Kr]/(1000 ù mv_sp) (3. 16. 2)

4.12.3.17 Prescribed 1-pool Kt/V and eKt/V

The prescribed 1-pool and equilibrated Kt/Vs based on running mean volume immediately preceding current session are calculated as:

ktv_rx = (Kdp)(Tp)/(1000 ù mv_splag) (3. 17. 1)

ektv_rx = (Kdp)(Tp)/(1000 ù mv_splag) - (.6)(60)(Kdp)/(1000 ù mv_splag) + 0.03 (3. 17. 2)

The prescribed 1-pool and equilibrated Kt/Vs based on the running mean volume at the time of the last prescription change (denoted ktv_rxa and ektv_rxa) are calculated as in 3.17.1 and 3.17.2 with mv_splag replaced by the running mean volumes at the time of the last prescription change. (Recall that revised prescription reports are sent only when the running mean volume (mv_sp changes by over 5%). It is ktv_rxa and ektv_rxa that are given in the routine kinetic modelling report.

4.12.3.18 Single pool PCR and nPCR

pcr_sp = 9.35 ù g_sp + 0.29 ù mv_sp (3. 18. 1)

npcr_sp = pcr_sp ù (0.58/mv_sp) (3. 18. 2)

4.12.3.19 Equilibrated PCR and nPCR (epcr_d and enpcr_d)

epcr_d = 9.35 ù eg_d + 0.29 ù mv_sp (3. 19. 1)

enpcr_d = (epcr_d)(0.58/mv_sp) (3. 19. 2)

4.12.3.20 Urea reduction ratio (URR)

URR = 1 - Ct/C0 (3. 20. 1)

4.12.3.21 Solute Removal Index (SRI)

(3. 21. 1)

4.12.3.22 TACu

TACu is calculated by repeatedly applying equations (3.8.3) and (3.8.4) to estimate C(t) at 5 evenly spaced time points within each of the three weekly dialysis sessions and at 5 evenly spaced time points between each of the three dialysis sessions based on the inputs: C1 = C0/100, Kd, uf, Td, mv_sp, and g_sp. Then estimate the area under the C(t) curve for the week using the trapezoidal rule, and compute TACu by dividing this area by the number of minutes in the week (7 ù 1440) and multiplying by 0.93 to express the result as a whole blood concentration.

4.12.3.23 Equilibrated TACu

Equilibrated TACu (denoted tacu_d) is computed similarly to TACu, except that Kd is replaced by Kwb and g_sp by eg_d.

4.12.3.24 Computation of "effective" parameters.

The "effective" values are the values of parameters necessary to account for the observed deviation between v_sp and mv_splag. These are reported in the trouble shooting report.

4.12.3.24.1 Effective Time (Td_eff)

Td_eff = Td ù (mv_splag)/v_sp (3. 24. 1)

4.12.3.24.2 Effective blood flow, dialysate flow, and in-vitro K0A.

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The equations (3.33.2) and (3.33.3) are equivalent to the series of equations 3.7.1 - 3.7.4 used to compute the in-vivo Kd. The effective blood flow rate (denoted Qbeff) is obtained by solving 3.33.2 - 3.33.3 for Qb given the observed Keff and the reported Qd and K0A. Similarly, the effective dialysate flow rate (Qdeff) and K0A (K0Aeff) are calculated by solving for these parameters given the reported values of the remaining parameters.

4.12.3.24.4 Effective % recirculation (recireff)

4.12.3.24.5 Effective % reduction in fiber bundle volume (perclot)

perclot = 100 (1 - K0Aeff/K0A) (3. 24. 5)

5. DIETITIANS

5.1 Importance of Monitoring Nutritional Status and Dietary Intakes

Data from the National Cooperative Dialysis Study (NCDS) suggested but did not demonstrate that the dialysis prescription may have an important impact on nutritional parameters. There was a striking decline in dietary protein intake in patients with high TAC BUN and a short target time and, although it was not an independent variable, low protein intake was a powerful predictor of morbidity. A more recent retrospective analysis of a large population of patients found the nutritional parameter of serum albumin to be importantly associated with outcome. The risk of death in a HD patient significantly increased with decreasing serum albumin.

The prospective predictive value of different serum albumins needs to be determined. It is critical to determine whether altering the dialysis prescription to a higher value for Kt/V and more biocompatible membranes will lead to improved nutritional status through higher serum albumin and increased energy intake. The following describes the rationale for monitoring nutritional status and dietary intake in the HEMO Study:

1) An increasing number of studies report that for the adult hemodialysis patient population, serum albumin has an important relationship to the outcomes variables, morbidity and mortality. Hypoalbuminemia may exert an independent effect on such outcomes, and it may result from low dietary protein intake or low energy intakes/energy balance, among other causes. Nutritional status may be affected by new and more effective dialytic techniques, such as high flux vs. conventional dialysis and biocompatible vs. standard membranes. Since nutritional status may affect outcomes, it is important to document it in the HEMO Study, specifically with respect to protein and energy.
2) Monitoring of diet and nutritional status allows evaluation of the effect dialysis treatment has on nutritional status. Possibly variations in Kt/V and/or membrane type have positive impacts on patient nutritional status, which may be of importance clinically.

3) Evaluation of nutritional status includes assessing food intake. Normalized PCR (nPCR) cannot be relied on as the sole measure of protein intake since it has not been demonstrated to be valid under all circumstances without corroborating data. For example, nPCR is not an accurate measure of protein intake for patients who are catabolic due to illness and many patients in the HEMO study may develop catabolic illnesses. Oral food intake must be assessed in conjunction with the nPCR in order to obtain useful dietary intake information and to complete a meaningful nutrition assessment.

4) Monitoring dietary intake allows assessment of the impact of the independent variables of the HEMO study on patient's appetite. Appetite may be correlated with different types of dialysis treatment.

5) PCR provides estimate only of dietary protein intake. In order to ascertain that intakes of all other nutrients are adequate additional data are needed. Monitoring dietary intake also provides valuable assurance that intakes of all essential nutrients are satisfactory.

6) The HEMO study offers a unique opportunity to describe the dietary intake of a large population of well characterized hemodialysis patients who are receiving specific types of dialysis prescriptions. This type of information may lead to the identification of nutritional problems and of their association with morbidity and mortality rates.

5.2 Role of the HEMO Grant-Supported Dietitian

The role of the HEMO grant-supported dietitian is to guarantee that the HEMO Study Protocol is being followed with respect to diet and anthropometry. The HEMO grant-supported dietitian must ensure that both the monitoring of nutritional status of patients in the HEMO Study and nutrition intervention are successfully completed. The HEMO grant-supported dietitian is also responsible for ensuring and maintaining a mutually amicable arrangement between that individual and the dialysis unit dietitian so that it will be possible to complete all aspects of patient care in the HEMO Study successfully.

The roles of the HEMO grant-supported dietitian are as follows:

1. Collection of a Two-Day Diet Diary Assisted Recall (Form 30).
2. Collection of all other nutrition-related forms (i.e., Forms 29, 33, 34, 35).
3. Calculation of food intake from diet records using Nutritionist Five, version 2.1.1H, customized for the HEMO Study, purchased and supplied by the NIH to each Clinical Center
4. Performance of post-dialysis anthropometric measurements as specified in the Protocol and Manual of Operations
5. Ensure that response to two nutrition-related action items (i.e., declining serum albumin or undesired weight loss) is according to Protocol and that actions are appropriate. If responses to the action items have not been initiated, it is the HEMO grant-supported dietitian's responsibility to perform them.
6. Become certified in all of the above activities and remain certified throughout the Study.

5.3 Role of the Dialysis Unit Dietitian

It is essential that the dialysis unit dietitian work as a colleague and full team member for the HEMO Study to be a success. The goal of both the dialysis unit dietitians and the HEMO grant-supported dietitians is to maximize patient well-being in the HEMO Study. The excellent clinical judgment and active involvement of the dialysis unit dietitians are essential for this to occur. Teamwork is essential for the HEMO Study to succeed.

Both the monitoring of the nutritional status of patients in the HEMO Study and nutritional intervention are limited. The primary emphasis of the Study will be to examine the effects of Kt/V (urea) and flux of dialysis membranes on outcome. Nevertheless, it is vital to observe the nutritional status of HEMO Study participants to ensure that they receive the same excellent care they would receive in the dialysis center if they were not Study participants. The dialysis unit dietitian is therefore critical to the Study and is regarded as a key team member.

Dialysis facilities at each Clinical Center are staffed by a registered dietitian. Attempts will be made, whenever feasible, to use their already existing and mandated patient activities in support of the nutritional aspects of the Study Protocol. The National Institutes of Health HEMO grant-supported dietitian will assume some of the activities of the dialysis unit dietitian.

Therefore, the Steering Committee considers it justifiable to invite the dialysis unit dietitian to carry out some of the Study-related nutritional interventions.

The responsibilities of the dialysis unit dietitian are as follows:

1. Initial and continuing education/training of the patient on his/her diet.
2. Routine re-evaluation of the patient's dietary intakes and routine nutritional interventions in these patients.
3. Assist HEMO grant-supported dietitian in responding to nutrition-related action items:
    a. Declining serum albumin.
    b. Undesired weight loss.
4. Use relevant data from the HEMO Study, including dietary analysis, to improve patient care and well-being.

The Nutritionist Five, version 2.1.1H, dietary analysis program and the laptop computer should be made available to the dialysis unit dietitian when not being used for Study purposes. (The *Nutritionist Five User's Guide* was distributed at training in Orlando, and is available through First DataBank Division, The Hearst Corporation, 1111 Bayhill Drive, San Bruno, CA 94066.)

5.4 Role of the Nutrition Consultants

The responsibilities of the Nutrition Consultants are as follows, with the performance of supportive activities to ensure their successful completion:

1) Review, modify and develop new forms concerning nutrient intake.
2) Review and provide recommendations concerning nutritional aspects of the Study Protocol.
3) Periodically revise the nutritional sections of the Manual of Operations in collaboration with members of the Nutrition Committee.
4) Train HEMO grant-supported dietitians.
5) Provide computer software for local dietitian use to assist in evaluating nutrient intakes.

6) Assist dietitians to become certified and remain so, for the above activities throughout the Study.

7) Assist the Nutrition Committee and participate in writing papers and reports from the HEMO Study.

8) Collaborate with the Anthropometry Consultant to ensure appropriate training of dietitians in anthropometry. Development of the Manual of Operations in anthropometry, and development of relevant forms related to anthropometry.

5.5 Other Activities of Dietitians in the HEMO Study

The HEMO grant-supported and the dialysis unit dietitians play a vital role in the success of the HEMO Study. In order to best enhance and coordinate their efforts, during the HEMO Study the following activities will take place:

1) **Annual Dietitian Training Workshop:**

The purpose of the workshop is to introduce the Study, Diet Assessment and nutrient analysis software (Nutritionist Five, version 2.1.1H), anthropometry related techniques, the HEMO Protocol and Manual of Operations. The workshop will bring together nutrition experts, both in the dialysis unit and NIH funded, to strengthen collaborative efforts.

2) **Certification related activities:**

Participate in certification activities to ensure standardization and quality assurance in all dietary and anthropometric measurements and in application of standards of care, action items, etc. for all Study patients.

3) **Conference Calls:**

Conference calls will be held monthly with the Nutrition Consultants, the HEMO grant-supported dietitians from each center, and other relevant staff, to assist in resolving problems in dietary and anthropometry related protocols.

4) **Consultation:**

Registered dietitians will also be asked to provide advice and participate in other, selected aspects of the Study, as their expertise is required.

5) **Strategic Planning:**

Develop long-term strategies, ensure coordinated efforts among parts of the HEMO Study, ensure focus, and provide leadership for the Study in the dietetic area.

6) **Quality Care:**

Assist in assuring high quality patient care.

7) **Training Dietitians:**

Assist in training dietitians in the Study.

8) **Present and Publish:**

Participate in development of abstracts and papers (see Section 16 of the Protocol for detailed procedures).

5.6 The Two Day Diet Diary Assisted Recall (Form 30)

5.6.1 Purpose

The Two-Day Diet Diary Assisted Recall (Form 30) is an adaptation of the 24-hour recall for use with dialysis patients. Because dialysis patients are in the unit frequently during the week, and are usually able to answer questions while being dialyzed, this method was chosen to minimize respondent burden while supplying some information that is representative of the entire week. Thus, this dietary assessment method recognizes the special needs and problems of dialysis patients and is tailored to minimize burdens upon them while obtaining appropriately detailed information about their diets.

The purpose of obtaining dietary data is to describe intakes in a reproducible way, and describe representative intakes. It is recognized that the recording process may be useful in making patients more conscious about what they are eating, and in improving adherence to diet prescriptions. Nevertheless, ***diet diaries should always reflect actual and usual dietary intake.***

The diet instruction videotape, *On The Record*, is provided to each clinical center. Its use is optional, depending on patient wishes, accessibility of VCR, whether or not there is a language barrier, and/or on the dietitian’s judgment of the patient's abilities to produce research quality data. Normally, its use will save time and assist in standardizing procedures.

The days of dietary data collection are chosen so that data collection is done on one dialysis day and one non-dialysis day, immediately preceding a scheduled kinetic modeling session. The appetite of dialysis patients may differ on dialysis days from that on non-dialysis days. Therefore, a two-day diet diary will be collected for each patient (one 24 hour period that is a dialysis day and one 24 hour period that is not a dialysis day). This will give us the best representation of intakes we can devise, given the constraints of time and money that are at our disposal.

5.6.2 Who Administers

The certified HEMO grant-supported dietitian administers the Two Day Diet Diary Assisted Recall as scheduled - once during Baseline and every 12 months thereafter.

5.6.3 Orientation of the Patient to the Procedure

5.6.3.1 Videotape and Workbook

A videotape, entitled *On The Record*, is a brief, 14 minute videotape orienting the patient on how to keep diet diaries. A copy is available in each Clinical Center and it can be copied if desired for study uses. The workbook *Keeping Track of What You Eat* and the HEMO Two Day Diet Diary Assisted Recall (Form 30) are keyed to the film. The film and workbook orient the patient to the diet diary keeping process, and urges the patient not to change his/her food intake simply because intake is being recorded. The video helps standardize patient response and save dietitian time in orienting the patient to the task, so it is recommended. The patient can be shown the film the visit preceding the first day on which records will be collected. In any event a "practice" recall is required to assist patients and dietitians in collection techniques prior to collection of records that will be entered into the study database.

5.6.3.2 Dietitian Orientation and Practice

After the patient has seen the videotape and completed the workbook, the dietitian orients the patient to collecting a Two Day Diet Diary Assisted Recall, making the following points when instructing the patient:

1) The patient will be asked to keep track of what he/she eats for a 2 day period, (1 dialysis day and 1 non dialysis day) and will be queried about intakes at the next dialysis session.
2) Food intake should be just as he/she would usually eat. The patient is asked to bring in any labels or details about recipes if possible for items he/she is not sure about.
3) Emphasize the information is only for descriptive purposes and for obtaining intakes of groups of patients, not to judge individuals.
4) The dietitian administers a "practice" recall to the patient while the patient is on dialysis, prior to the scheduled two day diet diary assisted recall collection period.
5) The following visit the patient is given a diet diary (Form 30) and asked to keep track of what he or she eats, over the next two days, and to bring the record to the next dialysis treatment.
6) The patient is asked if there are any questions, and if so, the questions are answered.

In summary, one week prior to the scheduled Two Day Diet Diary Assisted Recall collection period the patient views a videotape (optional), *On The Record*, to orient him/her to keeping a diet diary. Next, he/she completes a "practice" recall with the dietitian to assist him/her in understanding the amount of detail required, and the reason for the diary. The dietitian's practice recall further provides the patient with an example of what is required. The workbook, *Keeping Track of What You Eat*, provides some examples of how to keep a diary. The dietitian instructs the patient about the level of detail needed and how to use the diary. Finally, if the patient has any questions, they are answered.

5.6.3.3 **Two Day Diet Diary Assisted Recall (Form 30)**

The HEMO Two Day Diet Diary Assisted Recall (Form 30) is distributed to the patient at the dialysis session prior to that session at which the recall will be taken. The patient is asked to return with it at the next dialysis session for completion of the recall with the dietitian. The

diary provides the patient with a convenient method of recording his/her dietary intake and asking any questions that might arise over the two days.

5.6.4 **When to Administer**

One Two Day Diet Diary Assisted Recall is collected for each study participant. It is required for each 48 hour period that one 24 hour period be during a dialysis day and that the second 24 hour period be during a non dialysis day.

The Diet Diary is collected once in Baseline and annually during Follow-up. **It is important to make sure the dietary recall is collected just prior to a Kinetic Modeling session** to ensure nPCR and dietary protein intake are within the same week.

5.6.5 **How to Administer The Two Day Diet Diary Assisted Recall (Form 30)**

The HEMO grant supported registered dietitian (HEMO dietitian) is responsible for completing this procedure. (The dialysis unit dietitian, if certified, may serve as a back-up to the HEMO dietitian).

1) Assemble these tools:
   a) Two Day Diet Diary Assisted Recall (Form 30)
   b) measuring cups and spoons, food models, etc.
2) Orient the Patient

   Thank the patient for keeping the diet diary and ask to look at it. Review any items you may need to ask the patient about during the interview.

   Tell the patient that starting with the last meal eaten, the two of you are going to review his or her food intake over the two days he/she has recorded. Ask the patient to refer to the food diary for details, and ask if he/she has any questions or problems. Show the measuring cups, spoons and food models and tell the patient that they are available to help specify portion sizes.
3) Proceed with review of the Two Day Diet Diary Assisted Recall (Form 30)

The dietitian requests the diary and reviews it. Obtain additional detail, if necessary, prior to beginning the recall. Write any notes in the diary in red ink (to make it clear as to what was the original data and what was added by the dietitian) in the section marked “For Dietitian Use Only." If clarification is needed on any items, request more information and record it. Instruct the patient that the recall should include all food, drink, oral enteral supplements, tube feedings, TPN, IDPN, and vitamins and minerals. Use the food diary to prompt the patient. Be sure to probe for oral enteral supplements, vitamins and minerals, and to probe for additional items. Use a separate diet diary for each 24-hour period. Probe at the end of each day "anything else you ate or drank that day?" Note that there may be additional items that the patient may recall that were not on the diary.

Close the interview, asking "Is there anything else you remember eating or drinking that day?"

If the patient finds it easier to recall food intake starting with the day before proceeding through the current day, then proceed in that order.

If the patient has not kept a diary, try the recall. If the recall is so vague as to be uninterpretable, schedule a repeat collection for the next week. Record notes on why the interview was unsuccessful.

4) Thank the patient and ask if there are any questions.

5) Make a file for the patient's diet diaries and any other materials. File all materials with the date and patient's Study ID and namecode.

6) Enter the data into the Nutritionist Five nutrient analysis system as described in the Manual of Operations Section 5.9. Be sure to include all foods, drinks, oral enteral supplements, tube feeding, TPN, IDPN, and vitamins and minerals in analysis.

7) Enter all nutrient analyses into the Study database each week in line with Study Protocols. Keep a hard paper copy of the Nutritionist Five file with your records. You may be asked to produce and copy your complete record for quality assurance purposes.

5.7 Baseline Nutrition Data Collection: Details

5.7.1 Introduction

The purpose of Baseline data collection is to provide information on a representative sample of the patient's dietary intake before the randomized phase of the Study begins. Refer to the Protocol Section 4.6-Measurements to be Performed Once During Baseline and Annually During Follow-Up and Protocol Section 6.2-Schedule of Measurements and Procedures for scheduling details. The nutrient data is collected during the first 2 weeks of Baseline while patients are on their original dialysis prescription. See MOP Section 5.11 for visit number and nutrition activities scheduled for each week during the Baseline period. Nutrition data consists of a practice recall, a two day diet diary assisted recall, the Diet Prescription and Supplement Documentation Form (Form 33), Appetite Assessment Form (Form 34), and Anthropometric Measurement Form (Form 29). The forms are described below:

5.7.1.1 Form 29: Anthropometry Form

This form is used to record the anthropometry data. It is entered into the study database.

Raw values for each measurement are written in the appropriate places. Means will be calculated at the Data Coordinating Center. Body mass index (BMI) and standard body weight will be calculated from actual measurements recorded by the Data Coordinating Center.

Purpose

The goal is to describe body size and composition in a standardized fashion, including measurements of subcutaneous adipose tissue, frame size (via elbow breadth), height (or knee height if stature is unavailable) and weight. Note that each measurement value should be recorded (twice). Averages will be calculated at the DCC.

Who Administers

The HEMO grant-supported dietitian or another study personnel who is certified in anthropometry.

How to Administer

See Manual of Operations Section 9.5-Anthropometry: Instructions for Measurements

When to Administer

See Manual of Operations Section 5.7.2.3.

5.7.1.2 Form 30: Diet Diary Assisted Recall

Purpose

This form is first entered into Nutritionist Five Program and the results are transmitted to the Study database. This form is used to record each 24 hour recall from the two day diet diary assisted recall procedure. All food, drink, oral enteral supplements, tube feedings, TPN, IDPN, vitamins and minerals are probed for and recorded if consumed during the recall period. There is a separate form for each day. This form and the Nutritionist Five reports remain in the patient's file at the Clinical Center.

Who Administers

The HEMO grant-supported dietitian administers the Two Day Diet Diary Assisted Recall.

How to Administer

See Section 5.6.4 - 5.6.5 above for a detailed description of the Two Day Diet Diary Assisted Recall procedure.

1) Administer practice two day recall and review results with patient.
2) Administer two day diet diary assisted recall just prior to a KM session.
3) Review diet diary assisted recall and query patient for additional information needed.
4) Analyze data on nutrient analysis program and transmit data into DCC database.

When to Administer

See Manual of Operations Section 5.7.2.1

5.7.1.3 **Form 33: Diet Prescription and Supplement Documentation Form**

Purpose

This form is entered into the Study database. The form is designed to fulfill these study purposes:

l) Document diet prescription at: a.) Baseline, b.) every 12 months during follow-up c.) in response to a permanent diet modification (e.g.. new diagnosis of hyperlipidemia or diabetes), and d) in response to a nutrition action item (undesired weight loss or decline in serum albumin).
2) Document use of any vitamin/mineral supplements, medical nutritional products, and/or intradialytic parenteral nutrition.
3) Document change in oral enteral supplements, tube feeding, TPN, and IDPN prescriptions in response to nutrition action items.

Who Administers

The HEMO grant-supported dietitian completes Form 33.

How to Administer

See Manual of Operations 5.7.2.4

When to Administer

See Manual of Operations Section 5.7.2.4

5.7.1.4 Form 34: Appetite Assessment Form

Purpose

This form will be entered into the Study database.

Its purpose is to document appetite changes at Baseline and throughout the Study.

The goals of this form are to:

1) Describe general appetite level and appetite on dialysis and non dialysis days
2) Describe general food habits at baseline
3) Correlate intakes at baseline with possible changes in appetite on either dialysis or non dialysis days associated with alterations in Kt/V or flux of dialysis membranes.

Who Administers

The HEMO grant-supported dietitian administers the Form 34.

How to Administer

See section 5.7.2.2 for a detailed description of how to administer this form.

When to Administer

See Manual of Operations section 5.7.2.2

5.7.1.5 Form 35: Supplement Distribution Form

Purpose

This form is used to track the dispensing of vitamin/mineral and oral enteral supplements. See MOP Section 5.16 for details on the supplements. This information is entered into the study database. Parenteral, enteral, and intradialytic parenteral nutrition is recorded on Form 33.

Who Administers

The HEMO grant-supported dietitian completes this form.

When to Administer

Complete this form when dispensing vitamins/minerals or enteral supplements.

5.7.2 Detailed Description of Procedures for Nutrition Data Collection

5.7.2.1 Two Day Diet Diary Assisted Recall (Form 30)

Purpose

This form is entered into the Study database. It describes two 24 hour results of dietary intake, one dialysis day and one non-dialysis day.

Who Administers

The HEMO grant-supported dietitian administers the 2-day diet diary assisted recall.

How to Administer

See Section 5.6.4 above for a detailed description of the procedure

1) Administer practice two day diet diary assisted recall and review results with patient.
2) Administer two day diet diary assisted recall.
3) Review diet diary assisted recall and query patient for any additional information.
4) Analyze data on nutrient analysis program and transmit data into DCC database.

When to Administer

The Two Day Diet Diary Assisted Recall is administered during the first two weeks of Baseline, while patient is on his/her original dialysis prescription, and just prior to a kinetic modeling session. The Two Day Diet Diary Assisted Recall is administered annually thereafter, while patient is on his/her randomized dialysis prescription, and just prior to a Kinetic Modeling session. If a two day diet record cannot be obtained and all possible measures have been taken to obtain a two day food record including a two day recall or contacting patient's family/friends, then the food record data will be treated as a missing form. If the patient's two day food record is deemed unreliable or inaccurate, please document that on Form 34.

Documentation of Tube Feedings, TPN, and IDPN on Form 30

All supplemental tube feedings, TPN, IDPN need to be recorded on Form 30 and analyzed with the food intake in Nutritionist Five. Total tube feeds and TPN should be recorded on Form 30 and analyzed in Nutritionist Five even if not eating by mouth.

5.7.2.2 Appetite Assessment Form (Form 34)

Purpose

Document appetite pre and post dialysis. Enter the Form 34 into the Study database.

Who Administers

The HEMO grant-supported dietitian administers the form. If the patient refuses to have the questionnaire administered at the designated visit, it should be completed at the next visit.

How to Administer

During the first half of dialysis complete the form interactively with the patient to minimize respondent burden. If the patient prefers to fill out the questionnaire by him/herself, tell the patient that you will return to answer questions and to ask a few additional things. Ask the patient to fill out as much of the questionnaire as is possible. Give the patient about 30 minutes and return. Review the form and probe for items not completed. Ask him/her if there are any questions; if so answer them. Check the form for completeness. This is a subjective appetite assessment form and requires the patient to answer the questions on the form. Other persons may aid the patient in filling out the form with the patient, but cannot answer the questions for the patient. All answers must be based on the patient's input. If the patient is not eating by mouth or is mentally incompetent and cannot complete this form, fill out only the patients identification information, date, dates of two day food records, and reliability questions for food records.

When to Administer

The Appetite Assessment Form is administered during the first two weeks of Baseline, while patient is receiving his/her original dialysis prescription and annually thereafter, while patient is receiving his/her randomized dialysis prescription.

5.7.2.3 Anthropometric Measurements Form (Form 29)

Purpose

Document relevant aspects of the body measurements and changes in them over the course of the study. See Section 9 of the Manual of Operations for details on Anthropometry.

Who Administers Measure

The HEMO grant-supported dietitian or another member of the HEMO team certified in anthropometrics.

How to Administer

See Section 9.5 of the Manual of Operations, Anthropometry: Instructions for Measurements, for a detailed description of how to administer anthropometric measurements.

When to Administer

Anthropometric measurements are taken at Baseline and annually during Follow-Up. The **body measurements are always taken after dialysis** in what is known as the "dry" weight condition. If absolutely necessary, post dialysis measurements other than the post weight must be measured within 10 hours of the end of the patients dialysis session.

5.7.2.4 Diet Prescription and Supplement Documentation Form (Form 33)

Purpose

The form is designed to fulfill these study purposes:

l) Document diet prescription at a.) Baseline, b.) every 12 months during follow-up, c.) in response to a permanent diet modification (e.g. new diagnosis of hyperlipidemia or diabetes), and d) in response to a nutrition action item (undesired weight loss or decline in serum albumin).

2) Document use of any vitamin mineral supplements, medical nutritional products, and/or intradialytic parenteral nutrition.

3) Document changes in oral enteral supplements, tube feedings, TPN, and IDPN prescriptions in response to nutrition action items.

Who Administers

The HEMO grant-supported dietitian completes this form.

How to Administer

The HEMO grant-supported dietitian fills out the form. After the interview with the patient, fill out Form 33 Diet Prescription and Supplement Documentation Form and enter into the Study database, using your worksheets and related records to complete all items.

When to Administer

The form is administered at these times:

1) Baseline
2) Every 12 months during follow up
3) In response to a permanent diet modification (e.g. new diagnosis of diabetes mellitus or lipid abnormalities).
4) Diet prescription change in response to a nutrition action item (undesired wight loss or decline in serum albumin).
5) Change in prescription of oran enteral supplements, tube feedings, TPN, or IDPN in response to a nutrition action item.

5.7.2.5 Supplement Distribution Form (Form 35)

Purpose

This form is used to track the dispensing of vitamin/mineral and enteral supplements. See Section 5.16 for details on the supplements. This information is entered into the study database.

Who Administers

The HEMO grant-supported dietitian completes this form.

When to Administer

Complete this form when dispensing vitamins/minerals or enteral supplements.

5.7.3 Summary of Procedures for Baseline Nutrition and Anthropometry Measures

In summary, one week prior to the scheduled Two Day Diet Diary Assisted Recall collection period the patient views a videotape (optional), *On The Record*, to orient him/her to keeping a diet diary. Next, he/she completes a "practice" recall with the dietitian to assist him/her in understanding the amount of detail required, and the reason for the diary. The HEMO Two Day Diet Diary is distributed to the patient. The patient is asked to record his/her intake, for a 48 hour period (one dialysis day and one non-dialysis day), on the diary and return with it at the next dialysis session for completion of the recall with the dietitian. The Two Day

Diet Diary Assisted Recall is conducted by the HEMO grant-supported dietitian while the patient is on dialysis. The HEMO grant-supported dietitian interviews the patient, using the two day diet diary the patient has maintained. The dietitian assists the patient in recalling and further specifying his intake over the past 48 hours-one 24 hour period at a time. Upon completion of the interview, the dietitian collects the diary and other materials used in the 48 hour assisted recall.

Collected diet diaries are further reviewed by the dietitian prior to data entry into the nutrient analysis program, with any marks and clarifications made in red pen. The recalls are then analyzed for nutrients as described in the Manual of Operations, Section 5.9, and entered into the Study database as described in Section 5.10 of the Manual of Operations. The Two Day Diet Diary Assisted Recall (Form 30), the Nutritionist Five diet analysis printout, and all notes on the interview are kept in the Study record file within the unit. Copies of them are forwarded on request to the DCC Nutrition Consultant for quality assurance purposes.

5.8 Follow-Up Nutrition Data Collection Details

5.8.1 Purpose

Follow-Up nutrition data collection provides a description of the dietary intake and anthropometric measurements every 12 months during follow up and also in response to nutrition action items.

The Follow-Up nutrition data collection Protocol is identical to that done at Baseline. See Manual of Operation Section 5.7 for a detailed summary of the nutrition data collection process.

5.8.2 Standards of Care

5.8.2.1 Nutrition Prescription

Purpose

The purpose of the nutrition prescription is to meet study diet goals by encouraging increased protein or energy intakes either by dietary modification or, if that fails, by use of oral nutritional supplements (Nepro or Suplena, or others).

Who Administers

The dialysis unit dietitian is responsible for the usual nutritional care of the HEMO Study patient. The HEMO grant-supported dietitian is responsible for intervening when nutrition action items (undesired weight loss and declining serum albumin) are reached, after consultation and in collaboration with the dialysis unit dietitian. The HEMO grant-supported dietitian is also responsible for consulting with the dialysis unit dietitian and the patient when the Study participant's nPCR is < 1 gm/kg/day, or when Calorie intake is < 28 Kilocalories/kg/day.

How to Administer

The principles for formulating the nutrition prescription, details of protein and energy intake, and diet recommendations are provided in Sections 10.1-10.4 of the HEMO Protocol.

When to Administer

Ongoing throughout the study

5.8.2.2 **Diet Recommendations**

Dietary recommendations for the Study are provided in Section 9.1 of the Protocol and listed in Manual of Operations Table 5.1.

5.8.2.3 **Supplements**

R & D Labs, Inc. of Marina Del Ray, California has graciously donated Nephro-Vite® RX vitamin supplements for the Full-Scale Study. These supplements, although not required, are strongly recommended. Ross Laboratories has kindly provided oral nutritional supplements for the HEMO Study. These supplements are strongly recommended and available free of charge. These supplements are described in detail in Section 5.16.

Purpose

To ensure that the nutritional status of HEMO patients is maintained.

Who Administers

All certified study personnel as needed.

How and When to Administer Vitamin Supplements

Nephro-Vite® RX is available free of charge. Nephro-Vite® RX contains vitamins B and C as listed in the Protocol. Nephro-Vite® RX is strongly recommended but not required. If it is prescribed (Table 5.1, Diet Recommendations), it should be taken daily after dialysis on dialysis days and two hours after eating on other days. All randomized study participants are strongly encouraged to take the Nephro-Vite® RX.

How and When to Administer Oral Nutrition Supplements

See section 5.13.

5.9 How to Analyze the Diet Recalls

5.9.1 General Information on the Database to be Used in the Study: Nutritionist Five

The Two Day Diet Diary Assisted Food Recalls will be analyzed using Nutritionist Five version 2.1.1H customized for the HEMO study. This program is available from the DCC. The database is comprised of over 17,000 foods. The program is capable of analyzing diet intake for 80^{+} nutrients. The sources used to compile the nutrient information for this database span in years from 1977-1999 and include analyses information for both fast foods and a large number of food manufacturers. The customized program permits analysis by food, by supplement, or both food and supplement, sources of nutrients. The program is user friendly and does not require a significant degree of computer literacy to use.

For patient counseling purposes, the database can report dietary recalls by individual nutrients, by diabetic food exchanges for the entire day and by meal. It can also present food groups displaying the Food Pyramid format if this is helpful for patient instruction. It is possible to identify foods on the recall that are within a reasonable range of intake for a given nutrient. For example, if the user requests screening a diet record for potassium content between 25 and 100 mg, the program will list the foods on the recall that fall within that range. Protein and calorie consumption patterns can be reported per meal, if desired.

5.9.2 Diet records will be analyzed by the HEMO grant-supported dietitian using the Nutritionist Five Program customized for the study.

Two Day Diet Diary Assisted Recalls will be collected from participating subjects by the certified HEMO grant-supported dietitian. The recalls will be collected using the study Diet

Diary Assisted Recall Form (Form 30). After completion of the recall, the HEMO grant-supported dietitian will use the Nutritionist Five "Diet Analysis" option to analyze the collected food intake information. Intakes should be analyzed for the following nutrients: total protein (gm/ day), energy (kcal/day), fat (% of kcal and gm/day), saturated, monounsaturated, polyunsaturated (gm/day), carbohydrate (% of kcal and gm/day), ethanol (% of kcal), phosphorus (mg/day and mg/kg/day), fluid (ml/day), sodium, potassium, calcium, magnesium, thiamin, riboflavin, pantothenic acid, niacinamide, pyridoxine, and vitamin C (all mg/ day); and vitamin B12, biotin, and folic acid (all mcg/day).

After completion of the analysis, the dietitian transmits the nutrient analysis information to the DCC database (see Appendix 5A - 5.1, Sending Nutritional Analysis Results to the DCC), prints out a copy of the nutrient analysis information, and keeps a copy of the nutrient analysis printout in the patient's file.

5.9.2.1 **Purpose**

The purpose is to describe the patient's intake at Baseline, after randomization, and in response to action items. Dialysis unit dietitians may wish to use the dietary analysis program for obtaining recalls on patients at other times as well for clinical counseling purposes.

5.9.2.2 **Procedure**

The laptop provided has the customized software for the Nutritionist Five Version 2.1.1H program installed. Enter the recalls by day from the Form 30 after you have obtained them from the patient. The food record file should be saved onto a back-up floppy disk when the analysis is complete. Be sure the file is saved onto the disk prior to exporting and transmitting to the DCC.

5.9.2.3 **Who Should Enter the Data**

The HEMO grant-supported dietitian should enter the data and keep all relevant records for study quality assurance purposes. Such records include the diet diaries on which the Two Day Diet Diary Assisted Recalls are obtained (Form 30), any labels or any other information the

patient may have brought in with the diary, the Nutritionist Five nutrient analysis printout, and the back-up floppy disk containing the Nutritionist Five nutrient analysis.

Before you proceed to enter the data, examine each day of the diet diary for completeness. Make sure that portion sizes are written down. Desegregate recipe data for items that are not likely to be in the database into their component parts so that they can be entered. If you are in doubt about an item, look it up in the database to see if it is there. If you need help in deciding how to desegregate a dietary record, consult the HEMO Study Coding Manual or fill out a coding assistance Request and fax it to the Nutrition Coordinating Center at (617) 636-8325 (see appendix 5B), or call the nutrition consultation hot line for help in coding. (Phone: 617/636-9349 or fax 617/636-8325)

5.9.2.4 **Database Changes**

Database changes at sites cannot be made because they will confuse centralized data analysis.

5.10 Entering Diet Analysis Data in the HEMO Study Database

Nutrient intakes are calculated from the patients' Two Day Diet Diary Assisted Recalls (Form 30) provided in the output from the Nutritionist Five software program.

Diet analysis data records are entered into Nutritionist Five. The output from the Nutritionist Five diet analysis program, in the required format, is transmitted electronically to the DCC across the Internet (see Appendix 5A - 5.1, Sending Nutritional Analysis Results to the DCC). Contact the DCC Study Coordinator via e-mail if transmitted Nutritionist Five data need to be modified. Be sure the food record Nutritionist Five nutrient analysis has been saved on the hard drive and on a back-up floppy disk prior to exporting and transmitting to the DCC. The Nutritionist Five program should be backed up periodically to ensure that all food records are saved and prevent files from being lost.

5.11 Baseline Nutritional Care and Principles

The dietitian assesses the patient's nutritional status by completing a baseline nutrition assessment. The assessment includes evaluation of patient appetite, current diet prescription,

current dietary intake, current weight parameters, serum chemistries (BUN, creatinine, potassium, phosphorus, sodium, calcium, bicarbonate, albumin and nPCR), and interdialytic fluid gains. Using all of this information the dietitian determines if the diet prescription is appropriate as specified in Table 5.1.

5.11.1 Overview of Baseline

Within the first fourteen weeks (Baseline Period) that a patient is enrolled in the Study, the following forms must be completed: the Anthropometry Form (Form 29), the Two Day Diet Diary Assisted Recall (Form 30), the Diet Prescription and Supplement Documentation Form (Form 33), and the Appetite Assessment Form (Form 34). The Supplement Distribution Form (Form 35) is to be completed as needed when supplements are distributed to patients. These are completed by the HEMO grant-supported dietitian.

During the first two weeks of the Baseline period, the HEMO grant-supported dietitian instructs the patient on diet diary keeping using the videotape, workbook for patients, a practice recall and distribution of two day diet diaries as specified in the Manual of Operations Section 5.6. The HEMO grant-supported dietitian also collects completed diaries and performs recalls.

5.11.1.1 Baseline Visit l

1) Review overall nutrition data collection plans with patient.
2) Ask patient to complete Appetite Assessment Form (Form 34).
3) Evaluate and document the current diet prescription for clinical appropriateness with regard to the patient's nutritional status and the HEMO Study Protocol either this week or at week two, using Form 33 (Diet Prescription and Supplement Documentation Form).
4) If the patient’s current diet prescription is not within the ranges specified in Table 5.1, the HEMO grant-supported dietitian should meet with the dialysis unit dietitian, and the HEMO Study physician to discuss recommended changes and to implement them in line with the physician’s directions.

5.11.1.2 Baseline Visit 2

1) Ask the patient to view the videotape, *On The Record*, (optional) and to complete the workbook *Keeping Track of What You Eat*.
2) Complete a practice recall with the patient.
3) Provide patient with a Two Day Diet Diary to take home and instruct the patient to record his/her intake for a 48 hour period (one dialysis day and one non-dialysis day) on it.

5.11.1.3 **Baseline Visit 3**

1) Collect the two day diet diary assisted recall form (Form 30) and review with patient as described in section 5.6.5.
2) Query patient for any additional information or for clarification of food items. Write any additional comments on the record in red ink.

Table 5.1 Diet Recommendations a

Protein (g/kg/day)	> 1.0
Energy (kcal/kg/day)	> 28 or usual intake b, c, d whichever is greater
Calcium (mg/day)	800 - 2500e
Phosphorus (mg/kg/day)	<14
Magnesium (mg/day)	150 - 300f,g
Sodium (mg/day)	500 - 5000g
Potassium (mEq/day)	40 - 150g
Fluid intake (L/day)	0.60 - 3.0g
Vitamin supplementsh	
Thiamin (B1) mg/day	1.5
Riboflavin (B2), mg/day	1.7
Pantothenic acid, mg/day	10

Niacinamide, mg/day	20
Pyridoxine HCl, mg/day[i]	10
Vitamin B12, µg/d	6
Vitamin C, mg/day	60
Biotin, ug/day	300
Folic acid, mg/day	1.0

[a] Please note that these are optimal ranges but may not apply in specific situations. Also, when nutrient intakes are related to body weight, body weight will be determined as actual dry body weight. The exceptions are people who are less than 90% or greater than 120% of standard body weight (SBW) as determined from the NHANES data (Abraham et al, 1979). For these individuals, adjusted body weight (ABW) will be used. The ABW will be calculated as follows: ABW = ((Patient's actual weight - SBW) x 0.25) + SBW.

[b] Determined during the Baseline period. If a patient is ingesting ≥28 kcal/kg/day, food supplements will not be used to maintain the patient's usual energy intake during follow up, unless the patient qualifies for this by reaching an action item.

[c] Energy intake will be increased if the patient is losing weight and is not obese.

[d] Energy intake will be decreased if the patient is obese.

[e] Includes calcium ingested in calcium salts (e.g., for phosphate binders) which will be prescribed on an individual basis. Patient's actual calcium intake may be below this range, depending on pertinent biochemistries (serum calcium, phosphorus, alkaline phosphatase, pTH).

[f] Magnesium intake will be reduced if predialysis serum magnesium is 3.0 mEq/L or greater.

[g] The prescribed intake for this nutrient will be determined by the patient's physician, but will be within the indicated range.

[h] Refers to the content of the recommended R and D Labs vitamin supplement (Nephro-Vite® RX). Depending on the vitamin content of foods ingested, the total (diet and supplements) quantities of the individual vitamins may be somewhat greater than the above values.

[i] Given as pyridoxine HCl

5.11.1.4 **Baseline Visit 4**

1) Analyze Form 30 using Nutritionist Five program customized for the Study.

2) Print out nutrient data and transmit data to DCC database as described in Section 5.10.

3) After review of nutrient data, serum chemistries, nPCR, and fluid gains, provide the patient with appropriate counseling, reinforcement, or education

5.11.1.5 **Baseline Visit 5**

1) Provide the patient with appropriate counseling, reinforcement, education, enteral supplements, or additional information after review of dietary intake, serum chemistries, fluid gain and nPCR values. If the patient's diet is outside of the ranges in Table 5.l, the HEMO grant supported dietitian should consult with the dialysis unit dietitian and meet the study physician to discuss recommended changes. Implement changes as directed by the physician.

2) Arrange for a visit with the patient to provide diet counseling for abnormal serum chemistries as follows.

The HEMO grant-supported dietitian, after consulting with the dialysis unit dietitian, (or, if the dialysis unit dietitian believes it is preferable, the dialysis unit dietitian) will:

a) counsel the patient in response to abnormal serum chemistries such as BUN, creatinine, potassium, phosphorus, sodium, calcium, bicarbonate, albumin, nPCR and /or interdialytic fluid gains.

b) evaluate abnormal chemistries or large fluctuations in chemistries with consideration being given to nutritional status, diet intake, active medical issues, dialysis prescription, and delivered Kt/V.

c) discuss any abnormalities in serum chemistries that cannot be explained by diet or patient food intake with the HEMO Study physician to determine the cause or causes of these abnormalities, and take appropriate measures to correct them.

5.11.1.6 **Baseline Visit 6**

1) Perform anthropometric measurements and complete anthropometry form (Form 29).
2) Enter all nutrition forms into DCC database.

Sample of Baseline Nutrition Data Collection for a patient receiving dialysis on a Monday, Wednesday and Friday

	Sun	Mon	Tues	Weds	Thurs	Fri	Sat
Wk 1		Review overall plans with patient Ask pt to complete Appetite Assessment (Form 34)	Evaluate current diet prescription using Form 33-Diet Prescription & Supplement Documentation Form. Make sure prescription within ranges specified in Table 5.1.	Show pt Video *On the Record* Complete a practice diet recall with pt Instruct pt to collect 2-day diet recall for Thurs & Fri. Bring to dialysis session on Monday		Check with pt to see if she/he has questions re: diet diary. Remind pt to bring diet diary on Mon.	
Wk 2		Collect 2-day diet recall & review with pt. Query pt for any additional information/ clarification.		Analyze diet diary using Nutritionist Five. Printout nutrient data & transmit data to DCC.		Provide pt with appropriate counseling/ reinforcement/ education or supplements after review of dietary intake.	
Wk 3							
Wk 4		Perform Anthro measures & complete Anthro Form-Form 29		Complete Form 35-Supplement Distribution Form Enter all Nutrition			

				Related forms into DCC database.			
Wk 5							
Wk 6							

5.12 **Follow-Up Nutritional Care and Principles**

5.12.1 **Follow-up Nutritional Assessment**

Follow-up nutritional assessment is completed every 12 months (range 11 - 13 months) during the Full-Scale Study. At that time the following forms are completed: the Two Day Diet Diary Assisted Recall (Form 30), the Anthropometry Form (Form 29), Appetite Assessment Form (Form 34), Diet Prescription and Supplement Documentation Form (Form 33).

The goal of follow up nutritional care is to meet or exceed recommendations of relevant professional organizations and textbooks for good nutritional status of renal patients, as specified in several recent references.

5.12.1.1 **Follow-Up Visit 1**

1) Review overall nutrition data collection plans with patient.
2) Ask patient to complete Appetite Assessment Form (Form 34).
3) Evaluate and document the current diet prescription for clinical appropriateness with regard to the patient's nutritional status and the HEMO Study Protocol either this week or at week two, using Form 33 (Diet Prescription and Supplement Documentation Form).
4) If the patient’s diet prescription is not within the ranges specified in Table 5.1, the HEMO grant-supported dietitian should meet with the dialysis unit dietitian, and the HEMO Study physician to discuss recommended changes and to implement them in line with the physician’s directions.

5.12.1.2 **Follow-Up Visit 2**

1) Ask the patient to view the videotape, *On The Record*, (optional) and to complete the Two Day Diet Diary Assisted Recall (Form 30).

2) Complete a practice recall with the patient.

3) Provide patient with a two day diet diary to take home and instruct the patient to record his/her intake for a 48 hour period (one dialysis day and one non-dialysis day) on it. **Make sure it is the same week as a kinetic modeling session.**

5.12.1.3 **Follow-Up Visit 3**

1) Collect the Two Day Diet Diary Assisted Recall (Form 30) and review with patient as described in section 5.6.5.

2) Query patient for any additional information or for clarification of food items. Write any additional comments on the record in red ink.

5.12.1.4 **Follow-Up Visit 4**

1) Analyze Form 30 to include: food description, amount, portion type, protein, energy and food code, using Nutritionist Five program customized for the Study.

2) Print out nutrient data and transmit data to DCC database.

3) After review of nutrient data, serum chemistries, nPCR, and fluid gains, provide the patient with appropriate counseling, reinforcement, or education.

5.12.1.5 **Follow-Up Visit 5**

1) Provide the patient with appropriate counseling, reinforcement, education, enteral supplements, or additional information after review of dietary intake, serum chemistries, fluid gain and nPCR values. If the patient's diet is outside of the ranges in Table 5.l the HEMO grant supported dietitian should consult with the dialysis unit dietitian and meet the study physician to discuss recommended changes. Implement changes as directed by the physician.

2) Arrange for a visit with the patient to provide diet counseling for abnormal serum chemistries as follows.

The HEMO grant supported dietitian, after consulting with the dialysis unit dietitian, (or, if the dialysis unit dietitian believes it is preferable, the dialysis unit dietitian) will:

a) counsel the patient in response to abnormal serum chemistries such as BUN, creatinine, potassium, phosphorus, sodium, calcium, bicarbonate, albumin, nPCR and /or interdialytic fluid gains.

b) evaluate abnormal chemistries or large fluctuations in chemistries with consideration being given to nutritional status, diet intake, active medical issues, dialysis prescription, and delivered Kt/V.

c) discuss any abnormalities in serum chemistries that cannot be explained by diet or patient food intake with the HEMO Study physician to determine the cause or causes of these abnormalities, and take appropriate measures to correct them.

5.12.1.6 **Follow-Up Visit 6**

1) Perform anthropometric measurements and complete anthropometry form (Form 29).
2) Enter all nutrition forms into DCC database.

5.13 Responding to Action Items

The two action items requiring intervention by the dietitian are declining serum albumin and undesired weight loss.

5.13.1.1 Declining Serum Albumin

Definition: Declining serum albumin is defined as a decline in serum albumin concentration by $\geq$ 10% from the mean Baseline value on two consecutive monthly measurements. Measurements are obtained from the Central Biochemistry Laboratory using nephelometry.

The initial response to this change is to identify the causes for the declining serum albumin. Evaluate dietary protein intake by assessing recent food intake by using a recent

(within 1 month) 24 hour recall and by the normalized Protein Catabolic Rate (nPCR, gms/kg/day). If dietary protein intake is less than or equal to 0.95 gms/kg/day or energy intake is 27 kcal/kg/day or lower, intervene by maximizing oral food intake, if necessary, initiate oral nutritional supplements, encourage and counsel the patient to eat more and meet the protein and energy goals of the study which are ≥1.0 grams/kg/day of protein and ≥28 kcal/kg/day. If protein or energy from usual foods is inadequate to achieve these goals, then offer the patient Nepro, Suplena, or other supplements (including IDPN) to meet these goals.

5.13.1.2 **Nutrition care to be delivered in response to a decline in serum albumin as described above.**

1) Complete and review 24-hour recall.

   The HEMO grant-supported dietitian should complete a 24 hour Food Recall to assess patient's dietary intake. Determine the patient's intake and most recent serum chemistries to evaluate the patient's total nutritional status. Calculate total protein and kilocalories intake using Nutritionist Five, version 2.1.1H, from the food recall. Decide if liberalization of the therapeutic diet is appropriate to help the patient to meet the study protein (1.0 gm/kg/day or more) and energy (28 kcal/ kg/day or more) goals. Based on the results of your evaluation proceed as follows:

   If dietary protein intake is less than or equal to 0.95 gm /kg/day or energy intake is 27 kcal/Kg/day or lower, meet with the patient at the next dialysis session and counsel the patient about his/her diet.

   Encourage the patient to eat more protein, energy, or both and provide appropriate counseling and nutritional supplements to help do this.

2) At the next dialysis session after the action item was declared and the 24 hour recall obtained, counsel the patient.

At this session the HEMO grant-supported dietitian, after consultation with the dialysis unit dietitian, develops a plan to help the patient meet protein and calorie goals. The dietitian should develop an individual meal plan with the patient that will meet the desired protein and energy goals. Provide the patient with a sample of Nepro and Suplena to taste test so that the patient may select a supplement he/she prefers. Make nutrition supplements available and provide them if the patient wants them. If the patient reports or if dietitian assessment reveals that the patient will have great difficulty or will be unable to meet the Study protein and energy goals by usual diet alone, then provide an oral enteral nutrition supplement in an amount that, together with current oral intake, will meet the study's protein and energy goals.

If the patient reports that he/she will be unable to eat the amount of food and supplement that is required to meet protein and energy goals, the dietitian will evaluate the patient for nutrition support. Options include tube feedings, TPN (total parenteral nutrition) and IDPN (intradialytic parenteral nutrition).

If the patient reports that he/she will be unable to eat the amount of food and supplement that is required to meet appropriate protein and energy goals, and if the patient refuses and/or does not qualify for medical or reimbursement reasons for any of the nutrition support options, provide the patient with guidelines and counseling to maximize the patient's protein and energy intakes as best as possible, focusing on diet liberalization, guided by the patient's food tolerances, preferences, and serum chemistries.

3) If the action item persists and remains unresolved, three months after the action item was declared, obtain a 24-hour food recall. Calculate the protein and energy intake of the food recall. Also review the patient's most recent serum albumin, nPCR and post dialysis weight. The dietitian will continue to monitor and obtain 24-hour food recall every three months if the action item persists.

5.13.2 Undesired Weight Loss

5.13.2.1 Definition: Undesired post-dialysis weight loss of ≥ 2.5kg or ≥ 5% of post dialysis body weight for two consecutive months during Follow-Up. Note: Weight loss refers to the change in post dialysis weight from the average of the last two Baseline weights (weight recorded on Form 2 item 12a) to any post dialysis weight measurement during Follow-Up. Undesired weight loss is defined as a loss of weight that is not part of a planned weight reduction program documented in the database.

The initial response to this change is to evaluate the causes of declining body weight by assessing recent food intake using a recent (within 1 month) 24 hour food recall and by the normalized Protein Catabolic Rate (nPCR, gms/kg/day).

If dietary protein intake is less than or equal to 0.95 gms/kg/day or energy intake is 27 kcal/kg/day or lower, intervene by maximizing oral food intake and if necessary, initiating oral enteral nutritional supplements, encourage and counsel the patient to meet the protein and energy goals of the study which are 1.0 grams/kg/day of protein and 28 kcal/kg/day. If protein or energy from usual foods is inadequate to achieve these goals, offer the patient Nepro, Suplena, or other supplements (including IDPN) to meet these goals.

5.13.2.2 **Nutrition Care to Respond to Undesired Weight Loss**

1) The HEMO grant-supported dietitian completes a 24 hour food recall with the patient. The dietitian calculates the food recall for total protein and calories, and proceeds as follows:

   If dietary protein intake is less than or equal to 0.95 gm/kg/day or energy intake is 27 kcal/kg/day or lower, the dietitian counsels the patient at the next dialysis session and offers suggestions for ways to increase them.

2) Next dialysis visit

   At the next dialysis session, the HEMO grant-supported dietitian after consultation with the dialysis unit dietitian, meets with the patient for counseling, and develops an individualized meal plan with the patient that will meet desired protein and energy goals. Provide the patient with samples of Nepro and Suplena to taste test so that the patient may choose a supplement he/she prefers. If the patient reports, or by dietitian assessment it is clear that the patient will have great difficulty, or will be unable to meet the protein and energy goals by diet alone

provide an oral enteral nutrition supplement in an amount that, together with current oral intake, will meet protein and energy goals. If the patient reports that he/she will be unable to eat the amount of food, including supplement, orally that is required to meet protein and energy goals, evaluate the patient for nutrition support. Options include tube feedings, TPN (total parenteral nutrition) and IDPN (intradialytic parenteral nutrition).

If the patient reports that he/she will be unable to eat the amount of food and oral nutritional supplement that are required to meet the appropriate protein and energy goals, or if the patient refuses, and/or does not qualify for medical or reimbursement reasons for any of the nutrition support options, provide the patient with the guidelines that maximize patient protein and energy intakes, focusing on liberalization of the diet, as guided by the patient's food tolerances and preferences, and serum chemistries.

3) After six months, if the action item persists and remains unresolved the HEMO grant-supported dietitian will obtain another 24-hour diet recall. The dietitian will calculate the protein and energy intake of the recall. The dietitian will also review the patient's most recent serum albumin, nPCR, and post dialysis weights. The dietitian will continue to monitor and obtain 24-hour food record every six months if action item persists.

5.13.3 **Completion of 24 Hour Dietary Recalls and Transmission of Nutrient Analyses to the**

DCC

Purpose

The transmission of the nutrient analyses from the 24 hour dietary recalls of patients with nutrition action items will allow for: a) description of dietary intake at and during the time of nutrition action items, b) observation of any dietary changes of these patients at and during time of nutrition action items, and c) follow-up on the progress of the patient’s nutritional status and intake during a nutrition action item.

5.13.3.1 **Decline in Serum Albumin Action Item**

When to Administer

1) Within 4 weeks of notification of an **initial** decline in serum albumin action item (≥10% decline from mean baseline values on two consecutive monthly measurements), as indicated by the nutrition follow-up summary report, a 24 hour dietary recall must be obtained. The nutrient analysis from Nutritionist Five must be transmitted to the DCC within 2 months of notification of the action item.
    a) Patients do not have to complete 24 hour recall if a two day diet diary assisted recall was completed 30 days prior to the KM session date that triggered the initial action item or during the month that the patient was to have a schedule 24 hour dietary recall completed for an action item.
2) If the decline in serum albumin action item **persists and remains unresolved**, obtain a 24 hour dietary recall from the patient and transmit the nutrient analysis to the DCC every six months until the action item is resolved. (Obtain 24 hour dietary recall within 4 weeks of the scheduled 6 month period and transmit the nutrient analysis within 2 months of the scheduled 6 months period.)
3) Patients with persistent serum albumin action items who meet the following exception criteria **and** are stable do not have to complete a 24 hour dietary recall.
    a) Exception criteria
        1) two day diet diary assisted recall was completed 30 days prior to the persistent action item or during the month that the patient was to have a scheduled 24 hour dietary recall completed for a nutrition action item
        2) patient with persistent albumin action item, however serum albumin (nephelometry) is > 4.0 gm/dL; patient is currently stable
    b) Definition of "patient is currently stable"; patient must meet both criteria to be deemed stable:

1) no decline in weight of >2.0 kg from the initial action item weight
2) no decline in serum albumin of >0.2 gm/dL from the initial action item serum albumin

4) Using the exception and patient stability criteria for persistent serum albumin action item patients, the DCC will determine whether the patient needs to have the 24 hour dietary recall completed at the designated six months action item follow-up period. On the nutrition follow-up summary report, the DCC will post a notification to indicate whether a 24 hour dietary recall is required for these persistent action item patients.
5) If the 24 hour dietary recall is not obtained and nutrient analysis is not transmitted within 2 months of the scheduled completion period, an inquiry will be sent to the clinical center.

5.13.3.2 **Undesired Weight Loss Action Item**

When to administer

1) Within 4 weeks of notification of an **initial** undesired weight loss action item in which the weight loss is ≥ 5.0 kg or ≥ 10% from the mean baseline weight on 2 consecutive monthly measurements, as indicated by the nutrition follow-up summary report and action item notification, a 24 hour dietary recall must be obtained. The nutrient analysis from Nutritionist Five must be transmitted to the DCC within 2 months of notification of the action item. **Please note that the criteria for weight loss has been widened for the purposes of obtaining dietary intake data. The undesired weight loss action item definition has not changed (≥ 2.5 kg or ≥5% drop from the mean baseline weight on two consecutive monthly measurements). Routine nutrition care to all patients who reach an undesired weight loss action item should be followed as outline in the MOP Section 5.13.2. Patients with initial undesired weight loss action item indicated by ≥ 2.5 kg or ≥5% drop from the mean baseline weight on two consecutive monthly measurements should be assessed by obtaining a 24 hour dietary recall and calculating intake using Nutritionist Five nutrient analysis. The nutrient analysis,

however, will not be transmitted to the DCC unless the patient has a weight loss of ≥ 5.0 kg or ≥ 10% from the mean baseline weight on 2 consecutive monthly measurements.

a) Patients do not have to complete 24 hour recall if a two day diet diary assisted recall was completed 30 days prior to the KM session date that triggered the initial action item or during the month that the patient was to have a schedule 24 hour dietary recall completed for an action item.

2) If the undesired weight loss action item **persists and remains unresolved**, obtain a 24 hour dietary recall from the patient and transmit the nutrient analysis to the DCC every 6 months until the action item is resolved. (Obtain 24 hour dietary recall within 4 weeks of the scheduled 6 month period and transmit the nutrient analysis within 2 months of the scheduled 6 month period.)

3) Patients with persistent weight loss action items who meet the following exception criteria **and** are stable do not have to complete a 24 hour dietary recall.

a) Exception criteria

1) two day diet diary assisted recall was completed 30 days prior to the KM session date that triggered the persistent action item or during the month that the patient was to have a scheduled 24 hour dietary recall completed for a nutrition action item

2) persistent weight loss action item due to weight loss from 6^{+} months ago, patient is currently stable

3) peristent weight loss action item due to amputation; patient is currently stable

4) persistent weight loss action item due to intentional weight loss; patient is currently stable

5) persistent weight loss action item due to nephrectomy; patient is currently stable

b) Definition of “patient is currently stable”; patient must meet both criteria to

be deemed stable:

1) no decline in weight of >2.0 kg from the initial action item weight
2) no decline in serum albumin of >0.2 gm/dL from the initial action item serum albumin

4) Using the exception and patient stability criteria for persistent undesired weight loss action item, the DCC will determine whether the patient needs to have the 24 hour dietary recall completed at the designated 6 months action item follow-up period. On the nutrition follow-up summary report, the DCC will post a notification to indicate whether a 24 hour dietary recall is required for these persistent action item patients.
5) If the 24 hour dietary recall is not obtained and nutrient analysis is not transmitted within 2 months of the scheduled completion period, an inquiry will be sent to the clinical center.

5.14 Nutritional Standards of Care: Modified Step l Diet

HEMO Study patients who meet the criteria for borderline high risk serum LDL cholesterol as defined in Section 9.16.2 of the HEMO Study Protocol (e.g. serum LDL is greater than or equal to 130 mg/dL after two measurements) should be considered for dietary therapy with the Modified National Cholesterol Education Program Step l Diet, assuming that the modifications are compatible with other HEMO Study goals and good medical care practice. The NCEP Step l Diet specifies 30% of total kilocalories from fat, with less than 10 percent of kilocalories from saturated fatty acids, no more than 10 percent of kilocalories from polyunsaturates, and with no more than 300 mg dietary cholesterol.

If an individual HEMO patient has any indications of malnutrition or if the patient cannot meet his/her renal diet energy needs with a diet which is in line with these objectives, maintenance of energy intake and weight gain take precedence over that goal.

5.15 Procedures to Ensure Standardized Dietary Data Coding

When distributed dietary data entry is used, procedures to standardize dietary data coding and analysis are mandatory if quality is to be assured. These steps are outlined below:

5.15.1 **Protocols and Worksheets**

Dietary data are only as good as the original recall. The patients are instructed in a standardized manner using workbooks and videotapes as well as standardized materials developed in conjunction with the dietitians in the HEMO Study. Standardized portion size estimates are included for use in all diet recalls.

Worksheets are provided for dietitians' use:

1) Diet Diary Assisted Recall Worksheet (Form 30)
   This set of worksheets documents the patient's food and beverage intake for a 48 hour period. This information is entered into Nutritionist Five to produce the nutrient analysis.
2) Request for Coding Assistance (Provided by the Nutrition Consultants) See Appendix 5B.
   A worksheet for requesting assistance from the Nutrition Consultant for coding a food record.
3) HEMO Coding Manual (Provided by the Nutrition Consultants)
   This manual is designed to simplify the process of coding patient’s diets. This should further simplify the coding of unknown items, with a clear specification of unknowns. This manual is perpetually updated as coding assists are received.

These worksheets were provided in the Dietitian Training Manual during the Annual HEMO Dietitian Training each Spring.

5.15.2 **Hot Line for Queries**

The Nutrition Consultant maintains a "hot line" (617/636-9349) for assistance at the central level to ensure uniformity, deal with obtaining information on food items that are not available in the program, to deal with problems that arise in coding recipes, and other data coding problems associated with nutrient analysis or completion of other nutrition forms. A log is kept of questions and responses to update coding manual; replies provided are consistent and standard to similar questions.

5.15.3 Procedures Followed in Selecting Recalls for Quality Assurance Purposes

5.15.3.1 Introduction

Quality assurance of dietary data begins with meticulous collection techniques and checks at the local level for data entry and transcription errors. In order to facilitate such checks at the local level, HEMO grant-supported dietitians will be provided with information on usual ranges for nutrients or intakes of interest (protein and calorie intakes) and asked to check their original data and analyses for errors if they fall outside these ranges. If the intakes are in fact verified, an unusual intake form is filled out and kept in the patient's file. In addition when forms (e.g. Form 30 and Form 33) are sent to the Data Coordinating Center, range checks will also be applied, and the dietitian will be notified immediately when a range check reveals a response that is outside usual limits. The upper outlier limit for energy intake is >45 kcals/kg/d and for protein intake is >2.0 gm/Kg/d. The lower outlier limit for energy intake is <10 kcals/kg/d and for protein intake is <0.3 gm/kg/d. The dietitian will be asked to check for data entry and transcription errors.

For later quality assurance purposes, a random sample of dietary diary assisted recalls will be reanalyzed by the Nutrition Consultants. The records selected will be drawn randomly, as described in 5.15.3.2

5.15.3.2 Random Checks of 5% Sample for Plausibility

1. Each year, the Data Coordinating Center (DCC) randomly selects a 5% sample of records that have been entered into the database. This is done at baseline and yearly thereafter, and is stratified by site and dietitian.
2. The records selected by the DCC will be drawn randomly, stratified by Clinical Center and dietitian. At least one diary from each dietitian who is responsible for dietary data collection will be included. Records will be drawn both during Baseline and during follow-up.
3. The DCC will send a request for the photocopy of the original Form 30 (Two-Day Diet Diary Assisted Recall) to be forwarded to the NCC within 14 days.

4. The NCC dietitian will re-enter the original record from the diet diary to compare the calculation from the Nutritionist Five to that performed in the unit.
5. Upon completion of the re-analysis, the NCC dietitian will forward the Nutritionist Five nutrient analyses to the DCC to determine the variance between the NCC dietitian and the clinical center dietitian.
6. If deviations exceed ± 10% of protein or kilocalories intakes on the re-analysis, the NCC dietitian will request for a photocopy of the Nutritionist Five food record printout that is in question to be sent to the NCC dietitian within 5 working days. The Nutritionist Five printout should include the food name, food code, serving, portion type, kilocalories, and protein intake.
7. The NCC dietitian will evaluate the Form 30 for a qualitative check in comparison to the Nutritionist Five printout to determine whether the foods and quantities entered into the Nutritionist Five program are correct, given the entries written in the food record (e.g.., types and cuts of meats entered are reasonable for description in food record, etc.).
8. Upon the completion of the review of both the original Form 30 and the Nutritionist Five nutrient analysis printout, a reconciliation query is sent on the record to the dietitian who collected the data. See Appendix for forms used for the QA reconciliation query.
9. The HEMO Study dietitian responds to the query within 5 working days to the NCC dietitian. Discussion between the Nutrition Consulting Group and the local clinical unit dietitian should clarify ambiguities if these are the causes of the differences. Other causes of differences will be resolved appropriately. The corrected food record is re-entered into the database by the Study dietitians and the patient's revised Nutritionist Five file is re-transmitted to the DCC.

5.15.3 **Plans for Outliers**

In addition, after the Data Coordinating Center analyzes the Baseline dietary data, any intake records with outliers (defined as <2.5th or > 97.5th percentile from the distributions of intakes of protein and kilocalories of the dialysis patients) will also be identified and selected for recoding and reanalysis during the Baseline period. The diet assisted diet diaries are recorded

from the dietary recall worksheet and entered into the nutrient analysis program. The calculation from Nutritionist Five will be compared to that performed in the unit.

When deviations exceed 10% of protein or kilocalorie intakes on the reanalysis, a query is sent on the record to the clinical unit, to be transmitted to the dietitian who collected the data. Discussion between the Nutrition Consulting Group and the local clinical unit dietitian should clarify ambiguities if these are the causes of the differences. Other causes of differences will be resolved appropriately.

If recoded recalls remain discrepant by 10% or more for protein or calories, the dietitian who obtained the record will be provided with a practice recall to complete and submit to the Nutrition Consultant for review. The recall contains several common problems in coding, and will permit identification of possible errors in coding which will then be corrected by consultation between the consultant and the NIH grant supported dietitian.

5.15.4 How To Respond to a Request for a Record

Records are requested in writing or over electronic mail from the Data Coordinating Center. The patient's diet diary assisted recall (Form 30) will be requested by patient ID, name code and visit date.

When a patient's record is requested, Xerox a copy of the diet diary assisted recall worksheet, and send it to the Nutrition Consultant's office. Records should reach the consultant within 14 business days following initiation of the request. The recall will be recoded at the Nutrition Consultant unit, and any discrepancies between the coding rules and the recall will be noted. The analysis of the original recall and of the recoded recall will be compared by the DCC; if protein and /or calories differ by more than 10%, causes will be sought and the results discussed with the HEMO grant-supported dietitian in the Clinical Center. Final results will be transferred to the Data Coordinating Center.

5.15.5 What to Do If the Recoded Recall and Your Recall Differ

You will receive the results of reanalysis by fax or Internet.

The standards for agreement between the recoded recall and the original recall are for protein and calories to agree within at least 10%. If they do not, the causes for this

disagreement must be sought, and standardized ways of coding the records used, so that records from all dietitians in all clinical units are the same.

The first step in resolving differences is for you to examine the two printouts and note any discrepancies between food or recipe entries. Make sure that you review any coding rules that the reviewer has questioned. If you have further questions, call the Nutrition Consultant's office and resolve the problem. If differences are due to inappropriate coding, as the NIH funded Clinical Center dietitian responsible for dietary data integrity at your Clinical Center, you will be asked to complete a diagnostic diet recall to highlight and correct some common coding errors, and to submit the completed record to the Nutrition Consultant's central unit. Consistent inaccuracy or non-response may result in de-certification.

5.16 Medical Nutritional Supplements

5.16.1 Rationale for Supplementation

The purpose of the nutritional supplements is to ensure that the nutritional status of HEMO patients is maintained. Oral nutritional supplementation is an effective means of increasing protein and/or energy intake in patients whose voluntary oral intake is insufficient to achieve Study nutrient goals.

Supplements may be provided to any patient enrolled in the Study as well as any patients in Baseline. Patients who do not get randomized or drop out of the Study, will no longer be eligible to receive the supplements free of charge.

5.16.2 Supplements Available for Use During the HEMO Study

Ross Products Division, Abbott Laboratories is providing the following medical nutritional supplements to patients for use during the HEMO Study.

1) Nepro® Specialized Liquid Nutrition

   Nepro is designed specifically to be appropriate for diet recommendations for patients on hemodialysis. Each 8 fl oz serving provides 475 kcal and 16.6 g of protein.

2) Suplena® Specialized Liquid Nutrition

Suplena is a lower protein high calorie product designed specifically to be appropriate for diet recommendations for predialysis patients, and is also useful for hemodialysis requiring primarily energy, rather than energy and protein, supplementation. Each 8 fl oz serving provides 475 kcal and 7.1 g of protein.

3) Glucerna OS

Glucerna Os is a great tasting nutritional supplement designated for people with diabetes or abnormal glucose tolerance, or anyone who would benefit from a low-carbohydrate, modified-fat formula. Each 8 fl oz serving provides 220 kcal and 10 g of protein

4) ProMod® Protein Supplement

ProMod is a bland tasting protein powder which can be incorporated into foods and beverages to augment protein intake without adding appreciable quantities of other nutrients or energy. Each 6.6 g scoop provides 5.0 g protein.

5) Polycose® Glucose Polymers

Polycose Powder and Polycose Liquid are non-sweet sources of carbohydrate which can be incorporated into foods and beverages to increase energy intake without appreciably altering fat, protein, or micro-nutrient intakes. Each 100 g of Polycose Powder provides 94 g of carbohydrate and 380 kcal. Each 100 mL of Polycose Liquid provides 50 g of carbohydrate and 200 kcal.

R& D Laboratories is providing Nephro-Vite® RX vitamin supplements for use during the HEMO Study. Nephro-Vite® RX is strongly recommended, but not required, and is available free of charge to patients actively participating in the HEMO Study.

1) Nephro-Vite® RX

Nephro-Vite® RX is a B and C multivitamin formulated to meet the specific replacement needs of the renal patient. Most importantly, it has been formulated to meet the increased vitamin B6 requirement of 10 mg per day to normalize the serum level of the active moiety, pyridoxal phosphate, and the increased folic acid requirement of 1 mg. In addition, it provides the appropriate USRDA amount of

vitamin C, 60 mg, which has been shown to normalize serum C levels without significantly increasing serum oxalate. Finally USRDA quantities of B1, B2, B12, pantothenic acid, niacinamide, and biotin are provided to assure that regardless of whether a patient is well nourished or poorly nourished, eats consistently or intermittently, adequate vitamin supplementation is provided to maintain body stores.

5.16.3 Indications for Use, Composition, and Storage of Supplements

5.16.3.1 Indications for Use

Enteral Supplements

The quantity of enteral supplements available during the study is adequate to raise the energy intake of the entire Study patient population by 1.5 kcal/kg/day. Supplementation can therefore be initiated, in patients whose intake is suboptimal, **essentially as soon as desired** and be as aggressive as needed to meet study energy and protein goals.

Vitamin/Mineral Supplements

Nephro-Vite® RX is formulated to meet the specific replacement needs of the renal patient. It assures that regardless of whether a patient is well nourished or poorly nourished, eats consistently or intermittently, adequate vitamin supplementation is provided to maintain body stores. It is available free of charge to patients actively participating in the Study. If Nephro-Vite® RX is the prescribed vitamin supplement, one tablet should be taken daily. This tablet should be taken daily after dialysis on dialysis days and two (2) hours after eating on other days. Nephro-Vite® RX is strongly recommended, but not required.

5.16.3.2 Composition and Ingredients

Product information, ingredients, and basic usage information for each of the Ross products available is provided in an Appendix at the end of Section 5.16. A comparison of the nutritional profiles of each product is provided in Table 5.2. For additional product related information, contact either the Nutrition Consultants or David Cockram, MS, RD at Ross at 614/ 624-7580.

Nephro-Vite® RX contains the following amounts of vitamins:

Vitamin	**Amount**	**% USRDA**
Thiamin B1	1.5 mg	100%
Riboflavin B2	1.7 mg	100%
Pyridoxine B6	10 mg	500%
Pantothenic Acid	10 mg	100%
Niacinamide	20 mg	100%
Cyanocobalamin B12	6 μg	100%
d-Biotin	300μg	100%
Folic Acid	1.0 mg	250%
Ascorbic Acid C	60 mg	100%

5.16.3.3 **Supplement Storage**

Products should be stored at room temperature under conditions appropriate for storage of any other food.

5.16.3.4 **Shelf Life**

The expiration date is stamped on the bottom of the cans (product expires at the end of the month listed). Please check the expiration dates of your product prior to providing it to patients to be assured that it will not be out of date before the patient's next visit. Expired product should be discarded.

5.16.4 **Dispensing Supplements**

5.16.4.1 **Nepro and Suplena**

To estimate the monthly quantity (*in cases of 24 8-fl-oz cans*) of product required, multiply the recommended number of cans to be consumed daily (probably in the range of 0.5 to 2.0 cans per day) by 1.5 and round the result up to the next whole case. The quantity of supplement distributed at any given visit should not exceed that which is needed to meet the

patient's requirements between two adjacent visits (the calculated amount includes a pad adequate for about 5 days). Keep in mind that cases of product weigh about 20 lbs each. Quantities of supplements dispensed to patients should be recorded on the Supplement Distribution Form (Form 35). Supplements may be distributed in between visits, if desired, to minimize the quantity that patients have to carry at any given time.

For oral use, Nepro and Suplena are usually served cold. For variety, consider mixing 1-2 Vari-Flavor packets into each can of product or using the recipe books provided.

5.16.4.2 ProMod

To estimate the quantity (*in 275 g cans*) of product required, multiply the recommended number of scoops to be consumed daily (probably will be in the range of 1 to 5 scoops per day) by 0.9 and round the result up to the next whole can. The quantity of supplement distributed at any given visit should not exceed that which is needed to meet the patient's requirements between two adjacent visits (the calculated amount includes a pad adequate for about 5 days). Quantities of supplements dispensed to patients should be recorded on the Supplement Distribution Form (Form 35). Supplements may be distributed in between visits, if desired, to minimize the quantity that patients have to carry at any given time.

5.16.4.3 Polycose Powder and Liquid

To estimate the monthly quantity (*in 350 g cans*) of Polycose Powder required, multiply each 100 kcal to be consumed daily (probably will be in the range of 1 to 6 100 kcal/day) by 2.75 and round the result up to the next whole can. To estimate the quantity (*in 120 ml bottles*) of Polycose Liquid required, multiply each 100 kcal to be consumed daily (probably in will be in the range of 1 to 6 100 kcal/day) by 15 and round the result up to the nearest whole can. The quantity of supplement distributed at any given visit should not exceed that which is needed to meet the patient's requirements between two adjacent visits (the calculated amount includes a pad adequate for about 5 days). Quantities of supplements dispensed to patients should be recorded on the Supplement Distribution Form (Form 35). Supplements may be distributed in between visits, if desired, to minimize the quantity that patients have to carry at any given time.

5.16.4.4 **Glucerna OS**

To estimate the monthly quantity (in cases of 24 8-fl-oz cans) of Glucerna required, multiply the number of cans to be consumed daily by 1.5 and round the result up to the nearest whole case. Please record the quantity of product distributed to patients on the appropriate form.

5.16.5 **Ordering Supplements**

Enteral Supplements

Medical nutritional supplements should be ordered in whole case quantities from Ross Laboratories. Products take approximately two weeks to arrive once ordered. Contact David Cockram, M.S., R.D. at Ross 614-624-7580, 614-727-7580 (fax), or e-mail dcockram@infinet.com (See Appendix for Product Shipment Form).

Vitamin/Mineral Supplements

Nephro-Vite® RX is a prescription product and a physician's signature is required. **See appendix for order form**. Supplements will be shipped at no charge to each dialysis unit or central receiving site as designated by the center. If there are any questions call R & D Laboratories, Inc. at 1-800-338-9066. For customer service information Extension 6, for technical information Extension 46--Jamie Weisenberg, RD or Extension 11--Rhoda Makoff, Ph.D. (See Appendix for Supplement Request Form).

Table 5.2

Nutrient Profile of Ross Products for the HEMO Study

Nutrient	Nepro® (8 fl oz)	Suplena® (8 fl oz)	ProMod® (6.6 g scoop)	Polycose® Liquid (100 ml)	Polycose® Powder (100 g)	Glucerna® (8 floz)	Glucerna OS (8 fl oz)
Energy, kcal	475	475	28	200	380	237	220
Protein, g	16.6	7.1	5	*	*	9.9	10
Fat, g	22.7	22.7	<0.60	*	*	12.9	11
Carbohydrate, g	52.8b	60.6	<0.67	50	94	22.7c	22
Water, ml	166	169	*	70	6	202	202
Vitamin A, IU	1000d	250	*	*	*	1500e	1750
Vitamin D, IU	20	20	*	*	*	66.7	100
Vitamin E, IU	11.3	11.3	*	*	*	7.5	30
Vitamin $K_{1,}$ μg	20	20	*	*	*	13.4	20
Vitamin C, mg	25	25	*	*	*	50	60
Folic acid, μg	250	250	*	*	*	100	100
Thiamine (Vitamin B_{1}), mg	0.60	0.60	*	*	*	0.38	0.58
Riboflavin (Vitamin B_{2}), mg	0.68	0.68	*	*	*	0.43	0.43
Pyridoxine (Vitamin B_{6}), mg	2.1	2.1	*	*	*	0.50	0.50
Vitamin $B_{12,}$ μg	2.40	2.4	*	*	*	1.5	1.5
Niacin, mg	8.0	8.0	*	*	*	5.0	5.0
Choline, mg	150	150	*	*	*	100	100
Biotin, μg	120	120	*	*	*	75	75
Pantothenic acid, mg	4.0	4.0	*	*	*	2.5	2.5
Sodium:	200	185	<15	<70	<110		210
mg[a]	8.6	8.1	<0.7	<3.0	<4.8	220	9.1
mEq						9.6	
Potassium:	251	265	<66	<6	<10	370	370
mg[a]	6.4	6.8	<1.7	<0.15	<0.3	9.5	9.5
mEq							
Chloride, mg	240	220	*	<140	<223	340	354
Calcium, mg	325	330	<40	<20	<30	167	250
Phosphorus, mg	165	175	<30	<3	<5	16.7	250
Magnesium, mg	50	50	*	*	*	66.7	100
Iodine, μg	38.5	38	*	*	*	25	38
Manganese, mg	1.3	1.3	*	*	*	0.84	1.25
Copper, mg	0.50	0.50	*	*	*	0.34	0.5
Iron, mg	4.5	4.5	*	*	*	3.0	4.5
Zinc, mg	5.6	5.6	*	*	*	3.75	3.8
Taurine, mg	38	38	*	*	*	25	20
L-carnitine, mg	62	38	*	*	*	34	25

Selenium, µg	24	18	*	*	*	11.7	18
Chromium, µg	*	*	*	*	*	16.7	60
Molybdenum, µg	*	*	*	*	*	25	38
M-inositol, g	*	*	*	*	*	0.20	0.20

[a] The electrolyte content of NEPRO and SUPLENA is low to facilitate individualization of intake based on residual renal function, underlying disease(s), and other sources of electrolytes. Because of the number of clinical factors that influence electrolyte requirements, nutritional care must be individualized and electrolyte intake adjusted as necessary.

[b] includes 3.7g of frutooligosaccharides

[c] includes 3.4g soy fiber

[d] includes 750 IU as beta-carotene

[e] includes 663 IU as beta-carotene

* Denotes nutrients with no label claim.

Product Request Form
HEMO Trial

Please complete the following and forward to David Cockram at Ross for shipment. Shipments take about 2 weeks once order is placed. Please try to anticipate your needs for at least a month at a time if possible.

Contacts: dcockram@infinet.com (use e-mail if possible)
614/624-7580 (phone)
614/727-7580 (fax)

Ship to: _____

Address: _____

_____

_____

_____

Phone: _____

The following products are available for use in this study:

Nepro, Vanilla (#50632, 24 cans/cs) _____

Nepro, Butter Pecan (#54104, 24 cans/cs) _____

Nepro, Cherry Supreme (#54106, 24 cans/cs) _____

Suplena, Vanilla (#50164, 24 cans/cs) _____

Polycose Liquid (#00432, 48 bottle/cs) _____

Polycose Powder (#00746, 6 cans/cs) _____

ProMod Powder (#0775, 6 cans/cs) _____

VariFlavors, Assorted (#00730, 24 pkt/cs) _____

Glucerna (#50240 24 cans/cs) _____

5.17 Purpose and Procedure for Estimating Within Individual Variability of Intake in the HEMO Study

In a recent Institute of Medicine publication on Dietary Reference Intakes and Applications in Dietary Assessment, it was suggested that the Estimated Average Requirement (EAR) be used for nutrient assessment of groups. Specifically, EAR is used to estimate the prevalence of inadequate intakes within a group. A method that has been proposed to allow for the determination of the prevalence of inadequacy in a group by determining the number of individuals with intakes below the EAR is called the EAR cut-point method. This method assumes that the correlation between intake and requirement is low and that the variability of intakes is greater than the variability of requirements. It also requires that the distribution be symmetrical. The prevalence of nutrient inadequacy for a group will usually be overestimated by this method if dietary intake data are not adjusted for day to day within person variation. In order to examine the within individual variability of intake, there would need to be a collection of extra food records on a subset of the population.

Since the Institute of Medicine has proposed the described methods, this will become a standard practice in the reporting of intake and nutrient assessment of groups. Within individual variability must be obtained in order to assess the adequacy of dietary intakes of groups of individuals in the HEMO Study. Without such information it is not possible to report dietary intake data in the manner recommended by the Food and Nutrition Board, Institute of Medicine, National Academy of Sciences. In order to examine the within individual variability of intake, there would need to be a collection of extra food records on a subset of the HEMO patients since at present we only have one two-day diet diary assisted recalls (one dialysis and one non-dialysis day) per year on each patient.

The number of patients estimated to provide adequate data on within individual variability is 240 (approximately 16 patients per clinical center). These patients will be selected randomly to represent patients at different time points in the Study (baseline and multiple follow-up years) with equal number of men (120) and women (120). This would provide a total of 480 extra food records on a subset of patients.

Two sets of two-day diet diary assisted recalls will be collected on each patient with each set 2 weeks apart from the other. Clinical center dietitians will collect the first set of two-day

diet diary assisted recalls on their patients at either their baseline visit or at their annual scheduled follow up date. After reviewing the two-day diet diary assisted recall with their patient and documenting the details of the food items, the clinical center dietitians will analyze the food records using the Nutritionist Five nutrient analysis software program. The second set of two-day diet diary assisted recalls will be completed within 1-2 weeks from the first set. After reviewing the two-day diet diary assisted recall with their patient and documenting the details of the food items, the clinical center dietitians will send the completed food records to the Nutrition Coordinating Center. Because of time constraints and the burden on the dietitian, the Nutrition Coordinating Center will analyze the two-day diet diary assisted recalls using the Nutritionist Five nutrient analysis software program. Clinical center dietitians will be consulted if food items on the diet diary assisted recall are not clear for nutrient analysis. The analyses will be transmitted from the NCC to the DCC database.

5.18 Protocol for Collection of Diet Records to Examine Within Individual Variability of Dietary Intake in the HEMO Study

5.18.1. Selection of Sample

A. The number of patients estimated to provide adequate data on within individual variability is 240 (approximately 16 patients per center). Equal number of males (120) and females (120) will be included in the sample.

B. Patients who will have an annual 2 day diet diary assisted recall scheduled between March 2001 and November 2001 will randomly be selected. On 3/5/01, a list of the first 50% of the patients selected will be given to the dietitians. On 7/1/01, a list of the second 50% of the patients selected will be given to the dietitians. The second 50% of patients selected should have the annual 2 day diet diary assisted recall scheduled after 8/1/01.

1. The dietitians will be notified via memorandum from the DCC of the list of patients selected for their center.

C. If the randomly selected patient can't do or refuses to do a 2 day food record (either the annual food record or the second set or even both sets), this will be treated as missing data.

D. There may be instances where patients refuse to keep records. If the dietitian has tried all alternatives to getting a food record on the patient with no success, the dietitian will request a 2 day recall instead.

E. If the randomly selected patient dies or drops out of the Study before this process can be completed, another patient will be selected and included on the second randomized list given to the dietitians on 7/1/01.

F. If possible, the DCC will avoid including patients from specially designated logistically inconvenient units when selecting the samples.

5.17.2. Protocol

A. Completion of Annual 2 Day Diet Diary Assisted Recalls

1. After patients are identified for the sample, the dietitians will be notified via memorandum from the DCC of the list of patients for their center.
2. Dietitians will identify and mark down the annual food record collection date for those selected patients.
3. At the annual food record collection date for those selected patients, the dietitian will instruct the patient and collect the annual 2 day diet diary assisted recalls from those patients, per protocol outlined in the Manual of Operations Section 5.6. If 2 day diet diary assisted recalls cannot be obtained, a combination of a one day diet diary and one day recall or 2 day recall is permitted.
    a. Dietitians will obtain and review the 2 day diet diary assisted recall with the patients. Food records should have complete documented description and dietitian comments of the food items consumed by the patient.
    b. Dietitians will analyze the 2 day diet diary assisted recalls using Nutritionist Five HEMO Study customized version 2.1.1.

c. Dietitians will transmit the 2 day diet diary assisted recalls to the Data Coordinating Center.

B. Completion of Second Set of 2 Day Diet Diary Assisted Recalls

1. Two weeks after the collection of the annual 2 day diet diary assisted recalls, the dietitians will instruct and collect a second set of 2 day diet diary assisted recalls from the same selected patients, per protocol outlined in the Manual of Operations Section 5.6. The instructions of the completion of the 2 day diet diary assisted recalls should be the same as that of the 1st set. If a 2 day diet diary assisted recall cannot be obtained, a combination of a one day diet diary and one day recall or 2 day recall is permitted. (The elapsed time limit between the first set and the second set should be no less than 1 week and no more than 2 weeks. Food records that exceed the 2 week time limit are not acceptable.)

a. Dietitians will obtain and review the 2 day diet diary assisted recalls with the patients. Food records should have complete documented description and dietitian comments of the food items consumed by the patient.

b. Dietitians will fill out Form 34 questions 1-3 and 51-53.

c. Dietitians will xerox a copy of the completed 2 day diet diary assisted recalls and the completed sections of the Form 34 and mail the originals to the Nutrition Coordinating Center as soon as the records are completed.

d. The dietitian at the Nutrition Coordinating Center will analyze the two day diet diary assisted recalls using the Nutritionist Five HEMO Study customized version 2.1.1 in a timely manner as they are received at the office by mail.

e. The dietitian at the Nutrition Coordinating Center will consult the center dietitian on the 2 day diet diary assisted recall if clarification or further details of food items are needed.

f. Once the nutrient analysis of the 2 day diet diary assisted recall is completed, the Nutrition Coordinating Center will print and fax a copy of the analysis to the center dietitian for review and agreement.

g. After the 2 day diet diary assisted recall has been reviewed and approved by the clinical center dietitian, the dietitian at the Nutrition Coordinating Center will transmit the 2 day diet diary assisted recalls to the Data Coordinating Center.

C. Gifts for Patients

1. Upon completion of the extra set of 2 day diet diary assisted recalls, the dietitians will provide the patient with a gift of patient's choice as a token of appreciation for the extra food records completed.

Manual of Operation Changes
Section 5-Dietitians

Page 5.2-Remove item #6. Move item #7 over to left under item #5.

Page 5.4-Change “periodically” to “monthly”

Page 5.9-Should read: Instruct the patient that the recall should include all food, drink and oral enteral supplements. **Delete:** (both Study and other), including vitamin and mineral supplements, enteral, parenteral and intradialytic.

Page 5.11, Sec. 5.6.1.2- First sentence should read:
This form is first entered into the Nutritionist Five program then exported into the Study database (See appendix 5A-5.1 Sending Nutritional Analysis Results to the DCC) and is kept on file for quality assurance purposes.

Page 5.12-Item #2 at the top of the page should read “Administer two day diet diary assisted recall just prior to a KM session.”

Page 5.14, Sec. 5.6.2.1- **When to Administer**:
“and just prior to a Kinetic Modeling session. The Diet Diary Assisted Recall is administered annually thereafter, while patient is on his/her randomized dialysis prescription, and just prior to a Kinetic Modeling session.”

Page 5.17-The patient is asked to record his/her intake, for a 48 hour period (one dialysis day and one non-dialysis day)

Page 5.18, Sec. 5.7.2.3-

R&D Labs, Inc. of Marina Del Ray, California has graciously donated vitamin supplements for the Full-Scale Study. These supplements, though not required, are strongly recommended. Ross Laboratories has kindly provided oral nutritional supplements for the HEMO Study. These supplements are described in detail in Section 5.15.

Page 5.19-**How and When to Administer Vitamin Supplements**:
A vitamin supplement has been made available to all patients. Nephro-Vite®RX contains vitamins B and C as listed in the Protocol. If Nephro-Vite®RX is the prescribed supplement, it should be taken daily after dialysis on dialysis days and two hours after eating on other days. All randomized study participants are strongly encouraged to take the Nephro-Vite® RX.
Page 5.20-
After completion of the analysis, the dietitian transmits the nutrient analysis information to the DCC database (See appendix 5A-5.1 Sending Nutritional Analysis Results to the DCC). prints out a copy of the nutrient analysis information and keeps a copy of the nutrient analysis printout in the patient's file.

Page 5.21-
If you need help in deciding how to desegregate a dietary record, consult the coding manual, send a coding assistance request to the Nutrition Consultant, or call the nutrition consultation hot line for help in coding. (Phone 617/636-5273 or FAX 617/636-8325)

Page 5.21 **Database Changes**
Delete "However, recipes may be entered and stored as a new food and linked to the patient's code number."

Page 5.21, Sec. 5.9-
add at end of section: (See appendix 5A-5.1 Sending Nutritional Analysis Results to the DCC).

Page 5.22, Sec. 5.10.1.1 item #4:

If the patient's **current diet prescription** is not within the ranges specified in Table 5.1, the HEMO grant-supported dietitian should meet...

Page 5.28, Sec. 5.11.1.1 item #4:
If the patient's **diet prescription** is not within the ranges...

Page 5.28, Sec 5.11.1.2 item #3:
Make sure that the diet diary is collected just prior to a Kinetic Modeling session.

Page 5.30, Sec. 5.12.1.1 Declining Serum Albumin
Definition: Declining serum albumin is defined as a serum albumin which has (a) declined by 0.3 g/dl from the mean Baseline value and to a level ≤3.9 g/dl or (b) a serum albumin <3.5 g/dl. (These values refer to the BCG method.)

Sending Nutritional Analysis Results to the DCC

The Nutritionist Five program has a feature for exporting a diet analysis to an output data file. This means that the program will take the results of analysis of a patient's diet for a certain day and place those results in a file on the hard disk of your laptop. The results are placed there in a particular format such that once the file has been sent to the DCC, the DCC can read the results into the study database where it will be saved along with other study data being entered into the electronic entry screens.

Exporting Diet Record - NUTRITIONIST Five

1. While you are in the diet record screen, go to edit and select "analysis" or click on the "diet analysis" icon. This will give you a diet analysis drop down screen.

2. In the diet analysis drop down screen, go to file and select "export raw data". This will give you the export analysis data drop down screen. Note that all the boxes labeled "Complete food record","Oral enterals","Vitamins/Minerals" and "Foods only" should be checked off as a default.

3. Click on "export". This will give you a "Save Analysis Data As" drop down box.

4. Change the directory from Nutritionist Five to the folder that you are exporting the diet record to(i.e. export, diets, hemonut5 ... or what have you) and click "open". This is the same process as the one you used in exporting Nutritionist Five diet files. Remeber that you have to create this file folder outside of the Nutritionist Five program file.

5. Enter the appropriate filename(i.e. juleb1a, juleb1b, julef1a,julef2a ....). This should be the same filename that you gave when you saved the diet record. Click "save".

6. There is NO append function as there was in Nutritionist Five. Be careful not to save a different diet record to the same name as a previous file. If you do, you will lose the data in the previous file.

Sending the Output Data File to the DCC

There are three methods for transmitting the results file to the Data Coordinating Center. One or more may be available to you depending upon how your center's computers are set up for communicating with the DCC. These three methods are:

A: FTP transfer from a Clinical Center PC to the DCC.
B: Modem transfer to your local Internet provider computer, then FTP transfer to the DCC.
C: Modem transfer from the laptop to the DCC.

Option A is probably the easiest, and will be available if your center has a PC with network hardware, or SLIP or PPP software, and some version of FTP. FTP is a file transfer Protocol, or standard, that allows transfer of files between computers on the Internet. You may have FTP capability directly from your laptop (if you have an Ethernet adapter for your laptop, or have SLIP or PPP software).

Option B involves getting the results file to your local Internet computer that you dial with a modem, and then using FTP from there to send the file to the DCC, just as in A. This is a two-step process which is probably the least attractive.

Option C involves a file transfer via modem directly to the DCC. This will cost you long-distance charges, but given modem speeds today and the fact that these files will not be huge, the long distance involved will be negligible. If you don't have access to FTP from a PC, this is the recommended method.

Using FTP to Send the Data Output File to the DCC (Option A)

FTP is a software Protocol, not a particular piece of commercial software. This means that there are numerous implementations of FTP, from both commercial and non-commercial software suppliers. All these implementations are similar on a network level, but how the user

interacts with each program will differ to some extent. It is impossible to describe how to use all versions of FTP. The instructions that follow offer general guidelines based on how most versions work. Your version may vary. Confer with your local network personnel for assistance as needed.

If your laptop is set up with some version of the FTP software (either via network hardware or a SLIP/PPP connection), you can use FTP directly from the laptop to send the file to the DCC. Jump to Step 5 below. If you will be using another PC with FTP, you will need to copy the Nutritionist 5 output file to a diskette and read that diskette on the other PC to send the file. If so, begin at Step 1 below.

1. Insert a formatted diskette into your disk drive.

2. Either exit Windows to return to a DOS prompt (the C> prompt) or open a DOS session under Windows by double-clicking on the MS-DOS Prompt icon in the Main program group.

3. Type the follow at the DOS prompt and press Enter:

COPY C:\<<exported files directory>>\JULE???.DAT A:

Do this for every diet record file you need to copy. You can also go to the Windows Explorer, highlight all the files you want to copy and drag them onto the "A:" drive on the left side.

The Nutritionist 5 output files will be copied to the floppy.

4. Go to the PC from which FTP is available and insert the diskette into the diskette drive.

5. Verify that your network connection is active. If you have a network card, this is probably set up when you boot the computer. If you are using SLIP or PPP, you may have to dial via the modem at this time to establish the connection.

6. Start the FTP software. Again, how you do this will vary. You most likely will see an ftp>prompt, or your implementation may be completely menu driven.

7. Connect to the DCC computer. From the ftp> prompt, usually you will type

open bach.bio.ri.ccf.org

Some versions require you to just type the address.

8. Once connected, you will see the usual login> prompt that you will see if you were connecting with Telnet. Type in your HEMO account (mmhdxxxx) and press Enter. Don't forget that this must be in lowercase.

9. You will be prompted for your password. Type it in and press Enter. You should see some message indicating that you are logged in.

10a. FROM THE LAPTOP: To send the file, usually you will type the following at the ftp> prompt:

cd diets then press Enter (This puts you in the diets subdirectory in your home directory)

pwd then press Enter (This will echo the current directory for verification to the screen)

mput C:\<<exported files directory>>\ juleb1a.dat juleb1b.dat....

mput lets you send several files at one time with one statement.

10b. FROM ANOTHER PC: To send the file, usually you will type the following at the ftp> prompt:

cd diets then press Enter (This puts you in the diets subdirectory in your home directory)

pwd then press Enter (This will echo the current directory for verification to the screen)

mput A:\<<exported files directory>>\ juleb1a.dat juleb1b.dat....

mput lets you send several files at one time with one statement.. This assumes that the disk drive containing the diskette is drive A. If not, substitute the appropriate drive letter in this command.

11. The file will be transferred and you will be returned to the ftp> prompt. To disconnect from the DCC computer, type bye and press Enter.

Modem Transfer to Your Local Internet Provider, then FTP Transfer to the DCC (Option B)

This is the transfer method for which it is most difficult to give specific instructions. Transferring the file to the LIP computer will vary depending on the software the LIP computer offers, and the transfer Protocols available. You should have documentation or technical support available from your service. Consult that for assistance. The files you wish to transfer is C:\<<exported files directory>>\juleb1a and/or C:\<<exported files directory>>\juleb1b etc.

The FTP transfer will also depend on filename conventions of your LIP. Again, refer to the available documentation or technical support. The instructions for transfer from the laptop via FTP (Option A above) may be of some help.

Modem Transfer from the Laptop to the DCC (Option C)

The following describe how to send the output file to the DCC from the laptop using Crosstalk Mark IV Version 2 software. If you are using some other software for communication, consult its documentation for assistance. If you need more complete documentation on the DCC's versions of Kermit or Xmodem, contact the DCC.

1. Plug the modem into a wall phone jack. Consult your modem's user manual if you need assistance in doing so.

2. If you are in Microsoft Windows, exit to return the DOS C> prompt.

3. Type XTALK and press Enter to start Crosstalk.

4. You will be at the phonebook menu. Use the arrow keys to position the highlight on the phonebook entry which you created for calling the DCC (see the section "Setting Up Crosstalk to Send Nutritionist Five Output Data Files"). Press Enter.

5. The modem will dial the number. If you see a "Device Error" message, you may ignore it.

6. If a connection is successfully made, the screen will clear and you will see an Enter Username> prompt. You may type anything here, although you must type something. Your first and last name is a good choice. (This is NOT asking for your HEMO account name, by the way.) Press Enter.

7. You will see a Local> prompt. Type C and press Enter.

8. Now you will log into your account as usual. At the login: prompt type your username (mmhdxxxx) in lower case and press Enter.

9. You will next see the Password: prompt. Type in the password and press Enter. You will not see the password as you type it. Also remember that passwords are case sensitive.

10. Upon successful login, you will be at the bach% prompt.
Type:

cd diets then press Enter(This puts you in the diets subdirect. in your home directory)

pwd then press Enter(This will echo to the screen the current directory for verification)

kermit -x and press Enter.

11. Hold down the Alt key and press the A key. A Crosstalk Command: prompt will appear at the bottom of your screen. Type

SEND C:\<<exported files directory>>\JULEB1A.DAT

and press Enter. Repeat above for additional files substituting the next filename.

12. A box will appear display transfer progress. Upon completion, you will be returned to the Command: prompt. Type

SERVER FINISH

and press Enter. Press Enter again.

13. You should be returned to the bach% prompt. Type lo and press Enter to logoff the DCC computer.

14. You will be returned to the Local> prompt. Type lo and press Enter to disconnect and hangup the phone line.

15. Press Alt-Q to exit from Crosstalk.

Setting Up Crosstalk to Send Nutritionist 5 Output Data Files

1. If you are in Microsoft Windows, exit to return the DOS C> prompt.

2. Start Crosstalk by type XTALK at the DOS prompt and pressing Enter.

3. Press the Insert key to create a new phonebook entry.

4. You will be at the Name: field. Enter up to eight characters to identify this phonebook card. CALLHEMO might be a nice name.

5. Press Tab to move to the Description: field. Here you may type in a longer description of this phone book card.

6. Press tab to move to the Number: field. Here you must enter the phone number of the DCC's computer. That number is 216-444-3787 or 800-867-5515. However, you must also enter any numbers or codes that you typically need to enter to make a long-distance call. For example: when I'm calling long distance, I first dial 77. I hear a second dial tone. Then I dial a personal six digit
access code, after which I will hear a third dial tone. Then I dial 1 followed by the area code and number. So I would type into this field:

77,123456,1-216-444-3787 or

77,123456,1-800-867-5515

The commas cause the modem to pause a few seconds before continuing in order to wait for the second and third dial tones. The dashes in this number make it easier to read but are not necessary; they do not affect how the modem will dial.

7. Press the Down Arrow three times to move the cursor to the Device:field. This should already say MODEM. If not, type it into the field. Or you may press the slash key (/) to popup a list of devices. The arrow keys will scroll you through the list; when the MODEM device is highlighted, press Enter to select it.

8. Press Down Arrow to move to the Port: field. This is asking which communications port your modem is using. This should default to the correct port (probably 2) so for now let's leave it as is.

9. Press Down Arrow to move to the Speed: field. Type 9600 into this field, or press / to select from a popup list, as above.

10. Press Down Arrow to move to the WordFormat: field. If this does not already say 8-N-1, press the 8 key and that will appear in the field.

11. Press Up Arrow three times, and then press Tab twice to move the cursor to the Protocol: field. Type KERMIT into this field, or press / and choose KERMIT from the popup list.

12. Hold down the Control key and press the Enter key. The phonebook card will be saved, and you will return to the Phonebook menu.

Backing Up Your Nutritionist 5 Output Data Files

The reason for backing up the Nutritionist 5 export files is to save you from having to re-export your data in the event that your data is not transmitted successfully to the DCC and you have already deleted the original files on your hard drive. They will not serve as a database backup! To back up the files, do the following:

1. Obtain a blank, formatted diskette. Label it clearly; for example, "HEMO Nutritionist 5 Exported Data Files Backup".

2. If you are in Windows, either exit Windows to return to a DOS prompt (the C> prompt) or open a DOS session under Windows by double-clicking on the MS-DOS Prompt icon in the Main program group.

3. Type the following at the DOS prompt and press Enter:

    MKDIR A:\<<mmddyyyy>> This way you can track the files by date**
    CD A:\<<mmddyyyy>>
    COPY C:\<<exported files directory>>*.* A: /V

**Substitute for the mmddyy the current date in month, day, year format. For example, use 060399 if you were to back up datafiles on June 3 if this year.

4. The file will be copied from the C disk to the A diskette and removed from the C disk. You should see the message "1 file(s) copied." If you don't, or error messages appear, DON'T PROCEED until you've successfully copied the file.

5. The next step is to delete the export file from your C hard disk to avoid resending the analyses it contains to the DCC. To do so, type the following at the DOS prompt and press Enter:

    DEL C:\<<exported files directory>>*.*

6. Remove the diskette from the disk drive and store it in a safe location. Use this same disk for your next backup.

6. COMORBIDITY AND HEALTH ASSESSMENT

6.1 Comorbidity Assessment

In the USRDS 1993 Annual Data Report, comorbid conditions account for the majority of causes of death in the ESRD population. Comorbid conditions account for the majority of reasons for hospital admissions. Measuring comorbidity in end stage renal disease (ESRD) studies is important not only for case-mix adjustment but also because the incidence of a comorbid condition is a clinical outcome. The HEMO Study will use a modification of the Index of Coexisting Disease (ICED) (1-4). The ICED is a comorbidity classification system that measures the severity of each disease and takes into account the impact of the disease on the patient's physical function.

6.1.1 General Studies of Coexisting Disease

For twenty years, attempts have been made to quantify the effect of other unrelated diseases on the course of patients in whom an index disease is studied (5). These unrelated diseases are termed comorbidities or coexisting diseases. For a review of the literature, see the appendix in section 6.1.6. An early scheme which distinguished comorbidities with and without a direct impact on survival found that initial comorbidities influence outcomes in diabetes mellitus (6). It has also recently been shown that scoring systems which adjust for the severity of coexisting diseases can refine survival predictions. A technique which estimates the relative risk of death for each coexisting condition has been used to calculate a weighted index of comorbidity. A three grade severity system combined with a four grade scoring system predicted one year survival in a population of 685 women with breast cancer (7). This scheme relied on physician interpretation of clinical data.

The Index of Coexisting Disease (ICED) was first developed to measure the influence of

coexisting diseases on breast and prostate cancer treatment. The ICED consists of a rating of the severity of individual diseases from 0-4 and an estimate of physical impairment from each condition on a 0-2 scale. The ICED score is calculated using the highest severity of a coexisting disease and the highest level of impairment. Chart review for ICED classification has been performed by trained chart abstractors (1, 2, 4, 8).

6.1.2 Coexisting Disease and ESRD

Among patients beginning dialysis, the presence of diabetes mellitus, congestive heart failure, coronary artery disease, peripheral vascular disease and hypertension has each been shown independently to increase the risk of death in ESRD (9). This classification of coexisting disease was intended to compare mortality among dialysis patients with that of patients receiving transplants (10). Much of the difference was attributable to the presence of a greater number of coexisting diseases in dialysis patients. However, the severity of the coexisting diseases was not taken into account.

Tabulation of the number of coexisting diseases affecting dialysis patients shows that patients beginning dialysis now have more coexisting diseases than in the past. Elderly diabetic patients have been observed to have a greater number of coexisting diseases and to have higher mortality. The inference has been made that the higher mortality was due to the greater number of coexisting diseases (11-13).

Low functional status (as measured by the Karnofsky Index) and quality of life (as measured by the Spitzer Quality of Life Scale) have also been shown to be associated with higher dialysis mortality (14). The same study also showed increased mortality when patients with a coexisting disease were compared to patients lacking that coexisting disease. However, neither the interaction between coexisting disease and functional impairment nor the impact of more than one coexisting disease was explored. Subsequent multivariable analysis showed angina, congestive heart failure, nutritional impairment and low Karnofsky scores to be independent risk factors for dialysis mortality (15). Analysis of USRDS data has allowed estimation of the relative mortality risk associated with each of 25 coexisting conditions among 3399 incident hemodialysis patient (16). Peritoneal dialysis patients had fewer comorbid conditions than hemodialysis patients (17). However, this study did not classify coexisting diseases by their severity. Only one study of diseases coexisting with ESRD has considered their severity. A Cox proportional hazard model incorporated data from a retrospective review of 255 patients dialyzed at one Italian center during a 15 year period. The Index of Coexisting Disease (see above) predicted mortality independently of patient age, sex, the presence of diabetes or other systemic disease causing renal failure, or treatment modality (18).

Athienites et. al (63) examined ICED as a predictor of patient outcomes in peritoneal dialysis. Using the dialysis chart, a single reviewer assigned ICED scores to all 69 patients who began chronic PD at one center over 12 years. Mean follow up was 7 years. ICED level

correlated with hospitalizations (r=o.28, p=0.019) and cumulative ensuing hospital days (r=0.28, p=0.02). A multivariate model using age, diabetes and ICED level gave an excellent prediction of survival (area under the receiver operating characteristic ROC curve 86%) (63).

6.1.3 Selection of a Method to Assess Comorbidity in the HEMO Study

The development of a method to measure and classify comorbidity faces several difficulties. First, pathogenic connections can muddy the distinction between coexisting disease and complications of a primary disease. For example, the disease causing ESRD could also act as a comorbid disease (e.g. diabetes mellitus), and results of ESRD and ESRD treatment could act as independent comorbid conditions (e.g. secondary hyperparathyroidism). In order to avoid confusion, the study has adopted the following definition: a comorbid condition is any distinct additional clinical entity that has existed or that may occur during the clinical course of a patient who has end-stage renal disease (5).

Second, classification of diseases and their severity is a technically difficult task, especially if the data for the recording and classification of each condition are extracted from patient records. In fact, most comorbidity studies in ESRD have ignored variability in the severity of comorbid conditions. The ICED is the most appropriate tool available for this study because 1.) it was developed to be used on data extracted from patient charts, 2.) it has been validated in several other conditions and in one ESRD series and 3.) it takes into account the severity of each condition and the impact of the condition on patient functional status. For external validation, in addition to data required for ICED scoring, the study will collect all data requested on the abstraction forms of the USRDS Case Mix/Adequacy Study (19).

Third, in previous studies of comorbidity in ESRD, comorbid conditions reducing long-term survival were emphasized. In the HEMO Study, it is hypothesized that the Kt/V and membrane interventions may also affect hospitalizations, heart disease, infection, and impair functional status and quality of life. Hence, it is important that comorbid conditions which do not lead to death be included in the comorbidity assessment. In order to use the ICED for ESRD, it has been modified. The list of conditions which are scored has been lengthened to specify the conditions which commonly occur as comorbidity in ESRD treated by hemodialysis, and scoring of the severity of functional impairment has been adjusted to reflect the level of impairment commonly found in hemodialysis charts.

Fourth, the ICED is derived from data abstracted from patient records. For practical reasons, the study will use only dialysis unit charts as a data source. The selection of dialysis unit

charts over the hospital medical record will shorten and simplify the data collection process, but may increase the proportion of missing data. In addition, hemodialysis units use different charting systems. In addition, the occurrence of selected comorbid conditions will be assessed by personnel at the clinical centers when patients are hospitalized. The hospitalization forms (Forms 13 & 14) share the classification of disease categories for comorbid conditions used in the initial assessment and annual re-assessment.

6.1.4 Comorbidity Assessment in the MMHD Pilot Study

Comorbidity assessment in the MMHD Pilot Study was conducted at central site, the Comorbidity Assessment Center. Clinical center study coordinators upgraded and standardized the dialysis unit chart, photocopied requested sections and mailed them to the center. The median time to complete the comorbidity packets was 45 minutes. At the Comorbidity Assessment Center charts were reviewed by one individual, a former dialysis nurse, and then again by a nephrologist to allow assessment of interrater variability. Comorbidity assessments were entered into the DCC database and scored for the Index of Coexistent Disease (ICED). A consensus score was assigned for scores with disagreement and the reason for disagreement was identified. The interrater variability showed a kappa value of 0.77, indicating a high degree of agreement and showing evidence of the validity of chart scoring by ICED. The results of comorbidity assessment by ICED method in the pilot study showed the method to be plausible. Patient distribution in the ICED levels was: level 1: 51%, level 2: 12% level 3: 37%. Pilot study results were compared to previous studies where ICED was used. The Pilot Study patients appear to have higher scores than did the patients undergoing hip replacement whom Greenfield described. They appear to be comparable to the Italian dialysis patients whom Nicolucci studied, and perhaps to have slightly lower scores than the U.S. patients dialyzing at an academic center in the NEMC/DCI data set. Preliminary analysis of Pilot Study results significant negative correlations between ICED level and Karnofsky Index of Functional Ability as well between ICED level and serum albumin.

In the Full Scale Study, comorbidity will be obtained locally by the study coordinators. The Comorbidity Assessment form used in the Pilot Study has been significantly revised for ease of use. All MMHD Pilot Study charts have been reviewed again using the new chart upgrading system and new form. The was a high degree of correlation in the ICED scores between the both versions of the form, with a kappa value of .8.

6.1.5 Full Scale Study: Process for comorbidity review at the clinical centers

6.1.5.1 Frequency of assessment

Data will be collected at the Baseline and annually during the Full Scale Study. Each assessment will be cover a one year period. The Baseline comorbidity assessment will be the year prior to the date of the Baseline 5 visit. If a patient has not yet reached the high Kt/V goal,

the comorbidity assessment does not have to be done until the patient is eligible for randomization. However, the dates for the year to be reviewed remain one year prior to the Baseline 5 visit. The comorbidity assessment must be completed and entered into the database prior to randomization. Annual comorbidity will be done at F12, F24, F36 etc. with the review covering one year prior to that visit date.

6.1.5.2 Chart Upgrading

The clinical center study coordinator will obtain patients' consent to retrieve data from medical records of hospitalizations and reports of diagnostic tests. It is important that the chart be reviewed for missing data and consent obtained for data retrieval early in Baseline to facilitate data collection after the Baseline 5 visit. The Baseline comorbidity review must be completed and entered prior to randomization of the patient.

Categories of data to be reviewed have been listed below. All categories selected are included in the medical record model recommended by the ESRD Network Forum quality assurance committee (May 1992) . These categories will be recorded as present or absent on Form 3 to allow later assessment of completeness of charts at the various centers. Data will be reviewed and recorded on Form 3.

1. Discharge summaries from hospitalizations: Obtain discharge summary from most recent hospitalization if none in chart from last year. If patient has not been hospitalized in the past year, review the latest discharge summary available. Review all available summaries in the chart from the past year. A reasonable effort should be made to obtain a discharge summary if none are in the chart.
2. Medication record: The most recent medication review in past year.
3. Monthly progress notes by physician: Review past twelve months of MD progress notes.
4. Chest X-ray: Most Recent available.
5. Electrocardiogram : Most recent available.
6. Echocardiogram: Most recent available.
7. Physician's history and physical examination: Most recent available .
8. Problem list

If a reviewer has knowledge of a patient's condition not documented in the chart or if information is obtained during review of the chart from other areas than above, this may entered on the comorbidity assessment form but must be documented on the form 3.

6.1.5.3 Comorbidity Assessment : Form 3

The Index of Coexistent Disease (ICED) is a composite comorbidity index that incorporates the Individual Disease Severity (IDS) and the Index of Physical Impairment (IPI). The Comorbidity Assessment Form includes 19 disease individual disease categories, each of which has three levels, and allows for Individual Disease Severity (IDS) classification. The second component of the ICED, the Index of Physical Impairment is scored from Form 39.

6.1.5.3.1 General Guidelines of the Individual Disease Severity Classifications

The general guidelines which describe the Individual Disease Severity classifications are as follows:

IDS 0. Absence of coexistent disease in that category.

IDS 1. A comorbid condition which is asymptomatic or mildly symptomatic, where there is little or no morbidity. There are no complications and there is no indication for hospitalization. There is no limitation in activities of daily living.

IDS 2. A mild to moderate condition that is generally symptomatic and requires medical intervention. This also includes past conditions, presently benign, that still present a moderate risk of morbidity. There is need of medications: chronic administration from chronic conditions and short course administration for acute conditions (infections, etc.). Hospitalization, surgery or other invasive procedures may be indicated. complications may occur, but are not life threatening in the near future. There may be mild limitations in the activities of daily living.

IDS 3. An uncontrolled condition which causes moderate to severe disease manifestations during medical care. These conditions are usually acute or subactive and require medical intervention. Symptoms persist despite medical or surgical or other invasive treatment. Frequent hospitalizations may be necessary. Life threatening complications may occur. There is a high degree of morbidity and a moderate risk of mortality. There may be severe limitations in the activities of daily living.

6.5.1.3.2 Individual Disease Categories

Comorbid conditions are divided into the following 19 Individual Disease Severity categories. Although anticoagulation is not a specific disease category, it has been included because of the potential for comorbidity when a patient is anticoagulated. While it can be scored with a specific disease condition, review of the chart does not always identify reason for anticoagulation.

Ischemic Heart Disease

Congestive Heart Failure

Arrhythmias and Conduction Problems

Other Heart Disease and Conditions

Hypertension

Cerebral Vascular Disease

Peripheral Vascular Disease

Diabetes Mellitus (Type I or II)

Respiratory Disease

Musculoskeletal and Connective Tissue Diseases

Nonvascular Nervous System Disease

Gastrointestinal Disease

Hepatobiliary Disease

Urinary Tract Disease

Malignancy

HIV/AIDS

Ophthalmologic conditions

Hematologic Conditions (Non-Malignant)

Anticoagulation

6.1.5.3.3 Guidelines for Comorbidity Assessment Form Completion

Form 3 serves as a data abstraction and individual disease severity assessment form. The individual disease severity (IDS) component will be assessed by the study coordinators primarily by review of chart data. Occasionally, other undocumented knowledge of the patient's condition may exist. This should be recorded on the Form 3 and noted in the area provided. When the required data has been collected and identified in the dialysis chart, the study coordinator will review the data and complete Form 3 by marking all the conditions found in each of the 19 disease categories.

Conditions with an asterisk (*) on the form represent chronic or degenerating conditions and are marked if the patient has ANY history of the disease. Acute conditions will be recorded ONLY if they were active and required treatment in the past year. Although every attempt has been made to keep the form consistent throughout, there are some comorbid conditions which require clarifications. These will be noted in individual disease categories below. Do not score diseases/ conditions listed as " possible", "probable" or "rule out".

Ischemic Heart Disease

- Enter category if patient ever had diagnosis of ischemic heart disease. Most commonly documented as Coronary Artery Disease (CAD).

- Do not score chest pain episodes documented in the chart unless diagnosis of angina is made. Angina during dialysis is scored the same as stable or exertional angina.
- Score ischemia in EKG, exercise tolerance test (ETT), Persantine or Dobutamine Thallium scan only if diagnosis is firmly made. Do no score “possible” ischemia.
- Do not score hypertensive heart disease (if LVH exists, it will be scored under other conditions)
- Coronary angioplasty is frequently documented in the chart as percutaneous transluminal coronary angioplasty and abbreviated as PTCA.
- Angina at rest is unstable angina.

Congestive Heart Failure

- Volume overload resulting in CHF is common pre End Stage Renal Disease (ESRD) and should be scored as IDS 1, even if CHF requires medications and hospitalization in the past year. A diagnosis of cardiomyopathy should be scored as “1”, unless severity warrants a higher comorbidity score. Once patient has started therapy for ESRD, the it should be recorded as IDS 2 if this occurs in past year and requires medications (digoxin the most common) or hospitalization If the patient is on antihypertensives, and it is unclear whether for CHF, cardiomyopathy or hypertension, score under hypertension. Score severe cardiomyopathy as IDS 3.

Arrhythmias and Conduction Problems

- Score diagnosis of arrhythmia at any time in the past. Most common are atrial fibrillation, right or left bundle branch block, hemiblock, history of ventricular tachycardia (VT) or paroxysmal supraventricular tachycardia (PSVT).
- Sinus tachycardia and bradycardia are not considered arrhythmias.
- From the EKG report score all arrhythmias or conduction problems. Do not score " occasional premature ventricular complexes" or “possible” ischemia or “possible” myocardial infarct.
- If the patient now has a permanent pacemaker or a permanently implanted defibrillator score as IDS 3. If he required a temporary one with in the last year score as IDS 2.

Other Heart Disease and Conditions

- Score "pathologic" pericardial effusions as pericarditis. Pericardial effusions are common incidental findings in echocardiograms and reported as small or anterior pericardial effusion. Score all effusions of at least moderate size and all posterior effusions.
- Score all valve defects, unless reported as “trace insufficiency or regurgitation” If the patient has a prosthetic valve score IDS 2.
- If it is not clear from the chart that anticoagulation is for valve disease or prosthetic valve, score in item 33.

Hypertension

- Frequently patients are placed on medications which are indicated for both CHF and hypertension (e.g. ACE inhibitors and vasodilators) or angina and hypertension (b- blockers and Calcium channel blockers). If patient is on an antihypertensive medication and it is unclear if it is for another reason, score under hypertension.
- Score as IDS 2 if patient is on antihypertensive medications, even if there is no mention of any history of hypertension.
- Hypertension severe enough to require ER visit or hospitalization for treatment should be scored as IDS = 3.

Cerebral Vascular Disease

- Changes noted on CT scans do not have to be scored unless patient is symptomatic (e.g. cerebral atrophy)
- If patient has history of CVA and deficit is unclear from chart review, score as IDS 2.
- Aspirin, ticlopidine and Coumadin are considered anticoagulation medications.
- If it is not clear from the chart whether anticoagulation is for CVD, score it in item 33.

Peripheral Vascular Disease

- Vascular complications due to diabetes are scored in this category. Do not score renal artery stenosis.

- Amputation of unknown extent should be scored as IDS 2. Score aorto-iliac endarterectomy under bypass graft.

Diabetes Mellitus (Type I or II)

- If patient has been on both oral meds and insulin in the past year, score both.
- Score as IDS 3 for uncontrolled diabetes if frequent hypoglycemia occurs documented as "frequent hypoglycemic episodes", or at least 4 documented episodes of symptomatic hypoglycemia requiring intervention within the last year, or more than two episodes of ketoacidosis or hyperosmolar states within the last year requiring hospitalization.

Respiratory Disease

- Score diagnosis of chronic asthma\COPD but not isolated episode of asthmatic attack.
- Pulmonary complications from Wegner's or Goodpastures GN or sarcoidosis can be scored here.
- Common medications include inhalers, theophylline, prednisone.

Musculoskeletal and Connective Tissue Diseases

- Chronic musculoskeletal pain, includes low back pain, neck pain or other chronic pain.
- Renal osteodystrophy includes clinical diagnosis of renal osteodystrophy or other metabolic bone disease, X ray findings of osteopenia or hyperparathyroidism or diagnosis by bone biopsy.
- Do not score "hyperparathyroidism" by notes only
- Medications include: Non-steroidals (NSAIDS), prednisone, colchicine, opiates or other analgesics. Do not score a "2" for allopurinol unless patient has documented history of gout. Score if patient is on colchicine even if gout is not specifically mentioned.

Nonvascular Nervous System Disease

- Score paraplegia as IDS = 1. Complications should be scored under appropriate category (UTI's, etc.).
- Peripheral neuropathy from diabetes is scored in this category.

- If the patient is currently on anticonvulsant medication (e.g. dilantin, phenobarbital, tegretol or valproic acid) score as IDS 2 even in the absence of diagnosis of seizure disorder or peripheral neuropathy. Many of the conditions in this category are treated with the same medications.

Gastrointestinal Disease

- Do not score uremic gastritis.
- If the patient had a condition more than a year ago, but is still receiving medication for the condition, score as IDS 2. For example: patient had diagnosis of peptic ulcer disease more than a year ago and is still treated with ranitidine (Zantac), IDS=2. However, if the patient is on a medication without documentation of any history of the disease, do not score.
- Score gastroparesis from diabetes in this category.
- Score pancreatic conditions in this category.
- Ventral hernias and hernia repair do not need to be scored.
- Do not score IDS 3 if reflux persists on medications.

Hepatobiliary Disease

- Chronic hepatitis with chronically elevated transaminases, no symptoms and not on medications score IDS 2.
- IDS 3: Medications for chronic active hepatitis include prednisone and interferon.
- "Fatty liver" is not coded.

Urinary Tract Disease

- Asymptomatic polycystic kidney disease in not scored.
- Score IDS 3 if more than two hospitalizations in the last year were due to UTI's, renal cysts or stones.
- Score chronic prostatitis under chronic UTIs.
- UTI's requiring current treatment are scored as IDS = 1 unless complications arise or severity increases.

Malignancy

- Excluding basal cell cancer of the skin.

- Treatment refers to radiation, chemotherapy or surgery.

Ophthalmologic Conditions

- Retinopathy from diabetes is scored in this category.
- Glasses for nearsightedness, farsightedness or reading, IDS=0, unless patient has other chronic condition.

Hematologic Conditions (Non-Malignant)

- Excludes anemia of chronic renal disease, microcytic anemia (iron deficiency)
- Most common conditions: sickle cell anemia, idiopathic thrombocytopenic purpura (ITP), aplastic anemia, myelodysplastic syndrome, pernicious anemia (B12 deficiency), G6PD.

- Medication for IDS 2 include: prednisone, gamma-globulin, anabolic steroids or B12 injections .
- Score IDS 3 if frequent sickle cell crisis, requiring more than two hospitalizations in the last year or anemia is transfusion dependent.

Anticoagulation

- Aspirin, ticlopidine, persantine and Coumadin are considered anticoagulation medications.
- If patient is anticoagulated and has more than one disease which could require anticoagulation (fib, DVT, CVA, etc), score only ONE category as a IDS 2.
- If patient is anticoagulated and reason is unknown or unclear from chart review, score as IDS 2. This includes anticoagulation for dialysis access problems.

6.1.5.3.4 Classification of Diagnostic Tests

Common diagnostic tests may identify specific conditions that are included in certain disease categories. Study coordinators are not expected to interpret diagnostic tests, but only to use information that is provided in the test report. In reading reports of chest x-rays, EKG and echocardiograms the following chart is helpful in classifying the data in the correct individual disease category.

TEST	FINDING	DISEASE CATEGORY
Chest Xray	Cardiomegaly	Other Heart Disease
	COPD or chronic lung disease	Respiratory Diseases
	Osteopenia	Musculoskeletal
	Hyperparathyroidism	Musculoskeletal
EKG	Ischemia	Ischemic Heart Disease
	Evidence of old MI	Ischemic Heart Disease
	Conduction Defect (Fib, block)	Arrhythmia/Conduction
	Left Ventricular Hypertrophy (LVH)	Other Heart Disease.
Echocardiogram	Left Ventricular Hypertrophy (LVH)	Other Heart Disease
	Valve Disease	Other Heart Disease
	Large or posterior effusion (pericarditis)	Other Heart Disease

6.1.5.4 Index of Physical Impairment: Form 39

Coexistent diseases are often not considered consequential in an episode of care or hospitalization when they are medically well-controlled. Such diseases may actually have an impact on outcomes, but even a careful chart review may not identify and classify a given disease because little information is in the medical record. The concept underlying the assessment of physical impairment is that some not diagnosed but relevant diseases may have an impact on the function of the patient.

6.1.5.4.1 General Guidelines for Physical Impairment

The Index of Physical Impairment, Form 39, rates the patient in eleven areas or dimensions of physical function impairment using a three level scale, 0, 1 or 2. The Form 39 Worksheet provides specific information for each level of impairment for each category.

Level 0: No significant impairment, normal function,

Level 1: Mild / moderate impairment, symptomatic, may need assistance with ADL.

Level 2: Serious /severe impairment, symptomatic.

6.1.5.4.2 Categories of Physical Impairment:

Eleven categories of physical impairment scored in the Index of Physical Impairment.

Circulation	Feeding
Neurological	Ambulation
Respiration	Vision
Mental Status	Hearing
Urinary	Speech
Fecal	

6.1.5.4.3 Guidelines for Form Completion

Experience from the HEMO Pilot Study showed that documentation in the chart for physical impairment was often not present or updated. It is felt assessment of physical impairment by the staff person who knows the patient best is more accurate than chart based data and can be obtained with minimal burden to the dialysis staff. The Index of Physical Impairment should be completed by the hemodialysis unit staff person who is most familiar with the patient's functional ability, usually the dialysis nurse or unit social worker. The Karnofsky Index of Functional Ability, Form 37, and the Index of Physical Impairment, Form 39, should be completed by the same person. This minimizes the inter-rater variability for the two functional scales.

The study coordinator should identify the Dialysis unit staff person, nurse or social worker who is mostly familiar with particular patient's functional status and provide them with the Form 39 Worksheet and the Karnofsky Index, Form 37 (see section 6.2.1).

6.1.5.5 Summary of Comorbidity Assessment

1. **Early in baseline: review chart for items necessary for comorbidity review (see Form 3)**. The Baseline Demographic Form 2, item 51, asks for number of hospitalizations in past year. If there are no discharge summaries at all available in the chart and patient has been admitted in the past year, obtain discharge summary if possible. Reasonable attempts should be made to obtain discharge summaries. In Follow-up, discharge summaries are required to complete hospitalization forms and may already be in chart.
2. Obtain signed medical release from patient to request information from medical record.
3. Fax/mail request to appropriate medical records department.

4. When information is received, complete the Comorbidity Assessment Form 3 (6.1.5.3.3)
5. Have the Index of Physical Impairment Form 39 (6.1.5.4.3.) and the Karnofsky Index, Form 37 (6.1.5.4.3.) completed by appropriate staff member.
6. Enter forms into DCC database. The DCC will compute the ICED score which will be used in later analyses.

6.1.6 Appendix: Brief Review of the Literature on Assessment of Comorbidity and its Application in ESRD

Alvan Feinstein first described the impact of comorbidity on disease outcome in 1970 (5). In 1974, Kaplan and Feinstein showed the importance of classifying initial comorbidity in evaluating the outcome of diabetes mellitus. They introduced a three grade severity classification of comorbidity, and distinguished two types of comorbidity: comorbidity with a direct impact on survival, (e.g. cardiovascular comorbidity) and comorbidity with no direct impact on survival, (e.g. asymptomatic cholelithiasis) (6).

In 1987, Charlson developed a new method for classifying the severity of comorbid conditions (7). The relative risk of death for each condition was estimated, and a severity index called the "weighted index of comorbidity" calculated for each. When more than one comorbid condition existed, the patient was assigned the highest index.

In 1987, Greenfield et al introduced a chart-based comorbidity index to control for the influence of coexisting diseases on cancer management (2). Several studies have been published using this Index of Coexisting Disease (ICED)(2, 4, 8, 18). The ICED has two components: 1) the individual disease severity (IDS), which grades the severity of each condition from 0 to 4, and 2) the estimate of physical impairment from each condition, graded from 0 to 2. The peak severity of coexisting disease and peak severity of physical impairment are combined to form ICED levels 0 to 3.

In 1988, Pompei et al used a three grade severity system to classify comorbidity and used the system to predict one year survival (20). In ESRD, the issue of comorbidity was addressed by several investigators from the National Cooperative Dialysis Study. The presence of comorbid conditions was associated with death or removal from the study before 24 weeks, and accounted for 33% of hospitalizations (21).

In 1982 Hutchinson estimated the relative risks of death for coexisting conditions as diabetes mellitus, congestive heart failure, coronary artery disease, peripheral vascular disease and hypertension (9). Each condition was evaluated separately, but severity of condition was not taken into account. A subsequent study used the same method of measuring comorbidity in a prognostically controlled comparison of dialysis and renal transplantation (10).

Collins et al have showed the impact of comorbid conditions as death risk factors, the increasing number of diabetics with comorbid conditions entering dialysis, and the increasing number of patients with peripheral vascular disease comparing the periods 1976-1982 and 1983-1987(10-12, 22). Kjellstrand et al showed that both in a Swedish and a U.S. dialysis center, the number of patients with comorbid conditions entering dialysis was increasing (13).

McClellan et al found comorbid conditions, functional status and quality of life to predict early mortality among patients entering treatment for ESRD (14). A subsequent study showed variable mortality rates among dialysis treatment centers (15). The relative risk of death for comorbid diseases was estimated and comparison between units was made after adjusting for comorbidity.

The USRDS Case-Mix Severity Study estimated the relative mortality risk associated with each comorbid condition among 3399 incident hemodialysis patients (16). Another study compared patient selection to peritoneal dialysis versus hemodialysis according to comorbid conditions. Neither of these studies took the severity of comorbid conditions into account (17).

Nicolucci et al used the Index of Coexisting Disease (ICED) developed by Greenfield et al as a prognostic factor to predict mortality in a cohort ESRD patients. The study was retrospective. It showed ICED score to be an independent risk factor of death in ESRD patients (18).

6.2 Health Status Assessment

6.2.1 The Karnofsky Index of Functional Ability (KI): Form 37

The Karnofsky Index of Functional Ability will also be used to assess physical impairment in the HEMO Study. The Karnofsky Index is included in the USRDS 1993 Annual Data Report account of the special study on EPO and Quality of Life (23).

6.2.1.1 Frequency, Administration and General Guidelines

The Karnofsky Index will be completed at the Baseline 5 visit and annually at Follow-up 12, F24, F36 etc. The Karnofsky Index (KI) form should be completed by the hemodialysis unit staff person who is most familiar with the patient's functional ability, usually the unit social worker or a dialysis nurse. It should be clearly marked on the form whether the assessment of the KI was performed by the social worker, a nurse, or by another individual.

The study coordinator will provide the nurse or social worker with the definitions for specific terms used in the statement (see 6.2.1.2). The patient SHOULD NOT BE ASKED to assist in his assessment of his functional ability, nor should his family. The study coordinator should not influence by any means the person completing the form to choose a certain statement. The person completing the form will read the 10 statements and mark the statement that fits the patient's functional ability best. Only ONE statement should be marked for each patient. The dialysis unit patient record may be used for reference.

Choose ONE of the following statements that best describes the patients functional status:

(Circle number)

Normal; no complaints; no evidence of disease

1

Able to carry on normal activity; minor symptoms of disease

2

Normal activity with effort; some signs and symptoms of disease

3

Cares for self; unable to carry on normal activity or do active work

4

Requires occasional assistance but is able to care for most of own needs

5

Requires considerable assistance and frequent medical care

6

Disabled; requires special care and assistance

7

Severely disabled; hospitalization is indicated although death not imminent

8

Very sick; hospitalization necessary

9

Moribund; fatal processes progressing rapidly

10

6.2.1.2 Terminology for the Karnofsky Performance Scale (24)

The following definition of terms should be provided to the person completing the Karnofsky Index:

A.) "Normal activity" is defined as the amount of activity carried on by a patient when he/she is perfectly well. Normal activity includes:

1. Basic activities of daily living
    a. taking care of self
    b. moving in and out of a bed or chair
    c. walking indoors
2. Instrumental activities of daily living
    a. walking one block or climbing one flight of stairs
    b. doing work around the house
    c. doing errands
    d. driving a car or using public transportation
    e. doing vigorous activities
3. Social activities
    a. visiting with relatives or friends
    b. participating in community activities

c. taking care of other people

B.) "Active work" is defined as physical or mental activity which benefits oneself.

C.) "Cares for self" is defined as functioning independently in society except for the necessity of earning a living, which may depend on government or other outside support.

6.2.1.3 Assigning the Karnofsky Index Score

The numbered statements correspond to the following KI scores:

STATEMENT NUMBER	KARNOFSKY INDEX SCORE
1.	100
2.	90
3.	80
4.	70
5.	60
6.	50
7.	40
8.	30
9.	20
10.	10

6.2.2 The Quality of Life Questionnaire: Form 48/49

The Quality of Life Questionnaire combines questions from the Short Form 36 (SF 36)(56), the Index of Well-Being (IWB)(26), items modified from the Kidney and Dialysis Quality of Life™ questionnaire (KDQOL™)(64) and ESRD-specific/hemodialysis-specific questions developed for the HEMO Study.

To accommodate the largest number of study patients possible, the Form 48/49 has been provided in Interviewer-Administered format and in Spanish. The Spanish translation of the SF- 36 Form was done during the International Quality of Life Assessment (ICOLA) Project (65-67). The IWB, KDQOL™ and ESRD-specific questions were translated at New England Medical Center. There are a total of four Form 48/49 Quality of Life Questionnaires: English and Spanish Self-Administered and English and Spanish Interviewer-Administered.

6.2.2.1 Frequency and Administration of the Quality of Life Assessment: Form 48/49

The Quality of Life questionnaire will be administered once in Baseline at the B5 visit and annually at the Follow-up 12, 24, 36 etc. visits.

The Quality of Life questionnaire is designed to be self-administered by the patient. Depending on the ability of the patient, the form should take from 30-45 minutes to be completed. However, an Interviewer-Administered Form is provided for patients who are unable to self-administer the form due to an impairment in vision or reading ability, difficulty with manual dexterity or who state a strong preference for an interview format. It is important that patients be given an introduction to the form, proper materials for completing the form and consistent feedback if there are problems in completing the form. The following paragraphs are adapted from guidelines published in the *SF-36 Health Survey, Manual and Interpretation Guide* (25) and can be used for reference.

1.) Introduction of the Questionnaire

The questionnaire will take 30-45 minutes depending on the individual. It may be done anytime during dialysis, but should be done when the patient is feeling well. For some patients, early in the treatment may be the best time. Provide patients with a clipboard and pencil to complete the form The following introduction or a variation appropriately reworded to your style is suggested:

We would like to better understand how you and other persons in this study feel, and how well you are able to do your usual activities, and how you rate your own health. To help us better understand these things about you and other persons, please complete this questionnaire about your general health.

The questionnaire is simple to fill out. Remember, this is not a test and there are no right or wrong answers. Choose the response that best represents the way ***you*** *feel. I will quickly review the questionnaire when you are done to make sure all questions are completed.*

You should answer these questions by yourself. Spouses, other family members or visitors, **should not** assist you in completing the questionnaire.

2.) Completion of the Questionnaire

If a patient asks for help in completing the question, read and repeat the question verbatim. Tell patients to answer a question based on what they think the question

means**. Do not interpret or explain a question for the patient. Patients may leave a question blank if they are unable to or choose not to answer a particular question.**

Form 48/49: INSTRUCTIONS TO THE INTERVIEWER

Specific guidelines for the Interviewer-Administered Form are provided on the cover page of the form. The instructions are as follows:

1) Use this form to administer the Quality of Life Assessment Form by interview. Interviewer administration should be used with patients unable to self-administer or mark the forms due to an impairment in vision or reading ability, or difficulty in manual dexterity, and with patients who state a strong preference for an interview format.

2) Read each of the lead-in statements, questions, and response choices *verbatim* and in the order presented. Lead-in statements are enclosed in boxes and should be read to the respondent. Instructions to the interviewer are enclosed in brackets [] and should **not** be read to the respondent.

3) **Do not** lead respondents. If the respondent asks for clarification of a question, assist the respondent by re-reading the question and response choices for them *verbatim*. If they ask you what something means, **do not** rephrase the question, but gently tell them to use their own definition of the situation.

4) Circle the number corresponding to the one response choice selected by the respondent. If the respondent has difficulty selecting one response choice, gently guide them by acknowledging their difficulty and asking them which answer comes closest to what they are thinking or feeling. **Do not** lead the respondent.

5) Complete the entire questionnaire during one session.

6.2.2.2 Scoring and Interpretation (to be completed)

6.2.3 Appendix on Health Status Assessment

Instruments for health status assessment should provide information about physical functioning, mental health, social functioning and other domains which are related to health.

These include pain, fatigue, and the patient's overall perception of his or her well-being (3).

6.2.3.1 General Health Status Assessment Instruments Used in ESRD

Many instruments intended to measure quality of life or general health status assessment have been used in individual studies in ESRD. Only a few have been used in more than one or two studies. The Sickness Impact Profile (SIP)(27, 28) is a widely accepted general health status measure which has been used in a number of ESRD studies (27-35). It contains 135 items and takes 60 to 90 minutes to complete. Learning to administer the SIP requires extensive training. The Karnofsky Index has been used in several cross-sectional and longitudinal ESRD studies, and was used in the USRDS special study on Erythropoietin and Quality of Life (23). The instrument is easily administered, requires minimal interviewer training, and can be completed within ten minutes. Limitations include interobserver variability and limited scope (24, 29, 30, 36-46).

The Index of Well Being (IWB) has been used in many ESRD studies, and has yielded statistically significant results in clinically different patient groups (29-32, 35, 36, 43, 44, 46-52). The IWB is easily administered in less than 5 minutes, requires minimal interviewer training, and is easily scored. However, the scope of the IWB is also limited: it inquires only about the patient's own perception of overall well-being.

The Short Form 36 Health Survey was developed on the basis of experience in the Medical Outcomes Study. It assesses physical function, role limitations attributable to physical problems, pain, mental health, role limitations attributable to emotional problems, social function and vitality (23, 25, 29-32, 35, 36, 43, 44, 46-57). The SF-36 is available in a computer-scored format and can be completed in less than ten minutes. Minimal instruction is needed to administer the instrument. The SF-36 has been used extensively in ESRD and appears to be reliable and valid in this population (57-60).

6.2.3.2 ESRD-Specific Health Status Assessment Instruments

Several instruments focus particularly on the effect of ESRD on health. The Kidney Disease Questionnaire used in the Canadian Erythropoietin Study was derived from 130 items

identified from literature review and interviews with health care workers. Fifty patients ranked the importance of these items, and the 20 most important were retained. Dimensions covered include fatigue, physical symptoms, relationships with others, depression and frustration. In addition, patients completing the instrument were asked to enumerate up to six patient-specific items (30, 32, 33). Fatigue and physical symptom dimensions showed a clinically and statistically significant improvement with erythropoietin treatment.

Parfrey's Health Questionnaire for End-Stage Renal Disease asks about physical symptoms

selected because they were prevalent in a development cohort of ESRD patients or because they distinguished dialysis patients from transplant patients. It combines these questions with questions about emotional experiences which nephrologists considered important among ESRD patients, and with several established general health status indices (30, 32, 33, 44-46, 52, 61).

Burton and Lindsay developed a series of questionnaires assessing renal failure related and dialysis related stress mainly for peritoneal dialysis patients (62). Unfortunately, the details of the instrument used in these studies have neither been published nor made available to the HEMO study.

An ESRD-specific questionnaire designed to supplement the SF-36, "About Your Kidney Disease," is currently in use in the Network of New England Study of Health Status in Patients Beginning Dialysis. The KDQOL™ was recently developed at the RAND Corporation. It intersperses SF-36 questions among other questions from the Medical Outcomes Study long form questionnaire and ESRD-specific questions. Results of validation among 165 patients have been published.

It should be noted that although in presenting their instruments and findings, the authors of ESRD-specific instruments assert the necessity of supplementing generic health surveys, the value of the additional information in characterizing ESRD, in comparing treatment strategies or in improving care has never been demonstrated.

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7. FOLLOW-UP COMPLIANCE ENHANCEMENT

7.1 How to get participants to comply with time goals

Since 1983 there has been a decrease in the length of dialysis time. A relationship may exist between increasing mortality rates and the problem with the amount of dialysis prescribed vs delivered. The amount of dialysis may be inadequate if dialysis time is shortened, thus it is important for this study to have dialysis times of sufficient length to provide delivery of levels of treatment required for the study.

One of the goals to be evaluated for the HEMO Study is to determine if the higher Kt/V intervention is safe and acceptable to patients. Time is an inherent part of Kt/V; once maximally achievable blood flow and dialyzer KoA are reached, dialysis time may have to be increased in order to reach a Kt/V goal (see Table 9.2 of the protocol). Thus, patients are excluded from enrollment if they are unwilling to alter their time on dialysis.

Time may be altered for a number of reasons:

High flux randomization assignment may lead to shorter dialysis time in smaller sized patients.

Low flux assignment may lead to longer dialysis time.

Although the goal in the study will be to accomplish the treatment in the shortest time (minimum is 2.5 hours), time spent on dialysis will be determined in part by body size within the constraints imposed by available dialyzer KoA and access blood flow.

Time will be adjusted to meet the Kt/V goal up to 4.5 hours.

To enhance compliance to time from the inception of the study, discuss and review with the participant the purpose of the study and relationship to length of time on dialysis. Often, the patients have not been getting the dialysis prescribed for many reasons including shortened dialysis time. Problems related to dialysis may, in part, be related to time. A longer stay on dialysis may lead to more adequate dialysis and even improved appetite and nutritional state.

If non-compliance to assigned time on dialysis is identified, determine the cause and attempt to remedy the problem. Possible causes for non-compliance include:

Hemodynamic instability
Staff error
Staffing problems
Technical problems
Lack of quality control
Participant refusal
Transportation problems for participant
Access problems

To reverse the participant and/or staff non-compliance to time, consider using the following strategies:

1)Have the principal investigator discuss the non-compliance with the participant and participant's usual doctor.

2)Review with participant the purpose of the study including the possible risks and benefits of maintaining the time assignment. It is important to emphasize that the time assignment is integral to the dose delivered. The minimal time required for this dose is being employed in the study. A shortened dialysis time will lead to inadequate dialysis and the Kt/V will not be met. A longer time on dialysis which may be required may lead to more adequate dialysis, improved appetite and nutritional state. No apparent risk is involved in a longer dialysis time but a disadvantage my be the inconvenience.

3)Have the participant re-read the consent form that he/she signed.

4)Have the principal investigator discuss non-compliance with family member or support person.

5)Have participant talk with a time-compliant participant who has no complaints about the same time on dialysis.

6)Provide a reward or incentive to foster compliance to time, such as taxi fare, extra participation fee for added inconvenience.

If randomized participant refuses to continue the time goal, "loss to routine follow-up" can be considered .

8. COMPUTING AND DATA ENTRY

8.1 Computing Systems Overview

Computing for HEMO can be divided into two broad areas: computing at the Clinical Centers and their associated dialysis units, and computing at Data Coordinating Center (DCC). The purpose of this overview is to describe in general terms how these systems are organized and how they are connected.

Each Clinical Center has been provided with a personal laptop computer. These PC's will be used, for study purposes, to run software for communicating electronically to the DCC, and to run the Nutritionist IV software for entering diet diaries and recalls for nutrient analysis. They may additionally be used for a variety of tasks useful for the centers' work related to the study, such as word processing.

In addition to use of the laptop, clinical centers may use any other computers to which they have access. These do not necessarily have to be PC's, but could be a Macintosh, for example, with the stipulation that any computer so used must be able to adhere to a few communication standards. These will be detailed below.

To connect from your PC to the DCC (located in Cleveland, Ohio at the Cleveland Clinic), you will be making use of the Internet, a world-wide network of computers, composed of and supported by primarily academic, governmental, and non-profit institutions. Using the Internet, you will be able to interact with the DCC's computers in Cleveland.

The laptop PC that sits in your office is not directly connected to the Internet. You must first connect from your PC to a nearby computer that is "on" the Internet and then from that computer to the DCC. This nearby computer is called an Internet "node." Just what kind of computer each center will connect to in order to access the Internet will vary from center to center. Some will be connected to a computer at its institution that is an Internet node. This connection might be through a campus network, or it might involve dialing up the institution's computer over a phone line using a modem. Other centers will be utilizing a public provider of Internet access for a small monthly fee. Connecting to such a service will involve making a local phone call to connect using a modem. In either case, this manual will refer to the computer to which the laptop connects to gain Internet access as the Local Internet Provider (LIP).

Now, the DCC's computer is also connected to the Internet. Hence connecting from your laptop to your LIP allows you to reach the DCC across the Internet. In fact, you'll be using the DCC's computer directly when you enter data, and reports and mail messages from the DCC will be sent across the Internet to your LIP.

8.2 Your HEMO Study Laptop Computer

The laptop computer furnished to your center for the purposes of the HEMO study is a Compaq LTE Lite 4/25 or 4/40 computer. It features an Intel 80486SL 25 Mhz microprocessor, 4 MB of memory, and 120 MB or 170MB of hard disk storage. The laptops purchased for the pilot study centers have an active matrix LCD black and white display; other centers have and LCD color display. The PC will be running the DOS Version 6 operating system and Microsoft's Windows graphical user environment.

Your laptop is also equipped with an internal modem. A modem is a device that allows you to send and receive computer information over a standard telephone line. You will be using this modem to communicate to other computers, primarily your Local Internet Provider. Your modem can send up to 9,600 bits of information per second, and it also has fax capability as well.

The most important piece of software that you will be using on your laptop is a program that allows you to communicate to your LIP and then to the DCC's computer. This study will be using a communications package called Crosstalk Mk.IV. Crosstalk makes use of your modem to provide a friendly interface for using it to connect to your LIP.

When you connect to another computer from your PC, your communications software appears, to the remote computer, as if it were a dumb terminal, i.e., just a screen and keyboard without any processing power. This is known as terminal emulation. Crosstalk will be emulating a VT100 terminal. This is a very common, popular terminal, and might be considered a "least common denominator" among terminal emulation.

Another important software you will be using on your laptop computer is Nutritionist IV. This is a nutrient analysis program. You will be entering your patient's food records (diaries and recalls) into Nutritionist IV, it will analyze the foods they have eaten to determine their intake of certain nutrients, and then it will prepare a data record of those values. These data records will be sent to the Sun computer for inclusion in the study database.

Your laptop comes with the popular Microsoft Windows graphical user environment. The study will not be making use of Windows, but you may wish to take advantage of it for purposes related to the study.

8.3 Connecting to the DCC Computer

Connecting using the Crosstalk Mark IV Version 2.0 software installed on your laptop:

1. Start Crosstalk on your PC by typing XTALK4 at the C:\> prompt and pressing Enter.

2. After a few moments, you will see the Crosstalk phone book directory. This is a list of other computers which Crosstalk has been set up to connect to. Locate the entry called HEMO-DCC. Select this entry by moving the highlight bar using the arrow keys, then press the Enter key.

3. Crosstalk will dial the modem to establish the connection. Typically you will hear the dialing, the phone ringing, a high pitched sound (the "carrier"), a static sound, and then silence. In a few moments the screen should go blank and a login prompt to your LIP should appear.

4. Log into your LIP computer according to the instructions provided by your LIP.

5. Once you are connected to your LIP, you need to use Telnet in order to connect across the Internet to the DCC. How you access Telnet will depend upon how your LIP is set up. You should have some documentation as to how to do this. At some point you will be asked for an address or node name. The DCC has many SUN computers which compose its network. Which one you use will depend upon your clinical center number. The study is utilizing more than one computer to balance the load. Here is the address to use:

hemo.bio.ri.ccf.org

6. If the connection is successfully established, you will probably see a message that says "Connected to bach.bio.ri.ccf.org" (or "Connected to ashley.bio.ri.ccf.org if you telnet to ashley.)

7. You will then see the prompt "login:". Type in your Sun username, provided to you by the DCC, and press Enter. Your username will be of the form "mmhdxxxx" where "xxxx" is up to four letters of your institution's name. Your username must be entered in lowercase letters.

8. You will then see the prompt "Password:". Type in your Sun account password, and press Return. Note that your password will not be displayed on the screen as you type it, for reasons of security. Your password was originally provided to you by the DCC, but you should have changed it to something of your own choosing. Note that case matters in entering your password; you must enter it in upper, lower, or mixed case, according to how you entered it when your set your password, in order for it to be recognized.

9. If you have entered your username and password correctly, you will see the prompt bach% (or ashley %). This is the Unix operating system prompt. If not, you will see the message
"Login incorrect" and will be given an opportunity to try again.

10. When you are finished with your work on the DCC's computer, disconnect from it by typing lo at the bach% prompt and pressing Enter. You will be returned to your local Internet provider. Disconnect from that computer as usual to return to your PC.

8.4 How to Enter Study Data into the Database

The data in the HEMO Study is being maintained using a database management software called Oracle. This software will be used for both entry and maintenance of study data. To enter data upon connecting to the DCC's Sun computer, you will be running Oracle on that computer, and entering directly into the real database.

Each person who will be entering data will have their own Oracle username and password. The username will consist of your first initial followed by up to seven letters of your last name. Note that these are distinct from your center's Sun username and password.

1. At the bach% prompt, type hemo-entry and press Enter. This command (and all commands entered at the bach% prompt) must be entered in lowercase.

2. An Oracle login screen will appear. Type in your Oracle username and press Enter; then type in your Oracle password and press Enter. Note that your password will not appear on the screen as you type it. If you've made a mistake, you will be so informed and will be given another opportunity.

3. When successful, a menu title "The Hemodialysis Study" and subtitle "Main Menu" will be displayed on the screen. The menu choices allow you to get into various sets of electronic forms for entry of data, check on a patient's eligibility, read and respond to data inquiries from the DCC, and go to the Pine mail program.

Navigating the HEMO menu

1. The HEMO menu is a full-screen menu system. This means that choices will appear on the screen. One choice will always be "highlighted," or seen in reverse video (light characters on a dark background). To move the highlight bar from choice to choice, use the up and down arrow keys. When the choice you like is highlighted, press the Enter to proceed with the choice.

2. Each item of a menu is preceded by a number. Below the choices is a highlighted area with the prompt "Enter your choice." You may alternately choose a menu item by typing the number appearing before it and then pressing Enter.

3. The first menu choice of the Main Menu is called the "Patient Data Menu." This menu works slightly differently than any other. In this menu, you can only choose an item by typing its number in the highlighted box and pressing enter. That number will typically be the number of the form for which you wish to enter data. The screen displays a complete list of the study forms, each preceded by its number. For example: to enter Form 5, type 5 and then press Enter. The electronic form corresponding to Form 5 will be displayed.

Entering Data into the Oracle Form Application

1. Data is entered into fields on the Oracle form. Each field holds one item of data; it might

be numeric data, alphabetic characters, or a date.

2. Field areas should appear as highlighted areas on the screen, The cursor will always indicate where the field area is located. The screens have been set up to look like the paper forms as closely as possible. To enter data, simply type the appropriate information; it will appear in the field area as it is typed. To enter numbers, you may use either the number keys across the top of the main keyboard or the number keys on the numeric keypad. If you choose to use the keypad, make sure your PC is in NumLock mode. Typically, the keyboard will have a small light that will glow when you are in NumLock mode. If that light is not glowing, press the NumLock key. The NumLock key is typically located near the upper right of your keyboard.

3. When you have entered data for a field, press Enter to move the cursor to the next field. If your entered data length is shorter than the field length, you may just ignore the extra spaces. You do not need to enter leading zeroes although you may; Oracle will just remove them if you do.

4. The next to last line of your screen will be highlighted. This is known as the hint line. Text will be displayed on this line which will be a more verbose description of the expected data to be entered for this field. The hint line will change as you move from field to field, displaying information for the field at which the cursor is currently positioned.

5. Categorical fields; that is, fields which will take one of two or more discrete values, frequently have a List of Values associated with them. If so, at the end of the hint line it will say "List of values available" or just "LOV." You can also identify a field having a list of values by the characters "<List>" that will appear at the bottom right of the screen when positioned at the field (This is known as the "list lamp"). To display the list of values when positioned at the field, press the F7 key (located along the top of your main keyboard). A box appears listing all valid values for that field. The left column contains the possible field values, with each value's corresponding meaning listed in the right column. This is a pick list; that is, you may move the highlight up and down the list using the up and down arrows. When the value which you wish to enter into the field is highlighted, press Enter. The value is put into the field, and the list of values box is closed. Press Enter to accept that value for the field and move to the next. You are not required to display the List of Values for a field which has one; you may just type in the response to the field.

6. After completing the final field displayed on a page, pressing Enter at the field will scroll the form to the next enterable field.

7. When you have completed entering data for a form, pressing Enter upon entering the final field of the form will redisplay the beginning of the form.

8. To skip over a field that is to be left blank, simply press Enter while positioned at that field. To move back to a previous field, press the F2 key.

9. To display the meanings of all the keys, press Ctrl-K. A key map is displayed, listing a function (Previous Field, Exit, Next Block, etc.) followed by the key or key combination required to perform that function. Sometimes more than one key combination will perform the same function. When you see "KP-" on the key map screen, this is referring to the keypad. Hence KP-2 is the 2 key on the keypad, not on the main keyboard.

Saving Your Data and Exiting the Form

1. Entering data for one or more forms as described above does not automatically save it to the database. To save it, you must do what is called committing it to the database. This is accomplished by pressing the PF3 key. Upon committal, a message will be displayed at the bottom of the screen indicating how many new records (forms) were added to the database.

2. You may commit data as often as you like: after every form, or just prior to leaving that form type. Whatever needs to be saved is committed. If you attempt to leave the form without committing, you'll be warned that you are doing so and will be asked if you want to commit your data. Be sure to choose Yes, otherwise all of your hard data entry work will be lost. It is probably wise to commit after entry of each form, to limit your losses in case of network problems.

3. After you have entered and committed your data, exit the current form type by pressing the F4 key. You are returned to the menu of HEMO Study forms.

4. To enter forms for another form type, select that form type from the menu as before. A blank form will be displayed. Continue to enter data as before.

5. To get out of the Oracle data entry application, simply press the F4 key when at the menu of study forms. You will be returned to the bach% prompt.

Common Oracle Error Messages

When Oracle needs to display a message to you, the user, it will display it on the second line from the bottom of the screen (this is also the hint line, as described above). Some common messages you may see:

"Field must be entered": You attempted to skip over a field (by just pressing Enter) that must have a valued entered into it. These are typically important identification fields, as a visit date, or critical data that is collectable for every patient. Enter the value for the field and press Enter to continue to the next field.

"Invalid value for <fieldname>": You entered a value that is not a possible value for that field. For example, No/Yes fields may take only the values 0 and 1; anything else would generate such a message. Enter a valid value for the field and press Enter to continue.

"Legal characters are 0-9 + and -" You entered a non-numeric character (a letter or symbol) into a numeric field. You may enter only the digits 0 through 9, the plus sign (+), or the minus sign (-). Enter a numeric value to the field and press Enter.

8.5 How to Change Study Data in the Database

To protect the study data from being changed without notice months or years after data entry, the DCC uses the following system: Data which has been entered and committed to the database can be changed by that center if it is within a certain number of days of when it was originally entered. Typically, data can be modified within 7 days. Note: If more than 7 days has elapsed, you can request a formal data change by submitting a Data Inquiry Request to the DCC.

To change study data before the 7 day limit has passed,

1. Access the form from the HEMO menu for which a change is to be made.

2. Select, or query, the specific data form for the patient and visit. This is done by pressing F9 key, typing the patient ID and visit number information and then pressing the F10 key.

3. Position the cursor on the field requiring a change, and press the F5 key. A pop-up message will tell you that "change made enabled."

4. Key enter the desired value on the field

5. Since you have changed this record, you must again save it. Press the F3 key to commit the modification.

6. Continue to navigate through the data entry screen or press the F4 key to return to the HEMO menu.

To change study data after the 7 day time limit, follow steps 1, 2 & 3 above. Then,

4. After pressing the F5 key, another form titled "Submit a Data Inquiry to the DCC" form will be displayed on your screen. The identifying information, patient ID, visit number, etc. will be displayed in the screen as well as the specific field that is to be changed along with its original value.

5. Record the desired change by keyentering the "new" value that should replace the original value as well as any text that may further clarify the desired modification. You may bring up a box in which you may type a longer description by pressing the F8 key. When entry is completed in this pop-up box, you must press the F3 or exit key to either accept or abort the information typed into the field.

6. Press F3 to commit the data change information and return to the original (or calling) data entry screen. If you decide you do not wish to send this inquiry, press the F4 key.

7. A report will be sent to the DCC who will then follow through on the modification.

8. A report will be sent to the Clinical Center confirming the actual change made.

8.6 Responding to DCC Initiated Inquiries

In the event the DCC identifies data that they would like clarification on, an Inquiry Report will be sent to the Clinical Center. Upon receipt of this report;

1. Investigate the question and determine the response. (Look at patient charts, other records,...)

2. Access the HEMO study menu

3. a. Chose the "Data Change/Inquiry" menu option.
b. Chose the "Respond to a DCC Initiated Inquiry."

4. Retrieve the appropriate inquiry data from the database to your screen by:

a. Press the F9 key.
b. Enter the inquiry number of the inquiry to which you would like to respond.
c. Press the F10 key.

5. Key enter your reply in the appropriate fields. Enter a new value for the field in question, if appropriate. If the value is not to change, or if the value should become a blank, leave this blank, press Enter.

6. Enter a text explanation of your response. You may press the F8 key if you need more space for your reply.

7. Press F3 key to commit your reply and exit the screen.

8. To respond to another inquiry, repeat from item 4a. To exit and return to the HEMO menu, press the F4 key.

9. Upon receipt of your reply, the DCC will make any appropriate changes to the database. At that time, a report will be sent to the Clinical Center indicating the actual changes made.

8.7 Changing Your Password

For security reasons, it is highly recommended that all users of the Biostatistics & Epidemiology Sun computer network change their passwords periodically. Neither personal Oracle passwords, nor DCC Sun account passwords are not meant to be shared with other users; in the event that another user learns your password, the password needs to be changed in order to maintain the integrity of the system. Either the Sun account or Oracle account passwords can be modified after accessing the computer at the DCC (refer to steps 1-10 in Section 8.3).

Modifying Your Center's Sun Password

- At the bach% prompt, type passwd.
- You will get a prompt saying: Changing password for (your name) on bach. Old password: Type in your old password.
- At the next prompt (new password;) type in your new password.
- The computer will then display, retype new password.
    - Type the new password again to confirm it.

Modifying Your Personal Oracle Password

- At the bach% prompt, type sqlplus
- Enter your original Oracle username and password.
    - Type the following command at the sql> prompt.

Alter user <your username> identified by <new password>;

- You will receive a message indicating the user was altered.
- At the sql> prompt, type exit.

8.8 Electronic Mail

All database related reports and most routine correspondence will take place via electronic mail. Each clinical center and central lab will have an HEMO Study specific mail address (typically, hemoxxxx@.bio.ri.ccf.org).

When you log onto the DCC's computer you will have access to a mail utility called "Pine." Pine is a program for Internet News and Email. It is a screen-oriented message-handling tool (refer to Appendix D for more details). Pine's basic feature set includes:

- View, save, export, delete, print, reply, and forward messages.

- Compose messages in a simple editor (The editor is named PICO).

- Full screen selection and management of message folders.

- Address book to keep a list of long or frequently used addresses. Personal distribution lists may be defined (see 8.8.1 for public distribution lists).

- New mail checking and notification occurs automatically every 2.5 minutes and after certain commands, e.g., refresh screen (ctrl L).

- On-line help screens.

The following main menu-choices are available upon accessing Pine:

?	HELP	-	Get help using Pine
C	COMPOSE MESSAGE	-	Compose and send/post a message
I	FOLDER INDEX	-	View messages in current folder
L	FOLDER LIST	-	Select a folder OR news group to view
A	ADDRESS BOOK	-	Update address book
S	SETUP	-	Configure or update Pine
Q	QUIT	-	Exit the Pine program

8.8.1 Public Distribution Alias Lists

The DCC has set up some system aliases. An "alias" is just a group of e-mail addresses to which you may refer by a single name. That is, sending e-mail to that alias name causes the message to be sent to every address composing the alias.

To use the aliases, just send mail to <alias>@bio.ri.ccf.org, where <alias> is the name of the alias you wish to use. Currently 18 aliases are defined (see page 41 of the HEMO Study Address Directory for a current listing)

8.8.2 Complete Pine Documentation

THE "COMPOSE MESSAGE" command (available on MAIN MENU, FOLDER LIST, FOLDER INDEX, and MESSAGE TEXT screens) takes you into the Pine message composer and permits you to create and send a new message.

The "FOLDER INDEX" command (available on MAIN MENU, FOLDER LIST, and MESSAGE TEXT screens) takes you to the FOLDER INDEX screen which displays a summary caption for each message in the currently-open folder. One message will be highlighted; this is the "Current" message. The message commands available from this screen (e.g. View, Reply, Forward, Delete, Print, Save, etc) apply to the current message.

The "ADDRESS BOOK" command (available only from the MAIN MENU) takes you to the ADDRESS BOOK management screen. From here, your personal address book(s) may be updated.

To compose a message, select "C" from the Main Menu.

<u>The "To" Field</u>

The address you enter here must be a valid address which is reachable from your site. If it is not, you will get a error message after sending the message.

<u>E-mail Address Format</u>

You may enter a full name and address, a local address that Pine will complete for you, the nickname of someone in an address book, or a local mail alias defined by your system administrator. When you move the cursor out of this field, the nicknames will be expanded to the addresses in your address book, and the local names will be expanded to include the actual user name. You may enter as many addresses as you wish, but they must be separated by commas. You can move around this and other header fields with the arrow keys and use many of the usual composer editing keys.

A valid email address on the Internet has a user name, an "@" sign and then a domain. For example, jsmith@art.nowhere.edu is the email address of a person with the username "jsmith" who has an account with "art.nowhere.edu." The number of segments on the right of the "@" sign can vary depending on how the address is structured for the particular host.

If you are sending to someone on the same system as you are, you can leave the "@" and all the information to its right off of the address, and Pine will fill it in automatically. Sometimes you can also abbreviate the right part of the address if you are at the same domain. When sending message across gateways to other networks, the addresses get more complicated. Ask your local consultant for the correct syntax from your site to the network you are trying to reach.

Description of the FOLDER INDEX Screen

To view message in your current folder, choose "I" for folder index from the main menu. The Folder Index displays the headers or summary information of each message in the current folder. This is useful if you want to quickly scan new messages, or find a particular message without having to go through the text of each message, or to quickly get rid of junk messages, etc. If the list is too long to fit on one screen, you can page up and down in the list with the -/SPACE commands. The current message is always highlighted, and its message number is shown in the status line. Each message line contains the following columns:

STATUS: The markings on the left side of the message tell you about its status. You may see one or more of the following codes on any given message.

- "D" for Deleted. You have marked this message for deletion but not yet expunged the folder.

- "N" for New. You have not looked at the text of the message yet.

- "A" for Answered. Any time you reply to a message it is considered to be answered.

- "+" for direct-to-you. The "+" indicates that a message was sent directly to your account, your copy is not part of a cc: or a mailing list.

- "X" for selected. You have selected the message by using the "select" command. (Some systems may optionally allow selected messages to be denoted by the index list being displayed in bold type.)

- "*" for Important. You have previously used the "Flag" command to mark this message as "important."

NUMBER: Messages in a folder are numbered, from one through the number of messages in the folder, to help you know where you are in the folder.

DATE SENT: The date the message was sent. By default, messages are ordered by arrival time, not by date sent. Most of the time arrival time and date sent (effectively departure time) are similar. Sometimes, however, the index will appear to be out of order because a message took a long time in delivery.

SENDER: The name or email address of the sender. If you are the sender, then the first recipient's name is shown here.

SIZE: The number of parentheses is the number of characters in the message.

SUBJECT: As much of the message's subject line as will fit on the screen.

Description of the Address Book Screen

This screen lets you edit any and all entries in your address book. It also acts as a short-cut for composing messages to people in the address book. When, from this screen, you press "C" for Compose, the message starts "pre-addressed" to whatever address book entry is currently selected.

Pine's address book helps you keep a list of addresses you send mail to so you do not have to remember addresses that are often complex.

Delete, Reply, and Forward

After reading or viewing existing messages in the Folder Index, you will either want to delete, reply, and/or forward the message. To delete the message that is currently being viewed, simply type "D" to mark the message for deletion. When quitting from Pine you will be prompted to confirm the deletion of the market messages.

Replying (R) and Forwarding (F) are your two alternatives for following up on the message you are reading. You would use reply if you want to get email back to the author of the message and/ or the other people who have already seen it. You use forward if you want somebody new to see the message.

In the normal case, the only thing that you must supply when forwarding a message is the name/ email address of the new recipient. Pine will include the text of the forwarded message. Pine will also include any attachments to the message if you have requested them. There is space above the forwarded text for your to include any comments.

When replying, you usually have to answer some questions. If the message is to multiple people and/or specified with a Reply-to: header, then you will have to decide who should get the reply. you also need to decide whether or not to include the previous message in your reply. Some of this is configurable. Specifically, see the include-header-in-reply and include-text-in-reply configuration features.

Additional Help:

For additional help in any of these areas, choose the (context sensitive) help option which is available in every screen in the Pine program.

8.9 Quick Reference Pages

The following pages are copies of the overheads and handouts used at the HEMO training session. You may find it useful to copy some of these and post them near the computer you use for data entry for quick reference.

Data Entry in the HEMO Study

1. At the **%** prompt type **hemo-entry** and press Enter.

2. Type in your Oracle user ID at the **Username**: prompt and press Enter.

3. Type in your Oracle password at the **Password:** prompt and press Enter. You will not see the password as you type it.

4. The Hemodialysis Study Main Menu will be displayed. There are two ways to pick a choice from this menu:

   a. Use down arrow and up arrow and press Enter when your choice is highlighted, OR

   b. Type the number of your choice and press Enter.

5. By choosing "Patient Data Menu" and pressing Enter, a menu of the forms you will need to enter for the study will be displayed.

6. At the Patient Data Menu, type the number of the form you wish to enter and press Enter. (You cannot move through the choices with the arrow keys on this menu.)

Entering Data into the Oracle Form

--> The first field on every form will be the VERIFY field. When entering a form for the first time, just press Enter to advance to the first field on your form.

1. Data is entered into fields on the Oracle form.

2. Field areas should appear as highlighted areas on the screen.

3. When you have entered data for a field, press Enter. You will advance to the next field on the form.

4. The next-to-last line of your screen will be highlighted. This is the **hint** or **message** line. A description of the current field is displayed; messages are also seen here.

5. Fields which will take one of a few values, such as 0 or 1 for No or Yes, frequently have a **List of Values** associated with them.

This is indicated by the word **<List>** on the bottom right of the screen.

To display a List of Values, press the F7 key.

6. After completing the final field displayed on a screen, pressing Enter at the field will display the next screen and put you at the first enterable field of that screen.
7. When you have completed entering data for a form, pressing Enter upon entering the final field of the form will redisplay the beginning of the form.

==> At this time, you should press **F3** to save the data to the database. This is known as the **Commit** key.

Your data is not automatically saved; it is not safely entered until you have pressed the F3 key.

==> It is recommended, though not required, that you press F3 to commit your data after each form you enter.

Upon pressing F3, a message will be displayed that tells you how many "records" were committed. A record is just the information on one form.

8. To skip over a field that is to be left blank, simply press Enter while positioned at that field.

To move back to the previous field, press the **F2** key.

9. At any time you may press **Ctrl**-K to display the meanings of each key. To do so, hold down the Ctrl key (lower left of your keyboard), press the K key, and release both keys.

Verifying Data (Rekey Entry)

1. After you have entered and committed your data, you must enter and commit it a second time. This is known as **rekey entry** or **verification** of the data.

2. Press the **PgUp** key to move to the VERIFY field at the very beginning of the form.

3. Type a V and press Enter. The cursor will move to the ID field of the form. Type in the ID of the form you wish to verify. (You'll see a message at the bottom of the screen that says "Enter a Query").

4. Press Enter until the cursor is at the Date of Visit field. Type in the date of the form.

==> On some forms, this will be some other date, such as date of hospitalization.

Not every form needs such a date to identify it uniquely, such as Forms 1 and 2.

You may also, instead of the date, type in the Visit Type, Week or Month Number, and Day Number.

5. Press the F10 key. The screen will go blank except for the ID and the Visit Type, Week or Month Number, and Day Number.

6. Starting at Namecode, each value you type will be compared to what you typed the first time. When these are not the same, a box will appear in the middle of your screen that says "DISCREPANCY ENCOUNTERED -- Please reenter value." Type in the correct value and press Enter.

7. If what you type agrees with the first time through, that value is restored to the field. Continue with the next field as usual.

9. If what you type in the box does not agree with the first entry, you will be asked to "VERIFY DATA CORRECTION." Type the correct value. This time you must press the **F6** key to signal that this value is the correct one. The F6 is known as the **Accept Change** key.

10. When you have reached the end of the form after typing it in the second time, the cursor will remain at the last field (Certification Number of Person Completing Form). Press F3 to save (commit) the verified data. That data is now officially in the study database.

==> You must be at the last field of the form to commit the data after verifying it.

11. After you have entered and committed your verified data, you may **exit** the form by pressing the **F4** key. You will be returned to the Patient Data Menu.

Common Oracle Error Messages

When Oracle needs to display a message to you, the user, it will display it either:

1: on the second line from the bottom of the screen: the hint line or message line; or

2: it will be displayed in a pop-up message box on your screen.

Some common messages you may see:

"Field must be entered":

That data item cannot be left blank. Supply a value.

"Invalid value for <fieldname>":

That data item is restricted to certain values. Try the F7 key to display a List of those Values.

"Legal characters are 0-9 + and -"

You tried to type letters into a numeric data item field.

"Field is protected against update."

You need to be in change mode. Press the F5 key. If that doesn't work, you're not permitted to change that field.

How to Change Study Data in the Database

To protect the study data from being changed without notice months or years after entry, the DCC uses the following system:

==> Any patient data entered by a center may be changed by that center as much as desired within seven calendar days of the entry of the data.

==> After seven calendar days, the center must submit a Data Inquiry Request to the DCC in order to change the data.

To **change** study data **before the seven day limi**t has passed:

1. Access the form from the Patient Data Menu for which a change is to be made.

2. Retrieve the specific form for the patient and visit to be changed by entering a query.

3. Position the cursor on the field to be changed

4. Press F5 to indicate that you wish to change this data.

5. A pop-up message will tell you "Change Mode Enabled." Alter the the data in that field as desired. Press Enter when finished.

6. Since you have changed this record, you must again save or commit it. Press the F3 to commit this changed data.

To submit a **data inquiry after the seven calendar days:**

First, follow steps 1-4 as above.

5. After pressing the F5 key, another form titled "Submit a Data Inquiry to the DCC" form will be displayed on your screen.

6. Information needed to identify the patient form, usually Patient ID, Visit Type, and Week/Month Number, will be displayed on the screen as well as the name of the field that is to be changed along with its original value.

7. Type in the value you would like for this field and press Enter. Then type in text describing the reason for this request. You may bring up a box in which you may type a longer description by pressing the F8 key. This is known as the Edit key.

8. Press F3 to save (commit) the data inquiry information. If you decide you do not wish to send this inquiry, press F4 instead to exit.

9. You will be returned to the original form. Press F4 to exit to the menu.

10. A report of your request will be sent to the DCC who will then follow through on the modification.

11. A report will be sent to the Clinical Center confirming the actual change made.

Responding to DCC Data Inquiries

In the event the DCC identifies data concerning which we have a question, a DCC Data Inquiry Report will be sent to the Clinical Center. Upon receipt of this report:

1. Investigate the question and determine the response.

2. Access the HEMO Study Main Menu

3. Select the Data Inquiry menu

4. Select the Respond to DCC Data Inquiries item.

5. Press F9 to enter a query.

6. Type in the inquiry number of the inquiry to which you would like to respond.

7. Press F10 (Execute Query). The relevant information, as seen on your DCC Data Inquiry Report, will be displayed

8. Key a new value for the field in question, if appropriate. If the value is not to change, or if the value should become missing, leave this blank. Press Enter.

9. Enter a text explanation of your response. You may press the F8 (Edit) key if you need more space for your reply.

10. Press the F3 key to save (commit) your reply.

11. To respond to another inquiry, repeat from #5. To exit, press the F4 key.

Function and Movement Keys During Data Entry

F2 Go back to **Previous Field**

F3 **Commit** the data (i.e., save)

F4 **Exit** the form

F5 Enter **Change Mode** to change data

F6 **Accept a Change**d value during verification

F7 Show the **List** of possible values for the field

F8 **Edit** a text field

F9 **Enter a Query** to specify a previously entered form

F10 **Execute the Query** started with F9

F11 (Fn F1) **Clear the Field** you're currently in

F12 (Fn F2) **Clear the Form** you're currently entering

--> **Move Right** within the current field
<-- **Move Left** within the current field

Ø Show the **Next Record**
¦ Show the **Previous Record**

PgUp Go up to the VERIFY field

9. ANTHROPOMETRY

9.1 Principles

Anthropometry furnishes measurements of the human body in terms of dimensions of bone, muscle, and adipose (fat) tissue. Anthropometric measurements provide useful indicators of the participant's nutritional status, for purposes of assessing and monitoring nutritional status. In addition, these measurements will provide reference data for a population on dialysis. For these reasons, they are valuable for both clinical and research purposes in the HEMO Study.

The dialysis unit dietitian, who is also certified for anthropometric measurements, plays a critical role in quality assurance for taking anthropometric measurements, and as a back-up for the HEMO grant-funded dietitian.

9.2 Which Measures Are to Be Taken

The following measurements will be taken, using standardized procedures, by a dietitian certified in anthropometry:

Dry (post-dialysis) weight

Stature

Knee height

Mid-arm muscle circumference (taken twice)

Elbow breadth

Calf circumference (taken twice)

Skinfolds: triceps, biceps, subscapular (taken twice)

The body measurements are always taken after dialysis at what is known as the dry weight condition.

9.3 How Many Times per Patient per Year

For data collection purposes in the study, a complete set all of the measurements described in 9.2 is collected at Baseline and annually by the HEMO grant-funded dietitian.

Other measurements, such as dry weight post dialysis, are collected routinely after each dialysis session by the dialysis center dietitian. If an action item is triggered because of

declining body weight, the HEMO grant-funded dietitian initiates the intervention, after consultation with the dialysis center dietitian and the HEMO Study physician.

9.4 Instructions for Measurements

9.4.1 Who Takes Anthropometric Measurements

Only certified examiners take anthropometric measurements for the HEMO Study.

The HEMO grant-funded dietitian is certified to take anthropometric measurements and is responsible for carrying out the procedures. The HEMO grant-funded dietitian is also responsible for calibrating instruments. For weights taken at other times post dialysis, the HEMO grant-funded dietitian or the dialysis center dietitian may take the measurement. In all cases, the procedures specified in the protocol should be observed. These procedures are standard procedures and assure that data collected will be of high quality.

9.5 Certification Plans

Certification will be provided to those who successfully complete the dietitian workshop and the practice and certification measurement sessions. Certification is contingent upon successful updates of the Examiner Reliability Log, and on the individual examiner's agreement to follow appropriate procedures.

9.5.1 Initial Certification

Certification is essential because examiners must take measurements in an accurate and standardized fashion. Certification depends on three criteria: 1) attendance at the training session at the dietitians' workshop training session; 2) establishment of baseline reliability between observers at the workshop; and 3) agreement to follow procedures for taking anthropometric measurements as specified in the Manual of Operations for the HEMO Study.

At the training for the HEMO Study, the anthropometry consultant will present a workshop consisting of a demonstration and supervised practice in taking anthropometric measurements. The major concern is to ensure that the measurement technique is standardized across centers. The practice session will also establish baseline reliability levels of the

individuals who will be doing the measurements. Examiners who are able to perform the measurements reliably and validly will be certified.

9.5.2 Continuing Certification

Observer reliability is a major concern in all studies that use anthropometric measurements for guiding clinical actions. Therefore, continuing certification is based on continued demonstration of acceptable reliability between observers at the same center. At each center, the involved observers who are taking most of the measurements should double-measure on one subject every two months, so that inter-observer reliability can be checked. Summaries of these data are forwarded to the anthropometry consultant for review at the end of each grant year.

Either the certified HEMO grant-funded dietitian or the certified dialysis unit dietitian may take anthropometric measurements of weight associated with action items.

9.6 Role of the Anthropometric Examiners and Recorders

9.6.1 Role of HEMO Grant Funded and Dialysis Center Dietitian

The collection of anthropometric data is most easily done if two people help each other. The HEMO grant-funded dietitian is the examiner; the other person is the recorder. The certified HEMO grant-funded dietitian is always the examiner for Baseline and Follow-Up measurements; the recorder may be another dietitian or another person on the clinical staff.

The examiner (HEMO grant-funded dietitian) is the person responsible for positioning the patient, taking each measurement, and saying the measurement value aloud to the recorder for the value to be recorded. The recorder repeats the number, enters it onto the anthropometry form, and says the name of the next measurement (replicate) or next site of measurement listed on the form. The examiner should keep the measuring instrument set on the patient until the recorder repeats the number.

The recorder is responsible for ensuring that correct data are entered onto the form. The recorder has the role of assisting the examiner in obtaining correct measurements. This

includes helping the examiner to position the subjects correctly, and checking to make sure that the correct position is obtained and maintained.

9.6.2 Methods for Examination

The examiner will record values for a complete set of measurements. The examiner will then repeat the set of measurements. The pairs of values for those measurements will be reviewed to see if the differences exceed set limits. If a limit is exceeded for a measurement, the examiner will record a second set of values for that measurement.

There are no penalties for exceeding measurement limit values. These limits are there to help prevent recording errors and to see that additional measures are collected from certain subjects. It will generally be more common to repeat measurements from obese subjects.

9.7 Measuring and Recording Guidelines

Body measurements are usually taken on the right side of the body. However, some measurements may be taken on the left side of the body because of casts, amputation, or other reasons (including dialysis on the right arm). Under such circumstances, the left arm or leg can be used. When this occurs, this is noted and the reason is recorded on the anthropometry form.

All measurements, except for skinfolds, should be taken to the nearest tenth of a centimeter or l.0 millimeter. Skinfold measurements are taken to the nearest 0.1 millimeter. After each measurement is taken, its value is recorded in the appropriate space. If a recorder is present, the recorder should repeat the value that was called aloud by the examiner.

The set of measurements is repeated for each subject. If the two values for a measure differ by more than the acceptable amount, two additional measures are taken and recorded. The acceptable limits for differences between measurements are as follows:

Weight: Within 200 gm

Stature: Within l.0 cm

Elbow Breadth: Within 0.2 mm

Arm Circumference: Within 0.4 cm

Calf Circumference: Within 0.4 cm

Skinfolds: Within 4.0 mm

Knee Height: Within 0.5 cm

9.7.1 What Equipment is Used

9.7.1.1 Rationale for Standardizing Equipment

In order to ensure that standardized methods of taking physical measurements are used at each center, standard equipment for anthropometry is used in the HEMO Study, and measurements are taken by certified, trained personnel who are checked periodically for reliability.

9.7.1.2 Measurements and Equipment Employed

This equipment is furnished to each Clinical Center for making study-related measurements.

9.7.1.2.1 Elbow Breadth

Equipment: Small Sliding Caliper: Holtain Bicondylar Vernier Calipers

Purpose: Elbow breadth provides a very rough approximation of frame size. The measurement is taken twice, in centimeters.

Calibration: Calibrate using the calibrations step wedge every 3 months, using the wedge from 10-50 mm where appropriate. Calibrate the calipers every 3 months and record in the Equipment Calibration Log.

Method:

Ask the patient to stand erect, with feet together, facing the examiner.

Ask him to extend his or her right arm forward until it is perpendicular to the body.

Flex the individual's right arm so that the elbow forms a 90 degree angle with the fingers

pointing up, and the posterior part of the wrist is toward the examiner.

Hold the small sliding caliper (the Holtain Bicondylar Vernier calipers) at a 45 degree angle to the plane of the long axis of the upper arm, and find the greatest breadth across the epicondyles of the elbow.

Measure to the nearest 0.1 cm with the calipers at a slight angle (this may be necessary because the medial condyle is more distal than the lateral condyle). Record the measurement.

Repeat the measurement and record it.

If the two measurements differ by more than 0.2 mm, take two more measurements and record them.

9.7.1.2.2 Stature

Equipment: Accustat Stadiometer (Height Board)

Purpose: For measurement of stature

Calibration: Calibrate every three months as follows.

1) Place the horizontal bar of the stadiometer firmly against the top of each calibration rod (the first calibration rod is a piece of electrical conduit pipe 145 cm long; the second rod is 185 cm long)

2) Record the length of calibration rod #1 and #2 in the equipment calibration log for future reference. Note: if the rods you receive are not exactly 145 and 185 cm, record the actual length in centimeters of the rods in the calibration log.

3) Record the actual measurement with calibration rod #1 (145 cm) and calibration rod #2 (185 cm).

Method:

Ask the patient to stand with his or her back against the stadiometer, with heels together, and both heels touching the board.

Check to make sure that the patient's back (the scapulae) and buttocks are in contact with the board. Ask him or her to stand erect, naturally and comfortably. The back of the patient's head, the scapulae, the buttocks, and the patient's heels should be in vertical contact

with the board. (If the patient's buttocks are so large that the back is arched, then the buttocks and heels should be in contact with the board and the person stands erect from the waist up).

Check to make sure that the patient is standing erect, with no slouching. The heels should be together, with the medial borders of the feet at an angle of about 45 degrees from each other, with the weight equally distributed on each leg.

Check to make sure that the head is in the "Frankfort Horizontal Plane." Ask the patient to look straight ahead. A line running from the opening of the ear to the corner of the eye should be parallel to the floor.

Bring the movable headboard down firmly on top of the patient's head. Make sure that the headboard maintains a right angle and makes contact with the top of the scalp. If this is not possible remove or alter the patient's hairdressing until you can make contact with the head of the scalp. (Note: if the examiner is short, a small stepladder may be helpful to stand on to adjust the headboard).

Ask the patient to inhale deeply, and not to move his /her heels off the floor or otherwise alter position. Take the stature measurement before the patient exhales. Record the measurement.

Repeat the procedure and record the second measurement.

Check to see if the two measurements are within 1.0 cm of each other. If they are not, take two more measurements and record them.

9.7.1.2.3 Knee Height

Equipment: Ross Knee-Height Calipers

Purpose: Provides an approximation of stature, when reasons such as scoliosis or amputation prevent a stature measurement.

Calibration: Calibrate every three months.

Method:

Request the patient to sit on an examination table with his/her legs dangling.

Assist the patient to get onto the examination table if necessary.

Place the fixed blade of the large sliding caliper under the patient's heel on his right leg just below the lateral malleolus of the fibula.

Squat and raise the patient's leg so that the knee and ankle are both at a 90 degree angle. Do this by resting the patient's foot in the palm of your hand.

Place the movable blade of the caliper on the anterior surface of the right thigh, above the condyles of the femur, about two inches above the patella. Hold the shaft of the caliper parallel to the shaft of the tibia so that the shaft of the caliper passes over the lateral malleolus of the fibula and just posterior to the head of the fibula. Apply pressure to compress the tissue.

Ask the recorder to check the positioning of the leg and the caliper. Read the knee height to the nearest 0.1 cm. Check to see if the two measurements are within 0.5 cm of each other. If they are not, take two more measurements and record them.

9.7.1.2.4 Calf Circumference

Equipment: Steel measuring tape

Purpose: Index of fat-free mass

Calibration: Not applicable

Method:

The patient should be sitting with his/her right leg bent 90 degrees at the knee. The leg may be hanging off the side of a table, or if the patient is sitting in a chair, the right foot should be flat on the floor, with the right shoe removed. There should be no weight or force on the right leg.

Place the tape snugly around the right calf a few inches below the knee. Slowly slide the tape down the calf, noting the change in the measurement readings. These readings will increase in value and then start to decrease in value. The calf circumference is taken at the largest circumference of the calf. When the measures on the tape start to decrease, move the tape back up the calf to locate its maximum circumference.

Make sure the tape is not so tight that it causes dimpling of the skin. Record the measurement to the nearest millimeter.

Check to make sure that the two measurements are within 0.4 cm of each other. If they are not, take two more measurements and record them.

9.7.1.2.5 Weight

Purpose: Obtain a measurement of weight

Calibration: Calibrate every three months using standard 10 kg diver's weights. Place the weights on the center of the scale platform, where the patient stands, one weight on top of the other. Record the reading on the scales in the Equipment Calibration Log book. If the calibration is off by more than 0.2 kg (200 gm), ask your dealer to recalibrate the scales. Scales should not be moved. If they are moved, the scales will need to be recalibrated. Be sure that the scale is on a level, hard surface. Do not put the scales on carpeting. If the surface is carpeted, linoleum or other hard material should be placed under the scales and on top of the carpet.

Method:

Prepare the scales on each day they are used. Zero the horizontal beam. Check the scales to make sure they are balanced at zero every morning. To do this, remove everything from the scale. Place the main and fractional sliding beam weights directly over their respective zeroes, and, using the adjustment screws, move the adjustable zeroing weight until the beam is in zero balance. The measurement is always taken after dialysis, at what is the dry weight.

Ask the patient to remove his/her shoes and to put on a disposable gown over his/her underwear for the measurement.

Ask the patient to stand in the center of the scales and not to touch or support him- or herself on anything. Ask the patient to stand with his/her weight equally distributed on both feet.

Take the measurement and record it.

Ask the patient to step off the scales.

Reset the scales to zero.

Reposition the patient and take the measurement again. Record it.

Check to see if the two measurements agree within 200 gm. If they do not, take two more measurements and record them.

Leave the scales with the weights at zero when they are not in use.

9.7.1.2.6 Upper Arm Length (for Triceps and Biceps Skinfolds):

Equipment: Ross InsertTape

Purpose: The measurement is necessary to obtain triceps and biceps skinfolds.

Method:

Ask the patient to stand erect with his/her feet together. Stand behind the patient.

Ask the patient to flex his/her right arm 90 degrees at the elbow with the palm facing up.

Mark the uppermost edge of the posterior border of the acromion process of the scapula with a cosmetic pencil.

Hold the insertion tape at this point and extend the tape down the posterior surface of the arm to the tip of the olecranon process (the bony part of the mid-elbow). Keep the tape in position and find the distance halfway between the acromion and the olecranon process that is the midpoint of the upper arm, as indicated by the black triangle on the tape.

Mark a (+) at the midpoint on the posterior surface (back) of the arm.

Mark another (+) at the same level on the anterior (front) of the arm.

9.7.1.2.7 Mid-Arm Circumference

Equipment: Ross InserTape

Purpose: Necessary measurement for obtaining skinfolds

Calibration: Not applicable

Method:

Ask the patient to stand with his/her elbow relaxed, with the right arm hanging freely to the side.

Place the tape around the upper arm, directly over the pencil mark at the midpoint on the posterior aspect (back) of the upper arm. Keep the tape perpendicular to the shaft of the upper arm.

Pull the tape just snugly enough around the arm to ensure contact with the medial side of the arm and elsewhere. Make sure that the tape is not so tight that it causes dimpling of the skin.

Record the measurement to the nearest millimeter.

Check to see if the two measurements are within 0.4 cm of each other. If they are not, take two more measurements and record them. Note: When threading the narrow end of

the tap through the slots on the thick end of the tape, be sure to end up with the tape visible when it crosses the measurement line. Also, note that if the tape is threaded through backwards, the numbers are not visible.

9.7.1.2.8 Skinfolds

Equipment: Holtain Skinfold Calipers

Purpose: Measurement of biceps, triceps, and subscapular skinfold thicknesses.

Calibration: Calibrate the Holtain calipers every three months using the step wedge standard. First, zero the calipers. Place the step wedge standard between the caliper arms at each of the four steps in the wedge, and check that the reading on the scale corresponds to the standard measurement. Record the measurement taken at each step in the Equipment Calibration Log under the appropriate heading. An identical calibration should be done on a spare set of skinfold calipers if available, and these should also be recorded on a separate calibration log sheet labeled Instrument #2.

Method: General

Measure the skinfolds using the Holtain skinfold caliper. Take the measurement on the right side of the body. Grasp the fold of skin and underlying subcutaneous adipose tissue gently between the examiner's left thumb and forefingers. The amount to grasp will depend upon the thickness of the subcutaneous adipose tissue. Grasp enough skin and adipose tissue to form a distinct fold that separates from the underlying muscle. The sides of the skinfold should be roughly parallel.

Grasp the skinfold 2.0 cm above where the measurement is to be taken and hold the fold gently with the thumb and forefinger. Place the jaws of the calipers at the marked level, perpendicular to the length of the fold. Release the caliper tension but continue to hold the skinfold. After about three seconds, record the skinfold thickness to the nearest 0.1 mm. If skinfolds are too tight to be measured, so that the fold cannot be picked up for measurement, use the code for “skin too tight” (60.0) and record it in the space for that skinfold on the anthropometry form. If the skinfold is too loose to be measured, use the code for “skin too loose” (70.0) and record it in the space for that skinfold on the anthropometry form. If the skinfold is too large to measure, in which the skinfold is above the measurable limits of the

calipers, use the code for “too large to measure” (80.0) and record it in the space for that skinfold. Check to see if the two skinfold measurements are within 4.0 mm of each other. If they are not, take two more measurements and record them.

Method: Triceps Skinfold

Ask the patient to stand with his/her feet together, shoulders relaxed, and arms hanging freely at the sides. Stand to the patient's right side. Locate the point on the posterior surface of the right upper arm in the same area as the marked midpoint for the upper arm circumference.

Grasp the fold of skin and subcutaneous adipose tissue gently with your thumb and forefingers, approximately 1.0 cm above the point at which the skin is marked, with the skinfold parallel to the long axis of the upper arm. The jaws of the calipers should be placed at the level that has been marked on the skin with the marking pencil. The jaws should be perpendicular to the length of the fold, and the skinfold thickness measured to the nearest 0.1 mm, while the fingers continue to gently hold the skinfold gently.

Method: Biceps Skinfold

Follow the same procedure as for the triceps skinfold. The measurement of the biceps skinfold is at the front of the upper arm (instead of the back, as with the triceps). The level is the same as for the triceps and arm circumference, and the location is in the midline of the anterior part of the arm.

Ask the patient to stand with his/her feet together, shoulders relaxed, and arms hanging freely at the sides. Stand behind the patient's right side. Rotate the right arm so that the palm is facing forward. Locate the point on the anterior surface of the right upper arm in the same area as the marked midpoint for the upper arm circumference.

Grasp the fold of skin and subcutaneous adipose tissue on the anterior surface of the upper arm, in the midline of the upper arm, and about 1.0 cm above the marked line on the middle of the arm. Measure the skinfold thickness to the nearest 0.1 mm while you continue to hold the skinfold with your fingers.

Method: Subscapular Skinfold

Ask the patient to stand erect, with relaxed shoulders and arms.

Open the back of the examination gown or garment. Palpate for the inferior angle of the right scapula.

Grasp a fold of skin and subcutaneous adipose tissue directly below (1.0 cm) and medial to the inferior angle. This skinfold forms a line about 45 degrees below the horizontal, extending diagonally toward the right elbow.

Place the jaws of the caliper perpendicular to the length of the fold, about 1.0 cm lateral to the fingers, with the top jaw of the caliper on the mark over the inferior angle of the scapula.

Measure the skinfold thickness to the nearest 0.1 mm while the fingers continue to hold the skinfold. Record the measurement.

9.7.1.2.9 Adjusted Body Weight

Purpose: This is a statistic derived from anthropometric measurements after adjustment against normative tables. Its purpose is to provide a more suitable weight on which to base a prescription for protein and energy than would use of unadjusted weight for height data alone when a patient is less than 90% or greater than 120% of standard body weight, using the l979 NHANES data-based tables.

9.7.1.2.10 Adjustments for Amputees in Weight

Special adjustments will not be made for amputees in regard to weight. Existing standards for body weight and adjusted body weight, as stated above in sections 9.8.1.2.5 and 9.8.1.2.9 respectively, will apply for all study patients. The rationale is as follows:

Below the knee: Differences are small in weight and the effect on mobility are also quite low.

Above the knee: The RMR of a person missing a leg or legs should be slightly lower, but cost of movement is higher with one leg, probably lower with two legs gone since the person is likely to be in a wheelchair. However, it is unknown how best to estimate how much of the cost of activity is going to be affected or what the cost of loss of RMR will be due to the missing limb. Since there is no means of adjusting that has been validated (most are simply rules of thumb) The decision has been made to forego special adjustments for amputees.

9.7.1.2.11 Dry (post Dialysis) Weight

Purpose: Obtain a reliable healthy weight for the dialysis patient

Calibration: See weight

Reliability: Within 200 gm (see weight)

Method:

1) To minimize variability in measurement of weight, make sure that the patient is only lightly dressed; measure patients only in light clothing and without shoes.

2) Wait until the patient has finished his/her dialysis session; take dry weights post dialysis. Dry weight is defined as the weight below which the patient develops symptomatic hypotension or muscular cramps in the absence of interdialytic weight gain equal to or greater than 3 kg; edema not attributable to hypoalbuminemia, lower extremity venous insufficiency, or other anatomic causes; or symptomatic hypotension induced by other identifiable causes such as the use of antihypertensive medications immediately before hemodialysis or arrhythmias. Mitigating factors, such as the presence of significant cardiovascular or peripheral vascular disease, should be taken into account when estimating the dry weight. Attempt to keep the time of day of the measurement relatively constant, but in any event it should *always* be post dialysis.

The patient is weighed on a calibrated clinical scales. In order to calibrate the clinic scales, zero the horizontal beam with all materials off the scales and all the sliding beam weights to zero. Adjust the screws and the zeroing weight until the beam is balanced at zero.

9.7.1.2.12 Assesment of Edema

Method: Inspect the extremeties for edema, often manifested as a change in the usual contour of the leg. Press your index finger over the bony prominence of the tibia or medial malleolus for several seconds. A depression that does not rapidly refill and resume its original contour indicates pitting edema, which is not usually accompanied by thickening or pigmentation of the overlying skin.

Grading Scale: The severity of edema may be characterized by grading 1+ through 4+. Any concomitant pitting can be mild or severe, as evidenced by the following:

1+: slight pitting, no visible distortion

2+: a somewhat deeper pit than in 1 +, but again no readily detectable distortion

3+: the pit is noticeable deep; the dependent extremity looks fuller and swollen

4+: the pit is very deep,lasts a while, and the dependent extremity is grossly disfigured

9.8 Data Collection Form

Use Form 29, which is in the forms book for the HEMO Study.

9.9 Use of Anthropometry Data: Analysis Plans (Committee)

The anthropometric data will be used to describe groups of subjects with respect to their body mass index, stature, relative fatness, etc. For individuals, weight loss also signals the need for action to identify the causes of weight loss, and to assist the patient to gain weight if changes are correctable by nutritional means.

If skinfolds are too tight to be measured, so that the fold cannot be picked up for measurement, use the code for “skin too tight” (60.0) and record it in the space for that skinfold on the anthropometry form. If the skinfold is too loose to be measured, use the code for “skin too loose” (70.0) and record it in the space for that skinfold on the anthropometry form. If the skinfold is too large to measure, in which the skinfold is above the measurable limits of the calipers, use the code for “too large to measure” (80.0) and record it in the space for that skinfold.

9.10 Counseling Patients Regarding Anthropometric Measurements

Most patients are very interested in their anthropometric measurements. The goals in our study are to provide information to patients that does not bias their behavior during Baseline or Follow-up, but that alters when an action item (either low serum albumin or low weight) has been reached.

For Baseline anthropometric measurements, telling the patient his/her frame size, height, and weight is reasonable. Further interpretation of data, such as providing percent body-fat estimates from skinfolds, etc., is not advised. Simply provide the raw data if asked and provide the general explanation that the measurements are collected as another way of describing patients in the study and monitoring nutritional status. Mention also that skinfolds and arm-circumference measures are not sensitive enough to detect short-term changes in individuals, and that the data will be used primarily to evaluate changes in groups. Assure the patient that if changes in the measurement require alteration of his/her diet or dialysis schedule, the doctor and you will be sure to discuss it with him/her.

9.11 Equipment Calibration

The anthropometric measurements must be taken with the same set of instruments at each study center that are calibrated on a regular basis. The calibration schedule is the same for all instruments -- once every three months.

Mark each piece of equipment with a "set" number to identify that piece readily. Calibrate each piece of equipment and enter the data for each set on the attached logs.

9.12 Ordering Anthropometric Equipment

The Clinical Centers have been provided with equipment ordered by the Data Coordinating Center. If equipment is lost, damaged, or stolen, order replacements directly from these manufacturers:

For : Accustat Stadiometer $95.00 (03/97)

from

Cloverline
2431 W. Irving Park Road
Chicago, Illinois 60618
800-542-7322
FAX 312-509-9500

For: Holtain Skinfold Calipers Model #610, $459;

Bicondylar Vernier calipers Model #604, $415;

Calibration block Model #121, $16

from

Seritex Inc.
One Madison Street
East Rutherford, NJ 07073
201-472-4200
FAX 201-939-3468

For: Steel Tapes -- $10.66
(W606PM, diameter tape)
Cooper/Lufkin (#6822813)

from

McMaster-Carr Supply Company
PO Box 4355
Chicago, IL 60680

Knee-height calipers and InserTapes are supplied courtesy of Ross Laboratories.

CALIBRATION LOG

Instrument: Holtain Bicondylar Vernier Calipers

Calibration Method: Use step wedge at each of the five steps (10-50)

Frequency: Once every three months

Set 1:

Date	**Initials**	**Step 1** **10 mm**	**Step 2** **20 mm**	**Step 3** **30 mm**	**Step 4** **40 mm**	**Step 5** **50 mm**

Set 2:

CALIBRATION LOG

Instrument: Holtain Skinfold Calipers

Calibration Method: Every two weeks

Frequency: Once every three months

Set 1:

Date	**Initials**	**Step 1** **10 mm**	**Step 2** **20 mm**	**Step 3** **30 mm**	**Step 4** **40 mm**	**Step 5** **50 mm**

Set 2:

CALIBRATION LOG

Instrument: Ross Knee-Height Calipers

Calibration Method: Record date and initials and then the measurement.

Frequency: Once every three months

Set 1:

Date	**Initials**	**Step 1** **10 mm**	**Step 2** **20 mm**	**Step 3** **30 mm**	**Step 4** **40 mm**	**Step 5** **50 mm**

Set 2:

CALIBRATION LOG

Instrument: Stadiometer (Measuring Board)

Calibration Method: With the two calibration rods (145 cm and 185 cm).

Frequency: Once every three months.

Set 1:

Date	**Initials**	**Rod 1 (145) cm**	**Rod 1 (145) cm**	**Rod 2 (185) cm**	**Rod 2 (185) cm**

Set 2:

CALIBRATION LOG

Instrument: Scales

Calibration Method: Using Standard Weights

Frequency: Once every three months

Set 1:

Date	**Initials**	**Weight 50#**	**Weight 50#**

Set 2:

10. PROCESSING SPECIMENS FOR THE CENTRAL LABORATORY

Contents:

10.1 Introduction

Chapter 10 includes brief instructions for processing and shipping blood and urine and for ordering additional supplies. Forms and reports are also described.

10.2 Urine-Collection Procedures

START-UP PROCEDURE

Give the patient a jug at the end of a dialysis session. Describe the collection procedure to the patient, as follows.

COLLECTION PROCEDURE

See also section 4.7, Measurement of Residual Renal Function

1. The urine collection should begin any time after that session. Consider the morning before the day of the next dialysis session.

2. The patient should record the date and time of the first urine specimen. TELL THE PATIENT TO THROW THAT FIRST SPECIMEN AWAY.

3. Have the patient collect each subsequent urine specimen and pour it into the plastic container provided.

4. Have the patient record the date and time the urine collection is completed. Tell the patient to bring it to his or her next session, which must be a kinetic modelling session. The collection must be 24 hours or more.

5. Supply the start and stop times of urine collection and the volume on Form 9.

10.3 Blood Preparation Procedures

START-UP PROCEDURE

1. Freeze Super Ice the day before blood draw.

2. Call the courier the first thing on the day of the draw.

3. Fill out Form 9 requisition/mailing form appropriately.

4. Affix bar-code numbers to test tubes and requisition.

BLOOD PREPARATION PROCEDURE

1. Draw blood samples following the directions in Chapter 4 of this Manual, filling tubes completely.

2. Place SST tubes upright, allowing blood to clot at least 30 minutes (but no longer than 1-1/2 hours).

3. Centrifuge SST tubes at high speed (2000-3000 RPM) for 20 minutes.

4. Place all blood sample tubes in specimen tray.

5. Verify that all blood sample bar-code numbers on tubes and patient requisition/mailing Form 9 match.

6. Place specimen tray in bag, and requisition/mailing Form 9 in bag pouch.

7. Keep blood samples cool, using refrigeration.

10.4 Packaging Procedure

1. Fold shipping box.

2 Package blood sample(s) in shipping box with Form 9.

3. Fill out batch header and place in box.

4. Place Super Ice on box shelf.

5. Tape box with LifeChem tape.

6. Affix completed airbill label to box (if FedEx shipper).

7. Write name and address on box.

10.5 Asking Questions or Ordering Additional Supplies

Questions regarding procedures or supplies should be directed to Felix Wawra, Project Coordinator for the HEMO Study for LifeChem Laboratory Services. Felix can be reached at 1-800-205-5005, extension 5573.

10.6 Forms and Reports

Use Form 9 (NCR paper) to enter the mailing form; this form must be key-entered. (As noted, a copy of the mailing form must be sent with the specimens to the Central Biochemistry Laboratory. The original can be kept at the Clinical Center.)

The DCC will e-mail biochemistry reports for all protocol measures of albumin and Beta 2 microglobulin.

The DCC will report when a serum albumin action item has been reached.

10.7 Process for Doing the Split-Sample QC

1. Attempt to draw the bloods (predialysis and full-flow post-dialysis) on a non-kinetic modelling day for the first patient listed above. If the first patient is not feasible then go to the next one on the list. You must draw bloods from one of the three patients listed. (Be sure to inform the patient that additional bloods will be drawn on the non-modelling day.)

2. Draw the blood into 2 separate tubes for pre and post (two tubes for predialysis and two tubes for postdialysis bloods).
   NOTE: Since there may be a slight difference between the two post specimens, it is important to be consistent about this ordering, therefore always label the first tube with the real patient ID and namecode and the second tube with the QC ID and namecode.

3. Label one set (pre and post) of tubes and complete a Form 9 with the QC ID and QC namecode indicating a 2-BUN session.

4. Label the other set of tubes and complete a Form 9 with the real patient ID and Namecode indicating a 2-BUN session.

5. Send the real patient labeled tubes to the CBL with your normal batch of samples. Refrigerate and send the QC sample on the following day.

6. Complete a Form 25 (QC Matching Form) and key-enter immediately.

7. DO NOT complete a Form 5 for this non-modelling session.

8. Also, DO NOT key-enter either of the Form 9's (only mail the copy to the CBL and keep the other for your records).

If you have any questions, please contact the DCC.

APPENDIX 10.1 Baseline

The schedule of Baseline blood CBL measurements is provided below. The current plan is to discontinue the BCG and BCP samples after several months.

Recall that in addition to the blood measurements, urine samples will be drawn for determination of residual renal function in Weeks B1 or B2 for some patients, as defined by the protocol.

Schedule of Baseline Blood Draws

	B1	B2	B3	B4	B5	B6	B7
ALBUMIN							
Nephelometry	x	x					
BCG	x	x					
BCP	x	x					
BUNs							
Pre	x	x		x	x	x	x
Post-Inlet Full				x			
Post-Inlet Slow	x	x		x	x	x	x
AFTERTHOUGHT (5 ml)		x*					
CRP	x						

Notes: B1 refers to the Baseline Week 1, B2 to Baseline Week 2, and so on. The Pre and

Post-Inlet Slow samples may be drawn weekly after B7 if necessary to demonstrate achievability of the high eKt/V goal.

The majority of patients (at least 85%) should not require modeling after B6.

*The afterthought specimen should be drawn at the same time as the pre-dialysis BUN at either the Week 1 or the Week 2 modelling session.

Appendix 10.2 Follow-up Schedule of CBL Measurements

Month	Measurements
F1	Pre and post BUN, pre Albumin (nephelometry), pre and post Beta-2 (high and low flux)
F2	Pre and post BUN, pre Albumin (nephelometry), pre and post Beta-2 (high flux)
F3	Pre and post BUN, pre Albumin (nephelometry), CRP
F4	8 BUNs as specified in protocol, pre Albumin (nephelometry), pre- and post Beta-2, (high-flux - and every two months thereafter) Afterthought sample (5 ml)
F6	CRP
F5-F11	Pre and post BUN, pre Albumin (nephelometry)
F9	CRP
F12	Pre Albumin (nephelometry), pre- and post Beta-2, (high and low flux) Afterthought sample (5 ml), CRP
F13-17	Pre and post BUN, pre Albumin (nephelometry)
F15	CRP
F18	Pre and post BUN, pre Albumin (nephelometry), pre and post Beta-2 (high flux), CRP
F19-23	Pre and post BUN, pre Albumin (nephelometry)
F21	CRP
F24	Pre Albumin (nephelometry), pre- and post Beta-2, (high and low flux) Afterthought sample (5 ml), CRP
F25-29	Pre and post BUN, pre Albumin (nephelometry)
F27	CRP
F30	Pre and post BUN, pre Albumin (nephelometry), pre and post Beta-2 (high flux), CRP
F31-F35	Pre and post BUN, pre Albumin (nephelometry)

F33	CRP
F36	8 BUNs as specified in protocol, pre Albumin (nephelometry), pre- and post Beta-2, (high and low flux) Afterthought sample (5 ml), CRP
F37-41	Pre and post BUN, pre Albumin (nephelometry)
F39	CRP
F42	Pre and post BUN, pre Albumin (nephelometry), pre and post Beta-2 (high flux), CRP
F43-47	Pre and post BUN, pre Albumin (nephelometry)
F45	CRP
F48	Pre Albumin (nephelometry), pre- and post Beta-2, (high and low flux) Afterthought sample (5 ml), CRP
F49-53	Pre and post BUN, pre Albumin (nephelometry)
F51	CRP
F54	Pre and post BUN, pre Albumin (nephelometry), pre and post Beta-2 (high flux), CRP
F55-59	Pre and post BUN, pre Albumin (nephelometry)
F57	CRP
F60	Pre Albumin (nephelometry), pre- and post Beta-2, (high and low flux) Afterthought sample (5 ml), CRP
F61-65	Pre and post BUN, pre Albumin (nephelometry)
F63	CRP
F66	Pre Albumin (nephelometry), pre- and post Beta-2, (high flux), CRP
F69	CRP
F67-71	Pre and post BUN, pre Albumin (nephelometry)
F71	CRP

In addition to these measurements, there will be occasional special 6-BUN sessions for troubleshooting purposes. We will also be arranging for some split sample external quality control.

11. OUTCOME COMMITTEE MANUAL

Pages 11.2 through 11.36 include copies of practice vignettes, the final practice vignette classifications chart, a letter from Dr. Levey assigning classification questions and discussion leaders, rules for classification of deaths, and minutes of the committee's calls of 4/11/95, 4/25/95, and 5/2/95.

Frank Albers, MD
Practice Vignettes

Scenario 1

vas a 54-year-old black female with ESRD due to diabetes who was admitted after becoming acutely unresponsive one hour into a scheduled hemodialysis session. There was no hypotension, overt seizure activity, nor evidence of arrhythmia. Prior hemodialysis sessions were unremarkable. The patient had longstanding hypertension and type II diabetes complicated by retinopathy, peripheral neuropathy, and gastroparesis. She had a past left hemispheric CVA with resultant dense right hemiplegia. Most recently she had failure to thrive with a decreasing albumin level. On admission one month earlier, the patient was found to have a total occlusion of the subclavian vein ipsilateral to her peripheral AV graft, and a temporary dual lumen hemodialysis catheter was placed, The hospitalization was complicated by Staph aureas bacteremia, and the patient was still receiving vancomycin therapy. With the current admission, the patient was unresponsive and had flaccid hemiplegia on the left (previously unaffected) side. Heat CT and brain MRI showed no acute changes. Twenty-four hours after admission, the patient became hypotensive. Her antibiotic therapy was broadened, and the hypotension resolved with intravenous fluids. She had no improvement in her neurologic status over the ensuing 48 hours. Dialysis was withdrawn and the patient received conservative therapy. She died seven days after admission. No autopsy was obtained.

Scenario 2

was a 66 year old black female with a history of diabetic nephropathy, ESRD on hemodialysis, type II diabetes, hypertension, resected mucinous breast carcinoma, coronary artery disease, and peripheral vascular disease who was admitted for a left foot lesion and cellulitis. She was treated initially with parenteral antibiotics and local therapy, but the foot became gangrenous requiring a left BKA. She tolerated this procedure well but postoperatively the patient developed ischemic changes in the right foot prompting a BKA of this limb as well. After the second operation, the patient developed mental status changes. Brain CT raised the possibility of pontine infarct. There was slow improvement in the patient's mental status when she developed pronounced hematochezia, requiring 24 units of PRBC's over the ensuing days. The developed progressive deterioration in her mental status. After discussion with the patient's family a "do not resuscitate" status was instituted and dialysis was withdrawn. The patient died 45 days after admission, 7 days after hemodialysis was stopped. Autopsy showed a small resolving pontine infarct, old lacunar infarcts, three vessels coronary artery disease. There were no gastrointestinal lesions nor was there evidence of residual breast cancer. The pathologist felt the immediate cause of death was persistent gastrointestinal exsanguination.

Scenario 3

was a 39 year old black male with ESRD due to malignant hypertension. One year ago the patient was admitted in hypertensive crisis with acute renal failure and mental status changes. Brain CT showed white matter lucencies and ventricular narrowing consistent with cerebral edema. It was felt the patient had hypertensive encephalopathy. He did not recover renal function and was stated on maintenance hemodialysis. The patient tolerated hemodialysis well with blood pressure controlled on minimal antihypertensive agents. He was compliant with therapy and required no further hospitalizations. Two weeks prior to his demise, he developed problems with intraradialytic hypotension that recurred sporadically despite an increase in his dry weight and a reduction in antihypertensive agents. Physical examination and laboratory data were unremarkable. CXR showed cardiomegaly and EKG demonstrated only LVH with strain, both unchanged from previous evaluations. The patient failed to present for scheduled hemodialysis and, upon investigation, was found dead at his home. An autopsy could not be obtained.

Julia Breyer, MD
Practice Vignettes

Vignette 1

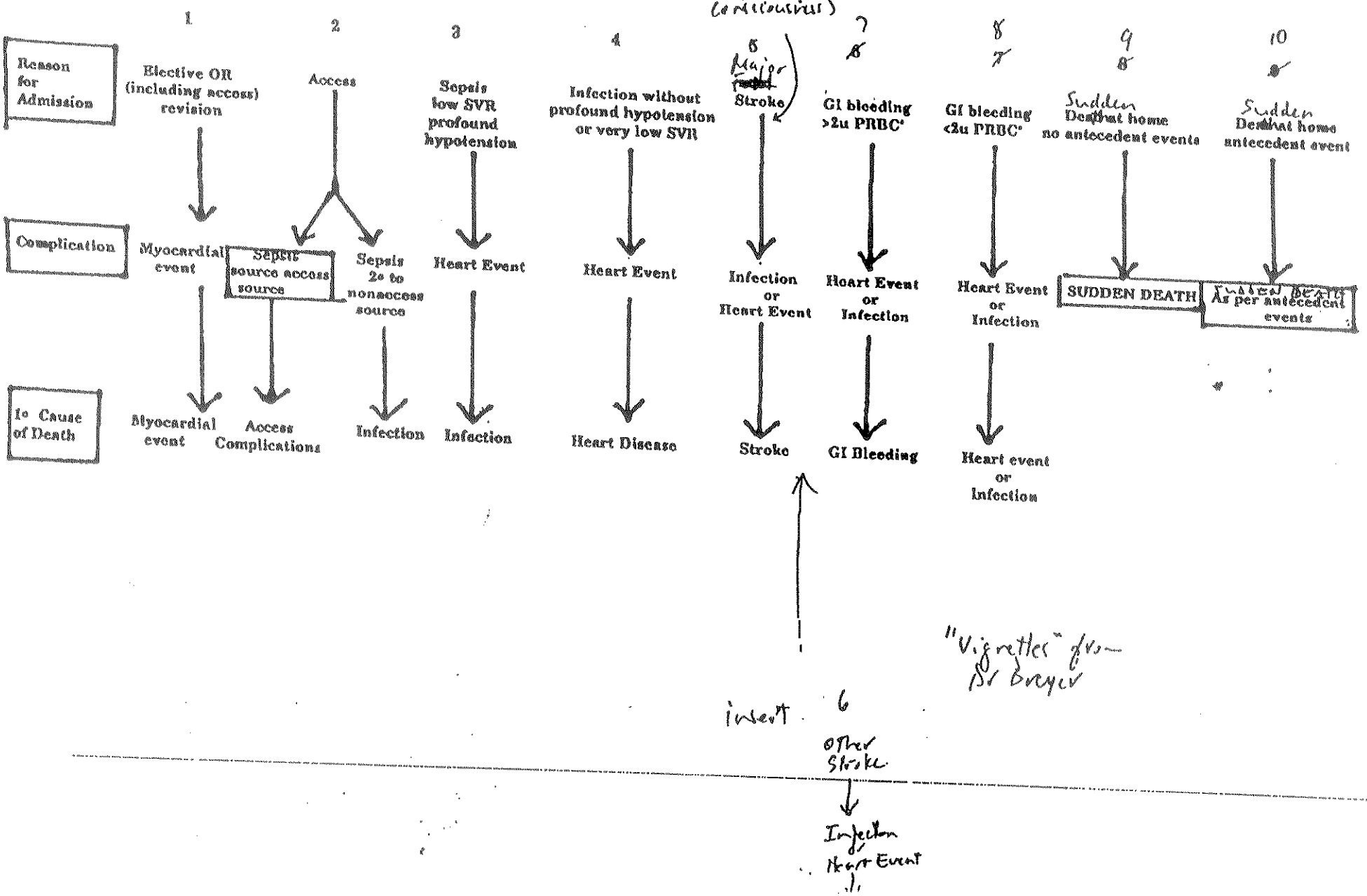
A 64-year-old black male while on HD complains of chest pain. The nurse checks his BP and he is stable at 130/85 mmHg. His heart rate is 110. Within 2 to 3 minutes of beginning that complaint, the patient becomes unconscious and repeat BP at that time is 60/50 mmHg. The patient is transported across the street to the ER. The patient goes on to become pulseless and apneic; CPR is begun, but fails to resuscitate the patient. No autopsy is performed and the patient is pronounced dead.

Vignette 2

The patient is a 64-year-old white male with a history of diabetes, hypertension, and coronary artery disease. Status post-coronary bypass graft 5 years previously who was attending a routine HD session in his outpatient HD unit. The pt. had gained approximately 10 kilos of fluid, which was an unusually large amount for him, in the previous interdialytic period. During the dialysis session, the pt. had multiple episodes of hypotension which responded to saline administration. During the fourth episode of hypotension while the nurse was administering saline, the pt. became pulseless and apneic. CPR was performed and the pt. was transferred to the ER where CPR was unsuccessful and he was pronounced dead.

Vignette 3

The patient is a 45-year-old white male with a history of diabetes mellitus and ESRD secondary to this. He is admitted electively to the hospital for cholecystectomy and preparation for kidney transplantation. Following the cholecystectomy, he develops fevers which are evidently found to be secondary to an abscess at the operative site. He develops bacteremia, hypotension, and dies.



CAMILLE JONES'S CASES FOR THE OUTCOMES COMMITTEE DEATH REVIEW

1. 53 yo black gentleman with hypertension, diabetes, peripheral vascular disease, and 40 pk year smoking history, with ESRD present for 4.5 years, presents to the hospital with worsening shortness of breath, tachycardia, hypoxemia and frequent PVC's on EKG. One hour after his arrival in the Emergency Room, he develops ventricular tachycardia, suffers cardiopulmonary arrest, and is resuscitated after 20 minutes. He remains unconcious, is moved to the ICU, and requires hemodynamic support for maintenance of blood pressure. He regains conciousness, but is confused. He suffers a repeat cardiac arrest with electro-mechanical dissociation 1 day after admission to the ICU. Resuscitation is unsuccessful.

2. 67 yo white lady is admitted with a history of membranous GN as the cause of ESRD 1 year ago. Breast cancer was diagnosed 6 months ago, being treated with chemotherapy. She has suffered two episodes of septicemia, once with staph aureus, and once with pnuemococcus in association with a community acquired pneumonia. She has had persistent trouble with clotting of her vascular access graft, and has had 1 surgical revision of the graft. She is admitted with shortness of breath, tachycardia, hypoxemia, with frequent PVC's on EKG. She has marked leg edema. She develops ventricular tachycardia, which is successfully treated with antiarrythmics. Progressive worsening of her pulmonary function is noted, with wooly patches seen in her lungs, progressing to complete opacification of the lung fields. Sputum cultures show normal flora. Ventilator support is required. She develops severe refractory hypotension, and expires in the ICU 1 week after admission.

3. 31 yo black lady with ESRD due to lupus nephritis, with severe lupus complicated by cerebritis and myocarditis. She has been treated with a prolonged course of prednisone. She is admitted with an acute upper GI bleed, with a hematocrit of 7 mg%, and a blood pressure of 70/p. She is successfully resuscitated with fluid and blood, with a blood pressure of 150/100 and a hematocrit of 28%. She has continued bleeding, requiring another 2 units of blood. One day after her last transfusion, she complains of back and chest pain, becomes short of breath, lightheaded, and goes into cardiopulmonary arrest. Resuscitation is unsuccessful.

4. 82 yo white gentleman with ESRD diagnosed 5 months ago. Previous history remarkable for alcohol abuse with cirrhosis and mild encephalopathy, mild hypertension, NIDDM, atherosclerotic heart disease, gout, venous insufficiency, and old CVA with residual weakness in the right hand. Cause of ESRD is unknown, since he has had no regular medical followup for the 4 years prior to presenting with ESRD. He is admitted for increasing confusion and agitation. He is dehydrated. He

has high blood ammonia levels and is treated with lactulose, without improvement of his mental status. Two days after admission, he develops a fever and a left lower lobe infiltrate, which enlarges and consolidates over the course of the day. He becomes increasingly hypoxemic, eventually requiring ventilator assistance for respirations without improvement of the hypoxemia. He suffers an acute drop in blood pressure, goes into cardiopulmonary arrest, and attempts at resuscitation are unsuccessful.

5. 67 yo black lady with ESRD due to atherosclerotic renal vascular disease, and history of myocardial infarction in the past 5 years with chronic angina, obesity, diabetes, and amputation of the toes on her left foot. She is admitted for intravenous antibiotics for a chronic osteomyelitis on the stump of her left foot. She complains of a transient episode of weakness in her legs, which resolves. Two days later, she is found unresponsive and cold in bed by the morning nursing staff. Attempts at resuscitation are unsuccessful.

6. 52 yo gentleman with ESRD due to polycystic kidney disease, with hypertension, atherosclerotic heart disease, obesity, and anxiety disorder treated with anxiolytics. He is admitted for surgery for a cancerous colonic polyp noted on sigmoidoscopy. His intraoperative course is remarkable for several brief episodes of severe hypertension (240/110). After surgery, he fails to wake up in the recovery room. Neurologic examination reveals an large hemorragic infarction with marked cerebral edema. After a week in the NICU with steroid treatment to reduce cerebral edema, the nurses note cloudy urine. Later that evening, he becomes feverish, and blood pressure drops to 80/40. He begins bleeding from his venipuncture sites, and around his surgical wound. Bleeding is extensive, and he expires 4 hours after onset of bleeding, despite aggressive medical management.

7. 36 yo gentleman with IDDM and ESRD for 4 years. Patient is blind, with coronary artery disease, autonomic dysfunction, chronic hyperkalemia, and severe peripheral vascular disease. He is admitted for bilateral cellulitis in the feet, and eventually requires bilateral below the knee amputations for gangrene. He develops marked shortness of breath in physical therapy two weeks after the operation, as he begins to do passive ROM exercises. He experiences syncope, and then cardiopulmonary arrest in the physical therapy suite. Resuscitation is unsuccessful.

8. 45 yo black lady with multiple sclerosis, with ESRD due to nephrotoxic antibiotics given for pyelonephritis. She is wheelchair bound, and has a tracheostomy. She is admitted with a severe aspiration pnuemonia, with hypoxemia (O2 30%). She refuses to allow mechanical ventilation, and expires 1 day after admission to the hospital.

9. 19 yo white lady with ESRD due to reflux nephritis, admitted for hypertension, tachycardia, difficulty breathing, and agitation. She has rales in her lungs, and EKG shown S-T segment elevation in the anterior leads. She develops ventricular tachycardia while being transferred to her hospital bed, which is not controllable with medications or electric shocks. Urine toxicology screen from the Emergency room reveals traces of cocaine in the urine.

10. 73 yo black man with ESRD due to streptococcal glomerulonephritis, with history of congestive heart failure, hypertension, hypothyroidism due to treated hyperthyroidism, and peripheral vascular disease. He was admitted for therapy of worsening congestive heart failure, and is found to have aortic stenosis. He is taken to surgery, with successful valve replacement. One day after surgery he is noted to have an ischemic hepatitis, with coagulopathy. He also develops a superficial staph aureus infection of the suture site for which he undergoes wound debridement. Two days later, he develops an upper GI bleed, a fever, drops his blood pressure, and suffers a cardiac arrest; resuscitation is unsuccessful.

Daniel B. Ornt, MD
University of Rochester

1) Patient was a 47 year old male with ESRD due to cryoglobulinemia of unknown etiology. He was doing well on chronic HD still receiving periodic plasmapheresis due to elevated cryocrits. He had sudden loss of consciousness and was brought to the hospital. On CT scan he had a large intracranial bleed and died several hours later. There was no post mortem exam.

2) Patient was a 45 year old male with ESRD due to type I DM. He was originally on PD but developed cryptococcal peritonitis. He was switched to hemodialysis and treated with two antifungal agents for 6 weeks. Three months later he died suddenly at his home. Post mortem showed a recent subendocardial MI and evidence of persistent cryptococcosis in lung and brain.

3) The patient was a 64 year old black female with suspected hypertensive renal disease on chronic HD for 5 years. She had a smoking history with the clinical diagnosis of mild COPD. She developed a GI bleed which required partial gastrectomy. In the recovery room, she had an acute respiratory event and was intubated. She suffered significant anoxic brain injury and was unresponsive. She was extubated in one week, but remained unresponsive for the next four weeks. The family elected to withdraw HD treatments and she died 5 days later. There was no post mortem exam.

Edwin Rutsky, M.D.
Practice Vignettes

Vignette 1

80 y/o MWM on chronic dialysis for 3 years was admitted with altered mental status, 4 days after a 3-week hospitalization for GI bleeding and pneumonia. He had ESRD of unknown cause, long-standing hypertensive and ischemic heart disease with cath-proven, 90% 3 vessel coronary atherosclerosis (for which he refused surgical intervention), atrial fibrillation with tachycardia-bradycardia syndrome (on quinidine and digoxin), recurrent GI bleeding due to peptic ulcer and more recently adenocarcinoma of the colon, and chronic cachexia. He had become unresponsive and disoriented on the day of admission, with no history of trauma or seizure. Physical exam revealed a BP of 120/80, HR 80, bilateral basilar crackles and a grade 4/6 systolic ejection murmur at the LSB. No evident volume overload or CHF. He was completely disoriented but had no focal neurological deficits. Arterial gas: pH 7.33, PCO2 36, PO2 67, PCV 28, WBC 13,000, glucose 119, and serum potassium 4.1. Chest X-ray showed a persistent infiltrate in the R base, unchanged from previous admission. He was treated with intravenous fluids with initial slight improvement in mental status, but was found in bed without pulse or respiration on the next morning. Since he had a DNR order, no resuscitation was attempted and he expired. Post-mortem exam was not done.

Vignette 2

63 y/o MWM on chronic hemodialysis x 4 1/2 yrs for ESRD due to chronic analgesic abuse, presented with acute generalized abdominal pain of less than 12 hours' duration. He had a long history of osteoarthritis with remote cervical spine fusion; radical left nephrectomy (2 yrs prior to starting dialysis) and radical right nephrectomy (4 yrs after starting hemodialysis) for renal cell carcinoma; chronic hypertensive and ischemic heart disease, with anterior MI and LVEF = 25%; S/P PTCA of 2 vessels for recurrent angina; atrial fibrillation and non-sustained ventricular ectopy; and recurrent hyperkalemia in spite of glucocorticoid/mineralocorticoid replacement and kayexalate. On admission, he was found to have diffuse fecal soiling of the peritoneum due to a perforated sigmoid diverticulum, requiring a diverting colostomy. His post-op course was long and complicated, remaining on ventilatory support because of persistent peritonitis/abscess formation in spite of multiple antibiotics, GI bleeding, ventricular ectopy and progressive respiratory dysfunction. He suffered a cardiac arrest,. and expired on the 38th hospital day. Post-mortem exam was not done.

Vignette 3

45 y/o SBM on chronic hemodialysis x 6 yrs for ESRD due to Type II DM. He was admitted from the ER with a 2-day history of left leg pain, fever and rigorous chills. He refused to seek medical attention and skipped dialysis on the morning of admission. He had a long history of diabetic neuropathy with recurrent foot ulcers, as well as treated osteomyelitis of the

R great toe, and more recent chronic osteomyelitis of the left great toe and ankle, and R index finger. Amputation had been advised but repeatedly refused by the patient. He also had long-standing hypertensive cardiovascular disease with cardiomegaly and intermittent pulmonary edema due to volume overload, renal osteodystrophy and a remote history of pulmonary thromboembolism. On admission, rectal temp was 104o, systolic BP 130/?, RR 44/min with no other pulmonary findings or evident volume overload. There were chronic ulcerations of the left great toe and ankle, and R index finger without purulent drainage. AV graft without evident infection. Chest X-ray showed only cardiomegaly. WBC 8000, glucose 400, arterial pH 7.21 with PCO2 17, PO2 99. Serum potassium was 7.1 and lactate 8.0. He was begun on gentamicin and nafcillin after blood cultures were obtained, and was started on hemodialysis. After 50 minutes of dialysis, he suffered a respiratory arrest with no prior hypotension. Although he was intubated promptly, and had an electrical heart rhythm, there was no palpable pulse or blood pressure. He expired after failing to respond to resuscitative efforts. Autopsy was refused. Blood cultures obtained prior to his arrest were positive for Pseudomonas species.

S.J. Schwab Cases for Outcome Committee

1. 62 year old black male with ESRD 2nd to NIDDM. S/P 2 vessel cabg 4 yr prior, s/p tplant rejection 4 months earlier. Presented to ER with fever 39.5 C. bp 100/50 and chest pain. No focus of infection apparent. Dialysis post tplant rejection uneventful. Admitted to ccu as probable sepsis and R/O MI. Loaded with Vancomycin and Gentamicin and hydrated to maintain BP. Cultures no growth clindamycin added. Developed progressive hypotension despite pressors and fluids. Was treated with CVVH for renal replacement. On 2nd post admit day developed hypotension and angina and asystole and could not be revived.

Post Mortem. RCA graft Occluded. Evidence of Acute MI in RCA distribution. Fungal Abcess in area of transplant nephrectomy.

2. 38 year old mentally impaired white male. ESRD 2nd to obstructive uropathy. S/P 2 valve replacement for rheumatic heart disease. Maintained on coumadin anticoagulation. BP intermittently elevated due to patient unwilling to take medication. Presented to ER with after being "found down" in nursing home. BP 180/120 PT 21 . CT scan large intercerebral bleed which was evacuated. No recovery of baseline mental function. With consent of guardian dialysis support withdrawn. Post Mortem not performed.

3. 71 year old black female. ESRD 2nd to NIDDM and HPT. Progressive cardiomyopathy with EF of 15% by echo. Refuses PD. Intermittent clinical angina without significant coronary lesions (assumed microvascular disease). Presented to dialysis unit feeling well. 4KG wt gain. 3hr into treatment developed hypotension followed by chest pain. Treatment terminated and patient transported to ER in unstable condition. Fluids and pressors in ER resulted in cardiopulmonary arrest. Rescue efforts unsuccessful. Post Mortem exam refused by family. ER EKG LBBB unchanged from previous.

Brendan Teehan, MD
Practice Vignettes

Case 1.

A 72-year-old white woman with ESRD due to ADPKD was found dead at home. She had a history of a seizure disorder which was inactive on Dilantin. In recent months, she was becoming more depressed, anorexic, and weak. There was no history of coronary disease, arrhythmias, or non-compliance.

Case 2.

A 49-year-old black woman with IDDM was hospitalized with fever, pneumonia, cachexia, and hyperglycemia. Serum potassium was 5.5. mEq/L. Cultures were drawn and antibiotics started. Blood cultures were positive for enterococci. Forty-eight hours later she vomited, aspirated, and has a cardiac arrest. Attempts at resuscitation were unsuccessful.

Case 3.

A 69-year-old white man was hospitalized from a nursing home because of fever. He had a past history of advanced multi-infarct dementia and was on dialysis for the past eight months because of hypertensive nephrosclerosis. The physical exam revealed dehydration, cachexia, and evidence of a right-lower-lobe pneumonia. BP = 90/60. Serum K+ = 7.8 mEq/L. Shortly after starting dialysis, ventricular fibrillation occurred. Attempts at resuscitation were unsuccessful.

Case 4.

A 39-year-old woman was admitted with fever and hypotension. She had been on dialysis for six months with ESRD attributed to AIDS nephropathy. During a recent admission, mycobacterium avium intercellulare had been cultured from her stools. A course of quadruple antibiotic therapy was ineffective. She was treated with pressors and empiric antibiotics but fever and hypotension persisted and she expired. Blood cultures were subsequently positive for resistant enterococci. An advanced directive for DNR was honored.

Case 5.

A 55-year-old black man was found dead at home. He had been on dialysis for five years. He had recurring vascular access thrombosis and recently had a right femoral permacath placed. The patient also had recurring episodes of angina in spite of a maximal medical regimen. Six months ago, a cardiac catheterization revealed inoperable triple vessel coronary disease.

Case 6.

A 76-year-old black female was found dead at home 24 hours after dialysis. She had a pst history of NIDDM, angina, a left BKA, and left subclavian vein thrombosis. Within the month prior to her death, a left upper arm Gortex graft was ligated because of severe edema. A right internal jugular permacath was placed and promptly became infected with both S. aureus and P. aeruginosa. Outpatient systemic antibiotic therapy with Gentamicin and Vancomycin did not affect a low-grade fever or the erythema and exudate at the exit site. The patient's husband who earlier refused permission for thrombolysis now refused to have the permacath removed. Blood cultures which were negative prior to antibiotic therapy remained so a week after a three-week course of antibiotics was completed.

Case 8.

An 80-year-old white man with a past history of NIDDM, hypertension, and a cerebrovascular accident underwent a routine hemodialysis on Friday and was returned to a nearby nursing home. The following Sunday afternoon, he developed intense melena and died en route to the hospital.

Case 9.

A 63-year-old African-American woman was admitted because of an infected pseudoaneurysm of a left upper arm Gortex graft. The temperature was 101 and the WBC count was 21,000. Blood cultures were taken (reported later as positive for S. aureus) and broad-spectrum antibiotics were started. She was scheduled for revision/ligation of the graft the following morning. During evening visiting hours, she complained of increasing pain in her graft arm. At 3:00 a.m. she was found dead with evidence of exsanguination from rupture of the graft pseudoaneurysm. There was no autopsy.

ESRD Vignettes

by

Robert D. Toto, M.D.

1. A 53 y/o black male has end-stage renal disease due to multiple myeloma on chronic hemodialysis for one year. The patient had a poor response to melphalan and prednisone. Chemotherapy was discontinued after 4 months at attempt to manage his tumor because of recurrent pneumonia. The patient was admitted to the hospital with fever, dry cough and dyspnea. Admission examination revealed a malnourished 53 y/o black male with tachypnea and labored respirations. BP 160/110 PR 110 RR 32 T 38.8. NECK: elevated neck veins, CHEST: Bilateral basilar rales, COR: 2/6 SEM, S4, EXT: bilateral pitting edema. Lab revealed WBC 14,000 Hgb 8 Hct 25. Total protein 10 g/dl, albumin 3.1g/dl. Room air ABG showed pO_2 54 mmHg, pCO_2 28, pH 7.36. CXR revealed bilateral pulmonary infiltrates and mild cardiomegaly. The patient was administered high flow oxygen and dialyzed. Blood cultures were obtained and he was started on broad spectrum antibiotics. His condition improved initially, but on the third hospital day he had increasing dyspnea, recurrent fever and hypotension. He was transferred to the intensive care unit, intubated and administered dopamine. CXR revealed worsening infiltrates and he became progressively more difficult to ventilate. A Swan-Ganz catheter was placed and the patient was found to have a high cardiac output with a low SVR. He was recultured and his antibiotic coverage was expanded. Blood cultures were positive for E. coli. On the following day he was dialyzed and transfused with packed red blood cells. Four hours after dialysis he developed ventricular ectopy which degenerated into ventricular tachycardia and he suffered a cardiac arrest. Attempts at resuscitation were unsuccessful. The family refused request for autopsy.

2. A 48 y/o Hispanic woman with end-stage renal disease due to type II diabetes on chronic hemodialysis for 3 years developed a 1 x 2 cm superficial ulcer on the plantar surface of 1st MTP joint of her right foot. The wound was managed with oral antibiotics, local wound care and hydrotherapy. The patient took her medication intermittently and was not compliant with local therapy. The lesion initially appeared to improve, but over the next month it enlarged in size and extended into the deeper tissue. Despite repeated attempts to control the lesion, cellulitis of the foot developed and persisted. Surgical consultation, local care and repeated courses of oral and intravenous antibiotics did not resolve the lesion. The patient was hospitalized for intravenous antibiotics to treat an advancing cellulitis and surgical services recommended amputation below the knee. The patient refused and was subsequently discharged on oral antibiotics. She continued to dialyze regularly with no improvement in the foot which began to develop dry gangrene over the ulcer site. The patient subsequently presented to the emergency room with a gangrenous foot and shock. Examination on admission revealed an obtunded Hispanic woman. BP 80 mmHg systolic, PR 120, RR 24 hyperpneic, T 36.0. EXT Deep ulcer over the 1st MTP. Dry gangrene of the big toe with cellulitis of the foot and lower leg. She was admitted to the intensive care unit and treated with antibiotics, pressors and

emergency hemodialysis for hyperkalemia and severe metabolic acidosis. Dialysis had to be terminated early because of hemodynamic instability. Despite continued supportive care with pressors and intravenous sodium bicarbonate, the patient's blood pressure remained low. She developed progressive hypotension, wide-QRS bradycardia and subsequently asystole. Efforts to resuscitate the patient were unsuccessful. No autopsy was performed.

3. A 60 y/o black male with end-stage renal disease due to hypertension had been on chronic hemodialysis for 3 years, dialyzing three times per week on a Monday Wednesday and Friday shift. He had a history of excessive interdialytic weight gain and his pre-dialysis blood pressure was frequently in the range of 16-200/100-110. He had been hospitalized numerous times in the past 4 years for pulmonary edema necessitating emergent ultrafiltration, usually on Sunday evening or on a weekday after missing a hemodialysis treatment. The patient was again hospitalized for sudden onset of dyspnea this time accompanied by chest pain. On admission the examination revealed a dyspneic black male in severe distress. BP 190/110 PR 96, RR 24, T 36.5. NECK: Elevated jugular venous pulse, CHEST: diffuse bilateral rales, COR: S3 and S4, EXT: 1+ pre-tibial edema. Room air ABG revealed pO_2 45 pCO_2 25 pH 7.42. CXR cardiomegaly and pulmonary edema. EKG revealed evidence for a new anterior wall myocardial infarction. The patient was admitted to the CCU and given thrombolytic therapy, intravenous nitroglycerin and heparin, and was dialyzed. He stabilized initially but subsequently developed ventricular tachycardia refractory to intravenous antiarrhythmics. Electrical cardioversion was successful but the patient's pulmonary status deteriorated because of pump failure. He developed recurrent ventricular arrhythmias and subsequently had a cardiac arrest. Resuscitative attempts were unsuccessful. No autopsy was performed.

HEMO STUDY
OUTCOME COMMITTEE PRACTICE CASES

Case (Name/#)	Cause of Death (Form 18 2/9/95) Primary	Secondary	Other	Other	Classification of Hospitalization (Form 15 2/9/95) Non-Access	Cardiovasc Disease	Infection
Jones/1	03DA						
Jones/2	09DU	10DG			Y	Y	N
Jones/3	24DA	13DA			Y	N	N
Jones/4	09DF	11DH	11DE		Y	N	N
Jones/5	24DA	01DD	06DE		Y	N	Y
Jones/6	06DD	18DC	22DC		Y	N	Y
Jones/7	04DA	01DD			Y	N	Y
Jones/8	09DS	23DK	14DP		Y	Y	Y
Jones/9	14DG				Y	N	Y
Jones/10	22DB	04DG			Y	N	N
					Y	Y	N
Toto/1	09DG	10DE					
Toto/2	07DK	08DH	23DK		Y	N	Y
Toto/3	01DB				Y	N	Y
					Y	Y	N
Albers/1	06DA	23DA	23DC				
Albers/2	13DB	23DA	06DA	08DH	Y	N	?
Albers/3	24DB				Y	N	Y
					NA	NA	NA
Ornt/1	06DD	19DI					
Ornt/2	01DB	18DI			Y	N	N
Ornt/3	22DB	14DM	13DA	23DA	Y	N	Y
					Y	N	N

HEMO STUDY
OUTCOME COMMITTEE PRACTICE CASES

Case (Name/#)	Cause of Death (Form 18 2/9/95) Primary	Secondary	Other	Other	Classification of Hospitalization (Form 15 2/9/95) Non-Access	Cardiovasc Disease	Infection
Teehan/1	24DB	23DC			NA	NA	NA
Teehan/2	09DG	09DS	23DC		Y	N	Y
Teehan/3	09DF	23DC	14DB		Y	N	Y
Teehan/4	16DC	18DE			N	N	Y
Teehan/5	01DA				NA	NA	NA
Teehan/6	20DE	23DK			NA	NA	NA
Teehan/8	12DA				NA	NA	NA
Teehan/9	20DB	20DE			N	N	Y
Schwab/1	18DA	01DB			Y	Y	Y
Schwab/2	06DD	23DA	04DG(H)	05DA	Y	N	N
Schwab/3	04DK	21DF			Y	Y	N
Breyer/1	01DB				Y	Y	N
Breyer/2	01DA	21DF			Y	Y	N
Breyer/3	13DS	22DB			Y	N	Y
Rutsky/1	24DA	10DF	01DD	23DC	Y	N	N
Rutsky/2	13DJ	09DT	01DD		Y	N	Y
Rutsky/3	18DC	08DH			Y	N	Y

HEMO Outcome Review Committee Members

April 4, 1995

Dear Friends,

Congratulations! We have completed the death classifications for the vignettes (36 cases in all). My thanks to everyone for creating them and then working to classify them. Under separate cover, you should receive the final classification of the practice cases. Please save this with the vignettes. You will need it for our next task.

We now need to resolve recurring questions that arose during the classification of the practice cases. In a previous letter (March 28), I summarized the most frequently recurring questions. My suggestion is to consider each question generally and define a "rule" that could be written for us to follow in future reviews. To stimulate our thinking, I have listed one or more of our practice cases that highlights each question. **In addition, as we discussed, I have assigned one of us to be a discussion leader for each question.**

Please review all the cases and consider the questions below for each case. If necessary we will re-classify them. We will begin this task on our next call (April 11). Good luck!

1. Degree of certainty. How certain must we be to assign a primary cause of death? For example, in a patient with one or more fatal conditions who dies in the hospital or dialysis unit, but the cause of death is not certain, shall we assign the probable cause of death as the primary cause or shall we list it as unknown?

   Examples: Teehan #6, Jones #3, Jones #5, Jones # 7, Rutsky #1, Ornt #2.
   Discussion leader: Breyer

2. Primary vs. secondary causes. What are the "rules" to follow regarding assigning primary and secondary status to "proximal vs. distal" events in the chain of events leading to death? For example, breast cancer causes lung metastases, is treated with chemotherapy, causes pancytopenia, causes sepsis and death. For example, diabetes causes peripheral vascular disease, causes gangrene, causes sepsis and death.

   Examples: Teehan #3
   Discussion leader: Toto

3. Definition of secondary causes. Shall we define secondary causes to be either "proximal" (rather than "distal") or unrelated to primary causes?

   Examples: Toto #3, Jones #1, Jones #6
   Discussion leader: Albers

4. Cardiac events. When shall we list the cardiac event as the primary cause of death or as a complication of the precipitating event? For example, septic shock complicated by acute MI, or dialysis-induced hypotension complicated by fatal arrhythmia?

Examples: Breyer #2
Discussion leader: Heyka

5. Sudden death. When shall we use the sudden death codes 01DA, 02DA, 03DA, 04DA and 24DA?

Examples: Breyer #2, Teehan #5, Jones #1
Discussion leader: Schwab

6. Access complications. Shall we expand the list to include more scenarios?

Example: Teehan #9
Discussion leader: Rocco

7. Concomitant conditions. When shall we list concomitant conditions as secondary causes? For example, shall we list diabetes, cancer, atherosclerotic heart disease whenever they occur or only if they are the cause of death?

Example: Jones #2, Toto #2, Teehan #2, Ornt #2, Albers #2, Rutsky #3
Discussion leader: Levey

8. Complications of treatment. When shall we consider a complications of treatment (Other Hemodialysis Complications, code 21; Other Surgical Complications, code 22) as the primary vs. the secondary cause of death?

Example: Breyer #3, Ornt #3
Discussion leader: Levey

I look forward to beginning these discussions. Best regards.

Sincerely,

Andrew S. Levey, M.D.

Julia A. Breyer, MD
Vanderbilt University Medical Center
Division of Nephrology
April 5, 1995

Dear Andy:

Thank you for asking me to comment on what our rules should be on degree of certainty in assigning primary causes of death. I think it is very important that we do not clutter our database with many "sudden death" or "unknown" cause of death classifications. Although in some cases we will not have absolute undeniable proof, such as autopsy data to support a primary cause of death, if in some common-sense way 5 out of 10 physicians would predict that a certain primary cause was the cause of death, that should be used as the primary cause of death. If less than 5 out of 10 physicians would likely classify a particular primary cause of death as the cause of death with insufficient data and might either list unknown or other primary causes, then those cases should be classified as sudden death -- cause unknown. In addition, in order for a primary cause to be listed when it is a situation of insufficient data, there must be some element of data to suggest that primary cause even if it is not sufficient to confirm it. For example, just a history of coronary artery disease in someone's past would not be sufficient to classify a person found dead at home, having been dead hours, as a coronary artery disease death. Rather, a patient with a history of coronary artery disease who is mowing his lawn, grabs his chest, and falls to the ground dead on the spot would be called coronary artery disease as the cause of death, since there was some element to support that primary cause other than just a history of a pre-existing illness predisposing him to such a thing.

In summary, I think we should have the following three guiding principles:

1. Have the fewest number possible "sudden death -- cause unknown" in our database.

2. There should be some element of supporting data for a primary cause even if it is not sufficient to confirm that primary cause.

3. There should be a common sense; more than 5 out of 10 physicians would classify a primary cause of death with the information available approach.

SOUTHWESTERN

THE UNIVERSITY OF TEXAS
SOUTHWESTERN MEDICAL CENTER
AT DALLAS

Department of Internal Medicine
Division of Nephrology

April 11, 1995

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TEL 617 636 5866
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Dear Andy:

Here are some of my thoughts and the "rules" for point # 2 on the list from April 4, 1995 FAX.

Background and Discussion

We have encountered several problems in assigning primary vs secondary causes of death during our exercises. I have listed three important ones:

1. A patient has several potentially lethal disorders at the time of death, e.g. pneumonia, hyperkalemia, sepsis, acute MI, etc.

2. There are several chronic underlying diseases which may contribute to a sudden fatal outcome.

3. The proximate cause of the "fatal" event is difficult to identify with a high degree of certainty. For example, ventricular fibrillation occurs on dialysis in a patient with pneumonia and a K of 7.8 mEq/L. Was it hypokalemia? respiratory failure?

We have to decide whether the underlying disease is the primary or the secondary cause.

In some cases they may be the same:

For example, a patient with known coronary artery disease has a massive MI or a lethal arrhythmia.

In other cases they may be different:

For example, in the patient with breast metastases who has sepsis after chemotherapy code the death as sepsis as primary cause and list breast cancer as the secondary cause.

Based on review of several cases and our discussion on the conference call it is suggested that we list immediate cause as the primary cause of death and the underlying disease as the secondary cause of death. (Otherwise a patient with diabetes could have this as their primray cause of death. It caused renal failure, which caused heart disease, which caused MI which caused arrhythmia, which caused death.)

Rules:

Rule # 1 In general, the proximate (immediate) cause of death, e.g. sepsis, an acute MI, pneumonia should be listed as the primary and underlying disease processes (e.g. diabetes) should be listed as secondary causes only. In some cases, there may be a clear temporal association between an underlying disease and death, e.g. some types of malignancies, cachexia, etc., and the terminal event. In these cases the underlying disease he may be the primary cause.

Rule # 2 If an underlying disease is thought to be contributing to primary cause of death list it as a secondary cause.

Rule # 3 When coding death we should focus on the cause of death rather than the mechanism of death.

I hope this will help the subcommittee. Please distribute this at your convenience.

Sincerely,

Bob

Robert D. Toto, M.D.
Associate Professor

Frank Albers, MD
Duke University Medical Center
Division of Nephrology
April 29, 1995

Dear Andy:

I have listed below the guidelines for secondary causes of death. I believe there are three principles that we should bear in mind when evaluating cases with regard to secondary events: (a) we should attempt to keep our list as concise as possible to avoid diluting meaningful data with incidental findings; (b) conditions existing before the primary cause of death should have more weight than conditions developing afterward (although exceptions to this will occur); and (c) we must consider the contribution of secondary conditions to the patient's clinical deterioration.

I. In cases where two different conditions have potential as being the primary cause of death, that condition not designated as the primary cause will be included as a secondary cause of death.

II. Pre-existent conditions that induce a significant deterioration in the patient's clinical condition, or without which the primary cause of death could not be possible, should be included as secondary causes of death. However, do not include conditions that would be redundant (e.g., acute MI and coronary artery disease).

Examples:

A patient with profound multiinfarct dementia dies from aspiration pneumonia -- the dementia is a secondary cause.

Patient with multiple myeloma dies of pneumonia -- multiple myeloma is secondary cause.

Patient dies of intraabdominal abscess and sepsis after elective cholecystectomy -- either "cholecystectomy" or "complications from surgery" must be included as a secondary cause.

III. Conditions that arise after the primary cause of death should be included as secondary causes if (1) they are not expected consequences of the primary cause of death or other noted secondary causes of death and (2) they result in a meaningful deterioration in the patient's clinical status.

Example:

Patient suffers cerebral hemorrhage with obtundation and later develops urosepsis -- cerebral hemorrhage is primary and urosepsis is secondary cause of death.

IV. Conditions or events should be excluded as secondary causes of death if they are expected or reasonable consequences of the primary cause of death or of a noted secondary cause of death.

Examples:
Patient has acute MI followed by cardiogenic pulmonary edema, refractory VT, and death. The cardiogenic pulmonary edema and VT are consequences of acute MI and are not included as causes of death.

Patient develops sepsis with development of DIC and rapid deterioration unto death. The DIC is a consequence of sepsis and is not included as cause of death.

Robert Heyka, MD
Cleveland Clinic Foundation
Division of Nephrology
May 1, 1995

Dear Andy:

Let me respond to your request for a summary of our discussions on cardiac death in the HEMO Study. (1) We should invoke the three principles of proximity, lethality, and inevitability as enumerated earlier to consider a cardiac event as the primary cause of death. Julia's worksheet from the Pilot Study still summarizes this very well. Thus in Breyer #2, the patient had a history of cardiac disease and objective findings -- i.e., repeated hypotension prior to the cardiac arrest -- so we can call this a primary cardiac event. Similarly, in the case of a recent MI or episode of CHF, either of these events are potentially lethal and would fulfill the requirements of a primary cause of death as long as they were proximate to the time of death. Expected associated events such as arrhythmias or LV failure would not need to be listed. I doubt that they would add much to the overall statistical analysis, according to the other DCC members. (2) The issue of an event more separated in time from an MI or episode of CHF would need to be judged on an individual basis. The question of an event like torsades de pointes with quinidine administration in the post MI setting could be evaluated *exceptis excipiendis*. (3) A cardiac event associated with other potentially lethal events such as sepsis should be considered a secondary cause of death using the principle of lethality. (4) However, in the absence of any symptomatic or objective evidence for cardiac events, we will probably accept "unknown" as the cause of death unless an Oracle committee feels differently.

Steve J. Schwab, MD
Duke University Medical Center
Division of Nephrology
May 22, 1995

Following is my comment regarding question #5 for the HEMO Outcome Committee:

The sudden-death codes -- 01DA cardiac arrest; 03DA cardiac arrest, arrhythmia induced; 04DA cardiac arrest, cause unknown -- should be used only when a more definitive diagnosis cannot be established. For instance, many diagnoses of 01DA or 03DA could be coded based on EKG or enzyme or clinical data as 01DB: myocardial infarction, acute. When a more specific diagnosis cannot be made, 01DA and 03DA remain useful diagnoses. Code 04DA -- cardiac arrest, cause unknown -- remains useful and should be used when more specific diagnostic data are not forthcoming.

To: HEMO Study Outcome Committee
From: Andrew S. Levey, M.D.
Re: Death Classification "Rules"
Date: May 2, 1995

Concomitant Conditions

We discussed the question, "When shall concomitant conditions (for example diabetes, atherosclerotic heart disease, cancer, dementia) be considered secondary causes of death?"

Concommitant conditions will be considered secondary causes of death if they contribute directly to death. Otherwise they will not be considered as secondary causes. (Of course, they can be considered primary causes of death if they meet the rules for this designation.)

Examples:

Jones #2 Breast cancer (10DG) is listed as a secondary cause because the patient was receiving chemotherapy, had prior infectious complications probably due to immunosuppresion, and died from respiratory failure of unknown cause (09DU) probably from another infectious complication.

Toto #2 Diabetic foot infection (08DH) is listed as a secondary cause because the patient died from gangrene with septicemia due to PVD (07DK) as a direct complication from the foot infection.

Rutsky #3 Diabetic foot infection (08DH) is listed as a secondary cause because the patient died from septic shock (18DC) as a direct complication of the foot infection.

Albers #2 Diabetic foot infection (08DH) is listed as a secondary cause because the lower GI bleeding (13DB) occurred following surgery to treat the foot infection.

Teehan #2 Type I diabetes (08DA) is not listed as a secondary cause because diabetes did not directly contribute to death from pneumonia-sepsis (09DG). If she had died from aspiration pneumonia as a consequence of non-ketotic hyperosmolar coma, the latter condition (08DE) could have been listed as a secondary (or primary) cause.

Ornt #2 Type I diabetes (08DA) is not listed as a secondary cause because diabetes did not directly contribute to death from myocardial infarction. Cryptococcal infection (18DI) is listed as a secondary cause of death, and diabetes may have contributed indirectly to persistence of cryptococcal infection after PD catheter removal. However, this is not sufficient for inclusion of type I diabetes as a secondary cause of death.

Complications from Treatment

We discussed the question, "When shall complications from treatment (for example surgical or anesthetic complications) be considered the primary cause of death?"

Complications from treatment will be considered the primary cause of death if the fatal complication occurs within 24-48 of the treatment, even though death may occur after a longer interval. For fatal complications that begin more than 24-48 hours after treatment, complications from treatment will be considered secondary causes of death. We anticipate that there will be exceptions to this general and arbitrary guideline.

Examples:

Ornt #3 Complications from surgery (22DB) is listed as the primary cause of death, because we assume the respiratory event occurred immediately after surgery. Anoxic brain injury (14DM) is the consequence of the complication of surgery.

Breyer #3 Complications from surgery (22DB) is listed as a secondary cause because intrabdominal abscess (13DS) presumably resulted from failure to clear bacterial seeding after surgery rather than the occurrence of bacterial seeding during surgery. If, however, abscess formation was caused by a retained surgical sponge, then the complication from surgery would be the primary cause of death.

To: Outcome Committee Members
HEMO Study
From: Andrew S. Levey, M.D.
Date: May 30, 1995
Re: a) Level of Concordance Regarding Classification of Death
b) Quality Control of Classification of Hospitalizations and Discharge Diagnoses

As you know, we completed the "rules" for classification of deaths during our conference call of May 23, 1995. Today, Tom Greene and Jennifer Gassman joined us to discuss the following issues:

a) Level of Concordance regarding Classification of Death

Deaths. **We decided, as discussed last week, that we would insist on agreement between the two Outcome Committee reviewers on the primary cause of death.** (If there is disagreement, the final classification will be assigned by the Chair or designee). **We decided today that we would require agreement on the major class of death, but not the exact classification.** For purposes of analysis, we anticipate reporting only the major classes of causes of death. **In contrast to last week's discussion, however, we decided that we would not require agreement on the secondary causes of death.** For analyses we will report only the "intersection" (causes listed by both reviewers) or "union" (causes listed by either reviewer) without regard to the rank order.

Hospitalizations. **We decided, as discussed last week, that we would insist on agreement between the Outcome Committee member and clinical center PI for classification of hospitalizations with regard to secondary outcomes (hospitalization for cardiovascular disease or infection).** (If there is disagreement, the final classification will be assigned by the Chair or designee). As discussed last week, concurrence is not required for discharge diagnoses. This will be addressed by quality control analyses (see below).

b) Quality Control of Classification of Hospitalizations and Discharge Diagnoses

We discussed three items related to this topic. For the record, the next three paragraphs are reprinted from last week's letter:

1. Classification of access vs. non-access hospitalizations (see Protocol p 4002 and question 4 on Form 14). In my view this requires a review (possibly masked) of a random sample of hospitalization packets to estimate the rate of agreement. We do not need to require concurrence of the clinical center and Outcome Committee.

2. Classification of hospitalizations for cardiovascular disease or infection. We are already reviewing all hospitalization classified by the clinical center as first hospitalizations for cardiovascular disease or infection (and requiring concurrence). We should also estimate the rate of agreement in classification of hospitalizations "not for cardiovascular disease or infection." Again, in my view, this requires a review (possibly masked) of a random sample of hospitalization packets to estimate the rate of agreement.

3. Classification of discharge diagnoses. It seems likely that we will wish to analyze these data. Thus, we must estimate their reliability. Again, in my view, this requires a review (possibly masked) of a random sample of hospitalization packets to estimate the rate of agreement.

The Data Coordinating Center is in agreement that items 1 and 2 should be subject to quality control. Questions remaining include:

1. What is the number of charts that should be reviewed by the Outcome Review Committee to assess the clinical center's classification?

2. Should the Outcome Review Committee members be blinded to the Clinical Center classification?

3. How should this review be implemented to minimize burden on the Clinical Center, Outcome Review Committee and DCC?

4. Should item 3 be subject to a similar quality control procedure?

The DCC will consider these questions further and advise us.

The Outcome Review Committee will give a report at the Steering Committee meeting next week. The report will focus on the progress we have made in death classification. Our next telephone conference call will be June 27, 10:00 AM (EDT).

MINUTES OF THE OUTCOME COMMITTEE CALL 4/11/95

TO: HEMO Outcome Committee

FROM: Lisle Benson
HEMO DCC

RE: Minutes of 4/11/95 Outcome Conference Call

DATE: April 18, 1995

We started to resolve the questions posed in Dr. Levey's letter dated April 4, 1995, by attempting to define rules to follow in future reviews.

2. *Primary vs. secondary causes issue* (discussion led by Dr. Toto):

How can we establish rules in assigning primary and secondary status to proximal vs. distal events leading to death? Potentially confounding problems include: (1) a pt. may have several potentially lethal disorders (e.g., pneumonia, hyperkalemia); (2) several such conditions may cause an acute condition that leads to rapid deterioration; (3) the proximal event may be difficult to determine.

The consensus, following a long discussion, was to use these main parameters: (1) code only fatal diseases as primary causes; (2) if there is a long interval between an event and death, code the event as primary only if there is an inevitable, clear-cut path leading from it to death. The former is important in capturing the diseases the pts. actually die from, rather than getting so far down the chain of events that all pts. are coded as dying from cardiac arrest or hypotension. The latter is important for the principle of inevitability, in that we consider whether something is absolutely inevitable as a consequence of a particular disease (e.g., metastases from breast cancer are inevitable, while complications from breast-cancer surgery are not). In all cases, we will have to rely rather heavily on the principal investigator for the "flavor" of the case.

1. *Degree of certainty issue* (discussion led by Dr. Breyer):

How can we establish the primary cause of death with some certainty? In a patient with more than one fatal condition for whom the cause of death is unclear, should we code the probable cause as the primary cause of death or code it unknown?

There was a strong consensus that we not clutter the database with "unknown" causes. The three suggested principles to follow in future review are to have: (1) the fewest number of unknowns; (2) supporting data or evidence for a coded cause of death; and (3) a simple majority vote (> 50%) of consensus among physicians for a coded cause.

* * * * * * *

Our next call will be Tuesday, April 25, at 10:00 EDT.

MINUTES OF THE OUTCOME COMMITTEE CALL 4/25/95

TO: HEMO Outcome Committee

FROM: Lisle Benson, HEMO DCC

RE: Minutes of 4/25/95 Conference Call

DATE: April 28, 1995

We continued our discussion of the issues in Dr. Levey's 4/4/95 letter.

3. *Definition of secondary causes* (discussion led by Dr. Albers):

Shall we define secondary causes as "proximal" rather than "distal," or unrelated to primary causes?

We had a long discussion and reached consensus on these parameters established by Dr. Albers: (1) if an event is an absolutely *unequivocal consequence* of the primary cause, there is no need to list that event as a secondary cause (but, as a corollary to this, if there is a known disease process with an acute event *prompted by* that process, that event should be listed as secondary); (2) where there are two causes of death, the choice of one as the primary cause makes the other the secondary cause; (3) pre-existing conditions distal to the main event are also to be listed as distal; and (4) conditions unrelated to the primary cause but causing significant deterioration are also to be listed as secondary causes of death.

Our choices will be directly influenced by the amount of data received. We will have to rely heavily on the PIs for adequate detail, particularly when there is a question of degree with a disease that may not be lethal *per se* (as in diabetes).

4. *Cardiac events* (discussion led by Dr. Heyka):

When shall we list a cardiac event as the primary cause of death or as a complication of the precipitating event?

We did not have time for a full discussion, but Dr. Heyka established some preliminary guiding principles similar to those in the issue #1 discussion: (1) proximity; (2) lethality; and (3) inevitability. We agreed that our multiple sudden-death codes are confusing and need streamlining. Before we ended, Dr. Levey re-emphasized that the amount of information would influence decisions re: primary cause of death, and that the degree of a problem would also be a significant factor.

* * * * * * *

Our next two calls will be at 10 EDT on Tuesdays, May 2 and May 9.

MINUTES OF THE 5/2/95 OUTCOME COMMITTEE CONFERENCE CALL

TO: HEMO Outcome Committee

FROM: Robert J. Heyka, M.D. RH

RE: Minutes of the 5/2/95 Conference Call

Date: May 10, 1995

Present: Andy Levey, Bob Heyka, Mike Rocco, Camille Jones, Bob Toto, Dan Ornt, Edwin Rutsky

AL raised issues related to the need for a meeting at the upcoming steering committee meeting in June.. He questioned whether we should meet for approximately 30 minutes on Monday, June 5, 1995 in the evening. The charge for the steering committee will be to present a progress report and to review data flow for hospital and death forms.

There will be no meeting on 5/9/95. On 5/16/95. the goal will be to complete the original questions. On 5/23/95 and 5/30/95, we will review documentation with the cases for steering committee records. We will also review our data flow sheets for hospitalizations and death. Hopefully, Jennifer Gassman from the DCC will be able to join us for this discussion.

We continued our discussion of the issues from AL's letter of 4/4/95:

6. *Access Complication* (discussion was led by MR):

Several cases were discussed related to access complication. Adjustments were made in the coding for those cases. A new code was proposed, namely 20DF, "Other complications of access placement." This will provide for complications that are mechanical, infectious or related to access placement. This will also cover complications related to access disconnection.

7. *Concomitant Conditions* (discussion was led by AL):

Several vignettes were discussed. Example was raised concerning diabetes mellitus. The consensus was that this should be listed only as a secondary cause when contributing in a direct way to patient's death. For atherosclerotic peripheral vascular disease, this should be considered only if an unexpected complication occurs early in the course of peripheral vascular disease. Otherwise, the same rules will apply as discussed in prior meetings for secondary causes. Several cases dealing with the diabetes for example, with DKA or hyperosmolar coma.

8. *Complications of Therapy being Listed as Primary Causes:*

General time rule of 24-48 hours relating to a particular treatment, for example, surgery, was enacted. Several vignettes were reviewed and reclassified. Lastly, a packet of notes and minutes containing all the cases and the listing of primary and secondary causes will be distributed to committee members as well as to the steering committee. Conference call was closed at approximately 11:00 AM

RJH:lmd