

An Opportunity for Comparative Effectiveness Research to Improve Quality of Care in the Medicare Program by Using *Enhanced Administrative Data*¹

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In February and March of this year, MTPPI conducted a series of seminars for the Congressional and Executive branches at which we presented the disconcerting results of comparative studies we conducted on risks and benefits related to epoetin therapy for dialysis related anemia patients. These studies^{1 2 3} mimicked clinical trials by modeling treatment information contained in Medicare claims and other administrative data. This work continued our earlier comparative assessment of anemia treatment variation across dialysis facilities.⁴ In a new MTPPI ongoing study using a composite cardiovascular/survival endpoint, preliminary findings suggest that high epoetin doses cause higher risks of adverse outcomes - a result consistent with a published re-analysis of a terminated epoetin clinical trial. Unlike other research of treatments for chronic conditions, our studies of epoetin are unique because, to gain Medicare payment (~\$2 billion/yr), providers are required to submit monthly epoetin dose and physiological response (hematocrit) data, information that is readily available to researchers on a continual basis. Consequently, this comparative effectiveness project serves as a good example of the benefit of modifying Medicare claims to obtain vital information in order to assess benefits of costly treatments.

A Case Study Of Today's Challenge

Importance: Treatment of chronic conditions accounts for ~80% of health care costs (~\$2.3 trillion/yr). Chronic anemia is a common condition among end-stage renal disease (ESRD) patients; the Medicare ESRD program serves as a microcosm of what universal healthcare could be.

We use epoetin (EPOGEN) treatment of chronic anemia, a common complication of chronic kidney disease and end-stage renal disease (ESRD), as a case study to exemplify (1) attempts to expand the market size of a drug, (2) studies necessary to assess market expansion, and (3) the translation of scientific evidence into policy formation. Documentation of epoetin therapy is unique because Medicare requires providers to submit monthly epoetin dosages and hematocrits for payment of this service. Medicare's epoetin reimbursement policy also created a perverse financial incentive to overuse this drug. These two phenomena make epoetin an excellent subject for a comparative effectiveness demonstration study that could be replicated.

Epoetin was introduced in 1989 to reduce the need for infusion of blood units for treatment of anemia among ESRD patients. Prior to availability of epoetin, blood units were frequently administered to approximately 10% of the ESRD patients (another 6% received an occasional blood unit for mild anemia). The remaining 84% of patients did not receive blood unit infusion for treatment of anemia. By 2005, however, 99% of in-center hemodialysis patients received epoetin treatment. How did this therapy diffuse to near-universal use among the dialysis population? Was this diffusion supported by sound scientific evidence (see Tables 2A & 2B below)? How can it be that a comprehensive technology assessment still has not been conducted more than two decades after epoetin has been widely marketed?

Epoetin dosing levels have changed dramatically since the substance's introduction into the U.S. market. The mean dose of epoetin has increased about fourfold in dialysis patients, and Medicare expenditures for epoetin rose to ~\$2 billion in 2004, constituting 11% of all Medicare ESRD costs. Unfortunately, other than studies documenting usefulness for a small group of patients who would otherwise be dependent on infusion of blood

¹ A more detailed discussion of this topic is located at: <http://www.mtppi.org/frameset.asp?Pg=/physio.asp&MI=>

units, there are no other clinical trials to guide policymakers on how to cover and/or reimburse this costly treatment. Despite this deficiency of valid scientific evidence, Medicare has consistently covered/reimbursed for the expanded use of epoetin, at a cost to the Medicare program of over \$20 billion to date.

In an attempt to both increase sales for approved indications and to expand epoetin use to other indications, proponents commissioned clinical trials and highly flawed observational studies which ended with conflicting results that raised more concerns. Justification for this prodigious drug expenditure continues to rest on the presumption that a positive change in the surrogate endpoint (in this case, hematocrit) is related to an improvement in a clinical endpoint (improved survival, quality of life, etc.), despite the fact that this presumption has been disproved by clinical trials and disallowed by the FDA.

MTPPI epoetin studies address the translation of epoetin research into practice (over 99% of dialysis patients today receive this drug continuously) and the role of government in requiring and applying scientific evidence for policy formation. The two existing clinical trials (Besarab, 1998, and Singh, 2006) were terminated due to higher mortality rates in the higher target hematocrit treatment arms. Unfortunately, there are no other clinical trials to guide policymakers on how to pay for this costly treatment. Our contention is that Medicare policymakers should base their decisions about future payment for these and other services on a reasonable demonstration of “real-world” clinical effectiveness (see Table 2B).

Conclusion

Rapid diffusion of costly health care technologies with undocumented benefits is endemic to the soaring costs of the U.S. health care system. Our case study is unique because epoetin dose and physiological response (hematocrit) data are readily available to assess, on a continuous basis, the benefits and risks of chronic anemia epoetin treatment. This case study is offered as an example of the advantage of expanding information required on Medicare claims in order to obtain vital data with which to assess treatment risks and benefits. It also serves as a cautionary tale of the pitfalls — both fiscally and in terms of patient safety — of not conducting comprehensive technology assessments.

Table 2A: Case Study Summary - Current status of what is known

1 Evaluation: FDA epoetin (EPO, EPOGEN) approval in June 1989, AHRQ assessment August 2001 concluded a lack of data to make definitive recommendations beyond those indications approved by FDA
2 Market Size: Prior to EPO, a small group (~10%) of anemic ESRD patients were treated with red blood cell transfusions (RBCT). EPO elevates hematocrit (Hct) to avoid the need for RBCT, but not much is known about EPO effects on the other 90% of ESRD patients who receive EPO therapy (20 yrs have passed and over \$20 billion in costs paid by Medicare since FDA approved EPO)
3 Treatment Target: EPO's first FDA treatment target hematocrit was 30-33% max 36%, changed in 1994 to 30-36% because of hematocrit variability, CMS eclipses FDA by allowing an upper Hct limit of 39%
4 Clinically Appropriate Target: No study has addressed an appropriate target hematocrit, but clinical trial attempts to expand EPO use resulted in higher mortality among those targeted to higher hematocrits
5 Effect of Policy on EPO Diffusion: Congress imposed a fee-for-dose policy that led to rapid increase in EPO use (well over 300% since 1991) because providers target hematocrit to 36%, aggressively treat EPO hypo-responsive patients and overshoot the target (Fall 2007 - 43% exceed the upper bound of FDA target hematocrit)

6 Lack of Science Supporting Policy: Medicare EPO policies are not based on science and provide perverse financial incentives to overuse EPO, and its policy is heavily weighted to accommodate hematocrit variability - hematocrit variability is no justification for picking an appropriate hematocrit target nor have there been any studies over the last 20 years to determine an appropriate target hematocrit

7 Effect of Financial Incentives on EPO Diffusion: Product discounts/rebates and Medicare payment policy are incentives for EPO overuse - providers use starting doses much higher than FDA's recommendations - over 56% of EPO is consumed by 24% of ESRD patients with EPO hypo-response

8 Risks Related to EPO: Based on recent causal "*EPO dose - composite CV²-mortality event modeling*" preliminary results indicate that higher doses (>40,000/wk) cause increased risk events (25% higher); placing over 20% of ESRD patients at increased CV-mortality risk

Table 2B: Case Study summary - *Opportunity today to make informed changes*

9 Product Labeling: Since there are no studies that address an appropriate target hematocrit, FDA should further restrict epoetin product labeling target hematocrit to 33% \pm 3% (thus achieving 30-36%), and emphasize lower titrated dose levels

10 Impact on Costs: Based on MTPPI causal "*EPO dose - hematocrit response modeling*" there is approx. 50% EPO overuse (~\$1 billion/yr), therefore, if based on EPO's historical overuse (directed by Congress), bundling EPO into the ESRD composite rate payment will reward providers with a ~\$1 billion/yr windfall

MTPPI is an independent non-profit institute whose mission is to provide research services related to safety, clinical effectiveness, patient outcome, cost, and cost effectiveness of new and emerging medical technologies. MTPPI has not received public or private funding for work related to this analysis.

1. Cotter D, et al The Effect of Epoetin Dose on Hematocrit, *Kidney Int.* 2007 Oct;72(8):1247.
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3. Thamer M et al Prednisone, lupus activity, and permanent organ damage *J Rheumatol* 2009 Mar;36(3):560-4
4. Thamer M et al Dialysis Facility Ownership and Epoetin Dosing in Patients Receiving Hemodialysis *JAMA*, 2007 Apr 18;297(15):1667-74.

²CV events include: myocardial infarct, stroke, and congestive heart failure