Chapter XIII

USRDS Research Studies

The USRDS conducts two different types of studies: "Existing Data Studies" and "Special Studies." "Existing Data Studies" analyze data that already have been collected; these studies will be discussed in the latter part of this chapter. "Special Studies," on the other hand, link existing data with additional clinical data or other information about patients, their health status, and their treatment.

Interim reports on the progress of Special and Existing Data Studies are made to NIDDK and HCFA, as well as to the USRDS committees and the ESRD Networks. Research analyses from several of the Special Studies can be found in the *USRDS 1992 Annual Data Report*. Selected study results have been reported in several scientific presentations and publications. Presentations and publications as of February, 1995 are listed in Appendix A.

Appreciation Of Renal Community Participation

HCFA, the ESRD Networks, and the renal community play an integral role in the ability of the USRDS to conduct Special Studies. Most of the on-site data collection has, until recently, been performed by the 18 ESRD Networks. In addition, surveys completed by ESRD dialysis and transplant units are an important source of Special Study data.

The USRDS thanks all those in the renal community who have cooperated with Special Studies to date, especially HCFA and the ESRD Networks, and the dialysis units and transplant centers that have directly submitted data on biopsies, EPO use, CAPD patients, and pediatric patients. The response by those units and Networks selected for the various studies has been excellent.

The USRDS is very grateful for the continued assistance of the renal community, since a high level of participation of the sample facilities selected for any study is vital to its success. With good response, the entire community can be represented by relatively few units and centers each year reporting on a relatively small number of their patients. Otherwise, data collection would have to be required of everyone, and much less could be accomplished at a higher cost.

Current USRDS Special Studies

The Dialysis Morbidity and Mortality Study (DMMS)--Special Study 8

DMMS Overview

Current plans for the DMMS call for the collection of data on a sample of 24,000 patients over a period of two years. The DMMS will be divided into four "waves" or phases of 6,000 patients each. In every phase, "core" data will be collected. Supplemental data will differ in each phase depending on the Special Studies that are designed in each of those phases. For example, plans for Wave 1 call for the collection of data on anemia, nutrition and vascular access. The information collected on all patients represent the core data. Supplemental data or the "non-core" components will be collected on various subsamples of the 6,000 patients.

We believe that a well-planned DMMS has the potential to answer many important research questions. Analyses of the "core" data collected on all 24,000 patients address questions related to the adequacy of dialysis, dialyzer membranes, and dialyzer reuse. The "core" data will also be used to develop a "comorbid infrastructure" from which analysis of many other important research studies can be conducted. Supplemental data in Wave 1 of the DMMS deals with the problems of anemia, nutrition, and vascular access in hemodialysis patients.

The DMMS Core

Five Special Studies will be included in the DMMS "core". Data aimed at addressing each of these research questions will be collected during all four Waves of the DMMS and will include a total of 24,000 cases.

- A study of the association between mortality and re-use of dialyzer membranes. This study will examine the relationship between mortality rates in hemodialysis patients and dialyzer re-use practices at the patient level.
- A study of the association between re-use of dialyzer membranes and patient morbidity. This study will investigate the relationship between patient morbidity and re-use of dialyzers. Are hospitalization rates greater for patients treated with re-used dialyzers and, if so, why are these patients being hospitalized?
- Development of a comorbid infrastructure. The "core" questionnaire will collect data pertaining to 20-25 comorbid patient conditions, ranging from cardiovascular disease to drug dependence and inability to ambulate. The most important objective is to expand the Standardized Mortality Ratio to many dimensions, including comorbid conditions and risk factors.
- A study of the adequacy of dialysis and the components of KT/V. This study will focus on the relationship between patient mortality and delivered dose of dialysis and will also examine the question of how much is enough dialysis, i.e. at which level of KT/V is there little benefit gained from a higher dialysis dose.
- A study of the relative importance of membrane type (cellulosic, synthetic, semisythetic) and dialyzer flux (conventional versus high flux). This study will investigate the relative importance of enhanced middle molecule removal accomplished with high flux dialysis and the avoidance of leukopenia and complement activation accomplished with biocompatible membranes.

Wave 1 of the DMMS

Wave 1 of the DMMS will include three additional Special Studies (Start date: March 1, 1995). "Non-core" data, collected on subsamples of the 6,000 patients over four months in Wave I, will provide the basis for the following Wave 1 analyses.

- A study of the relationship between vascular access and patient outcomes in the form of hospitalization and access procedures.
- A study of the relationship between EPO, hematocrit level and serum iron availability in dialysis patients.
- A preliminary study of the association between nutrition (based on serum albumin levels/ trends) and 1) mortality 2) protein catabolic rate and 3) KT/V.

Pretest of Wave I

As in all of our studies requiring special data collection activity, it is very important that the potential problems be removed before the full study is implemented. This is especially true of the first "wave" of the DMMS, which will establish a precedent for two of three subsequent waves of data collection that are planned as part of the DMMS. To ensure the commitment we have made to 90 minutes per patient abstraction, we have conducted an extensive pretest of the DMMS. Six ESRD Networks volunteered to take part in this pretest which included a sample of 50 patient abstractions from 20 dialysis units. Each dialysis unit completed approximately 3 patient abstractions from the draft questionnaires. This was to insure that the questionnaires were reasonable, that they could realistically be completed in an average of 90 minutes, and that the data collected were valid. In addition, the objectives of the pretest were 1) to receive feedback from the dialysis units for the refinement of the questionnaires and other logistical issues and 2) to ensure the reliability of the data collected.

Basic comparisons from the pretest and the Case Mix Adequacy Special Study for selected covariates are shown in Table XIII-1. KT/V with corrections for urea generation and weight loss were completed in 55 percent of the CMA, and 86 percent of the DMMS pretest. Overall the completion factor was higher for this DMMS pretest than for the CMA. In addition, the mean values from both studies are reasonably similar suggesting that the data from the pretest are reliable.

Comparison of Data Completion and Results from the DMMS Pretest and CMA

	DMMS Pretest			CMA		
Variables:	Mean	% Completed	n	Mean	% Completed	n
Kt/V	1.18	86	43	1.07	55	3570
Average Pre BUN	68.03	90	43	75.54	59	3570
Average Post BUN	25.32	90	43	31.04	60	3570
Average Predialysis Weight	78.96	90	43	72.61	94	3570
Average Postdialysis Weight	76.10	90	43	69.96	93	3570
Hematocrit	31.52	100	43	28.53	97	6319
Serum Creatinine	10.20	98	43	11.01	96	6276
Height (cm)	168.27	98	43	167.69	82	5531
Prescribed Hemodialysis (min.)	208.17	98	43	194.57	98	6380
Average Albumin over six month period	3.80	95	43	3.69	96	6246
Age at study start	59.58	98	43	58.46	100	6536

Table XIV-1

Data Validation

A rigorous Data Validation Study for Wave 1(a study of the quality of the data collected for the DMMS), has been planned for July 1995. The Data Validation Study will reabstract 30 questions for 1000 patients from 90 dialysis facilities. The validation will be conducted on an average of 55 patients per Network (total of 1000).

Future Waves of the DMMS: Waves 2-4

We anticipate that data collection for Wave 1 will be completed by July 1995. Wave 2 will start in August of 1995; the 3rd wave will start in April of 1996; and the 4th wave will start in October of 1996.

Waves 3 and 4 will be historical prospective studies. Wave 2 will be a prospective study.

We recognize that data collection is a burden on dialysis units and consequently we have always shaped study design to collect only the data needed for the particular research question. The DMMS is the first USRDS study which coordinates 4 substudies so that the analyses can be combined. This plan will permit the USRDS to test hypotheses that require a sample size of 24,000, in addition to the many issues that will be addressed with the substudies of 6,000, 3,000, and 2,000 each.

Some of the topics being considered for future waves of the DMMS include:

1. Comparison of long-term outcomes in CAPD versus hemodialysis patients including mortality, morbidity, hospitalization and quality of life.
2. A time variant analysis of nutritional factors, kt/v, and fluid intake affecting functional/physical decline over time for patients on dialysis.
3. Residual renal function: What role does it play in the hemodialysis relative risk of mortality story? How does residual renal function affect kt/v and adequacy of hemodialysis?
4. Study of facility variation as a predictor of mortality: What are the key measures of quality of care in a dialysis center?
5. What is the relationship between dose of peritoneal dialysis and outcome?
6. Study of racial/ethnic survival differences: What is it about being Black that creates an advantage in regard to ESRD mortality?
7. Why are hospitalization rates and morbidities higher for peritoneal dialysis patients versus hemodialysis patients?

The USRDS is also considering implementation of a new pediatric special study of growth in children, access to transplantation, and patient outcomes.

Summary

The DMMS will answer many important and relevant questions about the treatment of dialysis patients. All of us at the USRDS Coordinating Center, NIH, and HCFA are all grateful to the dialysis units and the 18 ESRD Networks. We sincerely appreciate their willingness to put forth a substantial effort on behalf of the DMMS.

The USRDS Coordinating Center would like to provide some meaningful assistance to the dialysis units in return for the important contribution they will be making. We will plan to calculate hospitalization data for each dialysis unit participating in the DMMS. These data, when compared to a national standard, will provide the dialysis units with an important measure of patient outcome.

Other USRDS Special Studies

Special Study topics are approved by NIDDK, with recommendations from HCFA, the USRDS Scientific Advisory Committees (Biomedical and Economic-Scientific Advisory Committees), the ESRD Networks, and the Renal Community Council (RCC). To date, seven Special Studies (requiring new data collection) have been undertaken by the USRDS. For each study, design and sampling plans were developed, samples were selected, and data collection forms and instructions were drafted, tested, and finalized. The current status of each study is summarized below. The data collection forms used for several of the USRDS Special Studies, including the Case Mix Severity, Case Mix Adequacy, CAPD and Peritonitis, Pediatrics, and Dialysis Morbidity and Mortality Studies, may be found in Appendix B.

Case Mix Severity (Special Study 1)

The objectives of the USRDS Case Mix Severity Study were to:

- Estimate the correlation of comorbid conditions and other potential factors existing at onset of ESRD regarding their association with subsequent mortality rates and hospitalization rates, while adjusting for age, sex, race, and primary diagnosis.
- Evaluate possible associations of these factors with reported causes of death.
- Assess the distribution of comorbid and other factors among patients utilizing different treatment modalities.
- Compare relative mortality rates by treatment modality with adjustment for selected comorbid conditions and other factors.

Initial data collection for this study was completed by the ESRD Networks in 1990. Data on nearly 5,000 patients (incident in 1986-87) were collected nationwide and have been entered into the database. However, due to errors in sampling it was necessary to collect data for a portion of the original sample that was skipped in the first round of data collection. This supplemental data collection was completed in mid-1991.

The Case Mix Severity study has been extensively analyzed by the USRDS Coordinating Center. These data have also been distributed to several independent investigators. Analyses based on data collected from the Case Mix Severity study have assessed the adequacy of dialysis, the association of comorbid factors with mortality, dialyzer reuse, access to renal transplantation, and differences in survival and selection (by comorbid factors) between CAPD and hemodialysis patients. Results have been presented to the SAC, the RCC, the ESRD Networks, and the American Society of Nephrology (ASN). A complete discussion of the basic mortality analysis can be found in the *USRDS 1992 Annual Data Report*, Chapter IV. Several additional papers based on these data have been published or are near publication, including a paper comparing CAPD and hemodialysis mortality which has been published in *Kidney International* (see list of publications in Appendix A).

Data Validation (Special Study 2)

The objectives of the USRDS Data Validation Studies were to:

- Document the reliability of the USRDS database.
- Identify those data items or sources that have high error rates.
- Determine the reliability of data that are derived from billing information.

In order to meet these objectives, three types of validation studies have been designed. The first type involves comparison of the USRDS database to other databases of known completion and validity. The second and most difficult type of USRDS data validation study involves comparison of reported data to source documents, (e.g., medical and hospital records, transplant summaries, billing records, etc.). Extensive results from these first two types of data validation were presented in the *USRDS 1992 Annual Data Report*, Chapters IX and X. The third type of data validation involves obtaining a "census" of patients from facilities and units to compare to the "census" tabulated from the USRDS database system. This type of study will allow identification of patients missing from the database. Significant progress is currently being made with plans for this validation study. Currently the USRDS Coordinating Center is comparing the census of all dialysis patients for December 31, 1993, recently conducted by HCFA, to the USRDS census of dialysis patients. This should prove to be a very important "Special Study" as it

will further ongoing efforts to validate and improve the database.

Renal Biopsy (Special Study 3)

The objective of the USRDS Renal Biopsy Study: Prognosis After ESRD is to test the hypothesis that outcomes vary for patients with different histologic renal diagnoses, even when adjusting for patient age, sex, and race. Prior research shows that biopsies are valuable diagnostic tools (Sobh) and that certain renal diagnoses are associated with a higher probability of recovery of renal function after renal failure (Sekkarie).

The study approach was to collect hard copies of biopsy reports for all cases incident between February, 1990 and January, 1991 with a report of a renal biopsy at any time prior to ESRD. Submission of hard copy biopsy reports by units and centers to the ESRD Networks was completed in early 1991. The data set includes over 2,700 patients. These are currently undergoing review for diagnostic confirmation by a panel of renal pathologists convened by NIDDK. Concurrently, epidemiological data on the biopsied patients are being extracted from the database and analyzed by the USRDS Coordinating Center. Preliminary demographic analyses of the first 400 cases have been presented to the SAC, the RCC, and the ESRD Networks. Demographic analyses and diagnostic confirmation of the full sample have not yet been conducted and the completion date for this study is, at this time, indeterminate.

EPO and Quality of Life (Special Study 4)

The drug recombinant human erythropoietin (EPO) is a specific treatment for the anemia of ESRD patients and was approved for use in 1989. Studies to date show that EPO improves patients' quality of life, i.e. their exercise capacity, energy, activity levels, and sense of well being (Eschbach; Winearls). The NMC/USRDS EPO and Quality of Life Special Study started in conjunction with National Medical Care, Inc. (NMC) in November 1989.

The objectives of the NMC/USRDS EPO and Quality of Life Study are to:

- Examine both cross-sectional data on patients receiving and not receiving EPO and longitudinal data on patients before and after they receive EPO.
- Establish a baseline for future EPO studies.

Data were collected by NMC social workers, nurses, and physicians on 2,248 patients prevalent in November 1989 at 284 NMC units for baseline and follow-up periods. The sample plan called for stratification by patients in the employable age groups. Patients selected represent a random sample of NMC patients and represent about 10 percent of NMC's prevalent patient population at the end of 1989. The data collected have been shared by NMC with the USRDS in return for support in study design, sample selection, and forms development and distribution. Preliminary analyses were shared with the Renal Community Council in November, 1992. In addition, data from this study were used to compare measurements of quality of life in the general population and the population of patients with chronic illnesses (data from the Medical Outcome Study in which quality of life was measured using the SF36 form) to measurements of quality of life in patients with End Stage Renal Disease. These comparisons were presented by the Coordinating Center at the NIH sponsored Workshop on Barriers to the Rehabilitation of Persons with ESRD and Chronic Urinary Incontinence in March, 1994. The Coordinating Center is still in the process of obtaining from NMC selected clinical and laboratory data necessary to complete the analyses.

CAPD and Peritonitis Rates (Special Study 5)

The objective of the USRDS CAPD and Peritonitis Rates Study was to compare peritonitis episodes in CAPD patients, with respect to connection device technology and other factors. The study population includes all patients newly starting CAPD in the first six months of 1989 (up to a maximum of 14 patients per dialysis unit). All units providing CAPD training participated in the study. The sample contains nearly 3,400 patients. The data have been added to the USRDS database, and extensive analyses have been completed. Early results were reported to the 11th Annual Peritoneal Dialysis Conference, the SAC, the RCC, the ESRD Networks, and the ASN. One paper on peritonitis risk has been published in *Kidney International* (see Appendix A), and a second study was presented as Chapter VI of the *USRDS 1992 Annual Data Report*.

Pediatric Growth and Development (Special Study 6)

The objectives of the USRDS Pediatric ESRD Growth and Development Study are to:

- Establish a baseline for assessing pediatric ESRD patient growth and sexual maturation by modality choice.
- Establish a prototype for ongoing collection of pediatric data.

All patients prevalent in 1990 who were born after December 31, 1970 are included in the study. The study population includes over 3,000 cases. The ESRD Networks began receiving data from units and centers with eligible patients in April, 1991. Data collection was completed by the Networks in the early fall of 1991; the data have been keyed, and analysis is underway. Extensive preliminary analyses of the data have been conducted and have been shared with the SAC and the RCC. A paper will be submitted shortly for publication. Discussions are underway with the Health Care Financing Administration to initiate the collection of data on pediatric patients incident after 1990.

Case Mix Adequacy Study (CMAS) of Dialysis (Special Study 7)

The objectives of the USRDS Case Mix Adequacy Study of Dialysis are to:

- Establish the relationship between the dose of delivered dialysis therapy and patient mortality.
- Determine the strength of this relationship when adjusting for comorbid conditions.
- Assess how this relationship changes at different doses of dialysis.
- Assess how this relationship is affected by re-use of dialyzers.
- Assess the impact of different dialysis membranes on patient morbidity and mortality.

Data collection started on April 1, 1992 and is now complete. The study consists of two groups of patients: an incident sample of patients starting hemodialysis for ESRD during 1990 and a prevalent sample of hemodialysis patients with onset of ESRD prior to 1990. As of March 1994, the sample now includes 7200 cases, approximately 3300 of which have the pre- and post- BUN values needed to calculate delivered dose of dialysis. We have matched 94% of these cases to the USRDS database, which will allow the data to be used for many extensive analyses. The ESRD Networks have collected these data in conjunction with their Medical Case Review data abstraction. This study was the first Special Study in which the Coordinating Center analyzed the data on a rolling basis, as they were received from HCFA. Now that all the data have been received, this process will enable final analyses to proceed rapidly. Preliminary results, based on the first 2,500 cases received, were presented to the RCC in November of 1992, and preliminary results based on 4,000 cases were presented to the SAC in January of 1994.

The following table XIII-2 provides a summary pertaining to the sample sizes of the Special Studies and the availability of Standard Analysis Files for each of the Special Studies.

USRDS Existing Data Studies

As previously noted, "Existing Data Studies" are analyses that use basic information routinely obtained from HCFA on all Medicare and some non-Medicare ESRD patients (e.g., transplant patients who have lost Medicare eligibility and DVA patients). Even without new data collection from Special Studies, important research is possible using these existing data. Depending upon their scope, a number of such studies are undertaken each year.

The first set of Existing Data Studies was chosen by NIDDK in November, 1989 with advice from the Existing Data Analysis Review Committee (EDARC). The EDARC, a committee that is no longer operational, reviewed nearly thirty study proposals in making its first recommendations to NIDDK on Existing Data Studies. Seven studies have been undertaken:

1. Racial Differences in the Incidence of Treated ESRD, 1982-1987

2a. The Influence of Donor and Recipient Sex and Age on Parent to Child Renal Transplantation

2b. Modality Distribution of Pediatric ESRD Patients

3. Trends in Mortality Rates Among Dialysis and Transplant Patients in the U.S.

4. Hospitalization Among Dialysis Patients and Transplant Recipients in the U.S.

5. A National Atlas: Geographic Variation in the Incidence of Treated ESRD

6a. The Impact of HLA Mismatches on Kidney Graft Survival

6b. Quantifying the Center Effect in Kidney Transplantation

USRDS Special Studies Data Files

Special Study	Number of Dialysis/Tx Units	Total Sample Size[1]	Proposed Schedule for SAF Availability
Case Mix Severity	328	5,255	May, 1994
Data Validation	348	1,692	N.A.[2]
Renal Biopsy	887	2,718	To be determined[3]
EPO and Quality of Life	284	2,248	To be determined[4]
CAPD and Peritonitis Rates	706	3,385	May, 1994
Pediatric Growth and Development	548	3,067	May, 1994
Case Mix Adequacy	523	7,096	June, 1995

[1] Total sample size may vary from previously reported numbers due to standardizing analysis files.

[2] No standard analysis file will be created from this study

[3] Data collection is not complete yet.

[4] Data belong to NMC, Inc., availability to be determined.

Table XIII-2

7. Investigation of the Limitations and Appropriate Use of Cox's Proportional Hazards Model for Observational Data

Studies 1 through 6a have been presented at various forums, as noted in Appendix A. Study 6a. has been published in the *New England Journal of Medicine*. Study 4 has been published in Chapter VIII of the *USRDS 1990 Annual Data Report*. A portion of Study 5 was recently published in the *American Journal of Kidney Diseases*. Studies 6b and 7 have been completed.

In addition, the following existing data research studies are in progress:

1. Comorbid predictors of patient outcomes.

2. The association of causes of death and kt/v.

3. Pediatric growth in ESRD patients.

4. Effect of dialyzer membrane on patient mortality.

5. Role of kt/v in patient mortality for hemodialysis patients.

6. Association of hemodialysis patient's blood pressure and patient mortality.

7. Relationship of dialyzer membrane and cause-specific mortality.

Access To USRDS Data

As discussed in Chapter I, Access to the USRDS Data, Standard Analysis Files (SAFs) and custom made data files are available to investigators in the renal research community for biomedical and economic research related to ESRD. These files contain both Existing and Special Studies data. Access to these files is discussed at length in Chapter I. The procedure for accessing these files is listed in Chapter I of this report.

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