FHN Daily and Nocturnal Trials

Talking Points - Core PI's to review these talking points with Site PIs
Version 1.2, February 2, 2006

1. Review Necessary Requirements for Site PI
    a. HIPAA certification. Have you taken a course? When were you last certified?
    b. IRB certification. Have you taken a course? When were you last certified?
    c. Basic GCP. Have you taken a course? When were you last certified?

2. General Principles of RCTs – Threats to a Study
    a. Equipoise - Before and after randomization, you and your staff must speak to a patient as if you are not certain which of the study arms is best. Otherwise, this could bias his performance on the physical function tests, for example, making him feel he has to do especially well if he is on the "good" treatment and making him sluggish if he knows he is in the "other" arm.'
    b. Bias. For example, in recruited population, ascertainment of endpoints (especially unblinded Quality of Life)
    c. Power. The power of the study is determined by recruitment of patients, completeness of follow-up, and maintenance of the targeted separation between groups (# treatments/week).

3. Protocol Design
    a. Review Study hypothesis - including endpoints
    b. Data analysis plan:
    There are two primary outcomes that are considered to be equally important. These are 1. 12-month change in the SF 36 physical health composite score or death, and 2. 12-month change in LV mass by a centrally-read cardiac MRI or death. The primary analysis will be conducted keeping each patient in the exact group the patient was randomized to, whether the patient ever received the protocol treatment assigned to that group or not. That is, the primary analysis plan is being done using Intent-To-Treat. For this reason, it is essential that all planned data be collected even for patients who are no longer following the planned treatment schedule.
    c. Review what happens to patients at the end of the study. (Nocturnal: may ask for NIH/CMS for extended follow-up).
    d. Do you have any issues with the study that preclude your involvement? Or preclude the involvement of your site?

4. Screening, Informed Consent and Randomization
    a. Sites must be absolutely sure that the patient fulfills all the inclusion criteria and does not fulfill any of the exclusion criteria. <u>For Nocturnal Study:</u> must have adequate home site, be able to pass the training, and does not need 4x a week dialysis on a regular basis. Evaluation of the likely suitability of the patient for nocturnal home dialysis during the baseline phase is essential, because if a substantial number of patients do not succeed in the training phase after randomization, the power of the study will be severely compromised. <u>For Daily Study:</u> must have adequate transportation.
    b. All baseline data must be collected before a patient can be randomized. If the patient is missing "just one thing" that is listed in the manual of operations as being required for

randomization, the patient is not eligible to be randomized until that piece of data is received. There are no special waivers

c. Once a patient is randomized, that patient is in the study throughout the scheduled follow-up period. All follow up data should be collected. This applies even if the patient is randomized to the experimental arm and stays on 3 times a week in center dialysis and never once receives the experimental (more frequent) therapy.

5. Good Clinical Practice (GCP) Record Keeping

a. Documentation & record keeping:

Essential Document file

Protocol and any amendments (& re-review)
Operations Manual & other written instructions
IRB-Approved consent forms
IRB correspondence
Information provided to patients
Recruitment advertising
Subject compensation/reimbursement
Serious Adverse Events / Safety Reports
Notes-To-File

Tracking logs for IRB submissions, SAEs, Safety Reports received from Sponsor, IRB-Approved Consent Form Versions, patient consent and re-consent, Signatures /Delegated Responsibilities, Researchers Training, Subject, Telephone, Notes-to-file

b. Recruitment procedure and consenting.

Allow sufficient time to consider all options
Provide opportunity for questions
Assess & reinforce comprehension as necessary
Sign & date form
Provide copy of signed form to patient

c. Baseline investigations
d. Treatment documentation
e. Discharge summary; important lab data for cause of hospitalization.
f. Adverse events reporting. What is an Adverse Event? What is a serious Adverse Event? Need to fill out forms

6. Clinical Care During the Trial

a. Dialysis Management. The need for strict adherence to the protocol for management of renal replacement therapy should be emphasized. Patient safety must, however, be the foremost concern. Investigator judgment must be used to ensure that rigid adherence to the protocol does not at any time result in compromise of patient safety.

b. Adherence and Planned reductions in therapy. The success of the study will be determined in large part by the extent to which patients randomized to 6 x/week dialysis maintain their 6x/week schedule. If a patient who is randomized to the frequent dialysis arm is unable or unwilling to maintain the 6x/week schedule, then guidelines in the protocol and MOP should be followed to maintain a treatment schedule which approximates the 6x/week schedule as closely as possible. These patients are retained in the statistical analysis under the intent-to-treat analysis plan.

Form 309 must be completed prior to known reductions in dialysis treatments (4 or more planned missed treatments within the next month) or in treatment time (planned average

time per session 30 minutes or more lower than minimum time under the study protocol for a period of at least 1 week). Treatment deviations due to hospitalizations are not counted. This form should be filed advance when you plan to deviate from the study plan for dialysis, including cases in which the deviation was requested by the patient.
c. Catheter malfunction. The most common cause of under-delivery of dialysis dose is likely to be catheter malfunction. Catheter malfunction should be suspected if the achieved blood flow rate is less than 90% of the prescribed rate or if catheter recirculation is > 15%, or high venous pressures (use your standard protocol). If the patient can't meet the targeted blood flow, you must prolong treatment to achieve the targeted Kt/V. Catheter replacement prior to the next planned dialysis treatment should be considered if catheter malfunction is present.

d. Monitoring Adequacy of Hemodialysis Treatments. The detailed algorithms for ensuring that the target dose of hemodialysis is achieved should be discussed. The use of calculation worksheets for the initial prescription of hemodialysis and modification of dose based on measurement of Kt/V should be described. Daily Study: Use Kt/V(2/3). Nocturnal Study: Patients must stay on dialysis 6 hrs a session for 6 days a week; with a std Kt/V of 4.0 or greater in experimental arm, and 3x wk meeting K/DOKI Kt/V goal in standard arm.
e. Isolated Ultrafiltration. The specific indications for isolated ultrafiltration will be left to the discretion of the primary physicians, however it is expected that the use of isolated ultrafiltration will be limited to patients with respiratory compromise or cardiac dysfunction manifested by objective criteria such as impaired oxygenation.
f. Associated therapy: monitoring so within K/DOQI for blood pressure, lipids, glucose

7. Vanguard Phase and DCC Status Reports

a. The performance of each center in recruiting patients, maintaining adherence to the targeted treatment schedules, completing the required case report forms, and obtaining the required measurements under the protocol will be summarized on a weekly basis in reports provided by the Data Coordinating Center.

b. The first year of the trial has been designated as a Vanguard phase. The DSMB will advise the NIH on whether the trial should be completed based on our performance during the Vanguard phase. Review the specific benchmark criteria which have been designated for the Vanguard.

8. Oversight Structure
   a. PI Steering Committee
   b. Executive Committee
   c. External DSMB