19. Kinetic Modeling - Nocturnal Trial

19.1 Introduction: Kinetic Modeling

The primary distinction betweens the treatment arms of the FHN Nocturnal Dialysis Study are in the frequency, duraction, and location of the treatments. In the nocturnal arm, 6 treatments will be conducted each week in the home, with each treatment lasting at least 6 hours. In the conventional HD group 3 treatments will be conducted in the dialysis unit each week, with each treatment typically lasting from 2.5 to 4.5 hours. The total weekly treatment time is expected to be approximatley 40 hours in the nocturnal treatment arm, compared to an average of approximately 10.5 hours in the conventional HD treatment group. Thus, in the conduct of the trial the main goal is to maintain the assigned duration and frequencies of the treatments in both treatment groups, and precise targeting of dialysis dose within a narrow range based on intricate kinetic modeling algorithms is not required. Nontheless, kinetic modeling will serve two important functions in this study: First, to provide minimum guidelines for the conduct of the interventions, and second, to characterize the targeted and achieved separation between the nocturnal HD and conventional HD interventions in treatment parameters related to solute clearance and to volume and blood pressure stability.

The guidelines for administration of the interventions are based on urea eKt/V are as follows:

i) *Conventional HD group:* Patients may remain on their usual dialysis prescription with 3 treatments per week subject to a minimum delivered eKt/V of 1.1 per session AND a minimum treatment time of 2.5 hours per session;
ii) *Nocturnal HD group:* Patients are dialyzed overnight in the home for 6 sessions per week, with a minimum treatment time of six hours AND a minimum delivered standardized Kt/V (stdKt/V) for urea of 4.0.

If the 6 times per week schedule is adhered to, simulation results indicate that the median sKt/V will be 5.12, with the 5^{th} and 95^{th} percentiles at 4.12 and 6.02, respectively. Thus, less than 5% of patients should have a stdKt/V of < 4.0 on their normal dialysis prescriptions. The patients whose stdKt/V falls below 4.0 will be advised to increase either their treatment times or other dialysis parameters (blood flow, dialysate flow, or dialyzer KoA).

If subjects in the nocturnal HD arm develop an unwillingness or inability to follow the 6x/week nocturnal treatment regimen specified by the protocol, efforts will be made to adopt a reduced treatment regimen which approximates the intended 6x/week nocturnal regimen as closely as possible.

As described in Section 19.2, an important aspect of the design of the study is that although the minimum dose target for the nocturnal arm is expressed in terms of the stdKt/V for urea, by varying both treatment frequency and total weekly treatment time the design is intended to achieve a large separation in the clearance of a wide range of solutes and in the stability of volume and blood pressure. The study design is not intended to determine the effects of each specific component of the nocturnal HD treatment regimen, but rather is based on the pragmatic objective of determining whether the combination of factors associated with the nocturnal HD regimen can improve outcomes.

19.1.2 Content of the Kinetic Modelling Chapter

Section 19.2 summarizes the targeted separation of selected treatment parameters between the nocturnal HD and the conventional HD treatment groups. Section 19.3 describes the computation of kinetic modeling parameters. The kinetic modeling measurement schedule is summarized in Section 19.4, and kinetic modeling procedures and data collection are reviewed in Section 19.5. Section 19.6 provies the DOQI standards for blood draws to be used in kinetic modelling.

19.2 Targeted Separation in Dialysis Parameters Between Treatment Arms

To understand the expected characteristics of the interventions in the two treatment arms, a simulation study was conducted to estimate the distributions of a number of key treatment parameters in the conventional HD and nocturnal HD interventions. We used a sample of 3285 patients from the 19XX Renal Research Institute data base to obtain estimates of the distribution of urea generation rate and urea distribution volume (V) for potential patients in the trial. Based on the protocol and a survey of participating clinical centers, we projected that treatment time would be uniformly distributed between 6 and 8 hours, dialysis blood flow would be distributed uniformly from 400 to 500 ml/min for 50% of patients on single needle dialysis and uniformly from 200 to 300 ml/min for the other 50% assumed to be using double needle dialysis; dialysate flow would be distributed uniformly from 200 to 350 ml/min, and that the typical urea KoA would be appoximately 450 ml/min. Based on these assumptions, we then simulated the targeted distributions of relevant parameters in the two treatment groups.

The results are presented in Table 19.1 below. The simulations assumed that all patients assigned to the nocturnal intervention actually received their targeted dialysis prescriptoin for 6 treatments per week, and that patients randomized to the conventional 3 times per week intervention actually received exactly 3 treatments per week. Thus, the results indicate the targeted rather than the achieved separation in the listed treatment parameters between the two treatment groups. The projected total weekly treatment time (median 40 hours for the nocturnal HD group vs. 10.5 hours for the conventional HD group) is almost 4-fold greater in the nocturnal HD group than in the conventional HD group. Largely due to the greater treatment time in the nocturnal HD group, the target equivalent renal clearance of β_2-microglobulin (a marker for clearance of middle molecular weight solutes) is 91% larger in the nocturnal HD group than in the conventional HD group, and the target standardized removal of phosphorus is over 4-fold larger in the nocturnal HD group. The targeted weekly standard Kt/V for urea, which is particularly sensitive to the frequency of dialysis treatments, is 108% higher in the nocturnal HD group. The greater frequency of the treatments and the greater total treatment time in the nocturnal HD arm compared to the conventional HD arm would provide a 50% reduction in the average amount of total ultrafiltration per dialysis treatment and a 74% reduction in the average ultrafiltration rate if patients fluid intake is the same in the two arms. Somewhat lower reductions in these ultrafiltration parameters would be projected if fluid intake is increased in the nocturnal HD arm compared to the conventional HD arm.

Table 19.1: Summary of the Dose Treatment Regimens

Parameter	Conventional HD (CHD)	Nocturnal HD (DHD)	% Difference in Medians (DHD vs. CHD)
Sessions per week	3	6	100%
Target prescription	Unspecified: eKt/V $\geq$ 1.10	sKt/V $\geq$ 4.0	-
Hours per session	$\geq$ 2.5 (median = 3.50)	6 to 8 (median = 7.0)	+100%
Maximum interdialytic interval (median, hours)	68.5	41.0	- 40.1%
Average interdialytic interval (median, hours)	52.5	21.0	- 60%
Hours per week (median, 5^{th} – 95^{th} percentile)	10.5 (9 – 13.1)	40 (36 – 45)	+ 281%
eKt/V urea per treatment (median, 5^{th} – 95^{th} percentile)	1.39 (1.12 – 1.75)	1.70 (1.07 – 2.40)	+ 22.3%
Weekly stdKt/V urea (median, 5^{th} – 95^{th} percentile)	2.46 (2.16 – 2.80)	5.12 (4.12 – 6.02)	+ 108%
Weekly eKR β_2-microglobulin (ml/min per 35 L total urea volume) (median, 5^{th} – 95^{th} percentile)	4.73 (4.12 – 5.32)	9.03 (7.84 - 10.67)	+ 90.9%
Standardized phosphorus removal (mg/day) (median, 5^{th} – 95^{th} percentile)	299 (254 - 374)	1281 (1036 - 1501)	+ 328%

eKt/V = equilibrated Kt/V, stdKt/V = standard weekly Kt/V, eKR = equilibrated equivalent renal clearance. Medians, 5^{th}, and 95^{th} percentiles based on simulations assuming distributions of patient characteristics from the Renal Research Institute Database, n=3285.

19.3 Calculation of Kinetic Modeling Treatment Parameters

Urea and Creatinine Kinetic Modeling Parameters

HD dosing is traditionally based on clearance of urea, expressed as Kt/V (K is the clearance of urea, t is the duration of the dialysis session, and V is the volume of distribution of urea in the patient). Traditionally, single-pool Kt/V (spKt/V), determined mostly from the pre- and postdialysis BUN values, was used to define and measure the dose in conventional HD [Gotch, 1985]. However,

because spKt/V overestimates the effective clearance due to the phenomenon of urea rebound, the concept of single pool Kt/V has been superseded by equilibrated Kt/V (eKt/V) [Daugirdas, 1995;Pedrini, 1988], which evaluates the clearance of urea while taking rebound into account. A further complication in the Nocturnal study is that due to the use of different treatment frequencies, per-treatment measures of urea clearance would not be expected to adequately compare dialysis dose between the two treatment arms. As a result, dialysis dose will be quantified using unified dose measures such as stdKt/V. Because residual renal function will be estimated as the average of the residual clearances of BUN and creatinine, both urea and creatinine kinetics will be performed. In the algorithm described below, per-treatment dose measures such as eKt/V are computed as an intermediate step for the estimation of residual renal function and the determination of stdKt/V. The urea kinetics parameters are computed first, followed by creatinine kinetics.

Step 0: Preliminary Estimate of Kru

The algorithm for calculating urea kinetic modeling parameters first obtains preliminary estimates using a ballpark approximation of the patient's residual urea clearance (Kru), and then repeats the calculations using a more refined estimate of Kru.

Step 0a. Initialize Kru to 0.

Step 0b. Using the anthropometric volume as a preliminary estimate of the urea volume (V), apply the iterative calculations of the 2-BUN algorithm of Depner and Cheer [Depner, 1989] to the predialysis and postdialysis BUN, the pre- and postdialysis weights, and the current estimate of Kru to solve for the equilibrated urea generation rate (eG). The patient's actual dialysis treatment schedule during the week preceding the kinetic modeling session will be employed in the iterative calculations.

Step 0c. Recompute Kru as:

Kru = { [UUN × (Urine Volume)] / (Collection Time) } / {time averaged concentration of BUN},

where UUN denotes the urine urea nitrogen concentration and the time averaged concentation during the collection period is computed from the final step of the algorithm of 0b.

Step 0d. Repeatedly apply steps 0b and 0c until convergence.

Step 1: Calculation of Predicted Dialyzer Clearance (Kd)

The first step is the calculation of single pool Kt/V and single pool V (Vsp) based on the data from a kinetic modeling session. To calculate these quantities for a single modeled dialysis session, the predicted extraction ratio (PER) and dialyzer clearance Kd will first be calculated using the formulas:

$$PER = \left[e^{\frac{K_0A}{Qb}\left(1-\frac{Q_b}{Q_d}\right)} - 1 \right] \Big/ \left[e^{\frac{K_0A}{Qb}\left(1-\frac{Q_b}{Q_d}\right)} - \frac{Q_b}{Q_d} \right]$$

and

$$Kd = 0.894(PER \times Qb) \times (1 - Qf/(0.894 \times Qb)) + Qf,$$

where Qb denotes the blood flow rate, Qd is the dialysate flow rate, KoA is the in-vivo dialyzer KoA, and Qf is the ultrafiltration rate. Based on results from the HEMO trial [Depner TA, *ASAIO J* 50:85-93, 2004], the in-vivo KoA will be estimated from the manufacturer's supplied in-vitro KoA at a Qd of 500 ml/min, using the expression:

$$K_0A = 0.84 \times [\text{Manufactur's in-vitro KoA at Qd = 500 ml/min}] \times [1 + \beta_{Qd} \times (Qd - 500)/300 + \beta_{reuse} \times (\text{reuse \#})]$$

where Qd denotes the dialysate flow using during the dialysis, (reuse #) denotes the number of reuses for the dialyzer used for the treatment, and β_{Qd} and β_{reuse} are constants which account for the effects of dialysate flow and reuse on the in-vivo KoA. Based on the HEMO Study results, β_{Qd} will be defined as 0.055, and β_{reuse} as -0.006. Due to reports of improvements in blood line pump segments since the HEMO trial, the actual blood flow Qb will be assumed to be equal to the nominal blood flow based on the blood pump speed, without the downward adjustments that were applied in the HEMO trial [Depner, 2004].

Step 2: Modeling single pool Kt/V and Vsp

Delivered spKt/V and Vsp will be determined from the above predicted Kd, the pre- and post-BUNs, the pre- and post weights, and the estimated Kru while taking into account the patient's dialysis treatment schedule using an iterative modelling program that employs the 2-BUN algorithm of Depner and Cheer [Depner, 1989].

Step 3: Estimation of double-pool parameters using the Tattersall rate equation

After determining Vsp and delivered spKt/V, the modification to the Tattersall rate equation developed in the HEMO Study [Daugirdas, 2004] will be used to estimate eKt/V from spKt/V according to the formula

$$eKt/V = spKt/V \times (t/(t+Tp))$$

where t denotes treatment time, and Tp = 30.7 minutes for AV accesses and 18.5 minutes for venous catheters. The equilibrated postdialysis BUN under the modified Tattersall equation is:

$$Ceq = C0 \times (Ct/C0)^{(t/t + Tp)}$$

As described in Daugirdas [1996], the more accurate double pool modeled volume of urea distribution (Vdp) will be estimated as:

$$Vdp = Vsp \times \log(Fdp \times (C0/Ct))/(Fdp \times \log(C0/Ct)), \qquad \text{(Eq 1)}$$

where C0 and Ct denote the pre and postdialysis BUNs, and Fdp is defined by

$$Fdp = Ct/Ceq.$$

Step 4: Computation of running medians for eKt/V and Vdp

In the fourth step of the kinetic modeling algorithm, running medians will be obtained for eKt/V and Vdp. Starting at the kinetic modeling session in Month 2 of follow-up, 4-session running median eKt/V and Vdp values (defined as meKt/V and mVdp) will be obtained as the medians of these quantities over the current session and the prior three modeling sessions. At baseline and the Month-1 follow-up sessions, the running medians will be calculated using the current session and all available prior modeling sessions. . Note that V is considered a physiologic constant whereas eKt/V may vary depending on conditions of the dialysis from session to session.

The calculation of the running medians is modified following access modifications to give increased emphasis to kinetic modeling sessions conducted after the latest access modification by making three copies of eKt/V and Vdp from sessions after the last access modification prior to calculating the running medians. Thus, for example, if the access was newly modified after the preceding dialysis but before the current dialysis, the 4-sesion running median is applied to three copies of eKt/V and Vdp from the current session and one copy from the three preceding modeling sessions.

Step 5: Calculation of equilibrated urea generation rate and whole body clearance

In the fifth step, calculate the whole body urea clearance as

$$Kwb = eKt/V \times mVdp/t.$$

Assuming a weekly steady state, the equilibrated urea generation rate (eG) is estimated by applying the 1-pool variable volume model with C0, mVdp, Kru, pre- and postdialysis weights, and Kwb as input parameters to calculate an estimated pre-dialysis BUN (C0) for a dialysis session beginning exactly 1 week after the current session.

Step 6: Obtain preliminary estimate of the BUN vs. time concentration curve for 1-week period

The BUN concentration curves will be generated using a 2-pool variable volume iterative model in which the postdialysis total volume of urea distribution is the running median V (mVdp) defined in Step 4, divided between the intracellular and extracellular compartments in a 2 to 1 ratio. Weekly steady state conditions will be assumed, including a constant urea generation rate [estimated as the equilibrated G (eG) from Step 5], a constant residual urea clearance (estimated in Step 2), and a constant weekly dialysis treatment schedule. The effective dialyzer clearance Kdeff and the intercompartment mass transfer coefficient (Kc) will be jointly estimated using the 2-pool model and fitting the BUN vs. time concentration curve in the extracellular compartment to the measured pre- and postdialysis BUNs, and the whole body urea concentration to the equilibrated BUN (Ceq) defined by the Tattersol method as described above.

Note that in this approach patient-specific estimates of Kc are not estimated from the data since no

delayed postdialysis BUNs are measured under the FHN protocol. Instead, Kc is imputed for each patient to be consistent with the modified Tattersol rate equation. Following estimation of Kc and Kdeff, the Runge-Kutta algorithm will be used to estimate the full BUN vs. time concentration curves for the intracellular and extracellular compartments.

Step 7: Recompute Kru

Kru = { [UUN × (Urine Volume)] / (Collection Time) } / {time averaged extracellular BUN}

where the time averaged extraccellular BUN concentration is computed, using the 2-compartment model described above, over the collection period.

Step 8:

Repeat Steps 1 – 4 using the updated estimate of Kru.

Step 9:

Repeat the calculation of spKt/V by applying the 2-BUN weekly iterative algorithm with the updated mVdp, Kru, C0, Ct, pre- and postdialysis weights as input parameters. Then update the estimates of eKt/V, eG, and the weekly BUN vs. time concentration curves by repeating Steps 5 and 6.

Computation of Standard Kt/V and Equivalent Renal Clearance

When patients are on conventional three times per week dialysis, urea Kt/V is generally accepted as a surrogate for dialysis dose. However, this trial requires consideration of a wider range of solutes and measures of clearance designed to generalize across different treatment schedules.

To compare different treatment schedules, clearance of urea have been expressed in terms of the quantity standard weekly Kt/V (stdKt/V), defined as:

stdKt/V = [eG/(mean predialysis peek)] × [total treatment time during 1 week] / V,

where eG denotes the equilibrated urea generation rate, the expression “mean predialysis peek” denotes the average of the predialysis BUN concentrations over all the dialysis in the 1 week period, and V denotes the volume of distribution for urea. The stdKt/V will be the primary measure of solute clearance in the study. An alternative measure is the so-called equivalent renal clearance (EKR), defined either as the ratio of the urea generation rate G to the time averaged concentration concentration (EKR_{ave}) [Casino 96]. The concept of EKR_{ave} can be also applied to a spectrum of other solutes besides urea to more fully characterize the clearance of solutes by dialysis.

The mean pre-dialysis peak concentration and the time-averaged concentration of BUN will be obtained from the full weekly curves estimated in Step 9 of the above algorithm. The values of $EKR_{peak,}$ EKR_{ave}, and stdKt/V are then computed based on the ratios of eG (also obtained in Step 9) to these values.

Step 10. Estimate the equilibrated postdialysis creatinine concentration by a modified Tattersall adjustment in which the time constant Tp for creatinine is estimated from data in the HEMO trial.

Step 11. Obtain preliminary estimates of residual clearance of creatinine (Krcr) and of the equilibrated creatinine generation rate (eGcr).

Step 11a. Initialize Krcr to 0.

Step 11b. Assuming that creatinine has the same distribution volume as urea, apply the same iterative calculations used in the 2-BUN algorithm to the predialysis creatinine, the estimated equilibrated postdialysis creatinine from Step 10, the pre- and postdialysis weights, the running median urea volume, and the current estimate of Krcr to solve for the equilibrated creatinine generation rate (eGcr). The patient's actual dialysis treatment schedule during the week preceding the kinetic modeling session will be employed in the iterative calculations.

Step 10c. Recompute Krcr as:

Krcr = { [Scr × (Urine Volume)] / (Collection Time) } / {time averaged concentration of Scr},

where the time averaged concentation during the collection period is computed from the final step of the algorithm of 10b.

Step 10d. Repeatedly apply steps 10b and 10c until convergence.

Step 11. Obtain preliminary estimate of creatinine vs. time concentration curve.

Similarly to BUN, the creatinine concentration curves will be generated using a 2-pool variable volume iterative model in which the postdialysis total volume of urea distribution is the running median V (mVdp), divided between the intracellular and extracellular compartments in a 2 to 1 ratio. Based on the estimates of Krcr and eGcr from Step 10, the effective dialyzer clearance for creatinine Kdcreff and the inter-compartment mass transfer coefficient for creatinine (Kccr) will be jointly estimated using the 2-pool model and fitting the creatinine vs. time concentration curve in the extracellular compartment to the measured pre- and postdialysis creatinine concentrations, and the whole body urea concentration to the equilibrated creatinine estimatd by the Tattersall method. The time constant Tp for creatinine will be estimated using data from the HEMO trial.

Following estimation of Kccr and Kdcreff, the Runge-Kutta algorithm will be used to estimate the full creatinine vs. time concentration curves for the intracellular and extracellular compartments.

Step 12. Update estimates of Krcr and eGcr, and estimate residual GFR.

Repeat Steps 10b and 10c to update Krcr and eGcr based on the creatinine concentration curve from Step 11. The estimated residual GFR, expressed in ml/min per 35 L of anthropometric urea volume, is:

Residual GFR = 0.5 × [Krcr + Kru] × [35/Vant]

Step 12. Repeat Step 11 with the updated values of Krcr and eGcr to obtain the final creatinine vs. time concentration curve.

19.4 Kinetic Modeling Measurement Schedule

Table 19.2 describes the schedule for kinetic modeling visits, the determination of residual renal function, and the retrospective acquisition of other information from the dialysis session run sheets.

Table 19.2: Schedule of Kinetic Modeling and Dialysis-Session Related Data

Visit Number	Type of Data Collection			
	Complete Kinetic Modeling **(Form 273)**	1-Week Retrospective Data from Run Sheets **(Form 274)**	Monthly Dialysis Treatment Attendence **(Form 275)**	Residual Renal Function **(Form 206)**
B-01	✓	✓	✓	✓
B-02*	✓		✓	
F-1	✓		✓	
F-2	✓		✓	
F-3	✓	✓	✓	
F-4	✓		✓	
F-5	✓	✓	✓	✓
F-6	✓		✓	
F-7	✓		✓	
F-8	✓		✓	
F-9	✓	✓	✓	
F-10	✓		✓	
F-11	✓		✓	
F-12	✓		✓	
F-13	✓		✓	
F-14	✓	✓	✓	✓

* One additional baseline kinetic modeling session must be conducted if the deviation between the estimates of the estimated urea volume (Vdp) for the first two baseline kinetic modeling sessions exceeds 28% of their mean value (corresponding to a coefficient of variation > 20%).

Baseline Period.

As shown in Table 19.2, two kinetic modelling sessions, designated B-01 and B-02, will be conducted during the baseline evaluation phase of the trial. The two sessions should be spaced at

least one week but no more than six weeks apart. Form 273 must be completed for each kinetic modelling session.

If the deviation between the estimates of the estimated urea volume (Vdp) for the first two baseline kinetic modeling sessions (B-01 and B-02) exceeds 28% of their mean value, a third baseline kinetic modeling session (labelled B-03) will be required. The median of all baseline urea volume estimates will be used to determine the initial post-randomization dialysis prescription.
In order to prevent randomization of patients who are unable to achieve an eKt/V close to the minimum level of 1.10 in the conventional HD arm, subjects must achieve a mean eKt/V of at least 1.00 on the final two baseline kinetic modeling sessions in order to be randomized. If the mean eKt/V for the final two of the baseline kinetic modeling indicated above is less than 1.00, then an additional kinetic modeling session may be scheduled, and the mean eKt/V recomputed from the last two baseline sessions. This process may be repeated up to 4 times, and the minimum eKt/V requirement will be met if at any of these tries the average eKt/V for the final two assessments exceeds 1.00. The baseline minimum threshold of 1.00 is set 0.10 eKt/V units below the minimum of 1.10 in the conventional HD arm, to take into account the random variation that can be expected from the average eKt/V over two modeling sessions.

Tables 19.3a – 19.3h in the Appendix provide a sample grid of prescribed dialysis times for patients ranging in size from 20 to 55 liters in 5 liter increments. The target eKt/V is 1.10 per dialysis. Treatment times equal to or larger than the values indicated in the tables will lead to target eKt/Vs of at least 1.10. It is recommended that the selected treatment time be at least 5% larger than the minimum values listed in the tables in order to reduce the likelihood that the achieved eKt/V will fall below 1.0. We expect that the prestudy dialysis prescriptions for the large majority of patients will already substantially exceed 1.10, so that prescription adjustments will be necessary for only a minority of patients during baseline. Selectable dialysate flow rates are either 500 or 800 ml/min and selectable blood flow ranges from 200 to 500 ml/min in 50 ml/min increments.

A timed urine collection of at least 24 hours should be performed for all patients producing urine prior to one of the first two kinetic modeling sessions during baseline. The duration of the timed collection is optional as long as it is at least 24 hours and it extends to the start of the kinetic modeling session. Although the timed urine collection may be obtained in the interdialytic interval prior to either of the first two modeling sessions, it is recommended that the collection be obtained prior to the first baseline kinetic modeling session (B-01) when this is feasible. Performing the collection at this time has the advantage that patients who exceed the maximum residual urea clearance limit of 3.0 ml/min per 35 Liters can be identified early in baseline, allowing them to be dropped from the trial before additional efforts are expended needlessly. If logisitical difficulties lead to a failed urine colleciton, the urine collection may be attempted again prior to the second baseline modeling sesssion.

The dialysis run sheet should be reviewed for the 1-week period preceding the initial B-01 kinetic modeling session in order to record on Form 274 information pertain to treatment time, blood pressure, weight, and hypotensive symptoms for each dialysis treatment performed during this period. The 1-week period for the retrospective data collection ends on the day prior to the kinetic modeling session, and will normally include the three preceding dialyses for patients on a 3 times per week treatment schedule.

Follow-up.

At randomization, a report from the DCC will notify the clinical center of the patient's assigned treatment arm. Patients assigned to the nocturnal treatment arm should conduct and complete training and preparation for the home environment for dialysis during the 1.5 months following randomization. Patients assigned to the nocturnal arm should normally initiate nocturnal dialysis by the end of the second month of follow-up. Throughout the training period, patients assigned to the nocturnal treatment arm may remain on their usual prescriptions as long as their prescribed eKt/V exceeds 1.10. The minimum dialysis prescriptions needed to achieve an eKt/V of 1.10 are summarized for 5L increments of urea voume in Tables 19.3a – 19.3h in the Appendix.

As described below, kinetic modeling sessions are conducted monthly throughout the follow-up period. After the running median volume Vdp is updated following the 1-month modeling session, the DCC will transmitt alternative dialysis prescriptions for a target stdKt/V of approximately 4.25 for a 6 treatment per week nocturnal dialysis treatment schedule. Subsequently, modeling data will be obtained monthly, and revised dialysis prescriptions will be provided if the running median V (over 4 months) increases by an amount that leads to a decrease in the updated prescribed stdKt/V to a value less than 4.0. These prescriptions represent lower bounds for the dialysis prescriptions under the protocol. As noted in Sections 19.1 and 19.2, it is expected that most patients assigned to the nocturnal arm will employ prescriptions with stdKt/V substantially higher than 4.0, so in practice it is expected that it will be relatively unusual that nocturnal dialysis prescriptions will need to be increased based on the DCC prescriptions.

The DCC will not transmit prescription reports for patients assigned to the conventional HD group, as these patients may continue on their usual prescriptions as long as their prescribed eKt/V exceeds 1.10. The minimum dialysis prescriptions needed to achieve an eKt/V of 1.10 are summarized for 5L increments of urea voume in Tables 19.3a – 19.3h in the Appendix.

The schedule for kinetic modeling during follow-up is based on calendar month. The calendar month following the month in which the patient is randomized is designated as F-1, with the subsequent month designated F-2, and so on. Thus, if a patient is randomized in the month of October, then F-1 corresponds to the month of November, F-2 to December, and so on for F-3 through F-12. Kinetic modeling sessions for the FHN Nocturnal Study are conducted monthly (in calendar months F-1, F-2, ….., F-12). For patients assigned to the conventional in-center HD group, it is desirable, if arrangements can be made, that the modeling sessions be conducted during midweek dialyses (either Wednesday or Thursday), but for logistical purposes, it is recommended that the FHN Study kinetic modeling sessions be conducted to coincide with the dialysis clinic's usual monthly kinetic modeling sessions to avoid additional blood draws.

Kinetic modeling sessions do not need to be repeated in the event of interuptions or missing data on the dialysate concentrations (Question 19 on Form 273). Kinetic modeling sessions should be repeated, however, if any of the responses to Questions 8 through 18 can not be obtained, or if either the pre- and postdialysis BUNs are not measured. Kinetic modeling may also be optionally repeated at the discretion of the FHN Study team.

For patients who continue to produce urine, timed urine collections of at least 24 hours should be performed preceding the kinetic modeling sessions at months F-5 and F-14. For patients assigned to the conventional in-center HD group, the duration of the collection period is optional, as long as it is at least 24 hours and it extends to the start of the kinetic modeling session. For logistical purposes, we recommend that the collection be initiated after the patient completes the dialysis preceding the kinetic modeling session.

For patients assigned to the nocturnal arm, follow-up urine collections should be initiated as the start of the dialysis session preceding the monthly kinetic modeling session, and should continue until the initiation of the modeled dialysis.

Similar to baseline, at months F-3, F-5, F-9, and F-14 the dialysis run sheet should be reviewed for the 1-week period prior to the kientic modeling session to record on Form 274 information pertaining to treatment time, blood pressure, weight, and hypotensive symptoms for each dialysis treatment performed during this period. As in baseline, the 1-week period for the retrospective data collection ends on the day prior to the kinetic modeling session, and will normally include the three preceding dialyses for patients on a 3 times per week treatment schedule, and six preceeding dialyses for patients on a 6 times per week nocturnal treatment schedule. If the kinetic modeling session is conducted during the first week of the calendar month, the period for retrospective data collection may extend into the preceding calendar month.

19.5 Procedures and Data Collection

Kinetic Modeling Sessions (Form 273)

For patients assigned to the conventional in-center HD treatment arm, it should not be necessary, in general, for the FHN Study coordinator to attend kinetic modeling sessions held during follow-up, since these sessions may coincide with the dialysis clinic's standard kinetic modeling. However, it is essential that arrangements be made to request measurement by the local laboratory of pre- and postdialysis creatinine and phosphorus in addition to the BUN. The pre and postdialysis blood samples should be drawn using DOQI standards (see Section 19.6). Because the baseline sessions will generally be held one to two weeks apart, it is likely that at least one of these will not coincide with dialysis clinic's regular monthly kinetic modeling.

Patients assigned to the nocturnal treatment arm will provide a copy of their "run sheets" to the home hemodialysis training center on a weekly basis. Patients will not need to provide a copy of the run sheets if they are being monitored centrally. The information on the paper copy run sheets will include start and stop times, blood and dialysate flow rates and blood pressure and pulse readings. This information will be reviewed by the principal investigator for each Clinical Center and will be used to both determine if the patient is compliant with therapy and also for safety evaluations.

Form 273 (the Kinetic Modeling Form) must be completed at each kinetic modeling session. The form should be completed for all available items even if certain items are missing. Question 5, which pertains to the type of kinetic modeling session, should be coded as "1 = Routine KM" unless

the kinetic modeling sessions is being conducted as a repeat session due to missing data or is being repeated at the discretion of the FHN staff, in which case the question should be answered as "2=Redo". During follow-up, repeat kinetic modeling sessions are preferably conducted in the same calendar month as the original kinetic modeling session (which is being repeated), but if necessary the repeat session can be conducted in the subsequent calendar month, as long as it is conducted prior to the standard kinetic modeling for that month. Thus, during follow-up, exactly one Form 273 with Question 5 designating "1 = Routine KM" should be completed during each calendar month from F-1 through F-14. Additional kinetic modeling sessions would be designated as redos.

Items 6 through 19 on Form 273 should be completed using information from the dialysis run sheet.

Item 7 (Reuse number) should be designated as 0 for the first use of the dialyzer, 1 for the second use, 2 for the third use, and so on. This may at first seem counterintuitive, but note, for example, that at the second use the dialyzer is being reused for the first time, and in general the number of resuses is one less than the number of uses.

Question 9b addresses whether there has been a surgical or radiological intervention since the previous kinetic modeling session. This is intended as a quality control check to assure that no access revisions are missed in the database. In the event that a surgical or radiological intervention has been performed, this intervention should be documented on Form 272 if it has not already been done.

Question 10 deals with the needle type for the dialysis (single vs. double needle).

Question 11 obtains the date of the dialysis preceding the modeling session, and is used to determine if the time-interval between the preceding and current dialysis was in accordance with the patients assigned treatment schedule. In the event of deviations from the standard interdialytic interval, kinetic variables which are senstive to predialysis solute concentrations will not be calculated.

Question 13 designates whether the total interruption time exceeded 15 minutes. Interruption time includes:

1) any lowering of the blood flow rate for greater than 15 minutes,
2) any time when dialysate was in bypass,
3) any time in the middle of dialysis when either blood or dialysate flow was interrupted due to problems with needle placement, clotting, water pressure, or other mechanical problems, etc.

Question 14 indicates the treatment time, in minutes. The treatment time should be based on the actual dialysis treatment time indicated on the machine readout for all delivery systems which provide this information. It is expected that almost all systems used for patients in the FHN Study include this information. In the event that the delivery system does not provide a machine readout of the treatment time, enter the difference between the start and end times of the treatment.

Question 15 asks for the average blood flow during dialysis if this is provided by the dialysis

machine. Otherwise, the initial blood flow reading indicated in the dialysis run sheet at or after 30 minutes from the start of dialysis should be indicated.

Question 18 asks for the dialysate flow rate. If the dialysis flow rate was modifed during the treatment, indicate the flow rate at 30 mintues following the start of the dialysis.

Question 17 regarding complications experienced during the dialysis treatment should be answered based on information in the dialysis run sheet.

Question 19 requests concentrations of selected substances in the dialysate. These fields may be skipped if the requested information is not present in the run sheet.

Question 20 is intended to documents the local laboratory measurements of the predialysis serum albumin and the pre- and postdialysis BUN, serum creatinine, and serum phosphate from the kinetic modeling session. Normally, the measurements will be transmitted by the dialysis clinic's local laboratory within two or three days following the dialysis treatment. The kinetic modeling session must be repeated if either the pre or postdialysis BUNs are missing. Every effort should be made to also collect the pre and postdialysis serum creatinines or serum phosphates, but the session need not be repeated in the event that these are missing.

Residual Renal Function (Form 206)

Timed urine collections of at least 24 hours are required once during baseline and at months 5 and 14 during follow-up. Urine is collected during the the interdialytic interval preceding kinetic modeling sessions. Form 206 is required to document the information needed to compute residual renal clearance. *The timed urine collection should be performed for all patients who produce urine.* However, the urine sample needs to be analyzed only if the total urine output from the collection is at least 100 ml/24 hours. If the volume is less than 100 ml, a sample need not be shipped for measurements at the dialysis facility's local laboratory.

Question 5 documents whether the urine output exceeded 100 ml/24 hours. If the urine output does not exceed 100 ml/24 hours, you may skip to the end of the form (Question Q200). If the urine output does exceed 100 ml/24 hours, continue with Question 6.

Questions 6 and 7 request the start and end times of the urine collection period.

For patients assigned to the conventional in-center HD arm, Questions 8 – 11 request the start and end times of the dialysis treatments immediately prior to and immediately subsequent to the urine collection. For patients assigned to the nocturnal arm, Questions 8 and 9 refer to the start and end times of the dialysis conducted duruing the collection period, and Questions 10 and 11 refer to the start and end time of the immediately subsequent dialysis.

Question 12 obtains the volume of the collection.

Questions 13 – 15 are intended to document the local laboratory measurements of urine urea nitrogen, urine creatinine, and urine phosphorus.

Retrospective Review of Dialysis Run Sheets (Form 274).

Form 274 should be completed to document retrospective data from the dialysis run sheets over 1-week periods at baseline and at months 3, 5, 9, and 14 of follow-up. The periods for the retrospective review extend for one week prior to the initial kinetic modeling session during baseline, and for one week prior to the F-3, F-5, F-9, and F-14 kinetic modeling sessions during follow-up, excluding the kinetic modeling session itself. Thus, for patients undergoing 6 times per week nocturnal dialysis, the 6 dialyses preceding (but not including) the kinetic modeling session should be documented on the form. For patients undergoing 3 times per week dialysis, the 3 dialyses preceding (but not including) the kinetic modeling session should be documented. The session immediately preceding the modeled dialysis is documented under Question 4, Session – 1. The prior session (2 dialyses before the modeling session) is documented under Question 5, Session – 2, and so on.

Attendence at In-Center Dialyses (Form 275)

Form 275 should be completed at the start of each calendar month in follow-up, beginning after month F-1, to document any missed dialyses during the preceding calendar month.

19.7 Procedures for Blood Draws

For patients assigned to the conventional 3 times per week in-center arm, pe and postdialysis blood samples may may be drawn using the dialysis clinic's usual procedures. When possible, the FHN Steering Committee recommends that DOQI standard be used. The current DOQI standards for blood draws for kinetic modeling are described below. **It is recommended that the stop flow technique (see subsection "Stopping dialysate flow prior to sampling" below) be employed for obtaining the postdialysis sample for patients assigned to the nocturnal treatment arm.**

DOQI Standards:

When dialysis adequacy is assessed by pre vs. postdialysis blood urea nitrogen concentration measurements, the blood samples must be drawn according to certain acceptable procedures.

1) Both samples (pre and post) must be drawn during the same session.
2) The risk of underestimating predialysis BUN due to saline dilution must be avoided by drawing blood before any saline has entered the patient during initiation of dialysis.
3) The risk of underestimating postdialysis BUN due to access recirculation must be avoided: Prior to sampling, one needs to either slow the blood flow through the dialyzer or to stop the dialysate flow to eliminate any re-entry of dialyzed blood back into the dialyzer.

Background
Summary of updated changes
The updated 2006 K/DOQI recommendations include the use of the dialysate stop flow method first recommended by Wu et al (Nephrol Dial Transplant. 1997 Oct;12(10):2124-7). The K/DOQI Committee was concerned about the risks of needlestick injury in trying to puncture a bloodline containing potentially hazardous infectious agents under time pressure, and for this reason, the time constraints of the slow blood flow method were relaxed, and a stop-blood flow method is preferred, as well as blood-drawing methods that don't involve needles at all (see CPR).

As was reviewed in the 2000 K/DOQI guidelines, there are 3 components of postdialysis urea nitrogen rebound. The first is due to access recirculation (AR), which resolved within seconds after stopping dialysis. The second is due to cardiopulmonary recirculation (CPR) which resolves within 1-2 minutes. The third is due to entry of urea from relatively undialyzed tissues and body compartments, which we will term remote-compartment (RC) rebound, which resolves withn 30-60 min after stopping dialysis.

The focus of the blood drawing guideline is to limit the effect of AR on the postdialysis BUN sample because AR can cause both large overestimations of the delivered dose and large reductions in the true delivered Kt/V, often below 0.8 (at which level mortality risk is strongly increased) in patients with apparent Kt/V values of 1.4 or more (Daugirdas, AJKD) . Since the K/DOQI 2000 guidelines were published, it has become clear that rebound is relatively predictable based on the rate of dialysis (HEMO Pilot and HEMO2). For these reasons, the recommendation remains to draw the postdialysis blood urea sample within several minutes (15-18 sec) after the end of dialysis. Since the 2000 guidelines were published, some papers have shown that sampling blood about 30 min prior to the end of dialysis can predict the blood urea nitrogen level 30 min after the end of

dialysis (Jean G et al, Kidney Int. 1999 Sep;56(3):1149-53.) This method is not recommended because of its relative complexity, because rebound is relatively predictable based on the rate of dialysis, and most importantly, because in the presence of AR, the dialysis dose can still be markedly overestimated,

Predialysis BUN. The predialysis BUN must be drawn before dialysis is started to prevent this sample from reflecting any impact of dialysis. Dilution of the predialysis sample with saline or heparin must be avoided. Underestimating predialysis BUN will result in underestimation of delivered Kt/V or URR, and the protein catabolic rate (PCR) will be underestimated.

Recommended method when utilizing an arteriovenous fistula or graft:

1. Obtain the blood specimen from the arterial needle prior to connecting the arterial blood tubing or flushing the needle. Be sure that no saline and/or heparin is in the arterial needle and tubing prior to drawing the sample for BUN measurement.

Purpose: Prevents dilution of the blood sample.

2. Do not draw a sample for use as a predialysis measure of BUN if hemodialysis has been initiated, or if saline or heparin is present in the lines.

Purpose: Prevents sampling of dialyzed blood or dilution of sample, respectively.

Recommended method when utilizing a venous catheter:

1. Withdraw any heparin and saline from the arterial port of the catheter, following the dialysis clinic's protocol.

Purpose: Prevents dilution of the blood sample.

2. For adult patients, using sterile technique, withdraw 10 mL of blood from the arterial port of the catheter. For pediatric patients, withdraw 3 to 5 mL, according to the fill volume of the catheter. Do not discard this blood if the intent is to reinfuse it after the sampling is complete (see step 4).

Purpose: To ensure that the blood sample will not be diluted by heparin. Ideally, all the contaminating diluent is removed in step 1. Step 2 provides an additional margin of security. Because pediatric patients and their catheters are smaller, recommended volumes are reduced.

3. Connect a new syringe or collection device and draw the sample for BUN measurement.

Purpose: Prevents dilution of the sample, and preserves the blood from step 2 for reinfusion, if so desired.

4. Complete initiation of hemodialysis per dialysis clinic protocol. (Optional step: reinfuse the blood drawn from step 2.)

Purpose: Reinfusion minimizes blood loss and may be particularly desirable in pediatric patients who have significantly smaller blood volumes.

Postdialysis blood sampling procedure.

Proper timing for acquisition of the postdialysis BUN sample is critical. Immediately upon completion of hemodialysis, if vascular access recirculation was present, some of the blood remaining in the angioaccess and extracorporeal circuit is actually recirculated blood. That is, some of the just-dialyzed blood has been routed through the angioaccess and the extracorporeal circuit for hemodialysis without that blood first having passed through waste product-rich tissues. If the blood sample is drawn immediately upon completion of dialysis, just-dialyzed blood that has recirculated into the angioaccess will dilute the sample. The consequence of sampling this admixture is a falsely reduced BUN value and artificially elevated Kt/V and URR. In this situation, the V will be falsely low and the K falsely elevated. Therefore, the amount of dialysis delivered will be overestimated.

Early urea rebound (≤3 minutes postdialysis) may be viewed as a two-component process.. The first component is secondary to blood recirculation within the angioaccess or catheter and is not present in patients without access recirculation. If access recirculation is present, urea rebound from recirculation begins immediately upon completion of hemodialysis and resolves in less than 1 minute, usually approximately 20 seconds. The second component of early urea rebound is cardiopulmonary recirculation that begins approximately 20 seconds after the completion of hemodialysis and is completed 2 to 3 minutes after slowing or stopping of the blood pump. Cardiopulmonary recirculation refers to the routing of just-dialyzed blood through the veins to the heart, through the pulmonary circuit, and back to the angioaccess without the passage of the just-dialyzed blood through any urea-rich tissues. The late phase of urea rebound (>3 minutes) is completed within 30 to 60 minutes after the cessation of dialysis. The late phase is a consequence of flow-volume disequilibrium (perfusion or parallel flow model) and/or of delayed transcellular movement of urea (diffusion model). Refer to K/DOQI Guideline 2: Method of Measurement of Delivered Dose of Hemodialysis, Single-Pool Versus Double-Pool Effects in Adult and Pediatric Patients. These components of urea rebound are schematically presented in Fig I-2.

Recommended methods for postdialysis blood sampling

Two alternative methods for postdiaylsis blood sampling are described below. The second method, referred to as “Stopping Dialysate Flow Prior to Sampling”, is recommended for patients assigned to nocturnal dialysis.

a. Rationale: Reducing blood flow to 50-100 ml/min reduces the entry of cleared blood into the access and stops AR (unless there is needle reversal, in which case it still greatly reduces AR). The deadspace of the bloodline attached to the access needle is usually 2-4 ml, and the deadspace between the tip of the arterial bloodline and sampling area is usually about 7-12 ml, giving a total deadspace of 10-15 mL. A flow rate of 50-100 ml/min is about 1 ml/sec. So waiting 15-20 sec will ensure that the column of blood at the blood sampling site has not been diluted with dialyzer outflow blood.

b. Method:

1) At the completion of hemodialysis, turn off the dialysate flow and decrease the ultrafiltration rate (UFR) to 50 mL/h, to the lowest transmembrane pressure (TMP)/UFR setting, or off. If the dialysis machine does not allow for turning off the dialysate flow, or if doing so violates the clinic's policy, decrease the dialysate flow to its minimum setting.

Purpose: Stop the hemodialysis treatment without stopping the blood flow completely. The risk of clotting the extracorporeal circuit is low.

2) Decrease the blood flow to 50 to 100 mL/min for 15-20 seconds (longer if the distance between the . To prevent pump shut-off as the blood flow rate is reduced, it may be necessary to manually adjust the venous pressure limits downward.

Purpose: Fills the arterial needle tubing and the arterial blood line with non-recirculated blood (in case there is any access recirculation) by clearing the dead space in the arterial needle tubing and the arterial blood line.

At this point, proceed with either the slow flow or stop pump technique:

2. Sampling

a. Continue slow flow while sampling

1) With the blood pump still running at 50 to 100 mL/min, draw the blood sample for postdialysis BUN measurement from the arterial sampling port closest to the patient.

Purpose: Drawing the blood from the arterial sampling port ensures the postdialysis BUN measurement is performed on undialyzed blood.

2) Stop the blood pump and complete the patient disconnection procedure as per dialysis clinic protocol.

2. Stop blood pump prior to sampling (initial slow flow period is STILL required!)

1) After the required slow flow period, stop the blood pump.

2) Clamp the arterial and venous blood lines. The arterial needle tubing distal to the blood sampling site.

3) Blood for postdialysis BUN measurement may be sampled by needle aspiration from the arterial sampling port closest to the patient (inlet bloodline). Alternatively, blood may be obtained from the inlet needle tubing after disconnection from the arterial blood line and attaching a vacutainer or syringe without a needle – method that may be preferred because it by definition limits the risk of needlestick injury.

4) Blood is returned to the patient and the patient disconnection procedure proceeds as per clinic protocol.

Stopping dialysate flow prior to sampling (preferred for patients assigned to Nocturnal Dialysis)

Rationale: The method is based on data in the paper by Wu et al. The principle is the same – when dialysate flow is stopped, the dialysate outlet urea concentration starts to approach the inlet level, and AR, if present, has a progressively lower dilutional effect on inlet blood flow. With this method, blood flow rate should NOT be reduced, because one wants to equilibrate the remaining dialysate in the dialyzer with blood as quickly as possible. There is no data regarding the time course of this equilibration. The length of time for which dialysate was stopped in the Wu et al paper was 3 min., and the K/DOQI recommendation is to follow this validated method. It should be realized that, 3 min after stopping dialysis, the CPR component of rebound, as well as some early components of the RC rebound will have resolved. Hence, the postdialysis BUN drawn using this method will be slightly higher than that obtained 15-20 sec after dialysis using the other methods.

Method:

1) Continue the blood flow rate at the prescribed rate, set the UF rate as close to zero as allowed, and put the dialysate into bypass.

2) Wait 3 min. At that point, sample the blood from either the sampling area in the inlet bloodline:

a) **Inlet bloodline sampling:** Take the sample from the inlet blood line – the blood can continue to flow during sampling or can be stopped.
b) **Inlet needle tubing sampling:** The blood pump is stopped, the inlet blood lines and needle tubing are clamped and disconnected from one another, and the blood is drawn using a Vacutainer screwed onto the luer lock connection on the inlet needle tubing.

3) After the sample is obtained, blood is returned in the usual fashion.

Appendix to Chapter 19

Tables 19.3a – 19.3h provide the minimum treatment times required to acheive a target eKt/V of 1.10 for alternative dialysis prescriptions for patients with modeled volume ranging from 20 L to 55 L. Patients on three times per week schedules should receive dialysis prescriptions at least as high as those indicated in these tables to assure adherence to DOQI standards for dialysis adequacy.

Table 19.3a

Treatment Times (min) Required to Achieve an eKt/V of 1.10

Modeled Volume = 20 L

Qb (ml/min)	Qd (ml/min)	KoA (ml/min) 500	600	700	800	900	1000	1100	1200
200	500	174	166	161	158	155	153	152	151
250	500	156	148	143	139	135	133	131	130
300	500	146	137	131	127	123	121	119	117
350	500	138	130	124	119	115	113	110	108
400	500	133	125	118	114	110	107	105	103
450	500	129	121	114	110	106	103	101	98
500	500	126	118	111	106	103	100	97	95
200	800	169	162	158	155	153	151	150	150
250	800	151	143	138	134	132	130	128	127
300	800	139	131	126	122	118	116	114	113
350	800	132	123	117	113	110	107	105	103
400	800	126	117	111	107	103	101	98	97
450	800	122	113	107	102	99	96	94	92
500	800	118	110	103	99	95	92	90	88

Table 19.3b

Treatment Times (min) Required to Achieve an eKt/V of 1.10

Modeled Volume = 25 L

Qb	Qd	KoA (ml/min)							
(ml/min)	(ml/min)	500	600	700	800	900	1000	1100	1200
200	500	213	203	197	192	189	187	185	184
250	500	191	181	174	168	165	162	159	157
300	500	178	167	160	154	150	146	144	141
350	500	169	158	150	144	140	136	133	131
400	500	163	152	144	138	133	129	126	124
450	500	158	147	139	133	128	124	121	119
500	500	154	143	135	129	124	120	117	115
200	800	207	198	192	189	186	184	183	182
250	800	184	174	168	163	160	157	155	154
300	800	170	160	152	147	143	140	138	136
350	800	160	150	142	137	132	129	127	124
400	800	153	143	135	129	125	121	118	116
450	800	148	137	129	124	119	115	112	110
500	800	144	133	125	119	115	111	108	105

Table 19.3c

Treatment Times (min) Required to Achieve an eKt/V of 1.10

Modeled Volume = 30 L

Qb (ml/min)	Qd (ml/min)	KoA (ml/min) 500	600	700	800	900	1000	1100	1200
200	500	251	240	232	226	223	220	218	216
250	500	226	213	204	198	193	190	187	184
300	500	210	197	188	181	176	171	168	165
350	500	199	186	176	169	164	160	156	153
400	500	192	178	169	161	156	151	148	145
450	500	186	172	163	156	150	145	142	139
500	500	182	168	158	151	145	141	137	134
200	800	244	233	227	222	219	217	215	214
250	800	217	205	197	191	187	184	182	180
300	800	200	188	179	173	168	164	161	159
350	800	189	176	167	160	155	151	148	145
400	800	180	167	158	151	146	142	138	135
450	800	174	161	151	144	139	135	131	128
500	800	169	156	146	139	134	129	126	123

Table 19.3d

Treatment Times (min) Required to Achieve an eKt/V of 1.10

Modeled Volume = 35 L

Qb	Qd	KoA (ml/min)							
(ml/min)	(ml/min)	500	600	700	800	900	1000	1100	1200
200	500	289	276	267	260	256	252	250	248
250	500	260	245	235	227	222	217	214	211
300	500	242	226	215	207	201	196	192	189
350	500	229	214	202	194	188	183	178	175
400	500	220	205	193	185	178	173	169	165
450	500	214	198	187	178	171	166	162	158
500	500	209	193	181	173	166	161	157	153
200	800	281	269	261	255	251	249	247	245
250	800	250	236	226	220	215	211	208	206
300	800	230	215	205	198	192	188	185	182
350	800	217	202	191	183	177	172	169	166
400	800	207	192	181	173	166	162	158	154
450	800	200	184	173	165	159	153	149	146
500	800	195	179	167	159	153	147	143	140

Table 19.3e

Treatment Times (min) Required to Achieve an eKt/V of 1.10

Modeled Volume = 40 L

Qb (ml/min)	Qd (ml/min)	KoA (ml/min) 500	600	700	800	900	1000	1100	1200
200	500	328	312	302	294	289	285	282	280
250	500	294	277	265	257	250	245	241	238
300	500	273	256	243	234	227	221	217	213
350	500	259	241	228	219	211	205	201	197
400	500	249	231	218	208	201	195	190	186
450	500	242	223	210	201	193	187	182	178
500	500	236	218	204	195	187	181	176	172
200	800	318	304	294	288	284	281	279	277
250	800	282	266	255	248	242	238	235	232
300	800	260	243	231	223	216	211	208	205
350	800	245	227	215	206	199	194	190	186
400	800	234	216	204	194	187	181	177	173
450	800	226	208	195	185	178	172	167	164
500	800	220	201	188	179	171	165	160	156

Table 19.3f

Treatment Times (min) Required to Achieve an eKt/V of 1.10

Modeled Volume = 45 L

Qb	Qd	KoA (ml/min)							
(ml/min)	(ml/min)	500	600	700	800	900	1000	1100	1200
200	500	366	348	336	328	322	318	314	312
250	500	328	309	295	286	278	273	268	265
300	500	305	285	271	260	252	246	241	237
350	500	289	269	254	243	235	228	223	218
400	500	278	257	243	232	223	216	211	206
450	500	269	249	234	223	214	207	202	197
500	500	263	242	227	216	208	201	195	190
200	800	355	339	328	321	316	313	310	308
250	800	315	297	284	276	269	265	261	258
300	800	290	271	257	248	240	235	231	227
350	800	273	253	239	229	221	215	210	206
400	800	261	241	226	216	208	201	196	192
450	800	252	231	217	206	198	191	186	181
500	800	244	224	209	198	190	183	178	173

Table 19.3g

Treatment Times (min) Required to Achieve an eKt/V of 1.10

Modeled Volume = 50 L

Qb (ml/min)	Qd (ml/min)	KoA (ml/min) 500	600	700	800	900	1000	1100	1200
200	500	404	384	371	361	355	350	346	344
250	500	362	340	325	315	306	300	295	291
300	500	336	314	298	286	277	270	265	260
350	500	319	296	280	268	258	251	245	240
400	500	306	283	267	255	245	238	231	226
450	500	297	274	258	245	236	228	222	216
500	500	290	267	250	238	228	220	214	209
200	800	392	373	362	354	348	344	342	340
250	800	347	327	313	303	296	291	287	284
300	800	319	298	283	272	264	258	253	250
350	800	301	279	263	252	243	236	231	227
400	800	287	265	249	237	228	221	215	210
450	800	277	254	238	226	217	210	204	199
500	800	269	246	230	218	208	201	195	190

Table 19.3h

Treatment Times (min) Required to Achieve an eKt/V of 1.10

Modeled Volume = 55 L

Qb (ml/min)	Qd (ml/min)	KoA (ml/min) 500	600	700	800	900	1000	1100	1200
200	500	442	420	405	395	388	382	378	375
250	500	396	372	356	344	335	328	322	318
300	500	367	343	325	312	303	295	289	284
350	500	348	323	305	292	282	274	267	261
400	500	335	309	291	278	267	259	252	246
450	500	325	299	281	267	257	248	241	235
500	500	317	291	273	259	249	240	233	227
200	800	428	408	395	386	380	376	373	371
250	800	379	357	342	331	323	318	313	310
300	800	349	325	309	297	288	281	276	272
350	800	329	304	287	274	265	257	252	247
400	800	314	289	271	258	248	240	234	229
450	800	303	278	260	246	236	228	221	216
500	800	294	269	251	237	227	219	212	206