Measuring Clinical Effectiveness in Practice: Evidence from EPO in Dialysis*

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We use a large change in financial incentives following a Medicare payment reform to measure the clinical effectiveness of epoetin alfa (EPO), Medicare's largest Part B drug expense before the reform. We find that a 1% increase in EPO successfully reduces anemia in dialysis patients by 0.09% but increases the risk of heart attack by 0.3% and death by 0.4%. Because clinical trials do not account for providers' responses to financial incentives or patient heterogeneity, our results provide novel evidence about the health consequences of drugs as used in the field and prospective payment models targeting their use.

JEL Codes: D43, I11, I18, L10

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1. Introduction

Health insurers use alternative payment models to restrain reimbursement costs (Shatto, 2016). Compared to traditional fee-for-service reimbursement schemes that give providers a separate payment for each treatment or service they render, alternative payment models such as prospective payment systems (PPSs) attempt to facilitate coordination and reduce unnecessary expenses by covering multiple aspects of care with a single reimbursement. Such alternative approaches may also create an incentive to undertreat patients, however, which requires policymakers to weigh the marginal costs and benefits of the care targeted by the payment reform. Although clinical trials often serve as the basis for these assessments, results from their controlled settings may not reflect how a drug or procedure is used in practice, as they ignore providers' endogenous responses to financial incentives and heterogeneity in the wider population covered by the policy (Alsan et al., 2022; Treasure and MacRae, 1998; Banerjee et al., 2020), making it difficult to predict how the such reforms will impact patients in practice.

In this paper, we use a major Medicare payment reform in the dialysis industry, a theoretical model of providers' treatment decisions, and a novel instrumental variable strategy to demonstrate how the results from clinical trials might diverge from those generated by providers' actual prescribing behavior. The payment reform we study was targeted at reducing excessive doses of epoetin alfa (EPO), a drug used to treat anemia among dialysis patients that was Medicare's largest Part B drug expense in 2010, totaling $2 billion (U.S. Government Accountability Office, 2012). Before 2011, Medicare had given dialysis facilities a fee-for-service reimbursement for the EPO they administered during treatment, with the drug accounting for as much as 25% of revenue for the largest dialysis chain, DaVita, and up to 40% of its profits (DaVita, 2005). Many patient advocates raised concerns about the pervasive use of EPO, however, as clinical trials had shown that excessive doses increase the risk of mortality and cardiovascular events (Besarab et al., 1998; Singh et al., 2006). In response to the escalating costs of EPO and the potential harm that it poses to patients, Medicare introduced a PPS in 2011 that covered both EPO and the dialysis session itself with a single payment to provide an incentive to use the drug more judiciously.

Although the move to include EPO in the PPS corresponded to a 49.4% drop in the average EPO dose given to patients each month from its peak during the fee-for-service era, its implications for patient welfare are not clear-cut: lower EPO doses could benefit those who were being overtreated prior

to the reform but could harm patients whose anemia is now undertreated. Determining the effect of these forgone doses is complicated by the fact that providers base their treatment decisions in part on patients' underlying health, making any correlation between drug doses and outcomes potentially confounded by unobserved attributes. Reflecting this possibility, we show that controlling for EPO doses in OLS regressions of hemoglobin, which measures the severity of a patient's anemia, and blood transfusions, a costly intervention used when anemia is especially acute, produce spurious negative and positive correlations, respectively, contradicting the results of clinical trials showing it in fact causes the opposite physiological responses (Eschbach et al., 1989).

To overcome the empirical challenges associated with patients' unobserved health conditions and coincidental changes in dialysis care, we use a novel source of exogenous variation in providers' treatment decisions to identify the marginal effect of EPO on outcomes: patients residing at higher elevations have less severe anemia at baseline and therefore naturally require less EPO to manage their condition (Winkelmayer et al., 2009; Brookhart et al., 2011). During the fee-for-service era, this physiological distinction made patients at higher elevations less profitable for providers, as they received smaller doses of EPO to keep their blood levels within clinical guidelines. After the switch to prospective payments, the financial incentives flipped, with patients at low elevations becoming less lucrative for providers who no longer receive separate reimbursements corresponding to these patients' larger doses. As a result, the uniformly applied payment reform effectively had different financial implications for facilities at different elevations.

Although promising as a source of exogenous variation, elevation is unlikely to be a valid instrument on its own; just as elevation directly affects hemoglobin levels, it may also directly affect other health outcomes. In light of this, we use the interaction between elevation and the payment reform as an excluded instrument to estimate the clinical effectiveness of EPO while controlling directly for time trends and elevation in our first- and second-stage regressions. By instrumenting for EPO doses with the interaction term, our first stage resembles a difference-in-differences estimation, with the first difference comparing EPO doses at high-elevation facilities with those at lower elevations, while the second difference compares doses during the fee-for-service era, when financial incentives favored higher doses, with those administered during the PPS era when the financial incentives reversed.

From our first-stage estimates, we find that facilities at lower elevations both used more EPO and disproportionately reduced their doses after the payment reform. The second stage then links the change

in EPO to its effect on outcomes. For this specification to have a causal interpretation, the interaction between a facility's elevation and Medicare's payment policy must only affect health outcomes through its influence on EPO, conditional on other controls, and we present several pieces of evidence that suggest our setting satisfies this requirement, such as parallel pre-trends for patients' EPO doses across high- and low-elevations and no meaningful changes in observable patient characteristics or other facility inputs.

To aid in the interpretation of our IV estimates and relate them to a treatment effect policymakers would find relevant, we use a simple model of providers' dosing decisions that demonstrates how, in equilibrium, they depend on both the clinical effectiveness of EPO and the financial incentives faced by providers. In this context, the impact of the payment reform depends on the health effects of the EPO forgone as a result of the policy change. We recover this quantity by combining our estimates with calibrations of the parameters governing provider altruism found elsewhere in the literature (Gaynor et al., 2020). We find that the equilibrium marginal effect of a 1% increase in EPO is a 0.09% increase in hemoglobin, a response well below those recovered from clinical trials. This difference highlights the importance of accounting for providers' equilibrium dosing behavior in forecasting how patients' health outcomes will change under a new reimbursement scheme.

We further show that the EPO forgone because of the payment reform had been harming patients. Our IV estimates indicate that a 1% increase in EPO raises the rate of cardiac hospitalization by 0.3% and mortality by 0.4%, suggesting that the financial incentives of fee-for-service reimbursements induced providers to overtreat patients in a way that led to severe adverse events. Finally, we present evidence that chain-owned and for-profit facilities reduced their doses more in response to the payment reform, consistent with these facilities being more responsive to financial incentives.

Using observed provider and patient behavior to study the effectiveness of EPO contributes to a growing literature on the limitations of clinical trials for assessing the impact of interventions in the field. Most notably, trial participants often differ from the general population in both observable and unobservable characteristics (e.g., Murthy et al., 2004; U.S. Government Accountability Office, 1992; Kramer and Shapiro, 1984; Heckman and Smith, 1995; Chan and Hamilton, 2006; Chassang and Feng, 2022; Treasure and MacRae, 1998; Banerjee et al., 2020), and failing to break out estimated treatment effects for important subgroups potentially limits our understanding of how an intervention will ultimately affect spending and outcomes (Green et al., 2022). In addition, gaps in representation contribute

to disparities in care and the uptake of newly developed drugs, with less-represented groups adopting new drugs more slowly (Alsan et al., 2022). Other well-known reasons why treatment effects estimated from clinical trials may differ from those in the field include various design features of randomized controlled trials (RCT) that can enhance the effectiveness of an intervention (Wennberg et al., 1998; Allcott, 2015) and institutional or general equilibrium differences that arise only when the intervention is deployed at scale (Bold et al., 2018; Oostrom, 2022). Building on this work, our paper highlights the role of providers' financial incentives in determining the equilibrium treatment effect of an intervention.

Our paper also relates to research that evaluates the effects of alternative payment models, such as the Bundled Payments for Care Improvement Initiative, introduced in 2011 with the goal of restraining health care costs by paying providers a bundled rate for specific episodes of care rather than traditional fee-for-service reimbursements (Agarwal et al., 2020; Rolnick et al., 2020). Several studies have since examined the initiative's impact, primarily through descriptive analyses that compare costs and patient outcomes across participating and nonparticipating hospitals, and have found lower costs at participating hospitals and mixed differences in outcomes (Maughan et al., 2019; Martin et al., 2018; Dummit et al., 2016; Navathe et al., 2017; Barnett et al., 2019). Most notably, Einav et al. (2020) find that when these programs are voluntary, hospitals elect to participate when they can increase revenue without making meaningful changes to their behavior, generating inefficient transfers to hospitals relative to the status quo. Importantly, the voluntary nature of many alternative payment programs has precluded researchers from using them to explore the effectiveness of the resulting forgone care, whereas the end-stage renal disease (ESRD) PPS that we study was mandatory and affected different patient populations with varying intensity, allowing us to identify the causal impact of EPO on health outcomes.

The switch to a PPS in dialysis has also been studied previously. Chertow et al. (2016), for example, document an abrupt decline in EPO doses beginning in late 2010 but find that all-cause mortality, cardiovascular mortality, and myocardial infarction did not change significantly, while Hirth et al. (2014) report an increase in blood transfusions following the start of the PPS. Our quasi-experimental research design allows us to add to this literature by identifying the causal effect of EPO on several health outcomes, informing recent discussions and policies designed to limit the unnecessary use of prescription drugs, particularly those covered by Medicare Part B, which paid $41 billion for drugs administered by infusion or injection in doctors' offices in 2020 (MEDPAC, 2022). As expenditures for this class of costly

drugs have increased at an average rate of 9% each year since 2009, policymakers have struggled to reduce expenses in ways that do not cut essential treatments for patients. Understanding the impact these drugs have on patients beyond clinical trials is therefore critical for making informed policy decisions.

Finally, our paper contributes to a recent literature specifically focused on the economics of the dialysis industry (e.g., Eliason et al., 2020; Dai, 2014; Cutler et al., 2017; Dai and Tang, 2015; Grieco and McDevitt, 2017; Eliason, 2021; Wilson, 2016a,b). Of particular relevance, Gaynor et al. (2020) study how dialysis providers balance patients' health with the financial incentives for EPO using a structural model of dosing decisions. Using data from before the payment reform, they find that fee-for-service payments resulted in an excessive use of EPO, with doses falling by a third under the optimal linear contract. We complement their work by examining how the change in drug reimbursements affected providers' treatment decisions in practice and the resulting impact on patient outcomes.

Our paper proceeds with Section 2, which discusses essential details of the U.S. dialysis industry. Section 3 describes our data. Section 4 lays out a simple model of providers' equilibrium dosing decisions and our instrumental variable research design. Section 5 presents our IV estimation results and our model-based measurement of EPO's impacts. Section 6 concludes. The appendix contains supplementary material referenced throughout the paper.

2. Institutional Details of Dialysis

2.1. Medical Background on Kidney Failure

Kidneys filter wastes and toxins from the blood and produce erythropoietin, a hormone that stimulates red blood cell production. For patients with chronic kidney failure, the kidneys no longer adequately perform these functions. To survive, those with ESRD must either receive a kidney transplant or undergo dialysis, a medical treatment that mechanically filters wastes and toxins from a patient's blood. The most common form of dialysis, hemodialysis, uses a machine to artificially clean blood outside the body, either at the patient's home or at a medical facility, whereas peritoneal dialysis uses the lining of the patient's abdomen to filter blood inside the body.[1] Because over 90% of dialysis patients in the U.S. use in-center hemodialysis, we focus on that modality for our analysis.[2]

[1] For more information, please see `https://www.niddk.nih.gov`.

[2] Please see Wang et al. (2018) for a discussion of the trends in dialysis modalities.

2.2. Medical Background on Anemia

Anemia results from deficient or dysfunctional red blood cells, which lead to reduced oxygen flow to the body's organs. To diagnose anemia and assess its severity, clinicians use either hematocrit concentration, which measures the volume of red blood cells as a percentage of total blood volume, or hemoglobin concentration, which measures the amount of hemoglobin, a protein contained in red blood cells, in terms of grams per deciliter of blood (g/dL).[3] We focus on hemoglobin levels in this paper, with accepted guidelines defining anemia as a hemoglobin level below 14 g/dL for men and 12 g/dL for women. Common symptoms relate mostly to a patient's quality of life, including fatigue, weakness, headaches, difficulty concentrating, a rapid heartbeat, and insomnia, but in some cases anemia can contribute to a greater risk of serious heart conditions, hospitalization, and death (Kliger et al., 2013).

Nearly all patients with kidney failure suffer from anemia. As mentioned above, healthy kidneys produce erythropoietin, which stimulates the production of red blood cells in bone marrow, so those with kidney failure have much lower levels of naturally occurring erythropoietin, which is why dialysis patients are often anemic (Babitt and Lin, 2006). Among these patients, anemia is typically managed using a cocktail of drugs, with acute instances requiring blood transfusions.

Chief among the drugs used to treat anemia is recombinant human erythropoietin or epoetin alfa, a biologic commonly known as EPO. Manufactured by Amgen under the brand name EPOGEN, EPO was approved by the Food and Drug Administration in 1989 to treat anemia in dialysis patients (Kalantar-Zadeh, 2017) and since then has been a standard of care for the condition, with those treated with EPO requiring fewer blood transfusions and reporting improved appetite, activity level, and sense of well-being (Eschbach et al., 1989; Valderrabano, 2000). By 2005, 99% of in-center hemodialysis patients regularly received EPO, and in some years it was Medicare's largest drug expenditure (U.S. Government Accountability Office, 2012).[4]

By the mid-2000s, randomized controlled trials had demonstrated that EPO may be harmful to some patients. Besarab et al. (1998), for example, found that ESRD patients with congestive heart failure treated with EPO to achieve normal or high hematocrit levels had a higher probability of death and myocardial infarction. Similarly, Singh et al. (2006) found an increased risk of death and cardiovascular

[3] Hematocrit is approximately equal to three times the measured hemoglobin (HGB) level (Bain et al., 2017).

[4] In addition to EPO, dialysis patients commonly receive a host of other drugs to combat the effects of ESRD, including intravenous iron for anemia management and vitamin D supplements and their analogues to treat hyperparathyroidism and bone mineral disease (Bhan and Thadhani, 2009).

events among patients treated with EPO to normal or high hematocrit levels who were diagnosed with chronic kidney disease but not on dialysis. Although these RCTs focused on specific patient populations, they raised concerns about the use of EPO more broadly, and in March 2007 the FDA issued a public health advisory for EPO, mandating a black box warning and advising physicians to adjust doses to target hemoglobin levels between 10 to 12 g/dL (Thamer et al., 2013). Over this period, observational studies suggested similar adverse effects (Zhang et al., 2004; Bradbury et al., 2009; Brookhart et al., 2010), although providers did not change doses much in response (Thamer et al., 2013) and the studies did not necessarily present causal effects. In June 2011, the FDA amended the original black box warning, instructing providers to use a dose no higher than what is necessary to avoid blood transfusions.

2.3. Medical Background on Elevation and EPO

ESRD patients do not respond uniformly to EPO, with the elevation at which a patient resides providing one source of variation. At higher elevations, the richness of oxygen in the blood decreases, activating an increase in both naturally occurring erythropoietin and the amount of iron in the blood stream. For those with healthy kidneys, erythropoietin stimulates bone marrow to use the available iron to produce red blood cells. In ESRD patients, however, higher elevation is associated with increased iron availability but little increase in erythropoietin, because their kidneys do not properly perform this function. However, iron makes erythropoietin more productive, so patients at higher elevations tend to have higher baseline levels of hemoglobin and consequently receive less EPO.[5]

Several observational studies in the medical literature have documented this phenomenon. Brookhart et al. (2008), for instance, show that patients living more than 6,000 ft. above sea level receive 19% less EPO than patients at sea level, while Brookhart et al. (2011) find that patients moving from low to high elevations exhibit large and persistent increases in hematocrit and decreases in EPO doses relative to a comparison group, with related results in Sibbel et al. (2017).

2.4. The Dialysis Industry

Dialysis patients choose their provider much like patients do in other parts of the U.S. health care system, with those covered under Medicare able to receive treatment at any facility that has an opening.

[5]Please see Winkelmayer et al. (2009) and Brookhart et al. (2011) for a more complete discussion of these physiological relationships.

Patients primarily receive treatment at one of the more than 6,000 dedicated dialysis facilities across the country, where they typically go three times per week for treatment that lasts three to four hours each visit. These facilities are run by a mix of for-profit and non-profit firms, with the two largest for-profit chains, DaVita and Fresenius, controlling over 60% of facilities and earning 90% of the industry's revenue (United States Renal Data System, 2014; Baker, 2019). Independent facilities comprise most of the remainder.

2.5. Medicare Payment Reform

Since 1972, Medicare has extended full benefits to all patients with ESRD, regardless of age, paying for both dialysis and anemia treatment under Part B. Those enrolled in an employer group health plan when diagnosed with ESRD retain their commercial insurance as a primary payer for 33 months, during which time Medicare acts as a secondary payer (Lin, 2021; League et al., 2022).

From the early 1980s to 2011, Medicare paid providers a composite rate of approximately $128 per dialysis session, which was intended to cover the labor, capital, supplies, and routine lab tests associated with each treatment. In addition, Medicare reimbursed providers for EPO and other injectable drugs on a fee-for-service basis, as is the case for many injectable drugs covered under Part B. Initially, Medicare set the reimbursement rate for EPO at $10 per 1000 IUs and then updated the rate in 2005 based on the average sales price plus a 6% markup, resulting in a slight decline in reimbursements to about $9.50 per 1000 IUs.[6] EPO doses and expenditures increased consistently during the fee-for-service era, with spending on erythropoietin stimulating agents (ESAs) such as EPO approaching $2.7 billion in 2007 (Whoriskey, 2012). Concerns that the distortionary incentives from fee-for-service reimbursements resulted in excessive costs for Medicare and harm to patients motivated policymakers to include ESRD payment reform as part of the Medicare Improvements for Patients and Providers Act (MIPPA) in 2008.

MIPPA mandated the bundling of dialysis services and all injectable drugs and biologics used in the treatment of ESRD into a single prospective payment that would take effect in 2011. Reimbursement for the bundle was initially set at about $230, a level chosen to reduce expected total federal payments to

[6]For more details, please see `https://www.gao.gov/assets/260/253347.pdf`.

dialysis providers by 2%.[7] Although EPO had an outsize effect on patient outcomes, Medicare spending, and provider revenues, the original PPS bundled together 21 other drugs, spanning anemia treatment, access management, and anti-infectives.[8] In addition, the reform explicitly stated that the use of drugs outside the PPS "as substitutes for any of these drugs" would be "ineligible for separate payment".[9]

To offset the incentives for providers to reduce their costs by providing lower-quality care following the payment reform, MIPPA also mandated the development of a quality incentive program (QIP) that reduces payments to providers that fail to meet certain clinical standards, such as standards for hemoglobin levels and hospitalization rates. Although the specific criteria assessed in the QIP change from year to year, in its inaugural year, 2012, the QIP standards targeted patients' hemoglobin levels and urea reduction ratio, a measure of dialysis filtration. Under the QIP, Medicare reduces the annual payments to a facility by between 0.5% and 2.0% if, for instance, the HGB levels of too many patients fall outside the regulated standards, with the size of the penalty determined by the extent of the shortfall. We discuss the QIP further in Appendix B, where we provide evidence that the QIP did not meaningfully contribute to the reduction in EPO use during our sample period, and evaluate providers' strategic responses to it in Bertuzzi et al. (2023).

3. Data, Descriptive Statistics, and Time Trends

The main dataset for our analysis comes from the U.S. Renal Data System (United States Renal Data System, 2019), a clearinghouse that collects and manages data from a variety of sources relevant to ESRD patients and health care providers. Included in these data are Medicare claims, treatment histories, patient attributes, and annual facility surveys. In addition, CMS Form 2728, known as the Medical Evidence Form, provides data on the health and clinical attributes of patients when they begin dialysis. We also geocode facilities' addresses and extract their elevations using data from the U.S. Geological Survey (U.S. Geological Survey Center for Earth Resources Observation and Science, 2014).

Table 1 presents summary statistics for our variables of interest. We limit our sample to hemodialysis

[7] See Federal Register, Volume 74, Issue 187, (September 29, 2009). Providers had the option to transition into the PPS either immediately in 2011 or gradually over four years starting in 2011. Over 90% opted for the immediate transition. In Appendix A, we demonstrate that our results are robust to using only the set of providers who opted in immediately.

[8] Since then, this list has been expanded to include over 50 products.

[9] Federal Register, Volume 75, Number 155, (August 12, 2010).

patients between the ages of 18 and 100 for whom Medicare is the primary payer. We further limit our sample to observations for which we observe all patient and facility characteristics used in our later analysis. These characteristics include demographic variables such as gender and age, comorbidities such as diabetes and cancer, patient behaviors such as smoking and drinking, and facility characteristics such as chain affiliation and elevation — a much richer source of patient attributes and at a much larger scale than typically available in clinical trials. Although in some figures we use data from 2005–2014 to provide a wider perspective, we conduct all statistical analyses on a sample restricted to 2009–2012, a window centered and narrowly focused on the start of the PPS. After these restrictions, our sample contains approximately 10 million patient-month observations. As will be important for our instrumental variable analysis in Section 4, the elevation of facilities varies substantially, with a standard deviation of 924 ft. We present summary statistics by elevation in Appendix C.

3.1. Time Trends

The 2011 payment reform combined reimbursements for two types of services, dialysis treatments and injectable drugs, into a single reimbursement. Figure 1 shows the evolution of several of these treatments, including anemia management and the quantity and quality of dialysis care. The primary measures of anemia management, EPO doses and transfusion rates, responded immediately to the payment reform. EPO doses were level going into 2010 but decreased substantially starting midway through 2010. The drop in EPO use moves in concert with the increase in transfusions shown in panel (b), consistent with EPO being used to increase patients' hemoglobin levels and reduce their need for transfusions. The sharp decline in EPO predates the payment reform in 2011 by a few months and matches Medicare's announcement of the final PPS rule.[10] For this reason, although we use January 2011 as the beginning of the PPS in our main analysis, we also show in Appendix D that our results are robust to changing the treatment period to include the anticipatory period between the announcement and the implementation of the payment reform.[11]

In contrast to the changes in anemia treatment, we find little evidence that dialysis care itself

[10]For more details, please see `https://www.gao.gov/assets/gao-13-190r.pdf`.

[11]In addition, as discussed in Section 2.2, during this period there were two other policy changes of note, a black box warning and the QIP. In Appendix B, we present evidence that these changes do not explain the decline in EPO doses in Figure 1—if anything, they would make our estimate of the change in EPO doses attributable to the payment reform conservative.

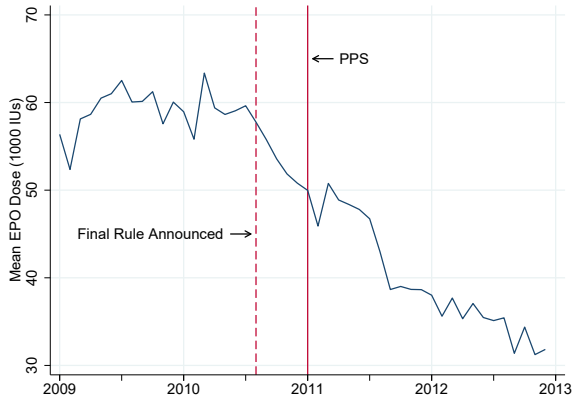
Table 1
PATIENT DESCRIPTIVE STATISTICS

	Mean	Std. Dev.
Patient Characteristics		
Predicted Mortality	0.016	0.011
Age (Years)	63.40	14.57
Months with ESRD	45.08	38.01
Black	0.385	0.487
Male	0.552	0.497
Diabetic	0.540	0.498
Hypertensive	0.906	0.292
Incident Hemoglobin	9.853	1.674
Facility Characteristics		
Facility Elevation (ft)	638.1	923.5
Independent Ownership	0.197	0.397
Resource Use		
EPO Dose (1000 IUs)	48.50	64.11
Receives Any EPO	0.755	0.430
Medicare Spending ($)		
Total	7,555	10,769
Inpatient	2,558	9,380
Dialysis	2,287	970
Part D	465	817
Outpatient	394	1,266
Health Outcomes		
Hemoglobin (g/dL)	11.12	1.22
Mortality	0.016	0.124
Hospitalizations		
Any Cause	0.1380	0.3449
Cardiac Event	0.0271	0.1625
Septicemia	0.0094	0.0965
Transfusions		
Total	0.0282	0.1655
Inpatient	0.0232	0.1504
Outpatient	0.0057	0.0750
Emergency Room	0.0001	0.0098
Unique Patients	461,477	
Patient-Months	10,077,289	

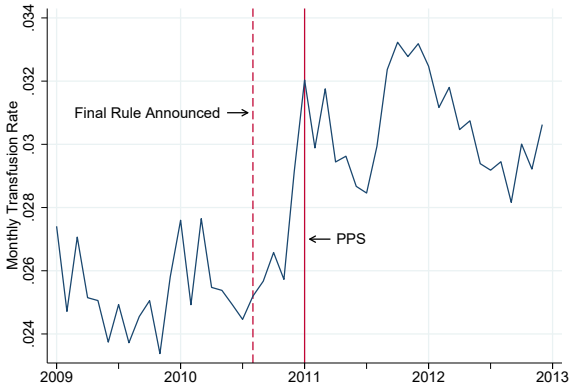
Notes: An observation is a patient-month. Sample consists of observations from January 2009 to December 2012 for in-center hemodialysis patients between the ages of 18 and 100 with Medicare as their primary payer for whom we observe all patient and facility controls used in the analyses in Section 3.1 and later. Predicted mortality is the predicted value for each observation using coefficients from a regression of mortality on patient controls and time fixed effects on observations from 2009 and 2010. Time fixed effects are not included in the prediction. Patient controls include dummy variables for incident comorbidities and characteristics reported on medical evidence forms, including diabetes, hypertension, BMI bin, GFR bin, HGB bin, high albumin, cancer, drug use, alcoholism, smoking behavior, necessity of assistance, COPD, ASHD, PVD, ischemic heart disease, and congestive heart disease, along with patient race, gender, and cubic functions of age and dialysis tenure. EPO doses are censored at the 99th percentile and measured in 1000 IUs. Hemoglobin is winsorized from below to 5 and from above to 20 and is measured in grams per deciliter. Facility elevation is measured in feet above sea level.

Figure 1
Time Trends in Treatments and Outcomes

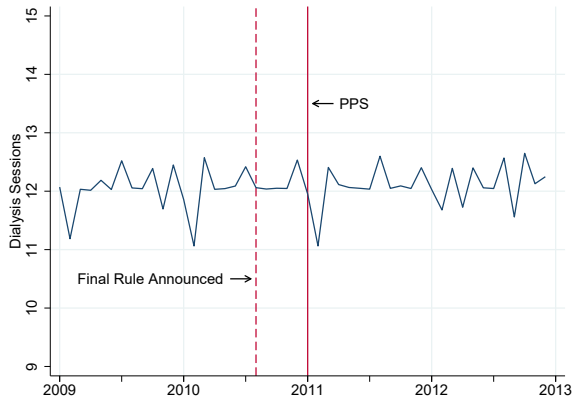
(a) Monthly EPO Dose



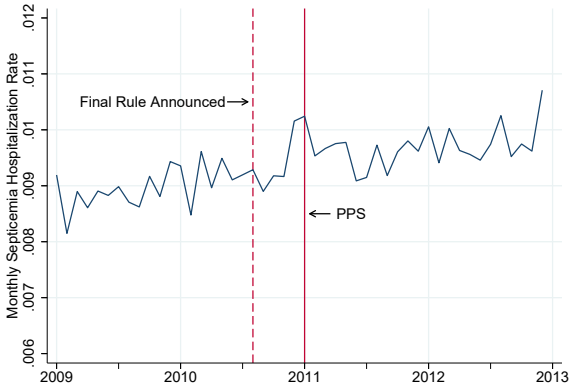
(b) Transfusion Rate



(c) Monthly Dialysis Sessions



(d) Hospitalizations for Septicemia



Notes: An observation is a patient-month. Sample consists of observations from January 2009 to December 2012 for in-center hemodialysis patients between the ages of 18 and 100 with Medicare as their primary payer for whom we observe all patient and facility controls used in the analyses in Section 3.1 and later. EPO doses are censored at the 99th percentile and measured in 1000 IUs. Injectable vitamin D drugs include Calcitriol, Doxercalciferol, and Paricalcitol. The solid vertical line indicates the start of the PPS in January 2011, while the dashed vertical line indicates the announcement of the final rule for the PPS.

changed in response to the payment reform, providing reassurance that we can use the payment reform to identify the equilibrium health effects of EPO. The average number of dialysis sessions per patient remained steady each month throughout the payment reform, for instance, and hospitalizations for septicemia, a class of infections that can arise from improper cleaning of dialysis facilities and reflects low-quality care, did not change.[12]

3.2. Preliminary Analysis of the Prospective Payment System

For a preliminary analysis of how the payment reform influenced provider behavior and patient outcomes, we consider the following regression that includes an indicator variable for the post-PPS period as well as patient- and facility-level controls:

$$y_{ijt} = \beta_0 + \beta_1 \mathbb{1}[PPS_t = 1] + X_{ijt}\Gamma + \varepsilon_{ijt}. \tag{1}$$

Estimates of equation (1) appear in Table 2, with column (4) including controls for patient and facility characteristics, along with calendar month, patient, and facility fixed effects. This specification suggests a within-patient decrease in EPO doses of over 9% from the pre-PPS mean.[13] In Table 3, we present results from estimating the same specification for other dependent variables, finding large changes after the payment reform: HGB levels declined 3.9%, transfusions increased 21.5%, overall hospitalizations dropped 3.4%, hospitalizations for cardiac events decreased 6.9%, and the monthly mortality rate fell 4.8%.[14]

Although easy to interpret, these initial time-series regressions may be biased by confounding time trends. Figure 1, for instance, suggests that the payment reform may have had an effect on both the level of EPO doses as well as the trend. In light of this, we enrich our prior specification by including a time trend interacted with the PPS indicator variable:

$$y_{ijt} = \beta_0 + \beta_1 t + \beta_2 \mathbb{1}[PPS_t = 1] + \beta_3 t_{Post\text{-}PPS} + X_{ijt}\Gamma + \varepsilon_{ijt}. \tag{2}$$

[12] Appendix E describes other channels through which the PPS may have affected patients.

[13] The smaller magnitude of the PPS coefficient in specification (4) that includes patient fixed effects is not driven by new patients, as the decrease in EPO was similar for both new and continuing patients. Furthermore, the reduction in EPO occurred for those who began dialysis before the final rule was announced just as much as for those beginning dialysis later.

[14] Table A4 in Appendix C gives the pre-PPS means for these variables, which are used as the denominators for these percentage change calculations.

Table 2
Change in EPO Dose After PPS

	(1) EPO	(2) EPO	(3) EPO	(4) EPO
PPS	-18.31***	-19.92***	-16.99***	-5.679***
	(0.245)	(0.238)	(0.417)	(0.266)
Pat/Fac Controls	0	1	1	1
Facility FE	0	0	1	1
Patient FE	0	0	0	1
Dep. Var. Mean	48.50	48.50	48.50	48.54
R-squared	0.0203	0.0777	0.134	0.531
Observations	10077289	10077289	10077264	10059269

Notes: OLS estimates from equation (1). Dependent variable is monthly EPO dose. EPO doses are censored at the 99th percentile and measured in 1000 IUs. PPS is an indicator variable for January 2011 or later. An observation is a patient-month. Sample consists of observations from January 2009 to December 2012 for in-center hemodialysis patients between the ages of 18 and 100 with Medicare as their primary payer for whom we observe all patient and facility controls used in the analyses in Section 3.1 and later. Patient controls include dummy variables for incident comorbidities and characteristics reported on medical evidence forms, including diabetes, hypertension, BMI bin, GFR bin, HGB bin, high albumin, cancer, drug use, alcoholism, smoking behavior, necessity of assistance, COPD, ASHD, PVD, ischemic heart disease, and congestive heart disease, along with patient race, gender, and cubic functions of age and dialysis tenure. Facility controls include facility elevation, whether the facility to freestanding or hospital-based, and chain ownership status. Further controls include calendar month fixed effects. Facility and patient fixed effects are also included when indicated. Standard errors clustered by facility are in parentheses. $^{+}$, *, **, and *** indicate significance at the 10%, 5%, 1%, and 0.1% level, respectively.

Table 3
Change in Other Outcomes After PPS

	(1) HGB	(2) Transfusion	(3) Hosp., Any Cause	(4) Hosp., Cardiac Event	(5) Mortality
PPS	-0.442***	0.00538***	-0.00490***	-0.00202***	-0.000815***
	(0.00888)	(0.000201)	(0.000460)	(0.000195)	(0.000124)
Pat/Fac Controls	1	1	1	1	1
Facility FE	1	1	1	1	1
Dep. Var. Mean	11.12	0.0282	0.138	0.0271	0.0157
R-squared	0.0749	0.0118	0.0215	0.00790	0.00850
Observations	8181736	10077264	10077264	10077264	10077264

Notes: OLS estimates from equation (1). Dependent variable in column (1) is hemoglobin. Hemoglobin is winsorized from below to 5 and from above to 20 and is measured in grams per deciliter. Dependent variables in columns (2)–(5) are binary outcome variables. PPS is an indicator variable for January 2011 or later. An observation is a patient-month. Sample consists of observations from January 2009 to December 2012 for in-center hemodialysis patients between the ages of 18 and 100 with Medicare as their primary payer for whom we observe all patient and facility controls used in the analyses in Section 3.1 and later. Patient controls include dummy variables for incident comorbidities and characteristics reported on medical evidence forms, including diabetes, hypertension, BMI bin, GFR bin, HGB bin, high albumin, cancer, drug use, alcoholism, smoking behavior, necessity of assistance, COPD, ASHD, PVD, ischemic heart disease, and congestive heart disease, along with patient race, gender, and cubic functions of age and dialysis tenure. Facility controls include facility elevation, whether the facility is freestanding or hospital-based, and chain ownership, as well as facility fixed effects. Further controls include calendar month fixed effects. Standard errors clustered by facility are in parentheses. $^{+}$, *, **, and *** indicate significance at the 10%, 5%, 1%, and 0.1% level, respectively.

Equation (2) differs from (1) in that it includes two time trend terms, t and $t_{Post\text{-}PPS}$. Here, t and $t_{Post\text{-}PPS}$ measure the number of months since the the start of the PPS in January 2011, and we therefore interpret β_1 as the average monthly change in EPO before the start of the PPS, while β_3 is the change in this trend after the PPS.[15] Complete estimates of equation (2) appear in Appendix F. Compared to our results from equation (1), the estimates of (2) suggest that the effects of the payment reform did not become fully realized in January 2011 but instead evolved more gradually over time. Regardless, the payment reform clearly coincided with a large reduction in EPO use and changes in measures of anemia management.

[15]The variable t takes on negative values prior to the start of the PPS in January 2011 such that in December 2010 $t = -1$, in November 2010 $t = -2$, and so on; $t_{Post\text{-}PPS}$ is set to 0 for all months prior to the start of the PPS. Please see Baicker and Svoronos (2019) for a discussion of the benefits of this definition of time trends.

4. The Causal Effect of EPO on Health Outcomes

Our descriptive results from Section 3 suggest that the payment reform had a large impact on the amount of EPO given to dialysis patients and their resulting health outcomes. Although clinical trials had previously shown how the drug affects patients in a controlled setting, the way providers respond to financial incentives and heterogenous patient populations may mean that the experience of Medicare beneficiaries differs from predictions based RCTs. To illustrate this point, we provide a simple model of providers' dosing decisions that incorporates the financial incentives and heterogeneous patient populations they face, and then introduce a novel instrumental variable design to estimate the causal effect of the drug's use on Medicare beneficiaries using observational data.

4.1. A Model of Provider Dosing Decisions

Suppose a provider chooses a patient's EPO dose to solve the problem

$$\max_{epo} \quad \alpha h(epo; a, x) + p \times epo,$$

where $\alpha \geq 0$ is the weight that providers place on patient health relative to profits; $h(epo; a, x)$ is the health of the patient, which depends on the dose of *epo*, elevation a, and other patient characteristics x; and p is the profit from each unit of *epo*. It is possible that p may be negative, as would be the case under the PPS, where higher doses of *epo* increase costs without a corresponding increase in reimbursements.

The first-order condition is

$$f(epo^*; a, p) = \alpha \frac{\partial h}{\partial epo^*}(epo; a, x) + p = 0,$$

which reveals that a provider influenced by financial incentives will overtreat patients if the profit margin of EPO is positive and undertreat them if it is negative. This mirrors policymakers' concerns both before the payment reform, when they suspected providers administered excessive EPO doses to patients, and after, when they feared the reform would result in insufficient doses due to the cut in reimbursements.

Using the implicit function theorem, the equilibrium level of EPO changes with respect to the profit

margin from administering the drug in the following way:[16]

$$\frac{\partial epo^*}{\partial p} = -\frac{\partial f}{\partial epo}^{-1}\frac{\partial f}{\partial p} = -\frac{1}{\alpha}\frac{\partial^2 h}{\partial epo\ \partial epo}^{-1}.$$

From the equation, the extent to which EPO doses change in response to a payment change depends on the altruism of providers, with more-altruistic providers responding less strongly, as well as the curvature of the health function with respect to EPO, where more rapidly diminishing returns result in a weaker response. The first point is well understood—health care providers are known to respond to financial incentives to varying degrees—whereas the second is not. If the second derivative of the health function with respect to treatment varies across patients, then providers will respond to payment changes differently for different patients, as we show below.

In Figure 2, for instance, we show that the change in EPO doses following the payment reform differed across elevations, suggesting that $\frac{\partial^2 h}{\partial epo\ \partial epo}$ depends on elevation. Furthermore, since we observe in the data that

$$\frac{\partial epo^*}{\partial p}(HighElevation) < \frac{\partial epo^*}{\partial p}(LowElevation),$$

it follows that

$$\frac{\partial^2 h}{\partial epo\ \partial epo}(HighElevation) < \frac{\partial^2 h}{\partial epo\ \partial epo}(LowElevation).$$

Assuming that EPO has decreasing marginal benefits, this implies that the marginal benefit from EPO at high elevations is decreasing more quickly than the marginal benefit of EPO at lower elevations, perhaps because physiological differences at high elevations make excessive EPO doses especially harmful or because the benefits of EPO are more rapidly diminishing at the lower doses that high-elevation patients receive. In short, the observed differences in how providers respond to payment changes reveal that the heterogeneous relationship between health and EPO influences their responses. Beyond elevation, other relevant sources of heterogeneity could include patient comorbidities like obesity or heart disease, or differences in the health function, which can be thought of as a composite function of many aspects of health: anemia, risk of adverse events, discomfort at being pricked with a needle, and so on.

When considering a reimbursement scheme that might induce providers to cut EPO doses, policymakers will need to evaluate how the reduction will affect the set of patients whose EPO doses will

[16]Here we assume differentiability of $f()$ with respect to a, x, and p around epo^*.

change because of the new policy. That is, any potential cost savings from the policy change must be weighed against $\frac{\partial h}{\partial epo^*}$, the equilibrium marginal impact of EPO on patient health. The optimal policy would eliminate doses that have a marginal cost exceeding the marginal benefits to a patient's health—recovering the marginal effect of EPO on health in equilibrium is therefore paramount to understanding the welfare implications of policy reforms that impact the use of the drug.

Notably, the model predicts that $\frac{\partial h}{\partial epo^*}$ will be the same for all patients for whom the financial margin on EPO, p, and the altruism of their provider, α, are the same.[17] At the same time, the health functions themselves may differ across patients and may vary nonlinearly in EPO, meaning that the amount of EPO used in equilibrium and the corresoponding level of health can—and likely will—vary across patients. This heterogeneity in equilibrium levels of dosing and health means that $\frac{\partial h}{\partial epo^*}$ is not practically attainable in clinical trials that do not typically account for providers' financial and altruistic considerations. Instead, these trials estimate an average of $\frac{\partial h}{\partial epo}$ that will not generally be the equilibrium levels of EPO used in practice. Therefore, estimating the central object of interest for policymakers, $\frac{\partial h}{\partial epo^*}$, necessitates the sort of empirical inquiry we present in this paper.

4.2. Identification Strategy

Using observed EPO doses before and after the policy change, we can estimate the causal effect of EPO on health outcomes, $\frac{\partial h}{\partial epo^*}$, from an IV strategy based on the following specification:

$$y_{ijt} = \beta_0 + \beta_1 EPO_{ijt} + X_{ijt}\Gamma + \varepsilon_{ijt}, \tag{3}$$

where y_{ijt} is the health outcome of patient i, treated at facility j, in month t. The main challenges in identifying the causal effect of EPO on health outcomes stem from reverse causality and simultaneity, which could bias OLS estimates in ambiguous ways. The estimates would be biased upward, for example, if only the healthiest patients receive EPO. Conversely, a downward bias may result from unobserved confounds, such as rapidly deteriorating kidneys, which would lead to both high EPO doses to combat anemia and low survival rates due to the patient's declining health.

To overcome these empirical challenges, we use two independent sources of variation in EPO doses

[17] Insofar as there are actually differences across patients in the equilibrium marginal effect of EPO on health for other reasons, such as provider uncertainty about a patient's health function or reliance on dosing heuristics, our estimates will recover a weighted average of these equilibrium marginal effects.

within an instrumental variables regression that, under a standard set of assumptions, returns a weighted average of marginal treatment effects, where the weighting follows from how the instrument shifts treatment. First, we use the time-series variation in EPO reimbursements associated with Medicare's payment reform. As Medicare imposed the change uniformly on all providers, rather than targeting specific payment changes to specific facilities, this policy introduced a plausibly exogenous shock to EPO doses due to the change in financial incentives. Second, we use a novel source of variation based on a physiological aspect of anemia management: patients living at higher elevations have higher baseline levels of HGB and consequently require lower doses of EPO to manage their anemia. With facilities considering both their own profits and a patient's well-being when administering EPO, those at lower elevations reduced their doses comparatively more after the PPS eliminated fee-for-service reimbursements. In other words, patients at low elevations experienced a larger shock to their EPO doses than patients at higher elevations did, and we can use the cross-sectional variation induced by patients' elevations along with the time-series variation induced by the payment reform to identify the causal effect of EPO on health outcomes.

We cannot simply use the payment reform and elevation as instruments directly in equation (3), however, as doing so may violate the exclusion restriction. To draw causal inferences on the basis of changes before and after Medicare introduced prospective payments, we would need to assume that the change in EPO was the only change that could have affected patients' health; other trends may be conflated with the payment reform, however, such as updated dialysis standards and related medical advances. Similarly, just as elevation directly affects patients' hemoglobin levels, it may also directly affect other health outcomes.

Rather than use either variable as an instrument on its own, we use the interaction of the post-PPS indicator variable and a facility's elevation as an instrument for EPO doses while controlling directly for time fixed effects and elevation in our first- and second-stage regressions. Our empirical strategy of interacting one variable with time-series variation and another with cross-sectional variation was first introduced by Bartik (1991) and is closely related to the strategies employed by Card (1995) to measure the returns to education, Nunn and Qian (2014) to study the effect of U.S. food aid on conflict in recipient countries, and Bettinger et al. (2017) to study the effect of online college courses on student

outcomes. Adapting this approach to our setting, we have a first-stage specification of

$$EPO_{ijt} = \alpha_1 Elevation_j + \alpha_2 PPS_t + \alpha_3 Elevation_j \times PPS_t + X_{ijt}\Gamma + u_{ijt}, \tag{4}$$

where the instrument $Elevation_j \times PPS_t$ varies by facility and time period, allowing us to include month-year fixed effects.

By instrumenting for EPO doses with the interaction term, our first stage resembles a difference-in-differences estimation, comparing EPO doses at facilities that typically use less of the drug due to their high elevation with those at lower elevations that typically use more of it, during the fee-for-service era when financial incentives favored higher doses relative to the PPS era when the financial incentives reversed. As outlined in Nunn and Qian (2014), the main distinction between this strategy and a typical difference-in-differences estimation is the continuous treatment variable.

For our second stage to have a causal interpretation, the interaction between a facility's elevation and Medicare's payment policy must affect health outcomes only through its influence on EPO doses, conditional on the controls. That is, the exclusion restriction in our setting requires that (i) any other mechanism through which elevation affects patients is constant over time and (ii) any other mechanism causing health outcomes to differ before and after the payment reform affects patients uniformly with respect to their elevation. As discussed above, if we were to use elevation alone as the instrument, the reduced-form slope would capture both the effect of EPO as well as other plausible mechanisms that affect health outcomes, such as patients living at higher elevations having more-active lifestyles (e.g., hiking and skiing) or elevation having direct consequences for patients' health. By interacting the two variables, however, the reduced-form coefficient measures only how the slope between elevation and outcomes changes when the reimbursement policy changes—the main effect of elevation included in both the first and second stages differences out any other plausible mechanisms that remain constant across the different payment schemes.

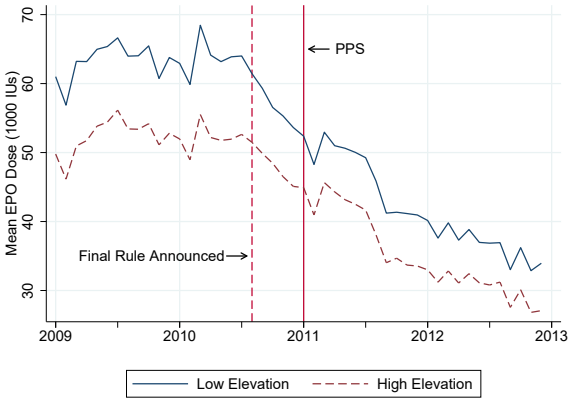
Although not directly testable, several pieces of evidence suggest that our empirical strategy satisfies these two requirements. In the same spirit as a traditional difference-in-differences estimation, the plot of EPO doses over time for the first and fifth elevation quintiles in the left panel of Figure 2 shows parallel trends in EPO doses prior to the payment reform.[18] On average, low-elevation patients received

[18] As discussed in Christian and Barrett (2017), non-parallel pre-trends would have suggested our difference-in-differences analog violated the exclusion restriction.

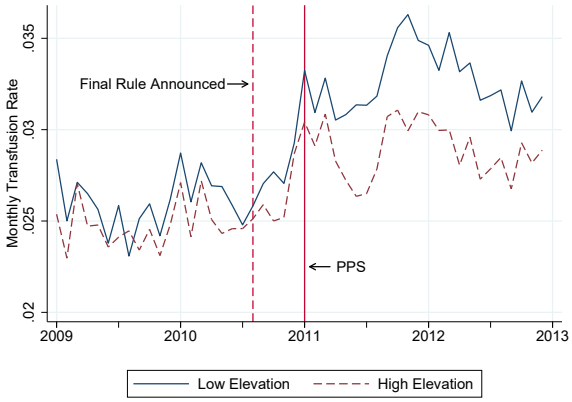
higher doses of EPO before prospective payments, with the difference between the two groups remaining constant during this period.[19] After the payment reform, average EPO doses declined in both quintiles, but the decline was much larger for low-elevation patients than for those at high elevations.[20] The second stage then links the change in EPO to related health outcomes like transfusions, with the right panel showing a larger increase for patients at lower elevations commensurate with their larger reductions in EPO.

Figure 2
Mean EPO Dose and Transfusion Rate over Time, by Elevation

(a) First Stage: EPO



(b) Second Stage: Transfusions



Notes: An observation is a patient-month. Sample consists of observations from January 2009 to December 2012 for in-center hemodialysis patients between the ages of 18 and 100 with Medicare as their primary payer for whom we observe all patient and facility controls used in the analyses in Section 3.1 and later. EPO doses are censored at the 99th percentile and measured in 1000 IUs. High (low) elevation denotes facility elevation in the fifth (first) quintile. This corresponds to being above 870 (below 73) feet above sea level. The solid vertical line indicates the start of the PPS in January 2011, while the dashed vertical line indicates the announcement of the final rule for the PPS.

A related threat to identification would be omitted variables that change disproportionately across elevations over time. From balance tables for observable patient characteristics at each elevation quintile in Appendix C, we find that although some differences across elevations do exist and change over time, the changes are not systematically moving toward better or worse outcomes. To assess more formally whether changes in unobserved patient characteristics might confound our analysis, we create

[19] A regression of EPO on facility elevation, a time trend, and the interaction of the two along with patient and facility controls using data prior to prospective payments indicates that the difference in time trends is small and not statistically significant (p=0.5777).

[20] This differential response to a uniform change in financial incentives suggests nonlinearities in the marginal effects of EPO across elevations and highlights the importance of interpreting our second-stage estimates as average causal effects from a heterogeneous effects model.

Table 4
Predicted Mortality by Elevation

	(1) Predicted Mortality	(2) Predicted Mortality	(3) Predicted Mortality
Facility Elevation	0.000000182**	0.000000165**	0.000000100
	(5.95e-08)	(6.05e-08)	(0.000000175)
Elevation × PPS	-7.62e-08***	-4.43e-08+	-3.20e-08
	(2.03e-08)	(2.37e-08)	(1.98e-08)
Year-Month FE	0	1	1
Pat/Fac Controls	0	0	0
Facility FE	0	0	1
R-squared	0.000167	0.000431	0.134
Dep. Var. Mean	0.0164	0.0164	0.0164
Observations	10077289	10077289	10077264

Notes: OLS estimates from equation (4). Dependent variable is predicted mortality. Predicted mortality is the predicted value for each observation using coefficients from a regression of mortality on patient controls and time fixed effects on observations from 2009 and 2010. Time fixed effects are not included in the prediction. PPS is an indicator variable for January 2011 or later. Facility elevation is measured in feet above sea level. An observation is a patient-month. Sample consists of observations from January 2009 to December 2012 for in-center hemodialysis patients between the ages of 18 and 100 with Medicare as their primary payer for whom we observe all patient and facility controls used in the analyses in Section 3.1 and later. Standard errors clustered by facility are in parentheses. +, *, **, and *** indicate significance at the 10%, 5%, 1%, and 0.1% level, respectively.

a composite measure of a patient's health status from an OLS regression of mortality on observable patient characteristics and month-year fixed effects, which we call predicted mortality, and then use the estimated coefficients to predict a patient's mortality risk. This predicted mortality variable is likely correlated with unobserved characteristics that affect their health, and we can detect changes in the composition of the patient population by testing if predicted mortality changed differentially by elevation after the payment reform.[21] Estimating equation (4) with predicted mortality as the dependent variable, we show in Table 4 that the differential change by elevation is a precisely estimated zero, which suggests that a changing mix of patients across elevations is unlikely to confound our analysis.

Another violation of the exclusion restriction could come from facilities reinvesting the additional profits they earn from administering less EPO after the payment reform. For instance, facilities at higher elevations use less EPO and therefore received a larger financial gain from Medicare's switch to a prospective payment system; these facilities may have reinvested their financial windfall in ways

[21] As the purpose of these regressions is to assess how predicted mortality correlates with the instrument, and predicted mortality is constructed as a direct function of patient comorbidities and demographics, we omit these patient controls from the specifications in Table 4.

Table 5
Facility Inputs by Elevation

	(1) Nurses Per Technician	(2) Patients Per Employee	(3) Patients Per Station	(4) Employees Per Station	(5) Hosp., Septicemia
Facility Elevation	0.0000230^{+}	-0.000175***	-0.000182***	-0.0000158**	-0.000000699***
	(0.0000128)	(0.0000196)	(0.0000260)	(0.00000598)	(0.000000129)
Elevation × PPS	0.00000839	0.0000345	0.00000562	-0.00000590^{+}	0.0000000336
	(0.00000858)	(0.0000232)	(0.0000167)	(0.00000357)	(0.0000000786)
Year-Month FE	1	1	1	1	1
Pat/Fac Controls	1	1	1	1	1
Facility FE	0	0	0	0	0
R-squared	0.00103	0.00628	0.00339	0.000968	0.00283
Dep. Var. Mean	0.910	5.402	3.988	0.766	0.00939
Observations	242917	254307	256712	256173	10077289

Notes: OLS estimates from equation (4). Dependent variables in columns (1)–(4) are facility-level ratios. Dependent variable in column (5) is an indicator for hospitalization with a primary diagnosis of septicemia. PPS is an indicator variable for January 2011 or later. Facility elevation is measured in feet above sea level. For columns (1)–(4) an observation is a facility-month. For column (5) an observation is a patient-month. Sample consists of observations from January 2009 to December 2012 for in-center hemodialysis patients between the ages of 18 and 100 with Medicare as their primary payer for whom we observe all patient and facility controls used in the analyses in Section 3.1 and later. Patient controls include dummy variables for incident comorbidities and characteristics reported on medical evidence forms, including diabetes, hypertension, BMI bin, GFR bin, HGB bin, high albumin, cancer, drug use, alcoholism, smoking behavior, necessity of assistance, COPD, ASHD, PVD, ischemic heart disease, and congestive heart disease, along with patient race, gender, and cubic functions of age and dialysis tenure. Facility controls include facility elevation, whether the facility to freestanding or hospital-based, and chain ownership status. For columns (1)–(4) controls are facility-month-level means of the patient-level controls. Standard errors clustered by facility are in parentheses. $^{+}$, *, **, and *** indicate significance at the 10%, 5%, 1%, and 0.1% level, respectively.

that improved patient care. As shown in Table 5, however, we find no evidence of such behavior, as conventional measures of a facility's investment in providing high-quality care, such as the number of patients per staff, the number of patients per station, and patient infection rates, did not differentially change by elevation after the payment reform.

With the approach outlined above, we can estimate the central object of interest to policymakers, $\frac{\partial h}{\partial epo^*}$, from our IV estimand: the ratio of (i) the differential effect of the payment reform on the outcome measure by elevation to (ii) the differential change in EPO. Using the model above, this can be expressed as

$$\frac{\frac{\partial^2 h}{\partial p\ \partial a}}{\frac{\partial^2 epo^*}{\partial p\ \partial a}} = \frac{\frac{\partial h}{\partial epo^*}\frac{\partial^2 epo^*}{\partial p\ \partial a} + \frac{1}{\alpha}\frac{\partial epo^*}{\partial a}}{\frac{\partial^2 epo^*}{\partial p\ \partial a}} = \frac{\partial h}{\partial epo^*} + \frac{\frac{\partial epo^*}{\partial a}}{\alpha\frac{\partial^2 epo^*}{\partial p\ \partial a}}. \quad (5)$$

[22]

That is, we can decompose our IV estimand into the object that we seek to recover, $\frac{\partial h}{\partial epo^*}$, and a second term that incorporates providers' financial incentives and patients' heterogeneous responses to EPO.

[22]Details on the derivation appear in Appendix G.

Taking hemoglobin as the relevant measure of health, we know from the data that $\frac{\partial epo^*}{\partial a} < 0$ and $\frac{\partial^2 epo^*}{\partial p \, \partial a} < 0$, so our IV estimate of the impact of EPO from the field is inflated above the equilibrium effect, provided that $\alpha > 0$. This wedge is proportional to the relative weight that providers place on profits: the more weight providers put on health, the closer our estimand is to the equilibrium effect of EPO. Moreover, this difference depends on the ratio of $\frac{\partial epo^*}{\partial a}$, which quantifies the heterogeneity in equilibrium EPO doses across elevations, and $\frac{\partial^2 epo^*}{\partial p \, \partial a}$, which captures dispersion in how that heterogeneity responds to changing financial incentives. Put simply, the more providers respond to financial incentives—and the more heterogeneity there is in how equilibrium EPO doses vary across elevations—the more our IV estimate will diverge from the equilibrium effect $\frac{\partial h}{\partial epo^*}$, motivating our analysis below that shows how to address the divergence between what the IV approach recovers and what is of ultimate interest to policymakers.[23]

5. Estimation Results

In this section, we present our estimation results for the impact of EPO on health outcomes, beginning with our IV estimates. We then return to the the model presented in Section 4.1, which demonstrates how to use our analysis, along with a measure of providers' financial incentives, to arrive at an estimate of the impact of EPO more relevant for policymakers.

5.1. Instrumental Variables Results

We present results from our first-stage estimates in Table 6, with an F-statistic of 49.1 demonstrating the instrument's relevance. Given the body's physiological response to elevation, EPO doses decrease with elevation in the expected way, but the rate of this decrease falls by over a quarter after the payment reform. Estimates from our preferred specification presented in column (3) indicate that patients at

[23]Because we identify the weighted average of the causal effect of EPO on outcomes for patients whose EPO dose changed due to the payment reform, our model provides valuable guidance for policymakers by establishing the causal effect of these forgone EPO doses. An alternative approach to estimating this policy-relevant treatment effect (PRTE) would have been to directly instrument for EPO doses using the policy change. We present these results in Appendix H, and while they are similar to our main results for some specifications, we provide evidence in the appendix that they rely on what are likely to be overly strong assumptions about excluded time trends. For this reason, we continue to focus our analysis on the interacted instrument instead, which relies on more defensible identifying assumptions and can still be used to recover the effect of equilibrium EPO doses on health outcomes.

sea level had their average monthly EPO dose reduced by 1,400 IUs more than patients living at 1,000 ft. Following the first-stage estimates, we recover the local average treatment effect of EPO on patient outcomes using two-stage least squares. In addition to instrumenting for EPO_{ijt}, we control for several patient covariates, month-year fixed effects, and facility fixed effects, estimating this equation for the main outcomes of interest: HGB levels, blood transfusions, hospitalizations, and mortality.

Table 6
First Stage Regression

	(1) EPO	(2) EPO	(3) EPO
Facility Elevation	-0.00477***	-0.00353***	-0.00542***
	(0.000341)	(0.000401)	(0.00157)
Elevation × PPS	0.00144***	0.00133***	0.00140***
	(0.000214)	(0.000203)	(0.000200)
Year-Month FE	1	1	1
Pat/Fac Controls	0	1	1
Facility FE	0	0	1
R-squared	0.0297	0.0835	0.139
Dep. Var. Mean	48.50	48.50	48.50
Observations	10077289	10077289	10077264

Notes: OLS estimates from equation (4). Dependent variable is monthly EPO dose. EPO doses are censored at the 99th percentile and measured in 1000 IUs. PPS is an indicator variable for January 2011 or later. Facility elevation is measured in feet above sea level. An observation is a patient-month. Sample consists of observations from January 2009 to December 2012 for in-center hemodialysis patients between the ages of 18 and 100 with Medicare as their primary payer for whom we observe all patient and facility controls used in the analyses in Section 3.1 and later. Patient controls include dummy variables for incident comorbidities and characteristics reported on medical evidence forms, including diabetes, hypertension, BMI bin, GFR bin, HGB bin, high albumin, cancer, drug use, alcoholism, smoking behavior, necessity of assistance, COPD, ASHD, PVD, ischemic heart disease, and congestive heart disease, along with patient race, gender, and cubic functions of age and dialysis tenure. Facility controls include facility elevation, whether the facility is freestanding or hospital-based, and chain ownership, as well as facility fixed effects. Standard errors clustered by facility are in parentheses. $^{+}$, *, **, and *** indicate significance at the 10%, 5%, 1%, and 0.1% level, respectively.

The results for HGB levels highlight the relevance of our empirical strategy. Based on randomized controlled trials, the FDA-approved indication for EPO is to increase HGB levels; that is, larger EPO doses have been clinically proven to have a causal effect on this outcome. The OLS specification results in Table 7 show the opposite effect, however, which reflects the nonrandom assignment of EPO to patients: more-anemic patients with lower HGB levels tend to be prescribed higher doses of EPO,

inducing a negative correlation between HGB and EPO if relevant patient attributes are not observed in the data. Our IV strategy corrects for these endogenous treatment decisions, as shown in column (2), where increasing EPO doses by 1000 IUs per month increases a patient's HGB by 0.0208 g/dL, on average, for an estimated elasticity of HGB with respect to EPO of 0.09, confirming the established medical fact that EPO effectively treats anemia. Table 7 also shows results with transfusions as the dependent variable. Similar to the results for HGB, the OLS coefficient suggests that EPO is associated with a need for more blood transfusions, once again contradicting established medical evidence. As with HGB, correcting for endogenous dosing decisions using our IV strategy reveals that larger EPO doses do indeed reduce the need for transfusions.

We show in Table 8 that larger EPO doses lead to more hospitalizations for cardiac events and higher mortality rates. For both all-cause and cardiac hospitalizations, the OLS and IV results suggest a positive correlation with EPO doses, although this effect does not remain statistically significant for all-cause hospitalizations in the IV specification. For mortality, the OLS estimates show a statistically significant, negative correlation with EPO, but the effect becomes positive while remaining statistically significant when we include our instruments. Interpreted as a local average treatment effect, our IV estimates suggest that a 1% increase in EPO raises the rate of cardiac hospitalization by 0.3% and mortality by 0.4%, meaning that the compliers—those patients whose EPO doses changed as a result of the instrument—had a 4.8% higher death rate during the pre-PPS period from excessive EPO doses.

As a placebo test, we also estimate equation (3) with septicemia as the dependent variable. Because septicemia, a severe blood infection resulting from poor cleaning protocols at facilities, has no known relation to EPO, a statistically significant effect of EPO on septicemia would suggest that an omitted variable confounds our analysis. As shown in Table 8, we do not find a causal effect of EPO on septicemia in our IV specification, providing further reassurance that our approach is valid.

Taken together, our results highlight the clinical tradeoffs associated with using EPO. Although EPO effectively treats patients' anemia, as reflected in higher HGB levels and fewer blood transfusions, these improvements must be weighed against a higher risk of cardiac events and death.

Table 7
The Effect of EPO on Hemoglobin Levels and Transfusions

	HGB		Transfusion	
	(1) OLS	(2) IV	(3) OLS	(4) IV
EPO	-0.00303***	0.0208***	0.000132***	-0.000574***
	(0.0000254)	(0.00542)	(0.00000256)	(0.000153)
Year-Month FE	1	1	1	1
Pat/Fac Controls	1	1	1	1
Facility FE	1	1	1	1
Dep. Var. Mean	11.12	11.12	0.0282	0.0282
Observations	8181736	8181736	10077264	10077264
First-Stage F-statistic		33.41		49.11

Notes: OLS and IV estimates from equation (3). Dependent variable in columns (1)–(2) is hemoglobin. Hemoglobin is winsorized from below to 5 and from above to 20 and is measured in grams per deciliter. Dependent variable in columns (3)–(4) is a binary variable for receiving a blood transfusion. EPO doses are censored at the 99th percentile and measured in 1000 IUs. An observation is a patient-month. Sample consists of observations from January 2009 to December 2012 for in-center hemodialysis patients between the ages of 18 and 100 with Medicare as their primary payer for whom we observe all patient and facility controls used in the analyses in Section 3.1 and later. Patient controls include dummy variables for incident comorbidities and characteristics reported on medical evidence forms, including diabetes, hypertension, BMI bin, GFR bin, HGB bin, high albumin, cancer, drug use, alcoholism, smoking behavior, necessity of assistance, COPD, ASHD, PVD, ischemic heart disease, and congestive heart disease, along with patient race, gender, and cubic functions of age and dialysis tenure. Facility controls include facility elevation, whether the facility is freestanding or hospital-based, and chain ownership, as well as facility fixed effects. Standard errors clustered by facility are in parentheses. $^{+}$, *, **, and *** indicate significance at the 10%, 5%, 1%, and 0.1% level, respectively.

Table 8
The Effect of EPO on Hospitalizations and Mortality

	Hosp., Any Cause		Hosp., Cardiac Event		Hosp., Septicemia		Mortality	
	OLS	IV	OLS	IV	OLS	IV	OLS	IV
EPO	0.000154***	0.000201	0.0000153***	0.000181^{+}	-0.000000269	0.0000351	-0.000112***	0.000126*
	(0.00000348)	(0.000249)	(0.00000121)	(0.0000942)	(0.000000602)	(0.0000538)	(0.000000893)	(0.0000631)
Year-Month FE	1	1	1	1	1	1	1	1
Pat/Fac Controls	1	1	1	1	1	1	1	1
Facility FE	1	1	1	1	1	1	1	1
Dep. Var. Mean	0.138	0.138	0.0271	0.0271	0.00939	0.00939	0.0157	0.0157
Observations	10077264	10077264	10077264	10077264	10077264	10077264	10077264	10077264
First-Stage F-statistic		49.11		49.11		49.11		49.11

Notes: OLS and IV estimates from equation (3). Dependent variables are binary outcomes. EPO doses are censored at the 99th percentile and measured in 1000 IUs. An observation is a patient-month. Sample consists of observations from January 2009 to December 2012 for in-center hemodialysis patients between the ages of 18 and 100 with Medicare as their primary payer for whom we observe all patient and facility controls used in the analyses in Section 3.1 and later. Patient controls include dummy variables for incident comorbidities and characteristics reported on medical evidence forms, including diabetes, hypertension, BMI bin, GFR bin, HGB bin, high albumin, cancer, drug use, alcoholism, smoking behavior, necessity of assistance, COPD, ASHD, PVD, ischemic heart disease, and congestive heart disease, along with patient race, gender, and cubic functions of age and dialysis tenure. Facility controls include facility elevation, whether the facility is freestanding or hospital-based, and chain ownership, as well as facility fixed effects. Standard errors clustered by facility are in parentheses. $^{+}$, *, **, and *** indicate significance at the 10%, 5%, 1%, and 0.1% level, respectively.

5.2. The Equilibrium Effect of EPO Outside Clinical Trials

As discussed above, the effect of EPO measured in clinical trials may not be the one experienced by Medicare beneficiaries due to providers' endogenous responses to financial incentives and the heterogenous responses of patients, potentially biasing forecasts of a payment reform's likely effects. We therefore use our model to recover the effects of EPO induced by the payment reform, an important element for evaluating the full impact of the policy change that accounts for the equilibrium dosing decisions of providers, something not attainable from clinical trials.

As explained in the previous section, we can use equation (5) to estimate the central object of interest, $\frac{\partial h}{\partial epo^*}$, by first estimating $\frac{\frac{\partial^2 h}{\partial p\ \partial a}}{\frac{\partial^2 epo^*}{\partial p\ \partial a}}$, $\frac{\partial epo^*}{\partial a}$, $\frac{\partial^2 epo^*}{\partial p\ \partial a}$, and α. The first three of these come directly from our estimation approach, while we appeal to Gaynor et al. (2020) for estimates of α, which they suggest may range from 89.49 to 899.59.[24] Using these estimates for α along with our estimates of $\frac{\partial epo^*}{\partial a}$ and $\frac{\partial^2 epo^*}{\partial p\ \partial a}$ from column (2) of Table 6, the difference ranges from 0.0003 to 0.0039, which implies that our estimate of the local average treatment effect of EPO on HGB, 0.0208, is slightly higher than the equilibrium marginal treatment effect. This implies our estimated value of $\frac{\partial h}{\partial epo^*}$ ranges from 0.0169 and 0.0205, meaning that the equilibrium effect of a 1% increase in EPO is to raise HGB by 0.074–0.089%.

Importantly, we can compare our estimate of the clinical effectiveness of EPO in equilibrium with those measured by clinical trials. As discussed above, clinical trials cannot measure effectiveness based on providers' equilibrium dosing decisions, and may therefore overstate the effectiveness of a drug if, for example, patients' behavior outside the lab differs from how they behave in a controlled setting or if the patients included in the study were selected based on how responsive they will be to treatment. To this point, the randomized controlled trials that we found in our review of the literature all estimate marginal effects of EPO in the same direction as ours, but of larger magnitude. For example, the original Phase III trial found an average effect per 1000 IUs of EPO of 0.0271 (Eschbach et al., 1989), while Tonelli et al. (2003) aggregated results from multiple clinical trials of EPO and found an average marginal effect ranging from 0.0338 to 0.0896. The distinction between these estimates and ours, which incorporates providers' equilibrium behavior and comes from actual dosing decisions, highlights the need for field studies to complement clinical trials, especially when the drug in question is the central target of a major payment reform, as it was for EPO in dialysis.

[24] For details, see Appendix G.

As our results make clear, the effectiveness of EPO outside of clinical trials depends on how providers trade off altruistic and financial incentives. Furthermore, this same tradeoff determines how providers respond to changes in regulations like payment reforms, and we show below that the relative weight providers place on patients' health and their own profits varies across facilities, which consequently affects the amount of EPO they administer and the overall impact of the payment reform.

The model shows that the amount of EPO administered by providers is increasing in its profit margin from EPO, p, such that patients are overtreated with a positive margin and undertreated with a negative one. The extent of this over- or undertreatment is determined by the level of altruism, α, with a larger weight on patients' health decreasing the deviation from the health-maximizing level of EPO. Similarly, the magnitude of the dosing response to the payment reform is informative about altruism, with a greater response indicating that providers put relatively more weight on financial considerations, because

$$\frac{\partial epo^*}{\partial p} = -\frac{1}{\alpha}\frac{\partial^2 h}{\partial epo\ \partial epo}^{-1}.$$

Thus, assuming the patient health function and the change in the profit margin of EPO are the same across facilities, a larger decrease in EPO doses following the payment reform indicates a relatively lower level of altruism.

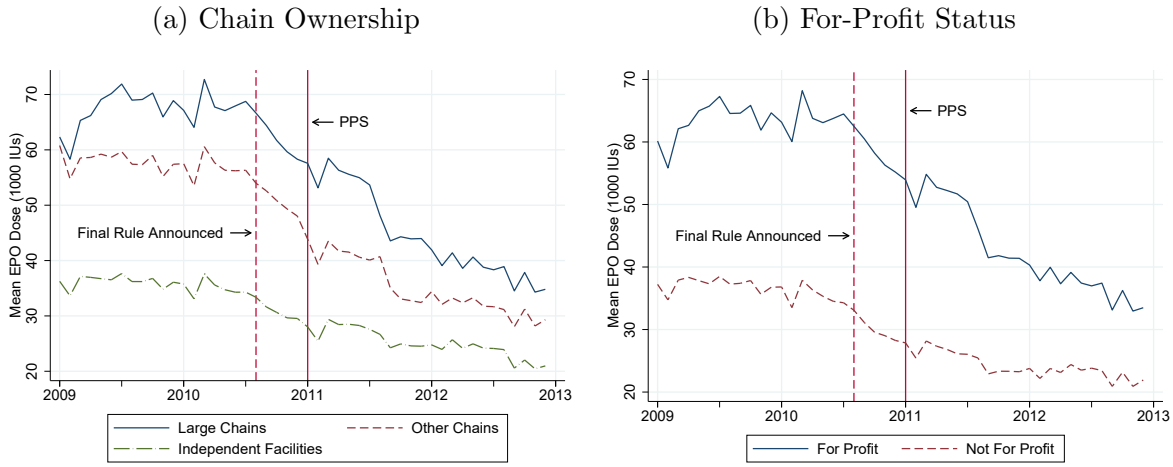
Figure 3 shows that, following the introduction of the PPS, facilities owned by large chains and for-profit facilities changed their doses more than independent and non-profit facilities did.[25] That these facilities responded more to the payment reform indicates that facilities owned by large chains and for-profit facilities place a greater weight on financial incentives relative to patient health.

6. Conclusion

In this paper, we use a major Medicare payment reform in the dialysis industry, along with a theoretical model of providers' treatment decisions and a novel instrumental variable strategy, to quantify the marginal costs and benefits of treatment with a heavily prescribed drug and demonstrate how the results from clinical trials might diverge from those generated by the actual prescribing behavior of providers. When providers respond to financial incentives, the results of randomized controlled trials

[25] These results are corroborated by the results in Appendix I, which allow for flexible differences in the change in doses by observable health characteristics.

Figure 3
Mean EPO Dose Over Time, by Facility Ownership



Notes: An observation is a patient-month. Sample consists of observations from January 2009 to December 2012 for in-center hemodialysis patients between the ages of 18 and 100 with Medicare as their primary payer for whom we observe all patient and facility controls used in the analyses in Section 3.1 and later. EPO doses are censored at the 99th percentile and measured in 1000 IUs. The solid vertical line indicates the start of the PPS in January 2011, while the dashed vertical line indicates the announcement of the final rule for the PPS.

may serve as a poor baseline for how a drug like EPO will affect health outcomes following a payment reform.

Our results support this contention, as we show that the causal impact of EPO based on actual provider behavior differs from that documented in RCTs. That we estimate a marginal effect below those found in clinical trials may suggest that the factors shaping providers' dosing decisions omitted from clinical trials ultimately led to EPO being used less effectively in practice. Moreover, we show that the response in EPO dosing behavior to the policy change depends on a dialysis facility's for-profit status, which further highlights the need to complement RCTs with evidence from the field.

Beyond dialysis, our results contribute to the broader discussion of alternative payment models within health care and the value of the services that they target. Over the past decade, Medicare has responded to allegations that traditional fee-for-service reimbursements lead to overtreatment by promoting accountable care organizations and bundled payments, to the point that these alternative payment models now constitute over 30% of Traditional Medicare spending (Shatto, 2016). As alternative payment models become more common, it will become even more important for policymakers to understand how changing financial incentives will affect the way providers care for patients, taking into

account that these financial incentives may change the effectiveness of the targeted treatments from those recovered from randomized controlled trials.

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Appendix: For Online Publication

The following appendices provide additional robustness checks, analyses, and details on our data.

Appendix A illustrates the robustness of our results to differences in the timing of PPS adoption.

Appendix B shows that neither the black box warnings nor the QIP can explain the patterns we observe for EPO doses.

Appendix C contains additional summary statistics by quintile of facility elevation.

Appendix D shows that our results are robust to a possible anticipatory response by providers.

Appendix E describes other channels through which the PPS may have affected patients.

Appendix F presents additional time series results.

Appendix G provides details on the derivation of our IV estimand.

Appendix H presents robustness of our results to instrumenting with a uniform PPS indicator.

Appendix I presents additional results on heterogeneity in provider altruism.

A. Differences in Timing of PPS Adoption

The PPS program allowed providers to gradually transition to the bundling of injectable drugs with the dialysis session such that this bundled payment comprised 25% of payments in 2011, 50% in 2012, 75% in 2013, and 100% in 2014. Alternatively, facilities could exercise a one-time option to opt in by November 2010 and immediately receive all payments under the PPS in 2011. Here, we present results showing the vast majority of providers chose to immediately transition to the new PPS and our baseline results are very similar to the results if we use only the subset of immediate-adopters.

First, we attempt to determine within our data the number of facilities that chose to immediately transition to the PPS by documenting whether a facility receives any positive payments for an injectable drug administered to a patient, which we view as a conservative measure of whether a facility has not fully adopted the PPS. We find that whereas more than 99.9% of facilities received payments for an injectable drug in each year prior to 2011, only 7.7% of facilities did afterwards, implying that over 92% of facilities immediately transitioned to the PPS based on this measure. The number increases to the point of full adoption by 2014, with independently owned facilities comprising 83.4% of those that transitioned gradually.

Next, we compare EPO use and patient outcomes by facility according to whether the facility immediately transitioned to the PPS ("Immediate") or not ("Gradual"). Table A1 shows this comparison using data from 2010. We find that patient outcomes are quite similar across these facilities, while those that opted for a gradual transition tended to use less EPO, primarily because most of the facilities that transitioned gradually were independent, which use less EPO on average. Furthermore, we do not find large elevation differences between the facilities. These facts, along with the small number of facilities that did not immediately transition, provide reassurance that selection bias does not undermine our estimates.

Nonetheless, we re-estimate our baseline results using only the sample of facilities that immediately transition to the PPS. The results, shown in Table A2, demonstrate that our baseline results are robust to focusing solely on this set of facilities.

Table A1
Summary Statistics by Immediate Transition to PPS

	PPS Without Transition?		
	Opts Out	Opts In	Total
Facility Characteristics			
Facility Elevation (ft)	644.9	639.6	641.3
Independent Ownership	0.835	0.152	0.209
EPO Use			
EPO Dose (1000 IUs)	39.13	59.09	57.02
Receives Any EPO	0.550	0.796	0.769
Health Outcomes			
Hemoglobin (g/dL)	11.26	11.33	11.32
Mortality	0.017	0.016	0.016
Hospitalizations			
Any Cause	0.1484	0.1412	0.1407
Cardiac Event	0.0282	0.0282	0.0280
Septicemia	0.0113	0.0092	0.0092
Transfusions			
Total	0.0324	0.0258	0.0261
Inpatient	0.0261	0.0213	0.0215
Outpatient	0.0071	0.0051	0.0052
Emergency Room	0.0001	0.0001	0.0001
Patient-Months	167,827	2,282,122	2,485,214

Notes: An observation is a patient-month. Sample consists of observations from January to December 2010 for in-center hemodialysis patients between the ages of 18 and 100 with Medicare as their primary payer for whom we observe all patient and facility controls used in the analyses in Section 3.1 and later and who are treated at a facility that does not permanently close before 2011. "Gradual" facilities are those for which positive payments for injectable drugs are observed in 2011 or 2012. "Immediate" facilities are those for which no payments for injectable drugs are observed in 2011 or 2012 but which received other payments. EPO doses are censored at the 99th percentile and measured in 1000 IUs. Hemoglobin is winsorized from below to 5 and from above to 20 and is measured in grams per deciliter. Facility elevation is measured in feet above sea level.

Table A2
Baseline Results Using only Facilities that Immediately Transition to PPS

	HGB	Transfusion	Mortality	Hosp., Any Cause	Hosp., Cardiac Event	Hosp., Septicemia
EPO	0.0285***	-0.000618**	0.000151*	0.000225	0.000211+	0.0000285
	(0.00823)	(0.000190)	(0.0000757)	(0.000306)	(0.000117)	(0.0000667)
Year-Month FE	1	1	1	1	1	1
Pat/Fac Controls	1	1	1	1	1	1
Facility FE	1	1	1	1	1	1
Dep. Var. Mean	11.13	0.0279	0.0157	0.138	0.0273	0.00932
Observations	7609185	9249810	9249810	9249810	9249810	9249810
First-Stage F-statistic	20.70	34.19	34.19	34.19	34.19	34.19

Notes: IV estimates from equation (3). Dependent variable in column (1) is hemoglobin. Hemoglobin is winsorized from below to 5 and from above to 20 and is measured in grams per deciliter. Dependent variable in column (2) is a binary variable for receiving a blood transfusion. Dependent variables in columns (3)–(6) are binary outcomes. EPO doses are censored at the 99th percentile and measured in 1000 IUs. An observation is a patient-month. Sample consists of observations from January 2009 to December 2012 for in-center hemodialysis patients between the ages of 18 and 100 with Medicare as their primary payer for whom we observe all patient and facility controls used in the analyses in Section 3.1 and later and who are treated at a facility that neither permanently closes before 2011 nor is observed to receive separate payment for injectable drugs in 2011 or later. Patient controls include dummy variables for incident comorbidities and characteristics reported on medical evidence forms, including diabetes, hypertension, BMI bin, GFR bin, HGB bin, high albumin, cancer, drug use, alcoholism, smoking behavior, necessity of assistance, COPD, ASHD, PVD, ischemic heart disease, and congestive heart disease, along with patient race, gender, and cubic functions of age and dialysis tenure. Facility controls include facility elevation, whether the facility is freestanding or hospital-based, and chain ownership, as well as facility fixed effects. Standard errors clustered by facility are in parentheses. $^{+}$, *, **, and *** indicate significance at the 10%, 5%, 1%, and 0.1% level, respectively.

B. The Effect of Black Box Warnings & QIP on EPO

Although the FDA's updated black box warning for EPO and Medicare's introduction of the QIP for dialysis facilities occurred around the same time as the payment reform, we present evidence that neither contributed meaningfully to the decline in EPO doses shown in the paper. For the black box warning, four institutional details suggest that it did not cause the decrease in EPO around 2011. First, we show in Appendix E that other injectable drugs, which did not receive black box warnings, follow a pattern similar to EPO's after the PPS. Second, as we discuss in Section 2.2, the FDA has issued two black box warnings for EPO, both of which recommend providers use EPO more judiciously, but the evolution of EPO doses in Figure A1 shows that they did not change following the first black box warning in 2007, an instance when the label changed but financial incentives did not. Third, the decline in EPO begins in October 2010, eight months before the black box warning update, and it is unclear why providers would have changed their behavior in anticipation of the new black box warning even if they had been aware of the FDA's looming decision given that they did not change their behavior following the first black box warning. Finally, as shown by Figure A2 a coincidental drop in EPO use stemmed from one large chain that renegotiated its contract with drug supplier Amgen in mid-2011, as other chains and independent facilities do not exhibit the same patterns for EPO doses.

The large dialysis chains DaVita and Fresenius have at times partnered with Amgen, a leading producer of ESAs, to make administering drugs such as EPO more profitable. In 2011, DaVita entered into a sourcing and supply agreement with Amgen, providing DaVita with discounts and rebates for Amgen's two ESAs, EPOGEN and Aranesp (DaVita Amgen Agreement 2011). In return, DaVita agreed to purchase at least 90% of its ESAs from Amgen. This 2011 contract ran through 2018 and was renewed in 2017 to extend through 2022 (DaVita Amgen Agreement 2017). Fresenius entered into a similar sourcing and supply agreement with Amgen in 2006, extending to 2011 (Fresenius Amgen Agreement 2006). Fresenius' contract lacked minimum purchase commitments, but did secure discounts for EPOGEN and Aranesp. Our understanding is that Fresenius now has year-to-year contracts with Amgen.

The distinct drop in average HGB levels in mid-2011 corresponds to the renegotiation of multiple large chains' contracts with Amgen, the monopoly supplier of EPO at the time. We see that the sharp drop in EPO and HGB levels in mid-2011 occurred only for patients at one of these large chains. This

provides further evidence that the cause of the discrete drop in EPO and HGB after the initial response to the payment reform was likely not the FDA black box warning but rather the renegotiation of this chain's supply agreement with Amgen. Because the contract renegotiation occurred at the same time as the PPS was implemented, the renegotiation likely reflected a change in this particular chain's strategy following the PPS. If this is the case, then the drop in EPO and HGB occurring in mid-2011 would be attributable to the PPS, with the delay highlighting the sticky nature of chains' supply agreements.

The other policy change around the start of the PPS was the QIP. As we explain in Section 2.5, Medicare instituted the QIP along with the PPS to provide facilities with incentives for maintaining high-quality care while still restraining reimbursement costs. In contrast to the PPS, which focuses on cost containment, the QIP aims to promote a high standard of care by reducing payments to poorly performing facilities.

To implement the QIP, each year Medicare announces the various performance measures that will comprise a facility's Total Performance Score (TPS). Facilities whose scores fall short of the benchmark that year face a reduction of their Medicare reimbursements of between 0.5%–2.0%, depending on the extent of the shortfall. During the sample period for our paper, Medicare used three clinical measures to construct the TPS: the percentage of patients with (i) HGB below 10 g/dL, (ii) HGB above 12g/dL, and (iii) urea reduction ratio (URR) above 0.65. For the first year of the QIP in 2012, Medicare used the facility's performance on these measures in 2010 to construct the TPS. For 2013 and 2014, only the latter two measures were used (based on facility performance in 2011 and 2012, respectively), with Medicare dropping low HGB levels as a criteria. The QIP also included a measure of vascular access in the TPS for 2014, although vascular access has no relation to EPO or other injectable drugs included in the payment reform, so we do not discuss it here.

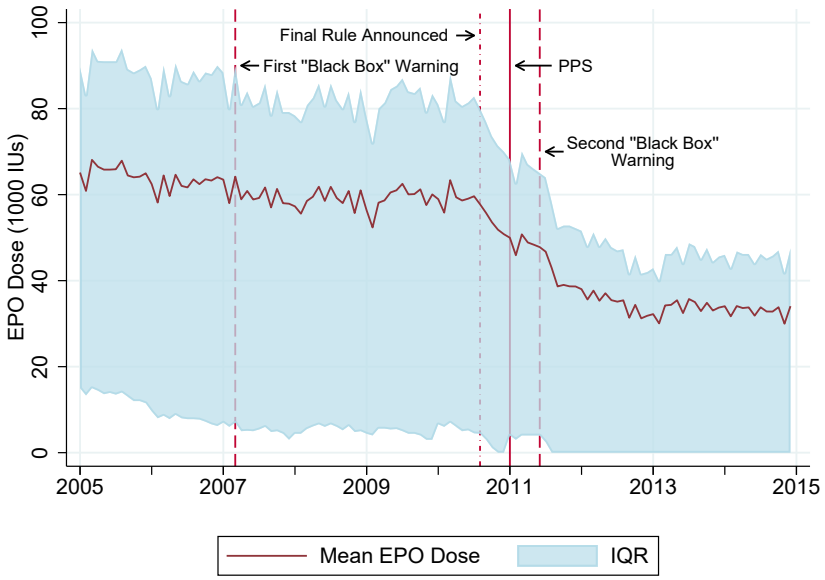
Although Medicare introduced the QIP to discipline facilities' behavior, Figures A3a and A3b show that it did not cause the decline in EPO doses during this period—if anything, the QIP likely makes our estimate of the PPS's impact on EPO doses a conservative one. In Figure A3a, which shows the percentage of patients with HGB greater than 12 g/dL, we see no change in trend following the announcement of this performance measure in 2010. Because EPO directly affects patients' HGB levels, the fact that the trend in the proportion of patients with high HGB levels remained constant after facilities began receiving penalties suggests this standard had little impact on dosing decisions.

Figure A3b shows the percentage of patients with HGB below 10 g/dL.[26] Again, facilities did not respond to the metric's introduction, with the trend remaining constant throughout 2010, although we do see evidence consistent with facilities responding to the metric's removal in 2011. The sharp rise in patients with HGB less than 10 g/dL after Medicare removed this metric from the QIP suggests that (i) our estimates of the PPS's impact on EPO and outcomes are potentially understated, because facilities may have continued giving EPO to low-HGB patients to avoid QIP penalties, and (ii) direct financial incentives from reimbursements predominately dictate facilities' dosing decisions, as facilities cut EPO doses to reduce their drug costs immediately upon Medicare's removal of the low-HGB guardrails.

In short, although the black box warning in 2011 and the QIP performance measures applied to 2010–2012 could have potentially confounded our analysis of the payment reform's effect on EPO doses, we find little evidence that they did, and, if anything, they suggest our results may be conservative. Moreover, because Medicare introduced the QIP in conjunction with the PPS, any potential confounding from the QIP would simply add nuance to our interpretation of the reforms rather than undermine our main findings. That is, we find that the financial incentives from the payment reform had a much stronger influence on facility behavior than the penalties from the QIP did, which provides valuable insights to policymakers aiming to restrain reimbursement costs while maintaining high standards for care. We consider the full effects of the QIP in Bertuzzi et al. (2021).

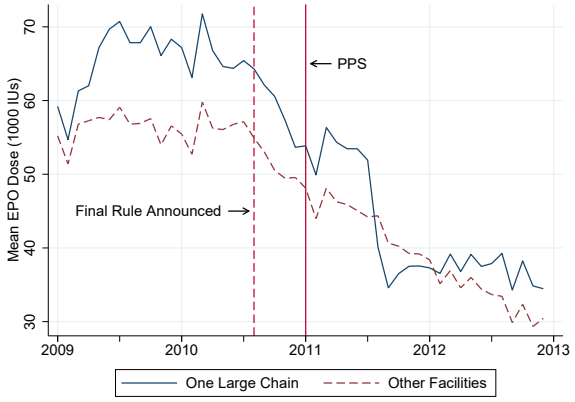
[26]The removal of the measure relating to the percentage of patients with HGB below 10 g/dL was announced in July 2011 and retroactively applied to the performance year beginning January 2011. This means that the TPS calculated using facilities' performances from January to December of 2011 did not include the percentage of patients with HGB below 10 g/dL, but facilities did not learn that this measure would not be used until midway through the year. This proposed rule change was finalized by Medicare in November 2011.

Figure A1
Monthly EPO Doses Over Time with Black Box Warnings

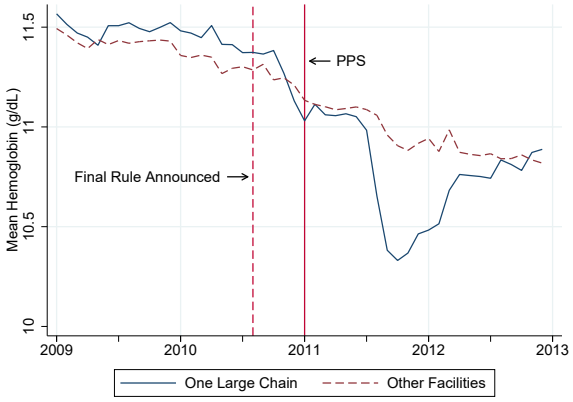


Notes: An observation is a patient-month. Sample consists of observations from January 2005 to December 2014 for in-center hemodialysis patients between the ages of 18 and 100 with Medicare as their primary payer for whom we observe all patient and facility controls used in the analyses in Section 3.1 and later. EPO doses are censored at the 99th percentile and measured in 1000 IUs. Vertical long-dashed lines indicate the release of official warnings from the FDA about the safety of high EPO doses. The solid vertical line indicates the start of the PPS in January 2011, while the dot-dashed vertical line indicates the announcement of the final rule for the PPS.

Figure A2
EPO Doses and HGB by Facility Ownership



(a) Monthly EPO Dose for One Large Chain and Other Facilities' Patients

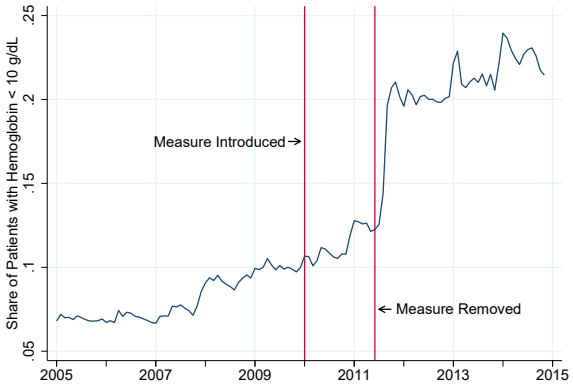


(b) Mean HGB for One Large Chain and Other Facilities' Patients

Notes: An observation is a patient-month. Sample consists of observations from January 2009 to December 2012 for in-center hemodialysis patients between the ages of 18 and 100 with Medicare as their primary payer for whom we observe all patient and facility controls used in the analyses in Section 3.1 and later. EPO doses are censored at the 99th percentile and measured in 1000 IUs. Hemoglobin is winsorized from below to 5 and from above to 20 and is measured in grams per deciliter. The solid vertical line indicates the start of the PPS in January 2011, while the dashed vertical line indicates the announcement of the final rule for the PPS.

Figure A3
QIP HGB Performance Measures

(a) HGB > 12 g/dL Over Time



(b) HGB < 10 g/dL Over Time

Notes: Hemoglobin is winsorized from below to 5 and from above to 20 and is measured in grams per deciliter. An observation is a patient-month. Sample consists of observations from January 2005 to December 2014 for in-center hemodialysis patients between the ages of 18 and 100 with Medicare as their primary payer for whom we observe all patient and facility controls used in the analyses in Section 3.1 and later. Vertical lines indicate the introduction and removal of the QIP performance measure.

C. Summary Statistics by Elevation

We provide additional summary statistics from our data by quintile of facility elevation. We see that patients at higher elevations tend to be somewhat less healthy than those at lower elevations, but these differences do not change following the start of the PPS. We do, however, see outcomes change differentially by elevation, providing descriptive evidence that the policy had different effects depending on a patient's elevation.

Table A3
Patient Descriptive Statistics by Elevation

	Elevation Quintile					
	First	Second	Third	Fourth	Fifth	Total
Patient Characteristics						
Predicted Mortality	0.016	0.015	0.016	0.017	0.017	0.016
Age (Years)	63.41	63.60	62.91	63.53	63.57	63.40
Months with ESRD	45.59	45.35	45.72	45.49	43.22	45.08
Black	0.447	0.440	0.452	0.375	0.211	0.385
Male	0.553	0.548	0.545	0.551	0.562	0.552
Diabetic	0.526	0.534	0.536	0.544	0.560	0.540
Hypertensive	0.910	0.906	0.909	0.905	0.900	0.906
Incident Hemoglobin	9.755	9.786	9.806	9.901	10.018	9.853
Facility Characteristics						
Facility Elevation (ft)	29.4	143.7	436.1	713.5	1875.9	638.1
Independent Ownership	0.185	0.183	0.177	0.231	0.208	0.197
Resource Use						
EPO Dose (1000 IUs)	51.50	50.24	50.94	46.84	42.90	48.50
Receives Any EPO	0.791	0.784	0.779	0.725	0.694	0.755
Medicare Spending ($)						
Total	8,019	8,042	7,342	7,389	6,980	7,555
Inpatient	2,788	2,759	2,443	2,469	2,328	2,558
Dialysis	2,320	2,372	2,266	2,262	2,215	2,287
Part D	499	493	464	442	428	465
Outpatient	352	389	410	424	394	394
Health Outcomes						
Hemoglobin (g/dL)	11.11	11.11	11.12	11.12	11.16	11.12
Mortality	0.015	0.015	0.015	0.016	0.017	0.016
Hospitalizations						
Any Cause	0.1406	0.1382	0.1355	0.1418	0.1340	0.1380
Cardiac Event	0.0280	0.0281	0.0268	0.0280	0.0248	0.0271
Septicemia	0.0097	0.0095	0.0091	0.0095	0.0090	0.0094
Transfusions						
Total	0.0297	0.0282	0.0278	0.0281	0.0270	0.0282
Inpatient	0.0255	0.0242	0.0226	0.0225	0.0210	0.0232
Outpatient	0.0047	0.0045	0.0059	0.0064	0.0068	0.0057
Emergency Room	0.0001	0.0001	0.0001	0.0001	0.0001	0.0001
Unique Patients	102,897	99,507	102,182	103,307	103,770	461,477
Patient-Months	2,043,637	1,989,978	2,033,229	2,000,408	2,010,037	10,077,289

Notes: An observation is a patient-month. Sample consists of observations from January 2009 to December 2012 for in-center hemodialysis patients between the ages of 18 and 100 with Medicare as their primary payer for whom we observe all patient and facility controls used in the analyses in Section 3.1 and later. Predicted mortality is the predicted value for each observation using coefficients from a regression of mortality on patient controls and time fixed effects on observations from 2009 and 2010. Time fixed effects are not included in the prediction. Patient controls include dummy variables for incident comorbidities and characteristics reported on medical evidence forms, including diabetes, hypertension, BMI bin, GFR bin, HGB bin, high albumin, cancer, drug use, alcoholism, smoking behavior, necessity of assistance, COPD, ASHD, PVD, ischemic heart disease, and congestive heart disease, along with patient race, gender, and cubic functions of age and dialysis tenure. EPO doses are censored at the 99th percentile and measured in 1000 IUs. Hemoglobin is winsorized from below to 5 and from above to 20 and is measured in grams per deciliter. Facility elevation is measured in feet above sea level. The cut points between elevation quintiles are 73, 260, 599, and 870 feet above sea level.

Table A4
Patient Descriptive Statistics by Elevation, 2009

	Elevation Quintile					
	First	Second	Third	Fourth	Fifth	Total
Patient Characteristics						
Predicted Mortality	0.016	0.015	0.016	0.017	0.017	0.016
Age (Years)	63.44	63.57	62.98	63.65	63.83	63.49
Months with ESRD	42.29	42.25	42.39	42.53	40.03	41.90
Black	0.446	0.438	0.447	0.370	0.207	0.382
Male	0.550	0.546	0.543	0.549	0.559	0.549
Diabetic	0.510	0.524	0.524	0.531	0.549	0.528
Hypertensive	0.908	0.905	0.910	0.904	0.899	0.905
Incident Hemoglobin	9.836	9.855	9.866	9.975	10.094	9.925
Facility Characteristics						
Facility Elevation (ft)	29.8	143.3	437.8	714.2	1868.8	638.0
Independent Ownership	0.199	0.202	0.195	0.267	0.229	0.218
Resource Use						
EPO Dose (1000 IUs)	63.28	61.73	62.19	55.73	52.35	59.07
Receives Any EPO	0.813	0.802	0.795	0.732	0.713	0.771
Medicare Spending ($)						
Total	8,016	7,999	7,305	7,299	6,801	7,483
Inpatient	2,846	2,818	2,492	2,520	2,320	2,599
Dialysis	2,283	2,326	2,236	2,211	2,145	2,240
Part D	442	445	417	394	382	416
Outpatient	332	364	377	387	361	364
Health Outcomes						
Hemoglobin (g/dL)	11.46	11.45	11.44	11.45	11.46	11.45
Mortality	0.016	0.016	0.017	0.018	0.017	0.017
Hospitalizations						
Any Cause	0.1471	0.1446	0.1420	0.1463	0.1391	0.1438
Cardiac Event	0.0307	0.0303	0.0289	0.0300	0.0267	0.0293
Septicemia	0.0093	0.0091	0.0088	0.0089	0.0084	0.0089
Transfusions						
Total	0.0256	0.0249	0.0247	0.0256	0.0244	0.0250
Inpatient	0.0219	0.0211	0.0201	0.0203	0.0188	0.0205
Outpatient	0.0042	0.0042	0.0051	0.0059	0.0063	0.0051
Emergency Room	0.0001	0.0001	0.0001	0.0001	0.0001	0.0001
Unique Patients	54,576	52,150	54,661	53,701	54,001	256,504
Patient-Months	477,695	457,844	478,139	467,866	468,898	2,350,442

Notes: An observation is a patient-month. Sample consists of observations from January to December 2009 for in-center hemodialysis patients between the ages of 18 and 100 with Medicare as their primary payer for whom we observe all patient and facility controls used in the analyses in Section 3.1 and later. Predicted mortality is the predicted value for each observation using coefficients from a regression of mortality on patient controls and time fixed effects on observations from 2009 and 2010. Time fixed effects are not included in the prediction. Patient controls include dummy variables for incident comorbidities and characteristics reported on medical evidence forms, including diabetes, hypertension, BMI bin, GFR bin, HGB bin, high albumin, cancer, drug use, alcoholism, smoking behavior, necessity of assistance, COPD, ASHD, PVD, ischemic heart disease, and congestive heart disease, along with patient race, gender, and cubic functions of age and dialysis tenure. EPO doses are censored at the 99th percentile and measured in 1000 IUs. Hemoglobin is winsorized from below to 5 and from above to 20 and is measured in grams per deciliter. Facility elevation is measured in feet above sea level. The cut points between elevation quintiles are 73, 260, 599, and 870 feet above sea level.

Table A5
Patient Descriptive Statistics by Elevation, 2012

	Elevation Quintile					
	First	Second	Third	Fourth	Fifth	Total
Patient Characteristics						
Predicted Mortality	0.016	0.016	0.016	0.017	0.017	0.016
Age (Years)	63.37	63.63	62.85	63.35	63.33	63.31
Months with ESRD	48.98	48.68	49.02	48.59	46.44	48.34
Black	0.448	0.443	0.454	0.379	0.213	0.388
Male	0.556	0.551	0.546	0.554	0.565	0.554
Diabetic	0.538	0.542	0.546	0.555	0.569	0.550
Hypertensive	0.911	0.908	0.909	0.906	0.902	0.907
Incident Hemoglobin	9.664	9.710	9.737	9.819	9.935	9.772
Facility Characteristics						
Facility Elevation (ft)	29.2	144.3	434.4	713.6	1886.7	637.2
Independent Ownership	0.172	0.161	0.150	0.197	0.184	0.173
Resource Use						
EPO Dose (1000 IUs)	36.71	36.11	36.75	34.27	30.43	34.87
Receives Any EPO	0.759	0.761	0.751	0.708	0.662	0.728
Medicare Spending ($)						
Total	7,884	7,890	7,224	7,290	6,959	7,453
Inpatient	2,637	2,564	2,277	2,301	2,196	2,397
Dialysis	2,390	2,456	2,334	2,353	2,322	2,371
Part D	571	550	523	499	480	525
Outpatient	373	417	441	463	427	424
Health Outcomes						
Hemoglobin (g/dL)	10.79	10.81	10.82	10.83	10.89	10.83
Mortality	0.015	0.014	0.015	0.015	0.015	0.015
Hospitalizations						
Any Cause	0.1344	0.1305	0.1283	0.1348	0.1275	0.1311
Cardiac Event	0.0257	0.0258	0.0246	0.0256	0.0227	0.0249
Septicemia	0.0103	0.0100	0.0094	0.0099	0.0094	0.0098
Transfusions						
Total	0.0326	0.0302	0.0296	0.0298	0.0288	0.0302
Inpatient	0.0279	0.0257	0.0236	0.0234	0.0221	0.0246
Outpatient	0.0053	0.0051	0.0067	0.0072	0.0075	0.0064
Emergency Room	0.0001	0.0001	0.0001	0.0001	0.0001	0.0001
Unique Patients	60,055	58,219	58,652	58,026	58,970	280,751
Patient-Months	543,541	528,788	531,440	518,537	527,525	2,649,831

Notes: An observation is a patient-month. Sample consists of observations from January to December 2012 for in-center hemodialysis patients between the ages of 18 and 100 with Medicare as their primary payer for whom we observe all patient and facility controls used in the analyses in Section 3.1 and later. Predicted mortality is the predicted value for each observation using coefficients from a regression of mortality on patient controls and time fixed effects on observations from 2009 and 2010. Time fixed effects are not included in the prediction. Patient controls include dummy variables for incident comorbidities and characteristics reported on medical evidence forms, including diabetes, hypertension, BMI bin, GFR bin, HGB bin, high albumin, cancer, drug use, alcoholism, smoking behavior, necessity of assistance, COPD, ASHD, PVD, ischemic heart disease, and congestive heart disease, along with patient race, gender, and cubic functions of age and dialysis tenure. EPO doses are censored at the 99th percentile and measured in 1000 IUs. Hemoglobin is winsorized from below to 5 and from above to 20 and is measured in grams per deciliter. Facility elevation is measured in feet above sea level. The cut points between elevation quintiles are 73, 260, 599, and 870 feet above sea level.

D. Potential Anticipatory Responses

Given the difficulty of changing clinical practices, we may expect them to change gradually and in anticipation of the PPS. Indeed, in Figure 2, among others, we see that EPO doses began to decrease in mid-2010, prior to the PPS's start in January 2011. In this appendix, we both quantify these anticipatory effects and show that our results are robust to including this period of anticipatory responses by providers in the post-PPS period.

To identify and quantify this possible anticipation, we use the methods of Brot-Goldberg et al. (2017). First, we estimate

$$\bar{Y}_t = \beta_0 + \beta_1 t + X_t \Gamma + \bar{\epsilon}_t, \tag{6}$$

where $\bar{Y}_t$ is the mean EPO dose in month t and X_t is a series of month-of-year fixed effects. We estimate this equation using only data from January 2005 through December 2009 and then use the estimated coefficients to calculate the predicted level of EPO for each month in 2010 and 2011. From the predicted and observed values in Table A6, we find that the first month in which the realized mean EPO dose is below the predicted level is October 2010, and that this drop continues to grow through 2011.

We corroborate our finding that the anticipatory response began in October 2010 by using a falsification test from Baicker and Svoronos (2019). To do so, we construct a test statistic from a series of Wald tests, testing each month in our data as a potential structural break in the time series of mean monthly EPO doses. From this, October 2010 returns the highest Wald statistic, 267, suggesting it is the most likely month of a structural break in the trend in EPO doses, which would indicate an anticipation of the PPS by providers.

In light of a possible anticipatory response, we consider the robustness of our main findings to this anticipation. In particular, we recreate the tables and figures presented in the main text while treating the start date of the PPS as October 2010 rather than the actual start date of January 2011. In this way, we treat the period during which facilities were modifying their behavior in anticipation of the PPS as part of the treatment period. Tables A7–A10 recreate our main results and show that they are robust to this alternative definition of the PPS period.

Table A6
Difference in EPO Relative to Trend

	Actual	Predicted	Difference
2010			
January	58.95	56.19	2.76
February	55.81	52.28	3.53
March	63.36	57.90	5.46
April	59.39	55.96	3.43
May	58.64	58.08	0.56
June	59.06	56.60	2.46
July	59.63	57.64	1.99
August	57.76	57.76	0.00
September	55.77	55.77	0.00
October	53.57	57.61	-4.04
November	51.85	55.03	-3.17
December	50.80	56.94	-6.14
2011			
January	49.98	54.64	-4.66
February	45.90	50.72	-4.82
March	50.77	56.34	-5.57
April	48.88	54.41	-5.52
May	48.36	56.52	-8.16
June	47.80	55.04	-7.25
July	46.74	56.09	-9.35
August	42.97	56.20	-13.24
September	38.66	54.21	-15.55
October	39.01	56.05	-17.03
November	38.68	53.47	-14.79
December	38.65	55.39	-16.74

Notes: Predicted values from OLS estimate of equation (6). Dependent variable is monthly EPO dose. EPO doses are censored at the 99th percentile and measured in 1000 IUs. An observation is a patient-month. Estimation sample consists of observations from January 2005 to December 2009 for in-center hemodialysis patients between the ages of 18 and 100 with Medicare as their primary payer for whom we observe all patient and facility controls used in the analyses in Section 3.1 and later. Sample presented in table consist of analogous observations from January 2010 to December 2011.

Table A7
Effect of PPS on EPO Dose

	(1) EPO	(2) EPO	(3) EPO	(4) EPO
PPS	-19.45***	-21.10***	-18.15***	-5.132***
	(0.246)	(0.237)	(0.421)	(0.226)
Pat/Fac Controls	0	1	1	1
Facility FE	0	0	1	1
Patient FE	0	0	0	1
Dep. Var. Mean	47.04	47.04	47.04	47.08
R-squared	0.0239	0.0804	0.134	0.532
Observations	10157714	10157714	10157683	10139936

Notes: OLS estimates from equation (1). Dependent variable is monthly EPO dose. EPO doses are censored at the 99th percentile and measured in 1000 IUs. PPS is an indicator variable for October 2010 or later. An observation is a patient-month. Sample consists of observations from October 2008 to September 2012 for in-center hemodialysis patients between the ages of 18 and 100 with Medicare as their primary payer for whom we observe all patient and facility controls used in the analyses in Section 3.1 and later. Patient controls include dummy variables for incident comorbidities and characteristics reported on medical evidence forms, including diabetes, hypertension, BMI bin, GFR bin, HGB bin, high albumin, cancer, drug use, alcoholism, smoking behavior, necessity of assistance, COPD, ASHD, PVD, ischemic heart disease, and congestive heart disease, along with patient race, gender, and cubic functions of age and dialysis tenure. Facility controls include facility elevation, whether the facility is freestanding or hospital-based, and chain ownership, as well as facility fixed effects. Further controls include calendar month fixed effects. Standard errors clustered by facility are in parentheses. $^{+}$, *, **, and *** indicate significance at the 10%, 5%, 1%, and 0.1% level, respectively.

Table A8
Effect of PPS on Health Outcomes

	(1) HGB	(2) Transfusion	(3) Hosp., Any Cause	(4) Hosp., Cardiac Event	(5) Mortality
PPS	-0.442***	0.00499***	-0.00560***	-0.00211***	-0.000829***
	(0.00815)	(0.000208)	(0.000452)	(0.000187)	(0.000116)
Pat/Fac Controls	1	1	1	1	1
Facility FE	1	1	1	1	1
Dep. Var. Mean	11.08	0.0287	0.137	0.0267	0.0156
R-squared	0.0758	0.0118	0.0212	0.00775	0.00843
Observations	8304637	10157683	10157683	10157683	10157683

Notes: OLS estimates from equation (1). Dependent variable in column (1) is hemoglobin. Hemoglobin is winsorized from below to 5 and from above to 20 and is measured in grams per deciliter. Dependent variables in columns (2)–(5) are binary outcome variables. PPS is an indicator variable for October 2010 or later. An observation is a patient-month. Sample consists of observations from October 2008 to September 2012 for in-center hemodialysis patients between the ages of 18 and 100 with Medicare as their primary payer for whom we observe all patient and facility controls used in the analyses in Section 3.1 and later. Patient controls include dummy variables for incident comorbidities and characteristics reported on medical evidence forms, including diabetes, hypertension, BMI bin, GFR bin, HGB bin, high albumin, cancer, drug use, alcoholism, smoking behavior, necessity of assistance, COPD, ASHD, PVD, ischemic heart disease, and congestive heart disease, along with patient race, gender, and cubic functions of age and dialysis tenure. Facility controls include facility elevation, whether the facility is freestanding or hospital-based, and chain ownership, as well as facility fixed effects. Further controls include calendar month fixed effects. Standard errors clustered by facility are in parentheses. $^{+}$, *, **, and *** indicate significance at the 10%, 5%, 1%, and 0.1% level, respectively.

Table A9
The Effect of EPO on Health Outcomes

	HGB		Transfusion	
	(1) OLS	(2) IV	(3) OLS	(4) IV
EPO	-0.00283***	0.0161***	0.000125***	-0.000568***
	(0.0000248)	(0.00454)	(0.00000250)	(0.000146)
Year-Month FE	1	1	1	1
Pat/Fac Controls	1	1	1	1
Facility FE	1	1	1	1
Dep. Var. Mean	11.17	11.17	0.0279	0.0279
Observations	8056164	8056164	9979284	9979284
First-Stage F-statistic		37.93		55.76

Notes: OLS and IV estimates from equation (3). Dependent variable in columns (1)–(2) is hemoglobin. Hemoglobin is winsorized from below to 5 and from above to 20 and is measured in grams per deciliter. Dependent variables in columns (3)–(4) is a binary outcome variable for receiving a blood transfusion. EPO doses are censored at the 99th percentile and measured in 1000 IUs. An observation is a patient-month. Sample consists of observations from October 2008 to September 2012 for in-center hemodialysis patients between the ages of 18 and 100 with Medicare as their primary payer for whom we observe all patient and facility controls used in the analyses in Section 3.1 and later. Patient controls include dummy variables for incident comorbidities and characteristics reported on medical evidence forms, including diabetes, hypertension, BMI bin, GFR bin, HGB bin, high albumin, cancer, drug use, alcoholism, smoking behavior, necessity of assistance, COPD, ASHD, PVD, ischemic heart disease, and congestive heart disease, along with patient race, gender, and cubic functions of age and dialysis tenure. Facility controls include facility elevation, whether the facility is freestanding or hospital-based, and chain ownership, as well as facility fixed effects. Standard errors clustered by facility are in parentheses. $^{+}$, *, **, and *** indicate significance at the 10%, 5%, 1%, and 0.1% level, respectively.

Table A10
The Effect of EPO on Hospitalizations and Mortality

	Hosp., Any Cause		Hosp., Cardiac Event		Hosp., Septicemia		Mortality	
	OLS	IV	OLS	IV	OLS	IV	OLS	IV
EPO	0.000147***	0.0000805	0.0000146***	0.000121	-0.000000784	0.0000275	-0.000112***	0.000144*
	(0.00000343)	(0.000237)	(0.00000119)	(0.0000957)	(0.000000586)	(0.0000524)	(0.000000871)	(0.0000646)
Year-Month FE	1	1	1	1	1	1	1	1
Pat/Fac Controls	1	1	1	1	1	1	1	1
Facility FE	1	1	1	1	1	1	1	1
Dep. Var. Mean	0.139	0.139	0.0274	0.0274	0.00930	0.00930	0.0159	0.0159
Observations	9979284	9979284	9979284	9979284	9979284	9979284	9979284	9979284
First-Stage F-statistic		55.76		55.76		55.76		55.76

Notes: OLS and IV estimates from equation (3). Dependent variables are binary outcomes. EPO doses are censored at the 99th percentile and measured in 1000 IUs. An observation is a patient-month. Sample consists of observations from October 2008 to September 2012 for in-center hemodialysis patients between the ages of 18 and 100 with Medicare as their primary payer for whom we observe all patient and facility controls used in the analyses in Section 3.1 and later. Patient controls include dummy variables for incident comorbidities and characteristics reported on medical evidence forms, including diabetes, hypertension, BMI bin, GFR bin, HGB bin, high albumin, cancer, drug use, alcoholism, smoking behavior, necessity of assistance, COPD, ASHD, PVD, ischemic heart disease, and congestive heart disease, along with patient race, gender, and cubic functions of age and dialysis tenure. Facility controls include facility elevation, whether the facility is freestanding or hospital-based, and chain ownership, as well as facility fixed effects. Standard errors clustered by facility are in parentheses. $^{+}$, *, **, and *** indicate significance at the 10%, 5%, 1%, and 0.1% level, respectively.

E. The PPS's Effect on Other Parts of Dialysis

E.1. Other Drugs

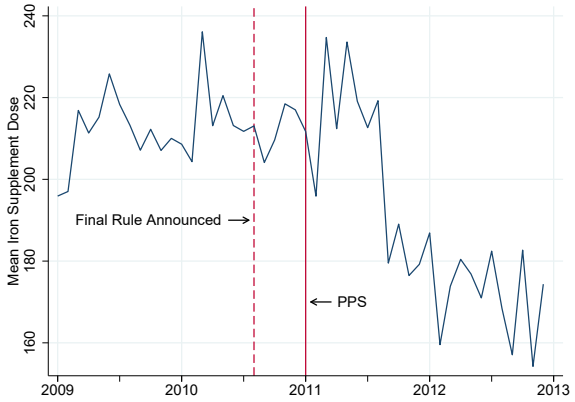
In addition to EPO, intravenous iron and vitamin D are common classes of injectable drugs administered to dialysis patients. Like EPO, these were separately billable prior to 2011, but were then bundled together with dialysis in the payment reform. Unlike EPO, these drugs were not the subject of any changes in clinical guidelines, such as the black box warning for EPO issued by the FDA in mid-2011. Figure A4 and Table A18 show that, similar to EPO, the use of these two classes of drugs declined, supporting our interpretation that financial incentives effectively reduced the quantity of injectable drugs given to dialysis patients. By contrast, we the use of Cinacalcet, a prescription drug for treating anemia that was excluded from the PPS during this period, increased substantially following the payment reform.

Table A11
Effect of PPS on Injectable Drugs

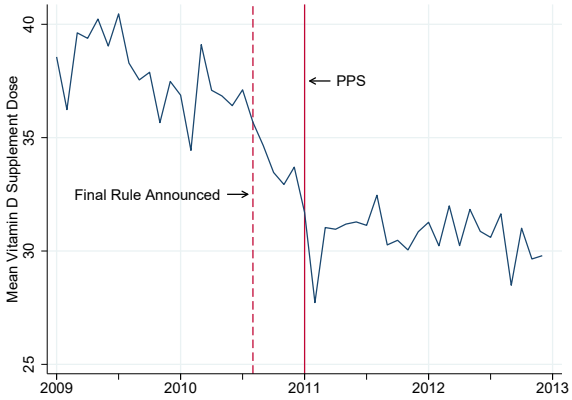
	(1) IV Iron	(2) IV Iron	(3) Vitamin D	(4) Vitamin D	(5) Cinacalcet	(6) Cinacalcet
PPS	-15.30***	4.922**	-6.219***	-3.527***	0.00701***	-0.00163**
	(1.727)	(1.650)	(0.250)	(0.210)	(0.000792)	(0.000618)
Time Trend		0.366***		-0.229***		-0.0000591
		(0.0941)		(0.0131)		(0.0000446)
Post-PPS Trend Change		-2.920***		0.191***		0.00104***
		(0.106)		(0.0134)		(0.0000558)
Pat/Fac Controls	1	1	1	1	1	1
Facility FE	1	1	1	1	1	1
Dep. Var. Mean	200.1	200.1	33.71	33.71	0.0990	0.0990
R-squared	0.0801	0.0821	0.0933	0.0936	0.0833	0.0835
Observations	10077264	10077264	10077264	10077264	10077264	10077264

Notes: OLS estimates from equations (1) and (2) in odd and even columns, respectively. Dependent variable in columns (1) and (2) is total intravenously injectable iron supplement dose in IUs. Injectable iron drugs include Ferrlecit, Venofer, Ferumoxytol, and Iron Dextran. Dependent variable in columns (3) and (4) is total injectable vitamin D supplement dose in IUs. Injectable vitamin D drugs include Calcitriol, Doxercalciferol, and Paricalcitol. Dependent variable in columns (5) and (6) is an indicator for prescription of Cinacalcet. PPS is an indicator variable for January 2011 or later. Time Trend is a continuous measure of months since January 2011. This means the value for January 2011 is zero, while it is positive for subsequent months and negative for prior months. Post-PPS Trend Change is the interaction of PPS and Time Trend. An observation is a patient-month. Sample consists of observations from January 2009 to December 2012 for in-center hemodialysis patients between the ages of 18 and 100 with Medicare as their primary payer for whom we observe all patient and facility controls used in the analyses in Section 3.1 and later. Patient controls include dummy variables for incident comorbidities and characteristics reported on medical evidence forms, including diabetes, hypertension, BMI bin, GFR bin, HGB bin, high albumin, cancer, drug use, alcoholism, smoking behavior, necessity of assistance, COPD, ASHD, PVD, ischemic heart disease, and congestive heart disease, along with patient race, gender, and cubic functions of age and dialysis tenure. Facility controls include facility elevation, whether the facility is freestanding or hospital-based, and chain ownership, as well as facility fixed effects. Further controls include calendar month fixed effects. Standard errors clustered by facility are in parentheses. $^{+}$, *, **, and *** indicate significance at the 10%, 5%, 1%, and 0.1% level, respectively.

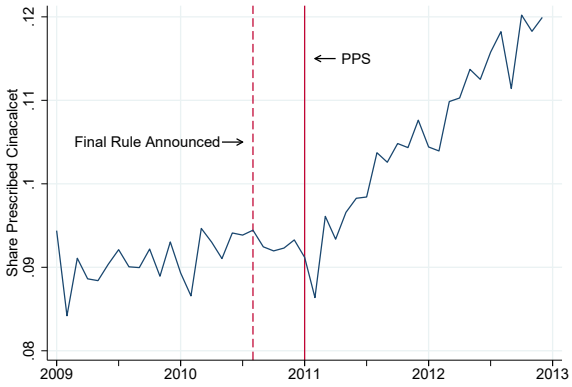
Figure A4
Use of Other Injectable Drugs



(a) Mean Monthly IV Iron Dose



(b) Mean Monthly Vitamin D Dose



(c) Share Prescribed Cinacalcet

Notes: An observation is a patient-month. Sample consists of observations from January 2009 to December 2012 for in-center hemodialysis patients between the ages of 18 and 100 with Medicare as their primary payer for whom we observe all patient and facility controls used in the analyses in Section 3.1 and later. Injectable iron drugs include Ferrlecit, Venofer, Ferumoxytol, and Iron Dextran. Injectable vitamin D drugs include Calcitriol, Doxercalciferol, and Paricalcitol. The solid vertical line indicates the start of the PPS in January 2011, while the dashed vertical line indicates the announcement of the final rule for the PPS.

Any change in providers' use of these drugs in response to the payment reform may violate the exclusion restriction for identifying the marginal effect of EPO on health outcomes. To address this, we present an alternative approach in which we account for intravenous iron in addition to EPO, although we exclude vitamin D because it was not used to treat anemia. Table A12 presents the summary statistics with information on the use of these other injectable drugs, which are used much less often than EPO.

We re-estimate our main specification using a combined measure of intravenous iron and EPO as our

Table A12
Summary Statistics including the Use of Other Drugs

	Mean	Std. Dev.
Resource Use		
EPO Dose (1000 IUs)	48.50	64.11
Receives Any EPO	0.755	0.430
IV Iron Dose (1000 IUs)	0.20	0.26
Receives Any Iron	0.571	0.495
Vitamin D Dose (1000 IUs)	0.03	0.06
Receives Any Vitamin D	0.659	0.474
Receives Any Cinacalcet	0.099	0.299
Dialysis Sessions	12.08	9.90
Unique Patients	461,477	
Patient-Months	10,077,289	

Notes: An observation is a patient-month. Sample consists of observations from January 2009 to December 2012 for in-center hemodialysis patients between the ages of 18 and 100 with Medicare as their primary payer for whom we observe all patient and facility controls used in the analyses in Section 3.1 and later. EPO doses are censored at the 99th percentile and measured in 1000 IUs. Injectable iron drugs include Ferrlecit, Venofer, Ferumoxytol, and Iron Dextran. Injectable vitamin D drugs include Calcitriol, Doxercalciferol, and Paricalcitol.

instrumented variable. Specifically, in each month we calculate each patient's Z-score for EPO based on the mean and standard deviation of EPO in our entire sample as well as a Z-score for intravenous iron. We sum those together for a combined total anemia drug dose Z-score, which captures each patient's position in the distribution of total anemia drug use. The results are presented in Table A13 and are very similar to our baseline results, demonstrating their robustness.

E.2. Peritoneal Dialysis

Table A14 shows a small shift from hemodialysis towards peritoneal dialysis, a change that may be due to the corresponding shift in relative profitability after the PPS that favored peritoneal dialysis (Zhang et al., 2017).

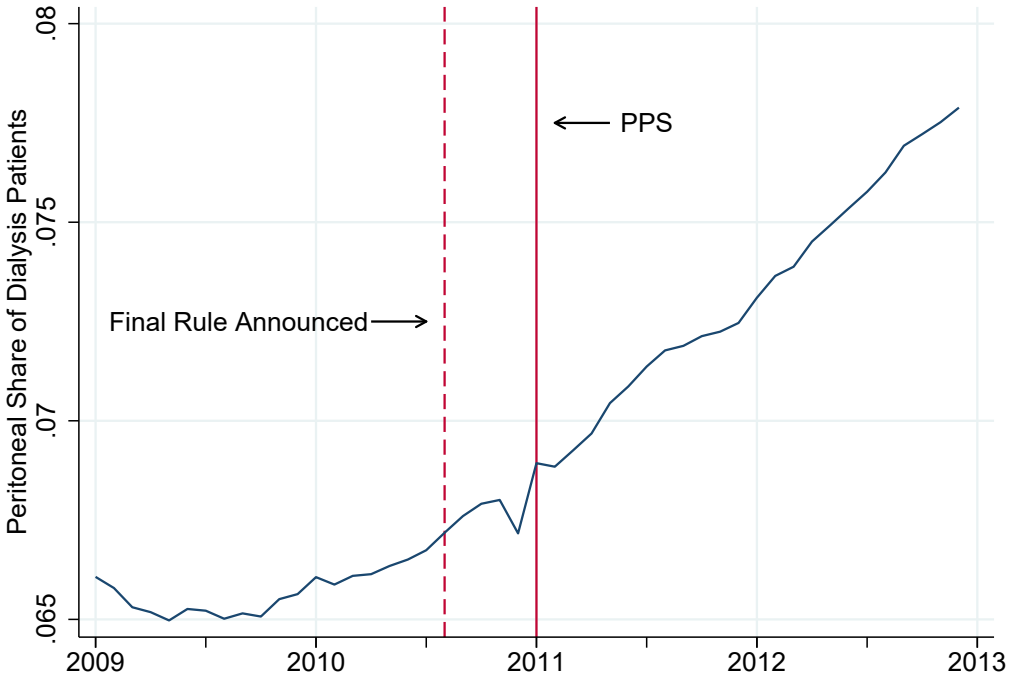
Like our results for other anemia drugs, the shift towards peritoneal dialysis may violate the exclusion restriction for identifying the marginal effect of EPO on health outcomes. In Table A15, we show that neither the share of patients receiving in-center hemodialysis nor the share receiving peritoneal dialysis changed differentially by elevation after the PPS, further supporting our identification strategy.

Table A13
Combined Injectable Anemia Drugs and Outcomes

	HGB	Transfusion	Mortality	Hosp., Any Cause	Hosp., Cardiac Event	Hosp., Septicemia
Combined Injectibles Z-score	1.584***	-0.0471***	0.0103+	0.0165	0.0148+	0.00288
	(0.384)	(0.0126)	(0.00533)	(0.0206)	(0.00795)	(0.00441)
Year-Month FE	1	1	1	1	1	1
Pat/Fac Controls	1	1	1	1	1	1
Facility FE	1	1	1	1	1	1
Dep. Var. Mean	11.12	0.0282	0.0157	0.138	0.0271	0.00939
Observations	8181736	10077264	10077264	10077264	10077264	10077264
First-Stage F-statistic	33.56	38.35	38.35	38.35	38.35	38.35

Notes: IV estimates from equation (3). Dependent variable in column (1) is hemoglobin. Hemoglobin is winsorized from below to 5 and from above to 20 and is measured in grams per deciliter. Dependent variables in columns (2)–(6) are binary outcomes. Combined injectables Z-score is the mean of the patient-month's Z-scores for EPO use and IV iron use. Injectable iron drugs include Ferrlecit, Venofer, Ferumoxytol, and Iron Dextran. An observation is a patient-month. Sample consists of observations from January 2009 to December 2012 for in-center hemodialysis patients between the ages of 18 and 100 with Medicare as their primary payer for whom we observe all patient and facility controls used in the analyses in Section 3.1 and later. Patient controls include dummy variables for incident comorbidities and characteristics reported on medical evidence forms, including diabetes, hypertension, BMI bin, GFR bin, HGB bin, high albumin, cancer, drug use, alcoholism, smoking behavior, necessity of assistance, COPD, ASHD, PVD, ischemic heart disease, and congestive heart disease, along with patient race, gender, and cubic functions of age and dialysis tenure. Facility controls include facility elevation, whether the facility is freestanding or hospital-based, and chain ownership, as well as facility fixed effects. Standard errors clustered by facility are in parentheses. +, *, **, and *** indicate significance at the 10%, 5%, 1%, and 0.1% level, respectively.

Figure A5
Share of Patients on Peritoneal Dialysis



Notes: An observation is a patient-month. Sample consists of observations from January 2009 to December 2012 for ESRD patients between the ages of 18 and 100 with Medicare as their primary payer for whom we observe all patient and facility controls used in the analyses in Section 3.1 and later. The solid vertical line indicates the start of the PPS in January 2011, while the dashed vertical line indicates the announcement of the final rule for the PPS.

Table A14
Effect of PPS on Dialysis Modality

	(1) Dialysis Sessions	(2) Dialysis Sessions	(3) In-Center Hemodialysis	(4) In-Center Hemodialysis	(5) Peritoneal Dialysis	(6) Peritoneal Dialysis	(7) Good URR	(8) Good URR
PPS	0.00316	-0.0224	-0.00701***	-0.00123*	0.00574***	0.000775	0.0235***	0.00701***
	(0.00829)	(0.0143)	(0.000987)	(0.000603)	(0.000860)	(0.000515)	(0.000959)	(0.000736)
Time Trend		0.000760		-0.000175**		0.000142**		-0.0000202
		(0.000790)		(0.0000602)		(0.0000508)		(0.0000511)
Post-PPS Trend Change		0.00117		-0.000253***		0.000234***		0.00182***
		(0.00129)		(0.0000658)		(0.0000573)		(0.0000686)
Pat/Fac Controls	1	1	1	1	1	1	1	1
Facility FE	1	1	1	1	1	1	1	1
Dep. Var. Mean	12.08	12.08	0.910	0.910	0.0707	0.0707	0.933	0.933
R-squared	0.00582	0.00583	0.292	0.292	0.269	0.269	0.0911	0.0921
Observations	8869420	8869420	10355669	10355669	10355669	10355669	8560825	8560825

Notes: OLS estimates from equation (1) in odd numbered columns and (2) in even numbered columns. Dependent variable in columns (1) and (2) is monthly number of dialysis sessions. Dependent variable in columns (3) and (4) is an indicator for receiving in-center hemodialysis treatment. Dependent variable in columns (5) and (6) is an indicator for receiving peritoneal dialysis treatment. Dependent variable in columns (7) and (8) is an indicator for having a urea reduction ratio above 0.85. PPS is an indicator variable for January 2011 or later. Time Trend is a continuous measure of months since January 2011. This means the value for January 2011 is zero, while it is positive for subsequent months and negative for prior months. Post-PPS Trend Change is the interaction of PPS and Time Trend. An observation is a patient-month. Sample consists of observations from January 2009 to December 2012 for ESRD patients between the ages of 18 and 100 with Medicare as their primary payer for whom we observe all patient and facility controls used in the analyses in Section 3.1 and later. Patient controls include dummy variables for incident comorbidities and characteristics reported on medical evidence forms, including diabetes, hypertension, BMI bin, GFR bin, HGB bin, high albumin, cancer, drug use, alcoholism, smoking behavior, necessity of assistance, COPD, ASHD, PVD, ischemic heart disease, and congestive heart disease, along with patient race, gender, and cubic functions of age and dialysis tenure. Facility controls include facility elevation, whether the facility is freestanding or hospital-based, and chain ownership, as well as facility fixed effects. Further controls include calendar month fixed effects. Standard errors clustered by facility are in parentheses. $^{+}$, *, **, and *** indicate significance at the 10%, 5%, 1%, and 0.1% level, respectively.

Table A15
Differential Change by Elevation for Dialysis Modality

	(1) Dialysis Sessions	(2) In-Center Hemodialysis	(3) Peritoneal Dialysis	(4) Good URR
Facility Elevation	-0.0000138	-0.00000595	0.00000581	-0.0000117**
	(0.0000343)	(0.00000736)	(0.00000690)	(0.00000377)
Elevation × PPS	-0.00000472	-0.00000110	0.000000955	0.000000987
	(0.00000560)	(0.000000683)	(0.000000636)	(0.000000696)
Year-Month FE	1	1	1	1
Pat/Fac Controls	1	1	1	1
Facility FE	1	1	1	1
R-squared	0.00617	0.291	0.270	0.0923
Dep. Var. Mean	12.08	0.913	0.0685	0.933
Observations	8869420	7488474	7488474	8560825

Notes: OLS estimates from equation (4). Dependent variable in column (1) is monthly number of dialysis sessions, in column (2) is an indicator for receiving in-center hemodialysis treatment, in column (3) is an indicator for receiving peritoneal dialysis treatment, and in column (4) is an indicator for having a urea reduction ratio above 0.85. PPS is an indicator variable for January 2011 or later. Facility elevation is measured in feet above sea level. An observation is a patient-month. Sample consists of observations from January 2009 to December 2012 for ESRD patients between the ages of 18 and 100 with Medicare as their primary payer for whom we observe all patient and facility controls used in the analyses in Section 3.1 and later. Patient controls include dummy variables for incident comorbidities and characteristics reported on medical evidence forms, including diabetes, hypertension, BMI bin, GFR bin, HGB bin, high albumin, cancer, drug use, alcoholism, smoking behavior, necessity of assistance, COPD, ASHD, PVD, ischemic heart disease, and congestive heart disease, along with patient race, gender, and cubic functions of age and dialysis tenure. Facility controls include facility elevation, whether the facility is freestanding or hospital-based, and chain ownership, as well as facility fixed effects. Standard errors clustered by facility are in parentheses. $^{+}$, *, **, and *** indicate significance at the 10%, 5%, 1%, and 0.1% level, respectively.

F. Additional Time Series Results

Column (1) of Table A17 presents results from estimating equation (2) with EPO as the dependent variable. We find that EPO doses were declining by approximately 0.4% each month prior to the start of the PPS, which increases in magnitude to 1.8% after the reform, in addition to the immediate decrease of approximately 14.1%. Compared to our results from equation (1), this suggests the effects of the payment reform did not become fully realized in January 2011, but instead evolved more gradually over time.

For other outcomes in Table A17, we find that, consistent with the contemporaneous reduction in EPO, transfusions increased after the payment reform, although with a moderated upward trend. For any-cause hospitalizations, we estimate a pre-existing downward trend that roughly doubles in magnitude after the start of the PPS, in line with the drop in EPO and the risks associated with the drug. By December of 2012, we find a 6.3% decrease in hospitalizations relative to December 2010. Rates of both hospitalization for cardiac events and mortality were decreasing in the pre-period and declined further following the start of the PPS, although the changes are not statistically significant. We similarly find that trends in Medicare spending changed following the reform, as shown in Table A18.

Table A16
Effect of PPS on Medicare Spending

	Medicare Spending				
	(1) Inpatient	(2) Outpatient	(3) Part D	(4) Dialysis	(5) Total
PPS	-83.23***	31.38***	53.61***	68.81***	-19.78
	(11.16)	(2.211)	(1.923)	(4.234)	(15.63)
Pat/Fac Controls	1	1	1	1	1
Facility FE	1	1	1	1	1
Dep. Var. Mean	2557.5	393.7	465.2	2286.8	7555.4
R-squared	0.0133	0.0168	0.0700	0.0819	0.0309
Observations	9771287	9771287	9771287	9771287	9771287

Notes: OLS estimates from equation (1). Dependent variables are components of Medicare spending, denominated in dollars. An observation is a patient-month. PPS is an indicator variable for January 2011 or later. Sample consists of observations from January 2009 to December 2012 for in-center hemodialysis patients between the ages of 18 and 100 with Medicare as their primary payer for whom we observe all patient and facility controls used in the analyses in Section 3.1 and later. Patient controls include dummy variables for incident comorbidities and characteristics reported on medical evidence forms, including diabetes, hypertension, BMI bin, GFR bin, HGB bin, high albumin, cancer, drug use, alcoholism, smoking behavior, necessity of assistance, COPD, ASHD, PVD, ischemic heart disease, and congestive heart disease, along with patient race, gender, and cubic functions of age and dialysis tenure. Facility controls include facility elevation, whether the facility is freestanding or hospital-based, and chain ownership, as well as facility fixed effects. Further controls include calendar month fixed effects. Standard errors clustered by facility are in parentheses. $^{+}$, *, **, and *** indicate significance at the 10%, 5%, 1%, and 0.1% level, respectively.

Table A17
Effect of PPS on EPO and Outcomes, Pre- and Post-Trends

	(1) EPO	(2) HGB	(3) Transfusion	(4) Hosp., Any Cause	(5) Hosp., Cardiac Event	(6) Mortality
PPS	-6.829***	-0.231***	0.00481***	0.00106+	0.000141	0.0000603
	(0.277)	(0.00645)	(0.000289)	(0.000585)	(0.000249)	(0.000181)
Time Trend	-0.189***	-0.00935***	0.0000707***	-0.000211***	-0.000102***	-0.0000397***
	(0.0189)	(0.000354)	(0.0000155)	(0.0000342)	(0.0000147)	(0.0000103)
Post-PPS Trend Change	-0.688***	-0.00271***	-0.0000868***	-0.000193***	-0.0000168	-0.0000104
	(0.0214)	(0.000420)	(0.0000209)	(0.0000440)	(0.0000179)	(0.0000120)
Pat/Fac Controls	1	1	1	1	1	1
Facility FE	1	1	1	1	1	1
Dep. Var. Mean	48.50	11.12	0.0282	0.138	0.0271	0.0157
R-squared	0.138	0.0772	0.0118	0.0215	0.00791	0.00850
Observations	10077264	8181736	10077264	10077264	10077264	10077264

Notes: OLS estimates from equation (2). Dependent variable in column (1) is monthly EPO dose. EPO doses are censored at the 99th percentile and measured in 1000 IUs. Dependent variable in column (2) is hemoglobin. Hemoglobin is winsorized from below to 5 and from above to 20 and is measured in grams per deciliter. Dependent variables in columns (3)–(6) are binary outcome variables. PPS is an indicator variable for January 2011 or later. Time Trend is a continuous measure of months since January 2011. This means the value for January 2011 is zero, while it is positive for subsequent months and negative for prior months. Post-PPS Trend Change is the interaction of PPS and Time Trend. An observation is a patient-month. Sample consists of observations from January 2009 to December 2012 for in-center hemodialysis patients between the ages of 18 and 100 with Medicare as their primary payer for whom we observe all patient and facility controls used in the analyses in Section 3.1 and later. Patient controls include dummy variables for incident comorbidities and characteristics reported on medical evidence forms, including diabetes, hypertension, BMI bin, GFR bin, HGB bin, high albumin, cancer, drug use, alcoholism, smoking behavior, necessity of assistance, COPD, ASHD, PVD, ischemic heart disease, and congestive heart disease, along with patient race, gender, and cubic functions of age and dialysis tenure. Facility controls include facility elevation, whether the facility is freestanding or hospital-based, and chain ownership, as well as facility fixed effects. Further controls include calendar month fixed effects. Standard errors clustered by facility are in parentheses. +, *, **, and *** indicate significance at the 10%, 5%, 1%, and 0.1% level, respectively.

Table A18
Effect of PPS on Medicare Spending, Pre- and Post-Trends

	Medicare Spending				
	(1) Inpatient	(2) Outpatient	(3) Part D	(4) Dialysis	(5) Total
PPS	19.89	-4.899*	12.07***	8.641*	-9.478
	(15.71)	(2.178)	(1.498)	(3.991)	(20.03)
Time Trend	2.399**	1.848***	1.232***	0.427+	10.62***
	(0.896)	(0.132)	(0.102)	(0.223)	(1.195)
Post-PPS Trend Change	-16.06***	0.0220	1.873***	5.553***	-23.30***
	(1.133)	(0.166)	(0.145)	(0.256)	(1.528)
Pat/Fac Controls	1	1	1	1	1
Facility FE	1	1	1	1	1
Dep. Var. Mean	2557.5	393.7	465.2	2286.8	7555.4
R-squared	0.0133	0.0168	0.0703	0.0827	0.0309
Observations	9771287	9771287	9771287	9771287	9771287

Notes: OLS estimates from equation (2). Dependent variables are components of Medicare spending, denominated in dollars. An observation is a patient-month. PPS is an indicator variable for January 2011 or later. Time Trend is a continuous measure of months since January 2011. This means the value for January 2011 is zero, while it is positive for subsequent months and negative for prior months. Post-PPS Trend Change is the interaction of PPS and Time Trend. Sample consists of observations from January 2009 to December 2012 for in-center hemodialysis patients between the ages of 18 and 100 with Medicare as their primary payer for whom we observe all patient and facility controls used in the analyses in Section 3.1 and later. Patient controls include dummy variables for incident comorbidities and characteristics reported on medical evidence forms, including diabetes, hypertension, BMI bin, GFR bin, HGB bin, high albumin, cancer, drug use, alcoholism, smoking behavior, necessity of assistance, COPD, ASHD, PVD, ischemic heart disease, and congestive heart disease, along with patient race, gender, and cubic functions of age and dialysis tenure. Facility controls include facility elevation, whether the facility is freestanding or hospital-based, and chain ownership, as well as facility fixed effects. Further controls include calendar month fixed effects. Standard errors clustered by facility are in parentheses. $^{+}$, *, **, and *** indicate significance at the 10%, 5%, 1%, and 0.1% level, respectively.

G. Additional Details on our Estimate of the Impact of EPO

In this appendix, we provide more details on the comparison of our IV estimates to those from other settings. First, we provide details on the derivation of our IV estimand, which is given by equation (5):

$$\frac{\frac{\partial^2 h}{\partial p\ \partial a}}{\frac{\partial^2 epo^*}{\partial p\ \partial a}} = \frac{\frac{\partial h}{\partial epo^*}\frac{\partial^2 epo^*}{\partial p\ \partial a} + \frac{1}{\alpha}\frac{\partial epo^*}{\partial a}}{\frac{\partial^2 epo^*}{\partial p\ \partial a}} = \frac{\partial h}{\partial epo^*} + \frac{\frac{\partial epo^*}{\partial a}}{\alpha\frac{\partial^2 epo^*}{\partial p\ \partial a}}$$

To derive this equation, note that the numerator (which is also the reduced form of the two-stage least squares estimate) is given by

$$\frac{\partial^2 h}{\partial p\ \partial a} = \frac{d}{da}\left(\frac{\partial h}{\partial epo^*}\frac{\partial epo^*}{\partial p}\right) = \frac{\partial h}{\partial epo^*}\frac{\partial^2 epo^*}{\partial p\ \partial a} + \frac{\partial^2 h}{\partial epo^*\ \partial a}\frac{\partial epo^*}{\partial p}$$

$$= \frac{\partial h}{\partial epo^*}\frac{\partial^2 epo^*}{\partial p\ \partial a} - \frac{1}{\alpha}\frac{\partial^2 h}{\partial epo^*\ \partial a}\frac{\partial^2 h}{\partial epo\ \partial epo}^{-1} = \frac{\partial h}{\partial epo^*}\frac{\partial^2 epo^*}{\partial p\ \partial a} + \frac{1}{\alpha}\frac{\partial epo^*}{\partial a},$$

where the second-to-last equality holds by the first-order condition and the last equality follows from the fact that

$$\frac{\partial epo^*}{\partial a} = -\frac{1}{\alpha}\frac{\partial^2 h}{\partial epo\ \partial epo}^{-1} \times \alpha\frac{\partial^2 h}{\partial epo^* \partial a} = -\frac{\partial^2 h}{\partial epo\ \partial a}\frac{\partial^2 h}{\partial epo\ \partial epo}^{-1}.$$

The denominator (which is also the first stage of the two-stage least squares estimate) is given by

$$\frac{\partial^2 epo^*}{\partial p\ \partial a} = \frac{1}{\alpha}\frac{\partial^3 h}{\partial epo\ \partial epo\ \partial a}\frac{\partial^2 h}{\partial epo\ \partial epo}^{-2}.$$

Here we also give more details on how we leverage the results in Gaynor et al. (2020), hereafter GMR, to assess the magnitude of the difference between our estimated treatment effect and the equilibrium average treatment effect. Estimates from GMR indicate that α may range from 89.49 to 899.59. In GMR's model, the physician values a one unit increase in HGB (b) equivalently to $3\alpha^{GMR}(\tau^{GMR} - 3b)$ dollars of income, while in our model the physician values it at α dollars, where GMR superscripts represent parameters in that model. Using the midpoints of the hemoglobin bins used by GMR to estimate their model along with their estimates of the mean values of τ^{GMR} and $\ln(\alpha^{GMR})$ reported in Table 3 of their paper ($\tau_k'\bar{x}$ and $\mu_{\alpha,k}$ in their notation), we get that the implied values of α are

$3e^{3.54}(40.2 - 3 \times 10.5) = 899.59$, $3e^{2.91}(43.7 - 3 \times 11.5) = 506.65$, and $3e^{2.99}(50.2 - 3 \times 12.5) = 757.64$, depending on the level of hemoglobin (10-11, 11-12, and 12-13 g/dL, respectively). Instead of using the GMR estimates of the target level of hematocrit, we can also use the upper limit of the guidelines supplied by the National Kidney Foundation in 2007, which is 39. Under this calibration, the implied values of α are $3e^{3.54}(39-3\times10.5) = 775.506$, $3e^{2.91}(39-3\times11.5) = 247.82$, and $3e^{2.99}(39-3\times12.5) = 89.49$, respectively. We also note that the coefficient we report in Table 6 is not exactly $\frac{\partial^2 epo^*}{\partial p\ \partial a}$, but rather the differential effect of the payment reform by elevation. We interpret the reform as a reduction in the profit margin on EPO of \$7.62, the average Medicare payment rate for EPO in 2010. This means the estimate we report (0.00133) translates into an estimate of $\frac{\partial^2 epo^*}{\partial p\ \partial a}$ of -0.0101. We could also use the Medicare base rate reported at `https://www.cms.gov/Medicare/Medicare-Fee-for-Service-Part-B-Drugs/McrPartBDrugAvgSalesPrice/01a19_2010aspfiles` for the final quarter of 2010, which is \$9.68. Using this value results in an estimate of $\frac{\partial^2 epo^*}{\partial p\ \partial a}$ of -0.0128. Finally, we calculate the range of our estimate using $\frac{-0.00353}{899.59\times-0.0101} = 0.0004 \leq \frac{\frac{\partial epo^*}{\partial a}}{\alpha\frac{\partial^2 epo^*}{\partial p\ \partial a}} \leq \frac{-0.00353}{89.49\times-0.0101} = 0.0039$ or $\frac{-0.00353}{899.59\times-0.0128} = 0.0003 \leq \frac{\frac{\partial epo^*}{\partial a}}{\alpha\frac{\partial^2 epo^*}{\partial p\ \partial a}} \leq \frac{-0.00353}{89.49\times-0.0101} = 0.0031$, depending on the value of the payment change.

H. Results from Instrumenting with a Uniform Indicator for PPS

This appendix presents an alternative instrumental variables approach that uses only time-series variation in the form of an indicator for post-PPS to instrument for EPO. There are two reasons for doing this. First, this approach estimates the effect of EPO on health outcomes using precisely the changes in EPO following the implementation of the PPS. Inasmuch as this change in EPO was precipitated by the PPS, this produces the policy-relevant treatment effect (PRTE) described in the literature (Heckman and Vytlacil, 2005; Carneiro et al., 2011). Second, in the context of our model the estimand directly identifies the equilibrium treatment effect of EPO. Specifically, the estimand can be represented as

$$\frac{\frac{\partial h}{\partial p}}{\frac{\partial epo^*}{\partial p}} = \frac{\frac{\partial h}{\partial epo^*}\frac{\partial epo^*}{\partial p}}{\frac{\partial epo^*}{\partial p}} = \frac{\partial h}{\partial epo^*}. \tag{7}$$

The expression $\frac{\partial h}{\partial epo^*}$ describes how health outcomes change with changes in equilibrium EPO doses, which directly depend on the underlying financial incentives. Under the standard identification assumptions, this estimand more directly returns the equilibrium effect of EPO than what is produced by interacting elevation with PPS (see equation (5)). However, because identification relies only on excluded time-series variation, controlling for a restricted set of time trends, these identifying assumptions are strong.

Tables A19 and A20 show these results when the outcome variables are hemoglobin and transfusions. In all cases the estimates here are similar in magnitude to those baseline estimates. Comparisons with the baseline estimates in Table 7, depend on how the specification controls for time trends. Comparing column 1 with column 2 (or column 3 with column 4), suggests a minor role for calendar-month fixed effects. However, controlling for a linear time trend produces larger effects on both HGB and transfusions. Without controlling for a time trend, these estimates are 22.8% smaller than the baseline results in the paper for how EPO affects HGB, while including a time trend inflates the estimate to be 66.4% larger than the baseline. Similar patterns emerge for the estimates of the equilibrium effect of EPO on transfusions. These differences could arise from either a bias introduced from either a faulty

exclusion restriction from the pre/post-PPS instrumental variable or from the simple fact that they are identifying different parameters.

As shown above, the pre/post-PPS IV ostensibly identifies the PRTE, $\frac{\partial h}{\partial epo^*}$, while our approach in the body of the paper relies on difference in change EPO doses across elevation, rather than overall changes in EPO. This interacted approach departs from PRTE by omitting a constant term whereby the policy shifted EPO doses downward across all elevations. Equation (5) describes this term, showing that it is inversely related to altruism (if providers were perfectly altruistic there would be no such downward shift) and proportional to the average gradient of EPO doses across elevations. In Section 5.1 we find that these features push our estimate to overstate the equilibrium effect for HGB, so the fact that the estimates here have larger magnitudes suggests that the differences are coming, at least in part, from a faulty exclusion restriction. This emphasizes the importance of our interacted instrument for credible identification.

Table A19
Pre/Post IV, Hemoglobin

	(1) HGB	(2) HGB	(3) HGB	(4) HGB
EPO	0.0216***	0.0367***	0.0216***	0.0466***
	(0.000522)	(0.00182)	(0.000521)	(0.00273)
Year-Month FE	0	0	0	0
Time Trend	0	1	0	1
Month FE	0	0	1	1
Pat/Fac Controls	1	1	1	1
Facility FE	1	1	1	1
Dep. Var. Mean	11.12	11.12	11.12	11.12
Observations	8181736	8181736	8181736	8181736
First-Stage F-statistic	1319.5	486.6	1315.4	305.4

Notes: IV estimates from equation (3) using PPS_t as the excluded instrument. Dependent variable is hemoglobin. Hemoglobin is winsorized from below to 5 and from above to 20 and is measured in grams per deciliter. EPO doses are censored at the 99th percentile and measured in 1000 IUs. An observation is a patient-month. Sample consists of observations from January 2009 to December 2012 for in-center hemodialysis patients between the ages of 18 and 100 with Medicare as their primary payer for whom we observe all patient and facility controls used in the analyses in Section 3.1 and later. Patient controls include dummy variables for incident comorbidities and characteristics reported on medical evidence forms, including diabetes, hypertension, BMI bin, GFR bin, HGB bin, high albumin, cancer, drug use, alcoholism, smoking behavior, necessity of assistance, COPD, ASHD, PVD, ischemic heart disease, and congestive heart disease, along with patient race, gender, and cubic functions of age and dialysis tenure. Facility controls include facility elevation, whether the facility is freestanding or hospital-based, and chain ownership, as well as facility fixed effects. Standard errors clustered by facility are in parentheses. $^{+}$, *, **, and *** indicate significance at the 10%, 5%, 1%, and 0.1% level, respectively.

Table A20
Pre/Post IV, Transfusions

	(1) Transfusion	(2) Transfusion	(3) Transfusion	(4) Transfusion
EPO	-0.000318***	-0.000820***	-0.000317***	-0.000777***
	(0.0000140)	(0.0000547)	(0.0000140)	(0.0000576)
Year-Month FE	0	0	0	0
Time Trend	0	1	0	1
Month FE	0	0	1	1
Pat/Fac Controls	1	1	1	1
Facility FE	1	1	1	1
Dep. Var. Mean	0.0282	0.0282	0.0282	0.0282
Observations	10077264	10077264	10077264	10077264
First-Stage F-statistic	1667.8	572.4	1660.7	520.4

Notes: IV estimates from equation (3) using PPS_t as the excluded instrument. Dependent variable is a binary variable for receiving a blood transfusion. EPO doses are censored at the 99th percentile and measured in 1000 IUs. An observation is a patient-month. Sample consists of observations from January 2009 to December 2012 for in-center hemodialysis patients between the ages of 18 and 100 with Medicare as their primary payer for whom we observe all patient and facility controls used in the analyses in Section 3.1 and later. Patient controls include dummy variables for incident comorbidities and characteristics reported on medical evidence forms, including diabetes, hypertension, BMI bin, GFR bin, HGB bin, high albumin, cancer, drug use, alcoholism, smoking behavior, necessity of assistance, COPD, ASHD, PVD, ischemic heart disease, and congestive heart disease, along with patient race, gender, and cubic functions of age and dialysis tenure. Facility controls include facility elevation, whether the facility is freestanding or hospital-based, and chain ownership, as well as facility fixed effects. Standard errors clustered by facility are in parentheses. $^{+}$, *, **, and *** indicate significance at the 10%, 5%, 1%, and 0.1% level, respectively.

I. Additional Results on Heterogeneity in Provider Altruism

In this appendix, we present evidence that large chains and for-profit facilities responded to the payment reform more than other facilities did. Assuming the patient health function and the change in profit margin on EPO are the same across these groups of providers, this differential response indicates less altruism and a greater weight placed on financial considerations. The requirement that the change in the profit margin on EPO is the same across providers is likely satisfied. While there may be differences in the acquisition costs for EPO across providers, the reduction in payment was uniform regardless of provider type. This means that unless there were differential changes in acquisition costs by provider type, the change in the profit margin was the same. The requirement that the health function of patients treated by different types of facilities is the same is less clearly satisfied. In order to address concerns that there may be differences in the types of patients treated by different facilities, we estimate

$$EPO_{ijt} = \alpha_1 Type_j + \alpha_2 PPS_t + \alpha_3 Type_j \times PPS_t + X_{ijt}\Gamma + u_{ijt}, \tag{8}$$

where $Type_j$ denotes the ownership characteristic of firm j. In X_{ijt} are a number of observable patient characteristics that are meant to capture the patient's unobserved health function. In our most conservative specification, the relationships between EPO dose and these observable characteristics are allowed to change after the implementation of the PPS.

The tables below present evidence that the larger reduction in EPO for large chains and for-profit facilities is robust to the inclusion of other controls. Table A21 shows that while there are no large differences between small and large chain facilities, independently owned facilities reduced their use of EPO by much less than those owned by chains. In our most conservative specification, we find that this reduction was over 7 thousand IUs per month less. Similarly, Table A22 shows that for-profit facilities reduced their EPO use much more than not-for-profit facilities. In Table A23, we limit the sample to only independent facilities and show that even within this sub-group, for-profit facilities reduced their EPO use by much more than their not-for-profit counterparts. That these differences remain after conditioning on rich and flexible parameterizations of patient and facility characteristics indicates that

Table A21
Differential Effect of PPS on EPO by Chain Status

	(1) EPO	(2) EPO	(3) EPO	(4) EPO
Large Chain × PPS	-0.390	0.0798	0.700	0.957
	(0.595)	(0.599)	(0.593)	(0.587)
Independent × PPS	11.39***	11.60***	11.30***	7.486***
	(0.881)	(0.882)	(0.882)	(0.982)
Year-Month FE	1	1	1	1
Pat/Fac Controls	0	1	1	1
Facility FE	0	0	1	1
Controls × PPS	0	0	0	1
R-squared	0.0533	0.0847	0.140	0.141
Dep. Var. Mean	48.50	48.50	48.50	48.50
Observations	10077289	10077289	10077264	10077264

Notes: OLS estimates from equation (8). Dependent variable is monthly EPO dose. EPO doses are censored at the 99th percentile and measured in 1000 IUs. PPS is an indicator variable for January 2011 or later. An observation is a patient-month. Sample consists of observations from January 2009 to December 2012 for in-center hemodialysis patients between the ages of 18 and 100 with Medicare as their primary payer for whom we observe all patient and facility controls used in the analyses in Section 3.1 and later. Patient controls include dummy variables for incident comorbidities and characteristics reported on medical evidence forms, including diabetes, hypertension, BMI bin, GFR bin, HGB bin, high albumin, cancer, drug use, alcoholism, smoking behavior, necessity of assistance, COPD, ASHD, PVD, ischemic heart disease, and congestive heart disease, along with patient race, gender, and cubic functions of age and dialysis tenure. Facility controls include facility elevation, whether the facility is freestanding or hospital-based, and chain ownership, as well as facility fixed effects. Standard errors clustered by facility are in parentheses. $^{+}$, *, **, and *** indicate significance at the 10%, 5%, 1%, and 0.1% level, respectively.

there are clear differences in the relative weights placed on patient health and financial outcomes by providers of different types, which is critical for policymakers to understand.

Table A22
Differential Effect of PPS on EPO by For-Profit Status

	(1) EPO	(2) EPO	(3) EPO	(4) EPO
For-Profit × PPS	-8.906***	-8.455***	-8.214***	-3.893***
	(0.796)	(0.785)	(0.764)	(0.865)
Year-Month FE	1	1	1	1
Pat/Fac Controls	0	1	1	1
Facility FE	0	0	1	1
Controls × PPS	0	0	0	1
R-squared	0.0434	0.0846	0.139	0.141
Dep. Var. Mean	48.50	48.50	48.50	48.50
Observations	10077289	10077289	10077264	10077264

Notes: OLS estimates from equation (8). Dependent variable is monthly EPO dose. EPO doses are censored at the 99th percentile and measured in 1000 IUs. PPS is an indicator variable for January 2011 or later. An observation is a patient-month. Sample consists of observations from January 2009 to December 2012 for in-center hemodialysis patients between the ages of 18 and 100 with Medicare as their primary payer for whom we observe all patient and facility controls used in the analyses in Section 3.1 and later. Patient controls include dummy variables for incident comorbidities and characteristics reported on medical evidence forms, including diabetes, hypertension, BMI bin, GFR bin, HGB bin, high albumin, cancer, drug use, alcoholism, smoking behavior, necessity of assistance, COPD, ASHD, PVD, ischemic heart disease, and congestive heart disease, along with patient race, gender, and cubic functions of age and dialysis tenure. Facility controls include facility elevation, whether the facility is freestanding or hospital-based, and chain ownership, as well as facility fixed effects. Standard errors clustered by facility are in parentheses. $^{+}$, *, **, and *** indicate significance at the 10%, 5%, 1%, and 0.1% level, respectively.

Table A23
Differential Effect of PPS on EPO by For-Profit Status Among Independent Facilities

	(1) EPO	(2) EPO	(3) EPO	(4) EPO
For-Profit × PPS	-6.341***	-6.239***	-6.297***	-7.822***
	(1.383)	(1.347)	(1.402)	(1.622)
Year-Month FE	1	1	1	1
Pat/Fac Controls	0	1	1	1
Facility FE	0	0	1	1
Controls × PPS	0	0	0	1
R-squared	0.0446	0.106	0.229	0.235
Dep. Var. Mean	30.14	30.14	30.14	30.14
Observations	1980611	1980611	1980598	1980598

Notes: OLS estimates from equation (8). Dependent variable is monthly EPO dose. EPO doses are censored at the 99th percentile and measured in 1000 IUs. PPS is an indicator variable for January 2011 or later. An observation is a patient-month. Sample consists of observations from January 2009 to December 2012 for in-center hemodialysis patients between the ages of 18 and 100 with Medicare as their primary payer for whom we observe all patient and facility controls used in the analyses in Section 3.1 and later. Sample is limited to patients treated at independently owned facilities. Patient controls include dummy variables for incident comorbidities and characteristics reported on medical evidence forms, including diabetes, hypertension, BMI bin, GFR bin, HGB bin, high albumin, cancer, drug use, alcoholism, smoking behavior, necessity of assistance, COPD, ASHD, PVD, ischemic heart disease, and congestive heart disease, along with patient race, gender, and cubic functions of age and dialysis tenure. Facility controls include facility elevation, whether the facility is freestanding or hospital-based, and chain ownership, as well as facility fixed effects. Standard errors clustered by facility are in parentheses. $^{+}$, *, **, and *** indicate significance at the 10%, 5%, 1%, and 0.1% level, respectively.