20. Standards of Care

20.1 Dialysis Co-Interventions Not Related to Dose

a. *Dialysis Machines*:

All dialysis units should employ the use of machines that allow volumetric control of ultrafiltration.

b. Water Quality

Patients undergoing nocturnal dialysis are required to use ultrapure water. Centers are encouraged to use ultrapure. All dialysate water should at a minimum meet Association for the Advancement of Medical Instrumentation (AAMI) standards for endotoxin units of <2.0 E.U/ml and bacterial counts of <200 CFU/ml. The limits for elemental and ionic impurities will also be maintained within AAMI standards in all centers. Dialysis unit water standards will be captured on Form 603 at the start of the study for all participating units in both studies

All dialysis units are encouraged to monitor their water quality on a monthly basis

Patients on home dialysis are encouraged to have monthly water tests. In the Nocturnal Study, the results of the home water quality tests will be entered into database twice during follow up.

c. Dialyzers:

Compared with conventional HD, patients on daily and nocturnal HD will have approximately twice the number of exposures to dialyzer membranes in a given time period. Because this could influence the interpretation of study results, standardized use of dialyzers is encouraged.

i) Flux: Subgroup analysis of the HEMO Study suggested a reduction in cardiac death with high-flux dialyzers (1). Only high-flux, high efficiency, biocompatible dialyzers should be used for all patients in both trials.

ii)Reuse: Reuse will not be permitted for any patients on home hemodialysis. For conventional HD patients in the Nocturnal trial, and for all patients in the daily study, non-reuse of dialyzers is encouraged.

If reuse is used, reuse techniques will follow manufacturers' recommendations and procedures approved by the medical directors of the Core Centers' dialysis units, with adherence to Association for the Advancement of Medical Instrumentation (AAMI) standards. Reuse number is collected monthly for each patient on the kinetic modeling Form 273.

d. *Dialysate Composition*:

i) *Acid Buffer*: Bicarbonate dialysate should be used in all patients in order to minimize intradialytic hypotension and cardiovascular instability (2). The dialysate bicarbonate concentration should be adjusted by the treating nephrologist in order to maintain a midweek predialysis serum bicarbonate of 20-27 mmmol/L (as determined by the local laboratory.

ii) *Sodium*: The dialysate sodium should be adjusted by the treating nephrologist. It is suggested that the dialysate sodium prescription should match the patient's predialysis serum sodium in order to maintain neutral sodium balance (6). In addition, to avoid increasing interdialytic thirst, weight gain,

and hypertension, the use of sodium ramping and high sodium dialysate is discouraged unless the center has biofeedback control or other mechanisms available to ensure patients maintain neutral sodium balance (7-10). Using dialysate sodium less than the patient's predialysis sodium is also be discouraged in order to avoid intradialytic hypotension and cardiovascular instability (11).

iii) *Potassium*: The dialysate potassium should be adjusted by the treating nephrologist. The suggested range is 1.5 – 4.0 mmol/L in order to maintain a predialysis serum potassium of 4.0 – 5.5 mmol/L. Dialysate potassium <1.5 should be avoided in order to decrease potential for intradialytic hypotension, cardiovascular instability, and arrhythmias (12;13).

iv) *Calcium*: The dialysate calcium should be adjusted by the treating nephrologist. The suggested range is suggested range is 1.25 to 1.5 mmol/L (2.5 to 3.0 mEq/L) in order to maintain a predialysis serum calcium (corrected for serum albumin) of 2.1 – 2.6 mmol/L (14). For subjects with intradialytic hypotension responsive to changes in dialysate calcium concentration, the dialysate calcium may be increased, provided that the adjusted pre-dialysis calcium concentration is maintained within target ranges (15-17) (see section 3.11.2 also).

v) Calcium-phosphate protocol for home nocturnal patients

Calcium- phosphate should be managed in home nocturnal patients according to the current standards of care.

vi) *Magnesium and Glucose*: The dialysate magnesium and glucose should be determined by the treating nephrologist according to clinical practice guidelines (18).

e. *Ultrafiltration and "Dry Weight" Targets*:

i) *Background*: Volume overload is the main cause of hypertension in ESRD patients, leading to left ventricular hypertrophy, pulmonary edema, and even sudden cardiac death (19). Volume depletion leads to symptomatic intradialytic hypotension, cramping, and fatigue, causing patient dissatisfaction with the dialysis procedure and poor quality of life (20). It is imperative that attempts be made to prescribe accurate ultrafiltration targets and attain dry weights equally in subjects from both groups. Using bioimpedance technology, it has been shown that the extracellular to intracellular fluid volume ratio is reduced toward normal physiologic values in daily HD patients, suggesting that improved blood pressure control may be at least partly due to closer attainment of true dry weight in these patients (London and RRI Studies, unpublished data). *It is difficult to determine if the daily HD procedure itself allows for easier fluid removal and thus closer attainment of dry weights, or if more effort was made to adjust dry weights in these patients.* Thus, for this study, it is critical to adopt a standardized approach for the determination and attainment of dry weight goals in both groups.

ii) *Setting the ultrafiltration prescription*: The ultrafiltration prescription will be determined by the treating nephrologist, and will be set to achieve the patient's goal "dry weight." (see below) It is suggested that the ultrafiltration rate during hemodialysis not exceed 2.0 L/hr in order to avoid intradialytic hypotension.

iii) *Determining the goal dry weight*:

Dry weight should be determined by the treating nephrologist by clinical examination, with emphasis on pre-dialysis blood pressure, jugular venous pressure, and pedal/sacral edema. It is suggested that the clinical examination be supplemented with a protocol to test the lowering of the patient's target weight. This involves to gradually lowering the target weight by 0.1L/session, until the patient cannot tolerate further lowering of the dry weight due to intradialytic hypotension or symptoms and the treating nephrologist deems that the true dry weight has been attained. The minimum tolerable

weight is then used as the patient's target weight for subsequent sessions, with reevaluation on a regular basis. Such an approach was utilized in the Renal Research Institute with success.

iv) *Approach to intradialytic hypotension*: Fluid overloaded patients often have intradialytic symptoms of hypotension and cramping due to slow plasma refilling (21). Patients with diastolic dysfunction may be particularly sensitive to filling pressures. Based on evidence, a standardized protocol is suggested for patients from both groups who experience intradialytic hypotension.

First, the subject should have a careful clinical examination by the attending nephrologist to assess volume status and to rule out non-volume causes of hypotension. If the patient is still deemed to be volume overloaded, he or she should be counseled to reduce sodium intake and interdialytic weight gains (22). The dialysate sodium should also be adjusted to the patient's predialysis sodium (23). In conjunction, the use of a blood volume monitor, such as continuous hematocrit monitor, may be used to guide ultrafiltration rate (24;25).

Where available, blood temperature monitoring may be used (26). If not available, constant cool temperature dialysate will be attempted, followed by ultrafiltration profiling or midodrine (27-30). Because of its adverse effects on interdialytic weight gain and hypertension (31;32), sodium profiling is discouraged, unless biofeedback or other mechanisms are available in order to ensure the patient remains in neutral sodium balance (10;33).

Failing these measures, under the discretion of the treating nephrologist, subjects may be advised to have additional dialysis treatments for ultrafiltration, until they are able to achieve their targeted dry weight. The treating nephrologist should adjust antihypertensive medications according to his or her discretion. Intradialytic hypotensive episodes and interventions will be recorded, along with the need for additional treatments. Regardless of the methods used to prevent, ameliorate, or correct intradialytic hypotension, the same methods should be applied uniformly to subjects randomized to both groups.

20.2 Non-Dialytic Co-Interventions

Recommendations regarding non-dialytic co-interventions are summarized in the table below.

Co-Interventions and Standards of Care Not Related to HD Prescription

Item	Recommendations*	Data Collection	Feedback
Tier 1			
Immunizations	Yearly Influenza Hepatitis B as per Appendix 2 Pneumovax as per Appendix 2	*None*	*None*
Diabetes Management	Target HbA1C <7.0%		
Lipid Management	Target LDL≤ 2.6 mmol/L		
Tier 2	*Targets (DOQI):*	*Regular local lab entry¥:*	*Automated feedback by DCC* to treating nephrologist and research coordinator for patients whose monthly labs fall outside of target for 3 consecutive months, or whose iron studies are out of target for 2 consecutive quarters
Anemia Management	hemoglobin 110 – 120 g/L ferritin 100 – 800 transferrin saturation ≥ 20%	hemoglobin ferritin transferrin saturation	
Calcium-Phosphate	phosphate <1.80 mmol/L calcium¶ 2.10 – 2.60 mmol/L	*phosphate* calcium	
Acid-Base Status	bicarbonate 20 – 27 mmol/L	bicarbonate	
Tier 3	*Routine monitoring frequency:*		
Ideal weight assessment	Weekly Monthly		
Formal vascular access monitoring	Weekly	*See "non-dialytic aspects of the intervention" in the protocol*	*None*
Visits by health-care professionals (other than nurses)			

*all lab values are pre-dialysis
¶corrected calcium (for albumin)
¥ all labs collected MONTHLY, except for transferrin saturation and ferritin which should be collected every 3 months (i.e. once per quarter)

The DCC will review the database monthly, and provide automated feedback for those items in Tier 2. These reports will be copied to designated members of the Standards of Care Committee. He/she will contact the local study coordinator for participants who generate 3 or more reports to determine the reason why the targets cannot be met. For those participants who are not able to meet targets despite adequate treatment, the further sending of automated reports may be discontinued. The Committee member will email the DCC to inform them of participants who should not have automated reports sent.

1) For those patients whose pre-dialysis Hgb is <110 g/L for 3 consecutive months, the following message will be sent to the study coordinator and/or local principal investigator:

> "As part of the FHN trial standards of care, the DCC is monitoring participants' laboratory values.
>
> Re: Patient ID # _____

We wish to bring to your attention that this patient's pre-dialysis hemoglobin has been less than the DQOI recommended target of 110g/L for the last 3 months. If you are already aware of this and have instituted appropriate treatment, please disregard this message."

2) For those patients who are on erythropoeitin AND whose pre-dialysis Hgb is >135 g/L for 3 consecutive months, the following message will be sent to the study coordinator and/or local principal investigator:

"As part of the FHN trial standards of care, the DCC is monitoring participants' laboratory values.

Re: Patient ID # _____

We wish to bring to your attention that this patient's pre-dialysis hemoglobin has been greater than the DQOI recommended target of 120g/L for the last 3 months. If you are already aware of this and have instituted appropriate treatment, please disregard this message."

3a) For those patients whose pre-dialysis phosphate is >1.80 mmol/L for 3 consecutive months, the following message will be sent to the study coordinator and/or local principal investigator:

"As part of the FHN trial standards of care, the DCC is monitoring participants' laboratory values.

Re: Patient ID # _____

We wish to bring to your attention that this patient's pre-dialysis phosphate has been greater than the recommended target of 1.8mmol/L for the last 3 months. If you are already aware of this and have instituted appropriate treatment, please disregard this message."

3b) For those patients who have pre dialysis serum phosphorus less than the lower limit of normal (for the lab where serum phosphorus was measured) for three consecutive months, the DCC will send a message to the Clinical Center.

4) Albumin corrected calcium is defined as Serum calcium + (0.8 x [Normal serum albumin - Patient's albumin]), where Normal serum albumin is defined as XXXXX.

For those patients whose pre-dialysis albumin-corrected calcium is <1.90 mmol/L for 3 consecutive months, the following message will be sent to the study coordinator and/or local principal investigator:

"As part of the FHN trial standards of care, the DCC is monitoring participants' laboratory values.

Re: Patient ID # _____

We wish to bring to your attention that this patient's pre-dialysis albumin corrected calcium has been less than the recommended target of 2.1mmol/L for the last 3 months. If you are already aware of this and have instituted appropriate treatment, please disregard this message."

5) Albumin corrected calcium is defined as Serum calcium + (0.8 x [Normal serum albumin - Patient's albumin]), where Normal serum albumin is defined as XXXXX.

For those patients whose pre-dialysis albumin corrected calcium is >2.90 mmol/L for 3 consecutive months, the following message will be sent to the study coordinator and/or local principal investigator:

> "As part of the FHN trial standards of care, the DCC is monitoring participants' laboratory values.
>
> Re: Patient ID # _____
>
> We wish to bring to your attention that this patient's pre-dialysis albumin corrected calcium has been greater than the recommended target of 2.6mmol/L for the last 3 months. If you are already aware of this and have instituted appropriate treatment, please disregard this message."

6) For those patients whose pre-dialysis bicarbonate is <20mmol/L for 3 consecutive months, the following message will be sent to the study coordinator and/or local principal investigator:

> "As part of the FHN trial standards of care, the DCC is monitoring participants' laboratory values.
>
> Re: Patient ID # _____
>
> We wish to bring to your attention that this patient's pre-dialysis bicarbonate has been less than the recommended target of 22mmol/L for the last 3 months. If you are already aware of this and have instituted appropriate treatment, please disregard this message."

7) For those patients whose pre-dialysis bicarbonate is >27mmol/L for 3 consecutive months, the following message will be sent to the study coordinator and/or local principal investigator:

> "As part of the FHN trial standards of care, the DCC is monitoring participants' laboratory values.
>
> Re: Patient ID # _____
>
> We wish to bring to your attention that this patient's pre-dialysis bicarbonate has been greater than the recommended target of 25mmol/L for the last 3 months. If you are already aware of this and have instituted appropriate treatment, please disregard this message."

20.3 Kinetic Modelling Action Items

a) DCC will report and the Adherence Committee will review (in conjunction with Kinetic Modeling Committee) any patient who has persistent underdialysis.

b) The Adherence Committee will review those patients who falling below target KT/V for 3 consecutive months.

c) DCC will report and the Adherence Committee will review any patient who has persistent nonadherence to therapy.

20.4 Core Facility Action Items

The Central HRQL Survey Center or Holter Reading Center or MRI Reading Center will report within 24 hours to the research coordinator or treating Nephrologist any patient who has potentially life-threatening findings on tests done exclusively for the purpose of the study. For quality assurance, the DCC will also report these findings to the study center when received by the database. These findings may include, but are not limited to:

1. answers 2 or 3 on question #9 of the Beck Depression Inventory ("would you kill yourself")
2. ventricular tachycardia or other life-threatening arrhythmias on the heart rate variability test
3. lung, mediastinal, esophageal, cardiac mass or large pericardial effusion on cardiac MRI.

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