

SUMMARY OF MINUTES

17th Meeting of MTPPI Technical Advisory Committee (TAC)
On Human Recombinant Erythropoietin Utilization
August 15, 2007

- Update of CMS EPO policies and research activities by Kim Long, Beth Koller and Maria Ciccanti.
- Update of NIH and NIDDK research activities and projects by Paul Eggers and Daniel Wright.
- Update on DVA Boston EPO research activities including hematocrit variability work by James Kaufman
- Update of MTPPI's research on epoetin practice patterns, hematocrit response relationship, dose and survival and future research projects by Mae Thamer and Yi Zhang.
- Discussion and review by TAC of three issue profiles (see attached pdf file): 1) Implications of survival research findings; 2) Design of anemia management strategies (for future grant work); and 3) Predictors of early mortality among CKD population.

Human Recombinant Erythropoietin Use in the Medicare Population

17th Meeting of the
Medical Technology and Practice Patterns Institute's
Technical Advisory Committee (TAC)

9:30 a.m. to 3:30 p.m.

Wednesday, August 15th

Calvert I & II Conference Rooms

Residence Inn Bethesda

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Technical Advisory Committee (TAC) Issue Profiles*

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** The N indicates that these are 'new' issue profiles in contrast to older issue profiles with the same number.*

Issue 26N: Implications of survival analysis

I. OVERVIEW

Since the introduction of epoetin treatment, a plethora of observational studies have shown that higher hematocrit is associated with better survival for dialysis patients. More recently, researchers have begun to focus on potentially harmful epoetin dose-dependent pathways after results of new clinical trials (along with several prior RCTs) demonstrated that patients targeted to higher hematocrit levels had increased risk of mortality, hospitalization, or cardiac outcomes. As a result of such concerns, the FDA has recently issued a Black Box warning to use the lowest epoetin dose among renal failure patients. The epoetin dose-survival relationship, however, has not yet been empirically determined. In this study, we aim to evaluate the effect of epoetin dose on dialysis patient survival using causal inference techniques.

II. METHODOLOGY and RESULTS

This observational study included 20,580 patients in the United States Renal Data System (USRDS) who started hemodialysis in 2003. Using marginal structural models (MSM), we estimated the relationship between cumulative average epoetin dose and patient survival during the first year of dialysis treatment.

Unlike results based on standard adjustment methods which suggest that higher epoetin dose is consistently associated with increased risk of mortality, using MSM, we found a U-shaped dose-survival curve. Risk of mortality appeared to be lowest at an epoetin dose in the range of 35,000-60,000 units per month and higher outside this range. In other words, this study found that, when compared to low epoetin doses, moderate epoetin doses were beneficial to the patients, instead of harmful as reported by the previous studies. However, a trend of sharply increased mortality risk was observed with increased levels of epoetin dose when monthly epoetin dose was higher than 60,000 units. Our findings are consistent with randomized controlled trials and suggest that moderate epoetin doses might be beneficial and have a protective effect while higher epoetin doses might not provide survival advantage for the hemodialysis population.

III. TAC ACTION REQUIRED

We ask the TAC to advise us on the following technical questions that will help us in the design of this and future studies:

1. How should we handle *epoetin use during hospitalizations*? Do ESRD patients routinely receive epoetin when they are hospitalized? Do they receive the same or different dose? Does it depend on the length of hospitalization? What assumptions can we make?
2. How should we handle *hematocrit values after a zero epoetin dose* [“hold dose”], since with no epoetin administration, no hematocrit is recorded? Currently we carry forward the last hematocrit of the previous month before epoetin was discontinued? Should we assume the hematocrit stays the same or decreases and by how much?

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We ask the TAC to advise us on the following clinical questions that will help us to interpret our dose-survival findings:

1. *Why does lower dose appear to be detrimental (i.e., below 35,000 units/month)? (threshold effect, inclusion of patients who do not require epoetin for accounting purposes, others?)*
2. *Why is high epoetin dose detrimental (i.e., above 60,000 units/month)? (What specific causal mechanisms or pathways might explain this? Limited epoetin receptors, cardiovascular complications, exacerbation of high blood pressure; are these pathways mediated through hematocrit or not?)*

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Issue 27N: Anemia management strategies

I. OVERVIEW

To address a question of clinical effectiveness, MTPPI has recently submitted a renewal NIH grant with the following research question, “*Given the wide variation in treatment strategies, what is the most effective anemia management strategy using epoetin therapy associated with improved survival among the dialysis population?*” Given the confounding demonstrated using conventional statistical techniques in observational studies, and the costs of conducting adequately powered randomized clinical trials (RCTs), we propose to answer these questions by applying so-called causal methods – inverse probability weighting and the parametric g-formula – to the analysis of a large administrative database.

We propose two clinical scenarios to examine the two issues that are of most concern with regard to anemia management, (and that must also be addressed if epoetin is subsequently bundled into the composite rate. The proposed clinical scenarios are:

- 1) What is the best hematocrit target for survival among the U.S. dialysis population; and
- 2) What is the most effective therapy (in terms of target hematocrit and dose) for patients who are hyporesponsive to epoetin therapy.

II. METHDOLOGY

Specifically, this is how we propose to operationalize these scenarios--

Research question 1: How does survival vary under different dynamic epoetin dosing regimes based on hematocrit targets?

Three hematocrit treatment strategies will be examined:

Strategy IA (Target HCT 30-<33%) is defined as follows: If the average patient hematocrit is between 30 -<33% at month 3 and the patient’s dose/administration is maintained +/-25% in month 4, that patient is first assigned to this strategy. Three clinical scenarios during the subsequent months will be considered as remaining in this category: (1) when HCT is <30%, epoetin dose/administration is increased by at least 25%, (2).when HCT is in the desired range of 30-<33%, epoetin dose/administration is maintained (+/-25%), and (3).when HCT is >33%, epoetin dose/administration is decreased by at least 25%.

Strategy IB (Target HCT 33-<36%) is defined as follows: If the average patient hematocrit is between 33-<36% at month 3 and the patient’s dose/administration is maintained (+/-25%) in month 4, that patient is first assigned to this strategy. Three clinical scenarios during the subsequent months will be considered as remaining in this category: (1) when HCT is <33%, epoetin dose/administration is increased, (2). when HCT is in the desired range of 33-<36%, epoetin dose/administration is maintained (+/-25%), and (3).when HCT is >36%, epoetin dose/administration is decreased.

Strategy IC (Target HCT 36-<39%) is defined as follows: If the average patient HCT is between 36 -<39% at month 3 and the patient’s dose/administration is maintained (+/-25%) in month 4, that patient is first assigned to this strategy. Three clinical scenarios during the

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subsequent months will be considered as remaining in this category: (1) when HCT is <36%, epoetin dose/ administration is increased, (2). when HCT is in the desired range of 36 -<39%, epoetin dose/administration is maintained (+/- 25%), and (3).when HCT is >39%, epoetin dose/ administration is decreased.

Since it is not known how low the hematocrit target could be without there being harm, we will also examine finer HCT target groups.

Significance. These strategies are dynamic treatment regimes because the epoetin treatment assigned to the patients depends upon the patient's evolving anemia history. Since no previous observational studies in the ESRD fields have compared dynamic treatment regimes and it is unlikely that long-term clinical trials will be ever conducted to compare each of these strategies, the proposed research, by applying appropriate analytical methods, will answer key clinical questions in anemia management. Research findings will provide the basis for improved clinical guidelines and more cost-effective payer policies.

Research question 2: How does survival vary in epoetin-hypo-responsive patients under different nondynamic epoetin dosing regimes?

Background: The greatest difference in epoetin dosing practice strategies has been found among non-responders, patients who had hematocrit less 30% with high dose epoetin treatment. To date, no formal assessment of the appropriate dosing levels has been conducted, nor has a payment policy been implemented to encourage appropriate dosing for unresponsive patients. However, findings of clinical trials have raised safety concerns possibly related to higher epoetin doses.

Three treatment strategies for nonresponsive patients will be examined. A cohort of non-responders will be first identified based on a prevalent group of patients with doses in the top 15%. Using this definition, we define three strategies to manage these non-responders will be compared:

Strategy 2A: Dose decreased by >25%.

Strategy 2B: Dose maintained +/- 25%.

Strategy 2C: Dose increased by >25%.

Significance. Our proposed study, by modeling the causal effect of the time-varying epoetin treatment on mortality, will allow us to determine whether higher epoetin dose is a better solution for patients with epoetin hypo-responsiveness.

III. TAC ACTION REQUIRED

1. Can the proposed scenarios be improved?
2. Are there other important scenarios in the area of anemia management to be examined?
3. Is there a better way to include both *dose and hematocrit* in a proposed scenario?

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Issue 28N: Predictors of early mortality among the ESRD population

I. OVERVIEW

Despite improvements in dialysis care, the mortality among end-stage renal disease (ESRD) patients in the United States remains high. Several studies have demonstrated a strong association between an increased risk of early death and suboptimal dose of dialysis, malnutrition, and non-renal co-morbidities. However, few studies have examined the impact of medical conditions and medical management prior to initiation of dialysis on early survival after becoming end-stage. Given the disproportionately high mortality rates during the first year after enrolling in the ESRD program (termed ‘early mortality’), accurate prediction of those destined for early death would be useful to patients and their families, providers, and society in making timely and optimal decisions about treatment strategy. We propose to construct a complete renal failure patient history by linking the pre and post dialysis data to assess the predictors of early death among the CKD population that progress to ESRD and dialysis therapy. The proposed study will link the 1992-2003 ESRD standard analytic files to the 5% CKD sample that have recently become available for research purposes.

II. METHODOLOGY

We propose to examine the entire mortality experience in the first year after enrollment in the ESRD program. Specifically, we will examine predictors of mortality among ESRD patients who died: a) during the hospitalization in which dialysis was first initiated; b) in the first 3 months after initiating a continuous course of outpatient dialysis; and c) in months 4 – 12 after starting outpatient dialysis. We hypothesize that early mortality after enrollment in the ESRD program is influenced by predialysis medical conditions combined with predialysis CKD management that does not prepare them appropriately for long-term dialysis. We propose to:

1. **Examine comorbid conditions seen within one year prior to dialysis** (e.g., cardiovascular events, acute renal failure, sepsis, hypertensive emergencies);
2. **Assess the medical management prior to dialysis** including involvement of a nephrologist, management of anemia and epoetin usage, nutritional status, and vascular access preparation (thus differentiating the ‘emergent versus elective’ transition from CKD to ESRD); and
3. **Quantify the intensity of health care services** utilized prior to dialysis including hospitalizations, emergency dialysis, intensive care stays, surgeries, outpatient visits, etc.

See Table 1. below for a list of the proposed variables to address each hypothesis.

III. TAC ACTION REQUIRED

Keeping in mind we are restricted to using data available from medicare administrative files, are there other useful predictors that can be examined to assess early mortality among the CRF population that progresses to ESRD.

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Table 1. Variables included in model to predict early mortality among dialysis patients

Variables	Unit	Code, if applicable	Missing data [^] (%)
Sociodemographics			
Age at first ESRD Service	years		
Gender			0
Race			<0.5
Hispanic ethnicity	Yes/No		<0.5
Marital status			<0.5
Socioeconomic status			<0.5
Median family income based on 5-digit zip code	\$		
Insurance status			<0.5
Clinical Characteristics at Initiation of ESRD			
Weight at onset of ESRD	kg		<0.5
Nutritional status at onset of ESRD			
Body mass index	kg/m ²		1.3
Serum albumin	g/dl		26.7
Cause of ESRD			
Diabetes	Yes/No		0
Glomerulonephritis	Yes/No		
Hypertension	Yes/No		
Other	Yes/No		
Severity-of-illness measures*			
Charlson Index (calculated at initiation of dialysis)			NA
Hospital Stay(s)	days		
Pre-dialysis epoetin use*	Yes/No		<0.5
Baseline Hematocrit at onset of ESRD	%		4.8
Serum Creatinine at onset of ESRD	mg/dl		1.0
Creatinine Clearance at onset of ESRD	ml/min		4.4
GFR at onset of ESRD	mg/dl		1.9
Vascular access placement*			
Permanent	Yes/No	CPT codes:, 36820, 36821, 36825,	
Temporary	Yes/No	CPT codes: 36011, 36012, 36488, 36489, 36490, 36491, 36533	
Co-Morbid Events Prior to ESRD*			
Cardiovascular Disease			NA
Coronary atherosclerosis	Yes/No	414.0	
Acute myocardial infarction	Yes/No	410.xx	
Angina pectoris	Yes/no	413.xx	
Heart Failure	Yes/No	428.xx	
Congestive heart failure	Yes/No	428.0	
Left heart failure	Yes/No	428.1	
Systolic heart failure	Yes/No	428.2	
Diastolic heart failure	Yes/No	428.3	
Combined systolic and diastolic heart failure	Yes/no	428.4	
Hypertensive heart disease	Yes/No	402.xx/404.xx	
Cardiomyopathy	Yes/No	425.xx	
Cardiac dysrhythmias	Yes/No	427.xx	
Cardiac arrest	Yes/No	427.5	
Acute and subacute endocarditis	Yes/No	421.00	

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Cardiogenic shock	Yes/no	785.51	
Acute pericarditis	Yes/No	420.xx	
Syncope and collapse	Yes/No	780.2	
Hypotension	Yes/No	458.xx	
Other co-morbidities			
Acute conditions			NA
Shock	Yes/No	639.5	
Septic shock	Yes/No	785.52, 785.59	
Septicemia	Yes/No	038	
Bacteremia	Yes/No	790.7	
Pneumonia and influenza	Yes/No	480-487	
Gastrointestinal hemorrhage	Yes/No	456.0, 456.20, 578	
Respiratory disorders			NA
Acute respiratory failure	Yes/No	518.81	
Acute or chronic respiratory failure	Yes/No	518.84	
Chronic respiratory failure	Yes/No	518.83	
Respiratory distress syndrome	Yes/No	769	
Respiratory arrest	Yes/No	799.1	
Chronic obstructive pulmonary disease	Yes/No	490.xx – 496.xx	
Acute renal conditons			NA
Acute renal failure	Yes/No	584.xx	
Nephritis, Nephrotic syndrome, and nephrosis	Yes/No	(580-589)	
Hypovolemia	Yes/No	276.52	
Volume depletion	Yes/No	276.5	
Volume depletion, unspecified	Yes/No	276.50	
Fluid overload	Yes/No	276.6	
Other non-cardiovascular co-morbidities			NA
Cerebrovascular disease, CVA, TIA	Yes/No	430-438	
Peripheral vascular disease	Yes/No	443.9	
Diabetes mellitus	Yes/No	250.xx	
Cancer	Yes/No		
Health Service Use Prior to ESRD*			
Hospital stays(s)	Total days		NA
Surgeries, procedures (e.g., emergent dialysis,		DRG and CPT codes	
Intensive care unit admission(s)	Total days		
Emergency room visit(s)	Counts		NA
Physician Visit			NA
Specialty (e.g., nephrologists, cardiologist, etc.)	Counts	Specialty code	

* All variables will be identified during the 12 months pre-dialysis period.

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