

Medicare Decision on Anemia Drugs Ignored Benefits of Drugs
Suggests That the Government Is Willing to Put Cost before Patient Care

New York, NY (March 11) – Today, the Center for Medicine in the Public Interest released a report on the decision by the Centers for Medicare and Medicaid Services to limit the ability of doctors to prescribe anti-anemia drugs to patients undergoing chemotherapy.

Last year, CMS limited (or outright prohibited) the use of anti-anemia drugs known as Erythropoiesis-Stimulating Agents (ESAs) in cancer patients on Medicare or Medicaid whose hemoglobin count exceeds 10 grams per deciliter of blood.

The report -- *The Impact of Medicare's Anemia Drug Coverage Decision on Cancer Patients: Comparative Effectiveness vs. Patient Centered-Care* -- found that CMS ignored the benefits of these medicines. The report also found that CMS ignored the risks of blood transfusions (a more aggressive anemia treatment) in order to dramatize potential safety problems.

“CMS made its decision by taking a one-size fits all approach to its review of anemia drugs. This does not bode well for cancer patients,” explained CMPI Vice President and study author, Robert Goldberg, PhD.

“This is yet another example of the government’s willingness to put cost before patient care. If CMS continues to make decisions in this way, both doctors and patients will see their access to new and existing treatments rationed in the name of cost containment,” explained Goldberg.

The study also reviewed a 1997 decision by CMS to limit payment for ESAs in the End Stage Renal Dialysis program. As a result of that decision, anemia levels soared and patients died. Only after CMS removed the cap did patient well-being improved.

Additionally, the report found that many new cancer drugs and treatments shown to prolong life are dependent on the use of anemia drugs that permit patients to undergo arduous therapies. CMS failed to consider the impact of reducing access to anemia drugs on cancer survival as a result of treatment.

Finally, the report found that CMS applied the Precautionary Principle in its most-recent anemia drug decision by focusing only on studies that averaged the results of generalized studies. CMS didn’t differentiate between type of cancer, chemotherapy regimen or severity of illness.

The report recommends that CMS, private insurers, companies, and researchers develop more patient-centered approaches to determining what medicines and treatments to use.

“CMS should establish a Critical Path for comparative effectiveness that seeks to integrate tools for personalizing medicine in the same way the Food and Drug

Administration has developed a Critical Path for modernizing medical product evaluation,” explained Peter Pitts, CMPI President and a former FDA Associate Commissioner. “The choice about cancer care should ultimately be made by oncologists, not by CMS bureaucrats.”

The report which includes information on how to evaluate online medical advice is available at www.cmpi.org.

About CMPI

The Center for Medicine in the Public Interest is nonprofit, nonpartisan research and educational organization that seeks to advance the discussion and development of patient-centered health care.

HYPERLINK

**The Impact of Medicare's Anemia Drug Coverage
Decision On Cancer Patients:
Comparative Effectiveness vs. Patient Centered-
Care**

The Center for Medicine in the Public Interest

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Robert Goldberg, Ph.D.

The Impact of Medicare's Anemia Drug Coverage Decision On Cancer
Patients:
Comparative Effectiveness vs. Patient-Centered Care

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Executive Summary

The Centers for Medicare and Medicaid Services (CMS) recently issued a National Coverage Decision (NCD) that concluded drugs called erythropoiesis stimulating agents (ESAs), which are used to reduce anemia caused by chemotherapy, were not safe to use in Medicare patients in most cases.

CMS came to this decision because it claimed it did not have enough evidence that ESA use beyond a certain hemoglobin was safe. As CMS puts it: "The absence of adverse events in a setting of potential harm with an absence of adequate safety data cannot be interpreted as proof of no harm." Lacking "adequate data" to establish proof of no harm, CMS will no longer cover ESAs

beyond a hemoglobin level of 10 g/dL and after a certain number of treatments.

Risk and technology assessment is not a purely objective enterprise. It is a social one that reflects views on how political and economic institutions should be organized. Specifically, CMS justified a specific dosing schedule and one-size-fits-all dose limit on all cancer patients needing treatment for anemia based on The Precautionary Principle. That principle states that "...if result of a given action may be to cause irreversible damage of some sort, in the absence of scientific consensus that such harm will not ensue, we must proceed as if there is evidence that such harm will indeed ensue. The result is that the burden of proof falls not on the regulator, but on those who advocate taking the action". The Precautionary Principle focuses on the inability of science to predict risk far into the future as a key weakness of all new technologies largely to the exclusion of potential benefits to individuals in the short term. Hence, a requirement to eliminate all risk at a population level as a precondition to individual access will certainly delay and reduce the use of innovative medical treatments.

Concerns about shorter survival and rapid tumor growth in patients receiving higher than indicated doses of ESAs are long standing and have been validated in recent years. However, in applying the precautionary principle and defending its decision in terms of patient safety, CMS assumed, without any evidence, that any form of blood transfusions were equally as safe and effective in reducing the burden of anemia imposed by chemotherapy at a level lower than labeled doses. CMS indirectly used a lower standard of evidence in making this assumption since the decision to begin transfusion has never been subjected to the same prospective clinical trials that ESAs have undergone over the years. Further, CMS ignored evidence from well-designed observational studies and controlled trials that measured quality of life and patient preferences, risks from transfusions, and the cumulative role ESAs have played in permitting more aggressive cancer agents, dosing cycles and new regimens that are related to increased cancer survivorship in the United States.

Further, a previous CMS effort to cap hemoglobin levels (in the Medicare reimbursed renal dialysis program) in a one-size fits all fashion led to an increase in anemia and deaths among patients. CMS is embarking on yet another experiment that places the effort to control costs by restricting dosing that could endanger patients. In this case, it is engaging in a double standard. In capping anemia drug use without regard to individual patient needs, CMS is ignoring scientific evidence and quality of life considerations that it has encouraged physicians, hospitals and medical technology developers to provide in support of other coverage decisions. For instance, in continuing to pay for the off-label use of drug eluting stents, CMS appropriately took into account quality of life concerns and reviewed data it claimed was not adequate proof of no harm

in the case of ESAs.

If the Precautionary Principle becomes part of the CMS method of comparative effectiveness of medical treatments or comparative effectiveness evaluation in general, it will deny Medicare patients a whole range of services and drugs now and in the future, not just ESAs. CMS will become a fourth hurdle for access to medical innovation while doctors, device and drug companies become more likely to shun the Medicare program. If the Precautionary Principle is used to compare clinical effectiveness, it will quickly be applied when deciding – as did CMS -- which service or treatment to cover.

Finally, the CMS decision is based on large scale trials and meta-analyses that ignore substantial variation – including genetic differences -- in individual responses to drugs and treatments that in fact do shape clinical outcomes. There are a wide variety of data sources that would permit CMS to come up with data and tools to improve clinical decision making. A collaborative research effort that prioritizes the well-being of the patient, linking treatment steps to outcomes and then to reimbursement makes more sense. Then patients could compare which plans and physicians provide the best care for them.

CMS should establish a Critical Path for comparative effectiveness that seeks to integrate tools for personalizing medicine in the same way the Food and Drug Administration has developed a Critical Path for modernizing medical product evaluation using genomics, health informatics and other advances. Promoting greater transparency, consumer choice and quality-based competition is consistent with other Health and Human Services initiatives. Such patient-centric information -- with the goal of providing the right treatment, at the right dose, at the right time for the right patient or not at all -- ensures that the choice about cancer care is ultimately made by doctors and patients, not by CMS bureaucrats.

The Precautionary Principle and Comparative Effectiveness: Medicare’s ESA Coverage Decision "Does No Harm" But At What Cost?

Robert Goldberg

*CMS and the fight over chemo-induced anemia and patient quality of life.
“This is a new paradigm – and it is not a welcome one.”*

The Centers for Medicare and Medicaid Services (CMS; Baltimore, MD; HYPERLINK "www.cms.hhs.gov" www.cms.hhs.gov), the agency that manages the nation’s Medicare program, recently announced its final national coverage determination (NCD) for the use of erythropoiesis stimulating agents (ESA) for patients with cancer and related neoplastic conditions. CMS outlined the limitations on coverage of ESAs in a letter issued by CMS chief medical officer, Barry Straube, to the American Society of Hematology (ASH; Washington, DC; HYPERLINK "www.hematology.org" www.hematology.org), US Oncology (Houston, TX; HYPERLINK "www.usoncology.com" www.usoncology.com) the and the American Society of Clinical Oncology (ASCO; Alexandria, VA; HYPERLINK "www.asco.org" www.asco.org).

The letter stated that CMS would only reconsider amending the cancer NCD for ESAs if evidence were submitted within 30 days, to challenge the ruling. The leading organizations representing those physicians who treat cancer patients submitted their reconsideration requests including the American Society of Hematology, the American Community Cancer Centers and the American Society of Clinical Oncology. The main CMS coverage decision points and the clinical concerns are highlighted below (Table 1):

Table 1. Clinical Concerns of Stakeholders Compared to CMS Coverage Decision(Ref. 1)	
CMS Position	Medical Community □
Patients with chemotherapy-induced anemia whose hemoglobin is >10 g/dL and whose physician recommends a transfusion, but who refuse to be transfused on personal, religious, or other grounds	CMS will not cover ESAs for patients who refuse transfusions out of quality of life concerns or infection concerns..
CMS will pay for one dose of ESA for each course of chemotherapy for 8 weeks of treatment at the 10 g d/L level regardless of chemotherapy regimen.	Cancer patients whose cancer has spread to other parts of their body often become resistant to one type of chemotherapy and need another right away or in combination. Each drug needs its own ESA boost at times, something CMS refuses to pay for. □
CMS will only pay for another dose of ESA (25	Patients respond differently to ESAs based on

percent higher than the starting dose) at the fifth week of treatment. CMS caps additional treatment at that dose at four weeks.	age, type of cancer, intensity of treatment, other illnesses that affect anemia, etc. Some people simply do not respond as quickly to ESAs. There is no accommodation for this clinical scenario, and there is the potential to negatively impact patient care.
Seeks to impose one approach to dosing to all patient for all ESAs	CMS has no evidence about paying for a one-size-fits-all dose increase will have on patients. Doctors should be guided by clinical and quality of life considerations.
CMS will only pay to achieve a hemoglobin level of 10g/dL	FDA's new label repeatedly notes the upper safety limit is 12 g/dL, and preserves physician discretion to use the lowest dose possible in order to avoid blood transfusions and to continue treatment within the range of 10-12 g/dL. Physician discretion remains the critical factor. FDA label supports anemia management protocols adopted by US Oncology, the American Society of Hematology (ASH), the American Society of Clinical Oncology (ASCO), and the European Agency for the Evaluation of Medicinal Products (EMA), and all major U.S. health insurance plans. All of these groups support the same physician-centric approach and reflect a target range of 10 g/dL and 12 g/dL.

ESAs are regarded as an integral part of treatment protocol for cancer patients undergoing radiation and chemotherapy. ESAs are synthetic form of erythropoietin, a protein made in the body that stimulates the production of red blood cells made through recombinant DNA technology. Administered by injection in a physician's office, recombinant ESA works similarly to its natural counterpart to increase oxygen-carrying blood in patients who are anemic due to chemotherapy treatments. The alternative to ESAs are blood transfusions, which are more invasive and require more patient preparation time as well as repeated trips to a blood center or hospital.

In medical practice, ESAs are FDA-approved to reduce the need for blood transfusions in patients with end-stage renal disease, chronic kidney disease, patients with cancer on chemotherapy, patients scheduled for certain major surgeries, and patients with human immunodeficiency virus (HIV) who are using Zidovudine (also known as AZT). With regard to the case of treating cancer-induced anemia, CMS proposed a national coverage decision that states Medicare coverage of ESA treatment in beneficiaries with cancer should be limited to circumstances in which the treatment is not likely to worsen the cancer and in cases where the beneficiary's anemia is responsive to the ESA. This proposal was prompted by the Food and Drug Administration's (FDA;

Washington, DC; HYPERLINK "<http://www.fda.gov>" www.fda.gov) “black box warning” regarding the use of ESAs such as Epogen (epoetin alfa), Aranesp (darbepoetin alfa), and Procrit (epoetin alfa). A black box warning means that medical studies indicate that the drug carries “a significant risk of serious or even life-threatening adverse effects.” Its moniker is a literal description of the frame appearing around such warnings on prescription packaging.

After reviewing more than 2,600 public comments and additional evidence in response to its proposed policy, CMS modified the ruling and decided that ESAs are not reasonable and necessary as a course of treatment for beneficiaries with certain clinical conditions, either because of a deleterious effect of the ESA on their underlying disease or because the underlying disease might increase their risk of adverse effects related to ESA use. The final national coverage determination (NCD) now limits payments for ESA use in cancer patients with hemoglobin levels less than or equal to 10 g/dL and stipulates that Medicare will cover ESAs that are used to treat anemia caused by chemotherapy, but not anemia caused by the cancer itself.

However, according to oncologists, limiting coverage for ESAs to Medicare beneficiaries with hemoglobin levels of 10 g/dL or lower leaves these patients at risk of dropping to hemoglobin levels at inappropriately low values. Government regulatory agencies and professional societies in the United States and Europe including the Food and Drug Administration and the European Medicines Agency recommend a higher hemoglobin concentration. For instance, the FDA has recommended treatment with ESAs, including Aranesp (darbepoetin alfa), Epogen (epoetin alfa), and Procrit (epoetin alfa), when hemoglobin levels are 12 g/dL or lower. Furthermore, in October 2007, the American Society of Hematology (ASH; Washington, DC; HYPERLINK "www.hematology.org" www.hematology.org) and the American Society of Clinical Oncology (ASCO; Alexandria, VA; HYPERLINK "www.asco.org" www.asco.org) updated their ESA guidelines, after reviewing and analyzing published clinical trials, to recommend maintaining a higher level of hemoglobin in the blood than that stated in government policy (Table 2).

Table 2. Erythropoiesis stimulating agents comparison					
<i>Manufacturer</i>	<i>FDA-approved ESA regimen, initial dosage*</i>	<i>Chemical □Name</i>	<i>Year of FDA approval</i>	<i>Baseline hemoglobin (Hb) in FDA- approved registration trial</i>	<i>News</i>
Amgen	Aranesp 500	Darbepoetin	2006	< 11 g/dL	

	mcg Q3W	alfa			
Amgen	Aranesp 2.25 mcg/kg QW	Darbepoetin alfa	2002	≤ 11 g/dL	
Amgen	Epogen A 150 Units/kg SC TIW□	Epoetin alfa		≤ 12 g/dL □	
Amgen	Epogen 40,000 Units SC	Epoetin alfa		≤ 12 g/dL □	
Ortho Biotech	PROCRIT 40,000 Units QW	Epoetin alfa	2004	< 10.5 g/dL females, < 11.5 males	
Ortho Biotech	PROCRIT 150 Units/kg TIW	Epoetin alfa	1993	≤ 10.5 g/dL	
Roche	Mircera		2007	≤ 12 g/dL □	Infringes 11 Amgen erythropoietin patent claims

* PROCRT Prescribing Information (03/07); Aranesp (04/07); Epogen

In the absence of what CMS considers adequate data to establish proof of no harm, CMS has mandated these provisions and limitations in its final NCD ruling for ESA usage:

The final NCD no longer distinguishes between cancers that have erythropoietin receptors and cancers without such receptors.

CMS has made no determination regarding ESA use for myelodysplastic syndrome (MDS) – a premalignant syndrome that transforms into acute myeloid leukemia in many patients. In cases where no determination is made, Medicare local contractors have the discretion to make reasonable and necessary determinations regarding ESA use.

The final NCD provides coverage with restrictions for the treatment of anemia induced by myelosuppressive anticancer chemotherapy in certain cancer conditions, such as solid tumors, multiple myeloma, lymphoma, and lymphocytic leukemia. The NCD details these restrictions, which include: limiting initiation of ESA therapy to when the hemoglobin level is less than 10 g/dL; limiting the ESA treatment duration to a maximum of eight weeks after a chemotherapy session ends; limiting the starting dose to the FDA-recommended starting dose; and limiting dose escalation levels. A belief that CMS should not include anemia of myelodysplastic syndrome or anemia associated with chemotherapy in the non-covered category.

CMS states that ESA use is not reasonable and necessary in beneficiaries who do not achieve a pre-specified hemoglobin response (i.e., have a poor drug response) in a pre-specified time period, even if their hemoglobin has stabilized. Evidence of poor drug response is characterized as a hemoglobin/hematocrit rise

of less than 10 g/dL or a change of less than 3% after four weeks of treatment. Lacking “adequate data” to establish proof of no harm, CMS will limit its coverage of ESAs in cases where it deems the treatment reasonable and necessary to a maximum treatment duration of 12 weeks/year, or a maximum covered four-week treatment dose of 126,000 units for erythropoietin beyond a hemoglobin level of 10 g/dL and after a certain number of treatments.

History of ESAs and Their Regulation

Erythropoietin is a protein made in the body by the kidneys that causes the bone marrow to produce oxygen-carrying red blood cells. When this natural mechanism is not working and the red blood cell count becomes too low (resulting in the condition known as anemia), it may be necessary to stimulate the bone marrow to produce red blood cells. The erythropoietin that is used to treat anemia is called epoetin alfa. Genetically engineered using recombinant DNA technology, epoetin alfa belongs to a class of drugs called erythropoietin stimulating agents or ESAs.

In 1989 and 1993, epoetin alfa was approved for the treatment of anemia associated with chronic renal failure and cancer chemotherapy, respectively. Since then, epoetin alfa and other recombinant epoetin therapies, such as darbepoetin alfa, have been used to treat anemia resulting from cancer chemotherapy. The risks and benefits of using ESAs to boost hemoglobin levels in patients who are not undergoing therapies that could cause anemia, or for other uses, also have been studied, and the results have been widely published.

Since their introduction in 1989, ESAs have generated significant clinical interest. Most of these studies address the impact of ESAs on quality of life during treatment for cancer patients receiving chemotherapies and for select patients with end-stage renal disease (ESRD) anemia.

The clinical trials of ESAs that were submitted for FDA approval (registration) were of relatively short duration (12-16 weeks). Further, these trials concentrated on effecting a change in hemoglobin concentration, reducing the need for transfusion, and improving quality of life. The results consistently have shown a relationship between the correction of anemia and improved cardiac function, cognitive ability, sexual function, and exercise capacity.

Medicare’s ongoing efforts to control its spending on ESAs are nothing new. The Medicare payment policy for ESA use in dialysis patients changed in January 1991 from a relatively fixed payment per treatment, which resulted in sub-therapeutic dosing, to a variable payment based on the amount of ESA administered with each treatment, which may have encouraged doses that were

unnecessarily high.

In 1997, Medicare initiated the Hematocrit Measurement Audit (HMA) policy for payment of ESA under the End-Stage Renal Dialysis Program. Under the HMA, Medicare refused to pay for ESAs when administered to ESRD patients at or above a certain hemoglobin level. The policy achieved its primary goal, but suffered a setback because the hemoglobin-level restriction implemented under HMA guidelines caused a reduction of the mean hematocrit as well, which meant many patients were falling below optimal hemoglobin levels. In fact, nearly half of the patients enrolled in Medicare's dialysis program were reported to have experienced hemoglobin levels that fell below 11 g/dL. This decline in hemoglobin (on an individual basis) was linked to a 40% increase in an associated risk for death. Medicare changed the HMA policy in 1998 in response to patient and provider concern.

Medicare, under Part B, pays for ESAs that are used to treat anemia in cancer patients. CMS determines the extent to which doctors who administer ESA treatments will be reimbursed. Typically that amount is equal to roughly 106% of the average sales' price of ESAs. In 2006, oncologists were eligible to receive \$130 per patient per visit from Medicare if they asked chemotherapy patients three invalidated questions about their experiences with the adverse effects of chemotherapy, including anemia. In 2007, CMS implemented an alternative demonstration project. The agency required oncologists to provide information on treatment patterns for patients with different cancers at different disease stages. Hence, while Medicare and manufacturers fight a battle over the costs and quantity of ESA use, the concern over quality of care and quality of life appears to be considered using varying standards, and late in the game, or as an afterthought, time after time.

The Precautionary Principle and CMS "Proof of No Harm" as New Standard for Reimbursement

Contrary to the cost considerations of the HMA policy, CMS has justified its decision to limit reimbursement for ESAs to treatment of non-dialysis patients on the grounds that any use of ESAs, other than those Medicare will pay for, is not proven safe. However, rather than providing evidence that the specific uses of ESAs, past or present, are unsafe, CMS maintains that it must make unilateral and swift decisions because of an entirely new safety standard: Whatever is not proven to be safe must be regarded as unsafe. Whatever is unsafe must not be

used. And, what must not be used must not be paid for.

This perspective that anything unknown and untested is potentially harmful – is known as the Precautionary Principle. The most widely used description of the precautionary principle is found in Article 15 of the United Nations Rio Declaration [on Environment and Development] of 1992, which states that in relation to a given action or state of affairs, “Where there are threats of serious or irreversible damage, lack of full scientific certainty shall not be used as a reason for postponing cost-effective measures to prevent environmental degradation.”³

The Precautionary Principle suggests that if the result of a given action were the cause of irreversible damage, such as permanent injury or death, then, in the absence of scientific consensus that such harm would not ensue, we must proceed as if there were evidence that such harm would indeed ensue. Consequently, the burden of proof falls not on the regulator, but on those who advocate taking the action.

In the practice of medicine, the precautionary principle has the following elements.

Preventing the use of new technologies because of uncertainty established from randomized clinical trials that exclude variations in individual response that mitigate fear or risk.

Shifting the burden of responsibility for proving safety and efficacy to the proponents of an activity. Demanding additional studies and restrictions designed to eliminate uncertainty.

Avoidance or rejection of evidence regarding the benefits of a technology on the grounds that such data fails to meet a specific scientific threshold. Ironically, those applying the precautionary principle often describe themselves as consumer advocates. Yet they reject observational studies that measure benefits of new technologies to individuals as unscientific in favor of their own unsupported assertions.

The new coverage guideline incorporates all these elements. CMS actually ignores quality of life and patient preferences, the risks posed by transfusions, and the cumulative role ESAs have played in permitting doctors to use more aggressive cancer-fighting agents, dosing cycles, and new regimens that are integral to increased cancer survivorship in the U.S.

The precautionary principle is not a scientific theorem. It is a political judgment used to rationalize the selection or presentation of a set of facts that are, in turn, used to justify a set of values. The following analysis of the CMS coverage decision portrays the agency as an authoritative body, presenting arguments in superficial scientific terms, and being selective in its use of science. Further, CMS’s interpretation of the data is influenced as much by existing agendas that

have little to do with science of safety as it is by relevant, sound research. The facts are presented to support the Precautionary Principle; the very foundation of the argument is predicated by the idea that we should refrain from scientific endeavors, the outcomes of which we cannot predict with certainty – which ultimately is a call to refrain from scientific intervention because the uncertainty of an outcome is at the very heart of the scientific enterprise.

As we shall see, CMS applies the precautionary principle to wrest control of clinical decision-making from doctors and to ignore patient demonstrations of well being. If applied across the board, CMS could thwart access to new technologies based on the premise that the outcome of implementation may be unsafe. CMS asserts that it has no choice but to limit access to ESAs, because this is how to proceed as if harm would ensue if it acted otherwise:

“We preface our consideration of the questions with a discussion of the evidence regarding appropriate outcomes (endpoints) for trials of ESA treatment. Because of concern about serious adverse effects, including death, we are focusing on evidence of morbidity and mortality.”

Most ESA registration trials have enrolled subjects with a variety of underlying diseases. This is best exemplified in the trials with cancer patients, where the subjects represent multiple cancer types. Although numerous qualitative and quantitative studies have been conducted for many cancers, by cancer type, we do not have enough data to draw a conclusion about safety because there are too few studies addressing ESA safety for each cancer. In light of evidence that the effect of ESA may vary by cancer type, it is possible that drug trials conducted on a group of subjects with different cancers may dilute the results, and thereby undermining the effect of ESA in some cancer patients.

CMS pointed to the fact that a number of ESA trials have been terminated, suspended, or otherwise not completed as proof of potential harm. It even went so far to accuse companies of only publishing studies that reflect a bias towards ESA use. Incredibly, in making it's decision it referred to a New York Times article mentioning that the Securities and Exchange Commission (SEC; Atlanta bureau) is reportedly investigating Amgen, Inc. (Thousand Oaks, CA; [HYPERLINK "www.amgen.com" www.amgen.com](http://www.amgen.com)), manufacturer of Aranesp (darbepoetin alfa) for failure to disclose to investors until February 2007 that a Danish study of darbepoetin use in head-and-neck cancer was terminated in October 2006 due to concerns for patient safety. This ad hominem attack on the conduct of a company had no place in what was – as CMS argued – was an evidence-based review of clinical literature.

CMS also claims that “the absence of adverse events in a setting of potential

harm with an absence of adequate safety data cannot be interpreted as proof of no harm.” In the process, CMS ignores any possible benefits of ESAs in a setting of possible harm that might offset the adverse effects. Further, it establishes a precautionary principle of medical technology: If you don’t have “adequate” safety data to prove that a treatment causes no harm, then don’t use it, no matter what the benefits of that treatment may be.

Adequacy, however, is in the eye of the beholder — and this beholder is also defining “risk.” In the regulatory environment, the standards used to characterize risk are ultimately from policy-based decisions, which are subsequently shaped by political, legal, and cultural factors. The evidence-based risk supports a policy decision, rarely the other way around. So the question is, what policy goal is CMS trying to achieve, beyond restricting access to ESAs, by making “proof of no harm” — independent of any benefit consideration?

What You Don’t Know Will Hurt You

A look at the “evidence-based review” CMS makes of clinical information and medical knowledge helps answer this question. For the most part, CMS ignores quality of life benefits and focuses on whether ESAs directly promote survival from cancer. Indeed, from 1994 forward most research on ESAs was designed to evaluate “ways to improve the response rate to epoetin alfa, the potential benefits of alternative dosing regimens and early treatment intervention, and non-anemia-related indications (e.g., cognitive impairment, asthenia). In addition, scientists are exploring the role of epoetin alfa in preventing apoptosis and ischemic brain injury, as well as its activity in other non-erythroid tissues.”

Nearly all the data and studies on ESAs examine the clinical circumstances under which the medicine could safely raise hemoglobin levels and reduce the need for blood transfusions. That is because the purpose and function of the drug, and not the improvement of patient survival rates (although prolonged survival may be an ancillary benefit of maintaining normal hemoglobin levels via the use of ESAs). Hence the sudden declaration of CMS that there are no data demonstrating a survival benefit from ESA, even though this was never the intention of the ESA treatment, is like being indignant that a baseball card provides no information about soccer players. The fact is that ESAs do increase patients’ quality of life and overall survival, while reducing their need for blood transfusions and protecting them from the hemoglobin roller-coaster experience (Figure 2).

Similarly, CMS seems to be implying that it is not concerned whether ESAs reduce the pain and suffering that goes along with chemotherapy, regardless if a

patient needs more product or individual treatments than CMS deems “safe.” Its primary objective is ensuring that it does not pay for drugs administered at hemoglobin level above 10 g/dL because that is the minimum concentration of hemoglobin required to sustain normal bodily functions before blood transfusions become mandatory.

After shifting the terms of the debate entirely away from the purpose for which ESAs are used, CMS seeks to determine whether or not the use of ESAs in patients undergoing chemotherapy might decrease survival. To this end, CMS looks at the use of ESAs in the non-adjuvant and experimental setting, ignoring any data that portrays their impact on the reduction of transfusions or quality of life in chemotherapy.

Meta-Analysis: Pooling Data to Drown Out Treatment Effects and Highlight Safety Risks

Meta-analysis has become the tool de jour for highlighting the risks of medicines. That’s because pooling data allows researchers to divert attention from clinical differences in outcome from a treatment to another issue. However, as an article in the British Medical Journal noted, “if the process of pooling data inadvertently drowns clinically important evidence from individual studies, then a meta-analysis can do more harm than good.”

It is important to describe these studies, since CMS consistently claims the absence of data as a reason for denying reimbursement. CMS relies heavily on two studies and one meta-analysis (an analysis in which the results from several independent studies are combined using different approaches to address a related set of research questions) in forming its conclusion. The Henke, et al., trial focusing on head and neck cancer and the Breast Cancer Erythropoietin Survival Trial (BEST) in metastatic breast cancer are the best -known examples of ESA studies reporting an adverse outcome.

However, both these trials studied investigational ESA use to maintain hemoglobin levels higher than FDA-approved prescription information. Further, as one commentator noted: “Both these trials were heavily criticized for their trial designs. The Henke, et al., trial used a target hemoglobin concentration above that set forth in the product-label recommendations, for the ESA-treated patients, and did not account for factors such as cigarette smoking, which can adversely impact survival in patients with head and neck cancer.” The data from these two studies should neither be dismissed nor quoted uncritically.

Authors of the meta-analysis assert that the studies reported by Henke, et al., and the BEST trial had several experimental limitations, including baseline

imbalances and protocol violations. Thus, despite intensive reanalysis, the exact causes of poorer survival [rates] associated with epoetin EPA treatment in these studies remain uncertain.”

A more recent meta-analysis in the Journal of the American Medical Association that added unpublished trials to the studies surveyed in the analysis cited above evaluated rates (rates of venous thromboembolism events (deep vein thrombosis and pulmonary embolism) and survival rates for all studies as well as according to prospective inclusion of survival as primary or secondary outcome measures.” These studies varied widely in duration, tumor stage and protocol violations. And individually no one trial exceeded 400 patients assigned to treatment. Three of the larger studies were terminated because of failure to enroll patients. A similar analysis conducted of the off-label use of drug-eluting stents – involving some of the same researchers associated with the JAMA re-analysis – also find a slight increase in mortality, again without adjusting for clinical variation or severity of illness.

All of the studies involved efforts to boost hemoglobin levels beyond 13g d/L. Indeed, many of the larger studies that could conceivably skew the results of the new study were also stopped mid point because of higher mortality in people receiving ESAs. In one such study, the researchers concluded that the reason for the “difference in mortality between groups could not be determined from additional subsequent analyses involving both study data and chart review.”

Further, the JAMA study did not include a most recent survival study. This study, an “open-label, randomized, multicenter study in patients with MBC treated with anthracycline- and/or taxane-based chemotherapy” found no difference in survival and an increase in thrombolytic events in the control group but no difference in serious thrombolytic events. Adding this study, which included 231 patients in the control group would have produced a very different picture than the one presented by the JAMA article. As is often said about meta-analysis, it is only as good as the best study you include and results will reflect the inclusion bias of researchers. In this regard, reliance on meta-analysis to determine clinical practice or reimbursement is based on a statistical tool that in other sciences is limited to generate hypotheses, not decisions.

A number of clinical studies have examined the effect of erythropoietin analogs on cancer progression and tumor growth (for head and neck cancer, lung cancer, lymphoproliferative disorders), apart from its effect on chemotherapy-induced anemia. These studies (e.g., Hedenus, et al., 2005) have found no improvements in progression-free survival or overall survival.

The Danish Head and Neck Cancer Study Group trial (DAHANCA 10), for example, conducted a randomized trial that compared radiation therapy alone to radiation plus darbepoetin alfa in the treatment of advanced head and neck cancer. Darbepoetin alfa, also known as novel erythropoiesis-stimulating protein (NESP), has roughly a three-fold longer terminal half-life than epoetin alfa when

administered as a single weekly injection, which should be slowly adjusted to achieve and maintain a target hemoglobin level of 12 g/dL. It was believed that the associated increased oxygen level would make the tumor more sensitive to radiotherapy. However, tumor growth was significantly worse for the darbepoetin patients, and overall survival favored the non-darbepoetin patients, although this difference was not statistically significant (Figure 4). This study was stopped because the cure appeared to be worse than the disease.

A separate study of darbepoetin in anemic cancer patients who were not receiving chemotherapy focused on the reduction in red blood cell transfusions, while maintaining hemoglobin levels at 12 g/dL. Unfortunately, darbepoetin did not reduce the need for red blood cell transfusions. Furthermore, patients receiving darbepoetin alfa had a higher mortality rate compared to those receiving placebo. These studies were funded by the companies that developed the ESAs.

Investigators in DANCA 10 note, “In view of these uncertainties, treatment with epoetin or darbepoetin to achieve hemoglobin levels beyond that of anemia (i.e., level greater than 12 g/dL) among cancer patients is potentially harmful and should be considered only in an experimental setting.” CMS uses this and similar statements to assert that it should not pay for the use of ESA until it sees the results of careful, prospective trials controlled for the type of tumor, its stage of growth and cell cycle, type of cancer treatment, endogenous systemic or paracrine/autocrine erythropoietin production, and the presence of the erythropoietin receptor on tumors and as soluble elements in the blood [to determine] whether ESAs provide a meaningful clinical benefit for the various oncologic populations.”

However, CMS excludes the observation made by the authors that “the apparent excess of thrombi-embolic events [was] observed in several trials that enrolled nonanemic patients and/or targeted hemoglobin levels that *were higher than product-label recommendations.*” (Emphasis added) Excluding these trials, a meta-analysis of patients with anemia who receive label-recommended ESA dosages demonstrates increased survival. According to this earlier study, “suggestive, but inconclusive, evidence that erythropoietin may improve overall survival.” Most recently, the FDA announced two additional studies showing that patients with breast or advanced cervical cancers who received ESAs or higher to treat anemia caused by chemotherapy died sooner or had more rapid tumor growth than similar patients who didn’t receive the anemia drug. But here too, many of those who died did not reach a hemoglobin level of 12 g/dL) any some of those that did in fact lived longer.

In other words, in order to show risk in approved uses of ESAs in cancer patients, CMS has to emphasize the risks in experimental populations and not

put them in the context of many other studies. CMS offers no explanation for doing so, except to say that previous studies were never designed or powered to test ESAs for safety.

Safety Is a Value Judgment

CMS essentially makes a value judgment that safety is more important than other considerations when making drug-coverage decisions for drugs. It rejects the validity of most of the published ESA studies, claiming these studies lack adequate safety data. In essence, CMS seeks to limit its evidence-based review to information gathered by and for the Oncologic Drugs Advisory Committee (ODAC; Rockville, MD; www.odac.org). That explains why the CMS decision is at odds with all the other experts, including those convened by the FDA to review the safety of ESAs. In this vein, the National Cancer Institute Cancer Bulletin noted:

None of the recommendations offered by the FDA's Oncologic Drugs Advisory Committee was highly specific. The committee did advise FDA to evaluate all available and forthcoming data to determine: if the use of these drugs, often called erythropoiesis-stimulating agents, should be limited in patients with certain tumor types; whether a specific hemoglobin level should be established to trigger the drugs' use in asymptomatic patients; and whether limits should be placed on the drugs' use within a certain time frame after chemotherapy is completed.

Specifically, ODAC chairperson S. Gail Eckhardt from the University of Colorado Health Sciences Center (Denver; HYPERLINK "www.uchsc.edu") stressed that the committee should not be looking to return to the "dark ages" when transfusions of red blood cells were the primary supportive care option for anemic cancer patients."

Similarly, when an FDA advisory committee was dealing with the safety of using ESAs to boost hemoglobin levels of patients with chronic kidney disease, or in efforts to boost hemoglobin levels beyond 12 g/dL in dialysis patients, it did not seek to impose a target hemoglobin level or cap because there was no evidence that this value would be safe (i.e., in absence of "proof of no harm," proceed as if harm would ensue). Despite the lack of data concerning appropriate ESA dosing levels for individual patients, the committee was more concerned that one-size-fits-all hemoglobin target would lead to abrupt dose modifications.

Panelists argued that the label should emphasize the distinction between a target dosage and a ceiling dosage. "I voted no [on the 'one-size-fits-all' hemoglobin

level required for ESA treatment] because I think the words ‘not to exceed’ are inappropriate,” says John Teerlink, associate clinical professor of cardiology at the University of California (UC; San Francisco; [HYPERLINK "www.ucsf.edu" www.ucsf.edu](http://www.ucsf.edu)) and a standing member of the UC’s cardiovascular advisory committee. Similarly, several patients told the panel that “lower hemoglobin targets do not take sufficient account of individual variability. “Having eleven as the magic number wouldn’t be practical,” says Malazia Scott, who served as a temporary patient representative. “I speak from personal experience. I know if I had a hemoglobin level of eleven, I wouldn’t be sitting here with you today.”

CMS also ignores and misrepresents the practice guidelines of the specialty community. In its coverage decision, CMS stated that it is “unaware of robust clinical evidence that transfusion is indicated for patients whose hemoglobin levels are more than 10 g/dL.” Yet, evidence-based reviews of transfusion thresholds generally note 7 or 8 g/dL as the clinically appropriate transfusion threshold which is far below what are regarded as acceptable levels to protect patients against anemia .* Indeed,, studies have shown that initiating transfusion in chemotherapy patients at such a low baseline are more likely to require additional blood transfusions.

Meanwhile, as a recent review article on blood transfusions notes: Blood transfusion utilization continues to rise, yet it has never undergone prospective safety and efficacy testing. Recent data regarding oxygen delivery, microcirculation, and inflammation all point toward potential problems with allogenic transfusion. Outcome data from retrospective data bases are sobering, calling to question the present practices of red cell transfusion.” CMS has judged blood transfusions as safe as ESAs absent any prospective evaluation of the treatment alternative it claims it has compared en route to making its coverage decision.

Furthermore, CMS overlooked a body of evidence known as the Dosing and Outcomes Study of Erythropoiesis Stimulating Therapies (DOSE). DOSE, an ongoing registry of oncology patients treated in over 80 U.S. community clinics and hospital centers, conducted an analysis of more than 960 patients to determine the relationship between hemoglobin concentration, ESA treatment and the need for transfusion. The study showed that a significantly greater proportion of chemotherapy-treated cancer patients required transfusion when ESAs were initiated at baseline hemoglobin level of less than 10 g/dL, compared with baseline levels of 10-11 g/dL (Table 3).

Table 3. Pre-transfusion hemoglobin concentrations reported from an ongoing ESA registry in chemotherapy-treated cancer patients. Data from an ongoing registry, which reflects real world practice, reported that 19% of transfusion episodes occurred at a pre-transfusion Hb level of > 9 g/dL. In a subset analysis of the Medicare population from this registry, 23% of transfusion episodes occurred at a Hb level > 9 g/dL. Review of these transfusion events reveals that the majority have occurred in patients with symptoms of anemia, e.g. ,dyspnea, fatigue, etc and/or co-morbid conditions.

Table 3. Pre-transfusion hemoglobin concentrations reported from an ongoing ESA registry in chemotherapy-treated cancer patients.

Transfusion trigger (g/dL)	<7	7-7.9	8-8.9	9-9.9	10-10.9	11-11.9
Total number of transfusions (%) (n=314)	14 (4%)					
Medicare patients (n=150)	8 (5%)	47 (31%)	61 (41%)	22 (15%)	12 (8%)	0 (0%)

This analysis also reported significantly greater blood utilization per transfusion, greater hospitalization risk, longer hospital stays, and more frequent transfusions when ESA was initiated at a baseline hemoglobin level of less than 10 g/dL, compared with a baseline hemoglobin of 10-11 g/dL (Table 4).

Table 4. Proportion of patients transfused stratified by Hb at ESA initiation. In a new analysis of > 960 patients, a significantly greater proportion of chemotherapy-treated cancer patients required transfusion in those initiated on ESAs at baseline Hb < 10 g/dL compared with baseline Hb 10-11 g/dL. This analysis also reported significantly greater blood utilization in patients initiated at baseline Hb < 10 g/dL compared with a baseline Hb of 10-11 g/dL.

Table 4. Patient transfusion requirements based on hemoglobin concentration at ESA initiation.			
Baseline hemoglobin (Hb) level	< 10 g/dL	10-11 g/dL	p value
Proportion of patients requiring blood transfusion	31%	14%	< 0.0001
Blood utilization (Units/study patient)	0.89	0.44	< 0.0001

The NCD memorandum states that the clinical practice guideline, jointly published in 2002 by the American Society of Clinical Oncology (ASCO; Alexandria, VSA; HYPERLINK "www.asco.org" www.asco.org) and the American Society of Hematology (ASH; Washington D.C; HYPERLINK "www.hematology.org" www.hematology.org) recommended evaluating patients for the need for ESA therapy when the hemoglobin is at or below 10 g/dL. However, CMS only cited a part of the ASH/ ASCO guidelines which continued to say, "For patients with declining hemoglobin levels, but less severe anemia (those with hemoglobin concentration of less than 12 g/dL, but who have never fallen below 10 g/dL), the decision of whether to use epoetin immediately or to wait until hemoglobin levels fall closer to 10 g/dL should be determined by clinical circumstances."

The recommendation for use of epoetin in patients with baseline hemoglobin levels of 10-12 g/dL, based on clinical judgment, is premised on the assumption

that patients with specific co-morbid conditions face a higher absolute probability of anemia, or a higher risk of adverse events related to this degree of anemia, than do other patients with this hemoglobin concentration. Examples of patients at this higher degree of absolute risk, who may be considered reasonable candidates for ESAs, based on clinical judgment, include but are not limited to elderly individuals with limited cardiopulmonary reserve or patients with underlying coronary artery disease and symptomatic angina.

Meanwhile, ASCO and ASH expanded and updated their guideline in 2007 to include a similar medication, called darbepoetin, and to take into account the most recent clinical trial results. It notes that ESAs “should be used cautiously with chemotherapy or in clinical states associated with elevated risk for thromboembolic complications.” The Committee also cautions against ESA use for patients with cancer who are not receiving chemotherapy, since recent trials report increased thromboembolic risks and decreased survival rates under these circumstances.” At the same time, the guideline still preserves physician discretion to raise hemoglobin levels at which ESAs are administered to between 10 and 12 g/dL.

CMS also based its argument for imposing a one-size-fits-all dosing limit on studies that explored erythropoietin receptors (or EPO receptors), which were implicated in erythropoietin-stimulated tumor progression and survival. The impact of ESAs on tumor growth has been studied in vivo and in vitro for nearly fifteen years. Much of the precautionary concern is based on epidemiological studies or meta-analysis that are designed to generate questions about safety rather than answer them. Hence, the briefing document developed by FDA scientists for the May 2007 Oncology Drug Advisory Committee stated that “a direct relationship between the presence of erythropoietin receptors on tumor and tumor proliferation, in response to exogenous erythropoietin, has not been established. In vitro and in vivo data do not provide convincing evidence that erythropoietin promotes tumor growth and proliferation.”

Additionally, Eckhardt commented that CMS acted prematurely when it based its dosing decision on the hypothesis that the body’s response to EPO is regulated by EPO receptors. “There is a huge amount of conflicting science on [the EPO receptor] issue, so I don’t think that anybody can say anything definitive one way or the other, certainly not at ODAC.” While CMS cites a study by Henke to support the EPO receptor basis for restricting coverage, Henke concludes that it is “ethically and clinically unwise to guide EPO administration by hematologic parameters alone.”

What CMS Forgot to Mention: Lack of Transparency

One of the key weaknesses of the NCD is the lack of transparency regarding the risks and benefits of ESAs compared with those of blood transfusions. CMS assumes that blood transfusions are as or more effective, and as safe as ESAs, but does not provide evidence in support of this theory. However, no evidence exists to refute this theory either. Further, CMS fails to provide information about the risks and benefits of transfusions, as it does with regard to ESAs, for which an arsenal of discouraging data is offered. In recent correspondence between CMS chief medical officer, Barry Straube, and co-chair of ASCO's Government Relations Council, Joseph S. Bailes, Straube stated that CMS would reconsider an NCD review when new evidence is provided or when arguments are presented to prove that CMS materially misinterpreted existing evidence.

To help facilitate this continued review, Straub posed questions that facilitated the presentation of evidence supporting a conclusion other than that which CMS had submitted in the NCD:

What is the evidence that using ESAs intermittently to maintain hemoglobin levels above 10 g/dL results in increased appropriate transfusions or higher adverse outcomes over the current practice of continuous use of ESAs?

What is the evidence that using ESAs intermittently to maintain hemoglobin levels above 10 g/dL results in increased appropriate transfusions or higher adverse outcomes over the current practice of continuous use of ESAs?

What is the evidence that cancer patients undergoing chemotherapy have better outcomes from ESA therapy vs. transfusions?

Straube maintains that providing this information to CMS would ensure an open and transparent evidence review. However, a more-transparent review process would have looked at quality of life considerations and the relative risks and benefits of transfusions compared to those of ESAs, for senior citizens undergoing chemotherapy. We will examine these issues next.

Whose Life Is It Anyway? Why CMS Ignored Quality of Life Considerations

A concerted effort seems to be underway to suggest that there is no benefit in providing patients with ESAs in lieu of performing blood transfusions. A recent letter from the FDA to Congressman Pete Stark, Jr. (D-CA), asserts that "there is no evidence that ESAs result in improved survival, tumor control or health-related quality of life, at any hemoglobin level, in cancer patients undergoing chemotherapy."

In fact, the FDA letter reflects the agency's guidance that quality of life claims based on patient-reported outcomes can only originate from randomized clinical trials using validated instruments and achieving statistical and "clinically

meaningful” differences, versus observational studies in post-market environments. CMS is not required to adhere to FDA’s regulatory standard for making a quality of life claim and has exercised this freedom on many other occasions.

Such behavior raises the issue of selective use of evidentiary standards – behavior that, once again, is subject to the influence of unstated goals. Several other reviews, including a health technology assessment cited by CMS in justifying its coverage decision, state that ESAs provide significant quality of life benefits. Indeed, a principal reason that the ASH/ ASCO guideline includes a dosing range is to help patients to improve their quality of life and reduce transfusions as quickly as possible.

The European Organization for the Research and Treatment of Cancer (EORTC; Brussels, Belgium; HYPERLINK "www.eortc.org" www.eortc.org) 2006 update for the use of erythropoietic proteins may be considered in asymptomatic anemic patients with hemoglobin levels of 11.9 g/dL, provided that individual factors like intensity and expected duration of chemotherapy are considered. Patients whose hemoglobin level is below 9 g/dL should primarily be evaluated for the need of transfusions, potentially followed by the application of erythropoietic proteins.

The total body of evidence indicates that red-blood-cell transfusion requirements are reduced (see Figure 1), following treatment with erythropoietic proteins. Moreover, this analysis confirms that, following erythropoietic protein therapy, quality of life is significantly improved in patients with chemotherapy-induced anemia and chronic anemia who also have cancer. Similarly, according to a health technology assessment conducted for the National Health Service in the U.K., “Health-related quality of life data were analyzed using vote counting and qualitative assessment, and a positive effect was observed in favor of an improved health-related quality of life for patients on erythropoietin.”

Figure 1. ESAs Safe As Placebo In Chemotherapy Setting When Used By Oncologists To Achieve Hemoglobin Levels Above 10 g/dL

An extensive body of evidence supports that ESA use is safe and effective when used in accordance with the FDA-approved label. Reports of a placebo-controlled trial of epoetin

alfa in 330 cancer patients receiving chemotherapy showed a median overall survival (OS) of 11.2 months for placebo-treated patients compared with 10.4 months for the epoetin alfa group (P= not significant). This difference was not considered significant. The study, which was intended for FDA registration purposes of weekly epoetin alfa dosing, did demonstrate significantly fewer transfusion requirements and better Hb changes in the epoetin alfa-treated group compared with the placebo group.

Is Transfusion Really As Safe and Effective? CMS Has Some Explaining to Do

At the heart of the CMS decision is an unspoken assertion that there is a safer and equally effective alternative to ESAs for raising hemoglobin levels to 10 g/dL: blood transfusion. Ironically, by failing to consider the relative risks of transfusions – because it is assumed that they are safe – the CMS preference for transfusions suffers from the same lack of adequate data needed to demonstrate “proof of no harm.”

In spite of what one would think, the practice of blood transfusion is not evidence-based. It was developed throughout the world, mostly empirically, since the late 1940s, with little or no published studies to validate the procedure or its risks and benefits. In the past 20 years, a concerted effort to improve the body of evidence regarding transfusions, fueled in part by the increasing numbers of lawsuits related to transfusion medicine, has materialized through prospective, well-controlled randomized clinical trials and consensus conferences.

The basic principles behind evidence-based medicine have been fairly well-known for many years. However, the concept of and approach to integrating evidenced-based decision-making into clinical practice on a day-to-day basis has only evolved over the past 15 years. Indeed, there are merely 56 randomized citations in Medline, an online database of peer-review medical literature ([HYPERLINK "www.pubmed.com" www.pubmed.com](http://www.pubmed.com)), that discuss blood transfusions and chemotherapy vs. 1,039 citations that discuss ESAs and chemotherapy.

Still, in its reference to transfusion as an alternative to ESAs, CMS failed to include evidence in the clinical literature about the risk associated with allogeneic blood transfusion. In this procedure, blood is obtained from a donor as opposed to autologous blood transfusion, where the donor and recipient are one and the same. Evidence from a variety of sources indicates that allogeneic blood transfusions can induce clinically significant immunosuppression in recipients. This clinical syndrome is also known as transfusion-associated

immunomodulation, or TRIM.

Clinical trials have shown that red-blood-cell transfusion, where the red blood cell components of blood from a donor are separated, isolated, and transferred to the patient, is correlated with an increased frequency of postoperative infection. Infections can occur when the patient has been given many transfusions, which causes the body to develop antibodies (immune cells) that react against donated blood cells, so that transfusions do not work well.

The acknowledgment that TRIM can increase morbidity and mortality in allogeneically transfused individuals has become a major concern for those involved in transfusion medicine. However, based on available randomized, controlled trials, the theory that TRIM predisposes recipients to increased risk for bacterial infection is still unproven.

Blood transfusion during primary radiotherapy for cervical cancer profoundly alters the magnitude and characteristics of radiation-induced immunosuppression, which in turn regulates tumor growth. Milasiene V, et. al., reported that red blood cell transfusions were associated with increased levels of interleukin-6 (IL-6) that could contribute to cancer recurrence. And Santin, et al., found that routine blood transfusion in anemic, cervical cancer patients does not improve outcome; transfusion on a regular basis may represent an independent variable that is predictive of diminished survival during primary radiation treatment for cervical cancer.

Since CMS deemed it appropriate to consider ESA-related safety problems that occurred in non-oncologic settings, such as surgery, it is noteworthy that blood transfusions have been linked to higher rates of mortality among people undergoing surgery. In addition blood transfusion in the setting of acute coronary syndromes (ACS) is associated with higher mortality, and this relationship persists after adjustment for other predictive factors and timing of events, according to the results of a post-hoc analysis of data from three large international trials published in the *Journal of the American Medical Association* in 2004 in which patients were grouped according to whether or not they received a blood transfusion during the hospitalization.

"Patients hospitalized for ACS are at risk of developing anemia acutely as a consequence of bleeding," explains Sunil V. Rao, M.D., from the Duke Clinical Research Institute in Durham, North Carolina ([HYPERLINK "www.dcri.duke.edu" www.dcri.duke.edu](http://www.dcri.duke.edu)). These patients are more than twice as likely to die during their first 30 days of hospitalization if they receive a blood transfusion to treat blood loss or anemia, or both, compared to non-transfused patients. A possible cause for increased mortality is that transfused blood may

stimulate an immune response that can exacerbate existing coronary artery disease (CAD). In addition, transfusion blood to anemic patients with ischemic heart disease (or myocardial ischemia, a disease characterized by reduced blood supply to the heart) may theoretically increase oxygen delivery to the cells and improve outcomes. However, there is no definitive evidence to support such a practice.

A third study of patients who underwent coronary artery bypass grafting found that five-year mortality was more than twice as high in those who received perioperative blood transfusions than in those who did not (15% vs. 7%, respectively). Even after the authors adjusted the data for demographic variables and co-morbidities, transfusion was still associated with a 70% rise in five-year mortality. These findings may seem counterintuitive, given the many investigations that have depicted a strong relationship between higher hemoglobin levels and better outcomes. However, achieving these hemoglobin levels via transfusion may be counterproductive to improving survival.

A randomized trial was conducted to assess the impact of blood transfusions on respiratory support, mortality, and long-term survival after curative surgery for colorectal cancer. Non-transfused patients had a significantly lower proportion of prolonged hospital stays and a dramatically increased survival rate, compared with transfused patients. Data from an ongoing registry of real-world ESA studies bear this out (Figures 2 and 3). Similarly, in a large, observational study of patients undergoing colorectal cancer resection, it was found that perioperative allogeneic blood transfusion was associated with an increased risk of thromboelitic complications in women, but not in men.

Figure 2: ESAs Reduce the Need for Blood Transfusions in Cancer Patients

These data also illustrate that blood transfusions are often an inferior substitute to ESAs for Hb maintenance. While blood transfusions readily correct the symptoms of anemia, this effect is transient. ESAs typically require 3-4 weeks of dosing to stimulate sustained erythropoiesis, and patients should be appropriately maintained on ESAs if chemotherapy is ongoing to avoid the cumulative myelosuppressive effects of cancer regimens. Accordingly, withholding ESA treatment because an Hb may transiently fluctuate above 10 g/dL during chemotherapy could result in Hb levels decreasing to the point where a patient would require transfusion support while waiting for resumption of ESA treatment and a sustained erythropoiesis response.

Figure 3: ESAs Maintain Hemoglobin More Reliably Than Repeated Blood Transfusions

Figure 3. There are data on the inability of blood transfusions to sustain Hb levels over time. The chart above depicts Hb levels over time in 11 multiple myeloma patients treated with either 150 IU/kg TIW epoetin alfa or blood transfusion. The vertical arrows indicate time points of allogeneic blood transfusion. The 'without epoetin alfa' line shows patients not receiving epoetin alfa who are repeatedly subjected to allogeneic red blood cell transfusions. (Couture 2005). It is apparent that blood transfusions provide only transient relief and fail to maintain Hb levels compared to continuous epoetin alfa therapy.

The CMS decision to restrict ESAs based on safety concerns was presented without publicly disclosing the risks associated with blood transfusions. Ironically, the argument in favor of limiting reimbursement for ESAs because the drug's safety is uncertain in certain populations comes to "center stage" at a time when CMS has announced it would not restrict payment for off-label (outside the categories approved by the FDA) use of drug-eluting stents. This decision was based on data from an ongoing registry, which reflects real world practice and observational studies that looked at both safety and quality of life, and show that drug-eluting stents decrease mortality and improve the quality of life of patients receiving them.

The FDA and Medicare had indicated they were concerned about the "off label" use of drug-eluting stents – they haven't been rigorously studied in patients with a history of heart attacks, small arteries, or multiple clogged arteries, although coated stents are used in these applications.

The FDA panel concluded that there was insufficient evidence to assess the risks and benefits of stents in patients with off-label applications, even though these individuals constitute roughly 85% of all stent patients, according to various estimates. So, while the FDA hasn't approved the marketing of such stents for off-label patients, Medicare generally pays for such uses. Last year, Medicare spent \$4.3 billion on coated-stent operations.

Effect on Blood Supply

Oncologists regard ESAs as an integral component of treatment protocols for cancer patients undergoing radiation and chemotherapy. An injectable biologic produced via recombinant DNA technology, ESA is a synthetic form of erythropoietin, a protein made in the body that stimulates the production of red blood cells, which contain hemoglobin (an oxygen-bearing protein). ESA works similarly to its natural counterpart to increase oxygen-carrying blood in patients who are anemic, due to chemotherapy treatments. The alternative to ESA therapy is blood transfusion – a more invasive process that poses various health risks, and, in the case of the NCD policy, could measurably reduce the nation’s blood supply, according to recent estimates.

Where will people get all the blood they need to replace the ESAs that CMS wants to deny them? The nation’s blood supply is a limited resource. Based on the 2005 Nationwide Blood Collection and Utilization Survey Report, 8.5% of surveyed hospitals reported postponement of elective surgeries on one or more days in 2004 because of blood- inventory shortages. In 2004 – the most current data available – a mere 4.5% more blood was available for transfusions than was used. This is the smallest margin ever measured.

The existing shortages are already putting pressure on the nation’s blood supply. “Blood suppliers aim to have a three- to five-day supply on hand to distribute to hospitals in case of emergencies.... [But,] at George Washington University Hospital (GWUH), officials came close to canceling non-emergency operations several times this summer,” says Dr. Gerald Sandler, the director of transfusion medicine at GWUH. “The hospital counts on having at least 130 units of this blood on hand. But, there have been times in the past few days where we’ve had only eight units. This is the worst blood shortage that I have experienced since I began directing transfusion services in 1968,” Sandler says, citing overseas travel restrictions as a major factor.

OrthoBiotech performed a modeling simulation using real-world data from an ongoing registry to estimate the impact that limiting the use of ESAs in chemotherapy-induced anemia would have on the U.S. blood supply. Upon analysis, Ortho Biotech found that up to a third of the marginal U.S. blood supply would be required to cover the incremental demand for blood resulting from a 25% decrease in the use of ESAs. Nearly two-thirds of the marginal blood supply could be compromised by a 50% reduction in the use of ESA to treat patients with chemotherapy-induced anemia.

Respondents in a survey conducted by the Association of Community Cancer Centers (ACCC; Rockville, MD; HYPERLINK "www.accc-cancer.org") expressed concern that the NCD will impact the nation's blood supply and hospital resources. As a result of the proposal by CMS, more patients with myelodysplastic syndrome and chemotherapy-induced anemia will require blood transfusions.

The ACCC survey measured just how much of an increase in blood transfusions would strain hospital resources and services, such as blood supply, bed space, personnel, and equipment (Figure 4). Of the 650 ACCC member hospitals that received the survey, 115 sites responded, including rural (20%), urban (39%), and suburban (41%) hospitals. The survey showed that 40.9% of respondents said that a 30% increase in demand for blood transfusions would cause problems in carrying out normal transfusion services. Another 16.5% said that an increase of 10% or less would cause problems, and 21.7% said any increase would result in problems.

Figure 4. Percentage of blood transfusions that would potentially cause a problem in hospitals if current proposed NCD on ESAs is adopted. Association of Community Cancer Centers, ACCC Hospital Survey, 2007.

Wall Street analysts have recently reported that the CMS Proposed Decision Memo on ESAs as written may decrease ESA sales by 25%–70%. Such changes in ESA utilization are associated with an incremental demand of 118,000–237,000 units of blood (Data on file, Ortho Biotech). This added pressure on the blood supply could be even greater, due to regional variation in the number of available units and the variable frequency of donation.

Securing a more-abundant supply of blood would be a time-consuming, costly endeavor. At the very least, it would increase blood-banking and acquisition expenditures. A possible, but less probable, result would be the weakening of safety and screening standards that are used to process blood donations. The CMS decision would place added strain on the blood supply, expose patients to delays in care, and drive up the total cost of care, as the collateral impact of delays in chemotherapy and surgery are realized. CMS failed to consider these health-related and financial risks during its decision-making process.

Impact of the Precautionary Principle on Health and Quality of Life of Cancer Patients

Application of the precautionary principle to the ESA coverage decision for cancer treatment could increase the death rate among Medicare patients. A study conducted by Frank Lichtenberg of Columbia University (New York; HYPERLINK "www.columbia.edu" www.columbia.edu) using the SEER Medicare-linked database looked at the effects of innovative chemotherapy techniques and other factors on cancer patients grouped into four major categories by cancer type (colorectal, lung, breast, and prostate), using longitudinal, state-level data in nine states during the period 1991-2003. An analysis of normalized data representative of 12.7 years of that study (1991-2002) revealed that the use of novel chemotherapy procedures implemented during that period increased the life expectancy of cancer survivors by 8-12 months, or about 10%.

Newer chemotherapy drugs have reduced mortality and increased survival. This conclusion is consistent with other studies that Lichtenberg has conducted, all of which suggest that the overall, long-term increase in life expectancy and health of cancer patients is due largely to use of newer drugs. Treatment plans that include more-aggressive agents – which are also more likely to cause anemia – in new combinations and with more frequent dosing schedules are primarily responsible for this positive outcome. ESAs have arguably made these novel treatments more tolerable and possible.

Ultimately, CMS's new approach to ESA reimbursement has created a fourth barrier between medical innovation and patient care. It demands randomized clinical trials to determine the safety of ESAs but can and may use these data to deny reimbursement and access to other cancer drugs. By setting up the precautionary principle as the new standard for reimbursement, CMS has established a precedent for "evidence-based medicine" that will inevitably delay access to new drugs with proven benefits on productivity, survival and well-being.

If CMS were to adopt a reimbursement policy that pays only for products that demonstrate – through randomized trials – quality of life benefits, it would eliminate reimbursement of hundreds of billions of dollars' worth of services that are or would have been covered under the current policy. Perhaps that is the point. The shift to the precautionary principle as the basis for NCD rulings, combined with the requirement for real-world data as "proof of no harm" would become the new "gold standard" for determining a treatment's health-related and quality of life benefits.

CMS Tries To Be 'NICE'

The use of “incomplete data” or “lack of real-world data” as a rationale for denying reimbursement is a policy-based decision, not a scientific one. What passes for the “right data” is a function of the political or procedural goals set by the organization that is reviewing the data. CMS claims that the coverage decision with respect to ESAs is evidence-based. Yet, the evidence CMS has selected reflects a larger policy goal: increase control over the practice of medicine by employing a process of healthcare technology assessment called “comparative effectiveness.”

Medicare’s Payment Advisory Commission, also known as MedPac (Washington, DC; HYPERLINK "<http://www.medpac.gov>" www.medpac.gov), describes comparative-effectiveness analysis as a comparison of the clinical effectiveness of a service or product (e.g., drugs, devices, medical services, diagnostic tests, and diagnostic and surgical procedures) against that of its alternatives. Bearing this in mind, CMS claims there is not enough credible, empirically based information about alternative treatments against which healthcare providers and patients can compare concurrent data or feedback; in turn, CMS maintains that it cannot make informed decisions about alternative diagnostic and treatment services for [even] the most-common clinical conditions. Many new services assimilate quickly into routine medical care, with little or no basis for determining whether they outperform existing treatments. If more information were available about the value of alternative health strategies it could improve the quality of, and reduce variation in, medical-treatment procedures.”

MedPAC predicted that if CMS were to base its reimbursement decisions on comparative-effectiveness studies, it would lead to increased federal administrative spending relative to current law due to a greater capacity to examine the comparative effectiveness of health care services; and improved decision-making by patients, providers, and payers by making information on the comparative effectiveness of health care services more accessible.

According to U.S. Congressional Budget Office Director Peter Orszag, “Perhaps the best-known example of comparative effectiveness is the coverage-determination process applied by the National Institute for Health and Clinical Excellence (NICE; London; HYPERLINK "www.nice.org.uk" www.nice.org.uk). This entity, which was established in 1999 as part of the U.K.’s National Health Service, provides guidance on the use of new and existing medicines, procedures and treatments, and on appropriate treatments for specific diseases. With a staff

of about 200 and an annual budget of about 30 million pounds (roughly \$60 million), NICE bases its determination for coverage on systematic reviews of existing research – i.e., conducts evidence-based reviews – and does not fund new clinical trials or other forms of primary data collection.”

CMS emulated NICE in its coverage decision for ESA when it selectively referred to one meta-analysis to describe impact of ESAs on survival, but omitted the impact of ESAs on quality of life. A closer look at the NICE methodology reveals how CMS anticipates making coverage decisions in the future. NICE has issued comparative-effectiveness decisions for many new medicines. However, NICE was intended to serve as an independent arbiter of cost-effective strategies for the U.K.’s National Health Service (NHS) – a role from which CMS is supposedly precluded by U.S. law. “But, many stakeholders that are affected by NICE’s recommendations no longer believe [NICE] agency is independent. Rather, they see it as an agent of government, tasked with deciding when the NHS should say ‘no’ to treatments that patients want. This drop in confidence is based partly on the perception that much of the agency’s guidance is negative, flies in the face of medical evidence and clinical practice elsewhere, and often is based solely on grounds of cost, not efficacy.”

The drugs that NICE has rejected or rationed include Gleevec(R) (imatinib mesylate), a medication manufactured by Novartis AG that disables certain cancer cells with a precise attack, while leaving normal cells uninjured. Gleevec is thought to work by blocking the pathway of a particular errant enzyme called KIT. This protein via signals to the nucleus directs the cell into abnormal overdrive, thereby creating the uncontrolled growth of gastrointestinal stromal tumors.

In 2001, Gleevec became first-line therapy for GIST in the U.S. It was the premier nonsurgical, effective treatment option against GIST tumors, which are known to spread readily and are generally fatal within 20 months. During Phase II clinical trials, 59% of the 148 patients taking Gleevec achieved remissions that lasted from 4.5 to 10 months, the latter being when the study ended; at that point, the cancer had not returned. To the outrage of most cancer specialists, the NICE decided after three years that it would use Gleevec as a last resort, in a limited dose. NICE took Gleevec away from patients who had some tumor sites that were responding to treatment, but some tumor sites that were not.

NICE also recommended against paying for Herceptin to treat metastatic breast cancer, as well as other drugs used to treat osteoporosis, Alzheimer’s disease, and multiple sclerosis, based on comparative effectiveness reviews. Independent review agencies in Australia, New Zealand, and Canada have done the same. The institute did not regard new drugs as clinically less effective than older

drugs. However, any additional benefits the new drugs provided, compared to existing treatments, were not commensurate with their higher costs – and were simply not worth paying for.

Similarly, CMS decided that ESAs are not necessarily less clinically effective than transfusions; they are just not worth paying for to achieve a hemoglobin level higher than that considered necessary and safe for all Medicare patients. CMS's ESA ruling, the product of an evidence-based review in which CMS found insufficient data proving no harm, combined with the lack of transparency in evaluating available information, is no different than the Hematocrit Audit Policy of 1997, which slapped a hemoglobin quota on all Medicare patients for cost-containment purposes. In the absence of transparency, how can patients be sure that CMS is not being self-serving in its technology assessment?

Two Tiers of Cancer Care

Cancer doctors across America are stunned at the government's ruling to restrict anemia-management protocols for cancer patients. It interferes with the practice of medicine, they say. US Oncology, the nation's leading oncology network representing over 1,100 oncologists across the country, maintains that the legislation creates a two-tiered system of cancer care in America, and potentially forces many cancer patients already receiving chemotherapy treatment to undergo avoidable blood transfusions.

This is true in one important respect: The coverage decision creates two separate approaches to health care – one in which doctors who follow the FDA or EMEA label are in control of medical decisions, and the other in which CMS is in charge of making such determinations. Meanwhile, Medicare beneficiaries with cancer would be forced to undergo chemotherapy without adequate treatment to avoid blood transfusions. It should come as no surprise when, a year from now, someone is conducting a study about how the CMS decision saved money on ESAs, only to drive up costs and risks somewhere else.

Further, regardless of whether an individual has other illnesses that would render transfusions risky, costly or inconvenient, Medicare will only pay for beneficiaries with hemoglobin levels up to 10 g/dL and for a certain number of ESA treatments, even if hemoglobin levels are persistently below 10 g/dL. Because ESAs are important in keeping patients on more aggressive cancer-fighting products, Medicare beneficiaries could lag in access to new

combinations of drugs. That's because as private insurers follow Medicare's lead in applying the precautionary principle to ESAs and other products, physicians and health technology firms will be more likely to launch new treatments in the private sector first, and only then seek Medicare reimbursement.

In October 2007, Aetna Inc. (Hartford, CT; [HYPERLINK "www.aetna.com" www.aetna.com](http://www.aetna.com)), one of the nation's largest insurers, quietly changed its reimbursement guidelines for two of Amgen's anemia drugs, echoing Medicare's new tighter reimbursement policy for the medicines. Aetna is the largest private insurer to make this move, and analysts expect others to follow suit. "That could seriously harm Amgen's financial outlook because payments by private insurers account for half of the company's sales among cancer patients," says Bear, Stearns & Co. biotech analyst Mark Schoenebaum.

Aetna's new policy is slightly less restrictive than Medicare's but severe nonetheless. It does include an exception for patients with higher hemoglobin levels who have demonstrated anemia symptoms. Another insurer, Blue Shield of California, attempted to change its policy during the summer of 2007 to restrict dosages of the anemia drugs, but partially reversed its decision weeks later after receiving complaints from members and some doctors.

Hence companies will have another reason not to enter the regulated federal market. Even trying to figure out how to rectify new ESA dosing schedules with CMS policies will discourage adoption in the Medicare program.

Finally, Medicare patients may apply secondary private insurance benefits towards the difference between what CMS covers and what they and their physician deem the optimal ESA treatment plan. However, since CMS is the primary insurer, its policies prevail in billing. Medicare determines what is appropriate for payment to a physician for a service, based on the physician's and his or her colleagues' histories of charge. Further, Medicare limits the maximum fee that a non-participating physician may charge a Medicare beneficiary to 115% above the Medicare-approved amount. The physician is prohibited from collecting the difference or balance between his/her regular fee and the balance billing limit. Basically, CMS is not averse to patients receiving ESA treatment beyond what CMS covers, as long as the physicians are willing to pay for it out of their own pockets.

A Shift in Technology Assessment Will Require a Shift in Values and Policy

The CMS approach to technology assessment is similar to that taken by some of

the staunchest critics of the FDA regulatory process and drug companies over the past decade. These critics maintain that the reason most drugs appear safe and efficacious is that the people in charge of drug testing and approval have not been collecting and analyzing enough data with the statistical power to detect safety problems, or to compare the effectiveness of two similar treatments. Against this backdrop, CMS, in an unprecedented demonstration of rule-making, claims that previous studies in which ESAs were used were not sufficient to uphold its new safety standard – “proof of no harm.” In other words, any evidence of a potential adverse event would be considered a demonstration of possible harm. Critics of the principle argue that it is impractical, since every implementation of a technology carries some risk of negative consequences. Proponents counter that the principle is not an absolute rule, but rather a conceptual tool to clarify arguments, and especially an issue of where the burden of proof lies.

In some applications, the Precautionary Principle may cause more harm than it alleviates. This is because when it is applied, people are more acutely aware of negative outcomes than they are positive outcomes. Because of this effect, a drug that brings great health benefits may be ruled out by the Precautionary Principle because of its potential for severe negative impacts, leaving the overriding positive benefits unrealized.

The Paralyzing Principle: Does the Precautionary Principle Point Us in Any Helpful Direction?

Even worse, CMS appears to be taking the stance that no additional reimbursement of ESAs will be made in the absence of data from randomized clinical trials. CMS states it will not pay for any use of ESA outside of the coverage parameters until it sees the results of “...careful, prospective trials controlled for the tumor, tumor stage, and perhaps tumor cell cycle, cancer treatment, and perhaps endogenous systemic or paracrine/autocrine erythropoietin production and the presence of erythropoietin receptor on tumors and as soluble elements in the blood” to determine “whether ESAs provide a meaningful clinical benefit for the various oncologic populations.”

According to this new standard, ESAs would be one of several treatments to be rationed. None of the conventional technologies used to measure patients’ response to treatment – including the use of biomarkers – would be deemed acceptable. Only randomized trials would be a suitable means of generating sufficient evidence to establish drug response or effectiveness. Pharmaceutical companies that manufacture biotech drugs may be negatively affected by the

precautionary principle, especially since fast-track FDA approval of new biotech medicines relies on the use of biomarkers in lieu of time-intensive clinical trials to show efficacy and safety. But, they would have bigger problems if one of their blockbuster drugs received FDA approval, based biomarker data, and was later found to be unsafe because CMS invoked an entirely different standard for establishing safety to justify not paying for new products.

Clearly, the impact of CMS's national coverage decision and its far reaching effects can impact the biotech playing field, the hospital community, and the individual in need of help. Policymakers' desire for comprehensive and definitive evidence of clinical effectiveness in the Medicare coverage process should not result in inappropriate government controls over the practice of medicine. The development of increasingly stringent evidentiary review criteria does not necessarily translate into better or more appropriate coverage decisions or patient care. Ultimately, decisions about how best to practice medicine should remain the clear domain of practicing physicians in consultation with their patients.

The shift in evidentiary standards at CMS reflects a shift in thinking about medical innovation. It is designed to centralize clinical decision-making in the hands of government bureaucrats at the expense of patients and physicians. It replaces data that capture significant patient variation with evidence that is derived from large, randomized trials, which result in one-size-fits-all decisions. CMS is using administrative tools to ensure it pays for the least amount of product. But, in the end, the money CMS saves will be squandered somewhere else, as it tries to undo or control the damage caused by its cost-saving actions.

A better approach would be one that focuses on setting appropriate ESA-dosing levels for a wide variety of patients (e.g., patients with heart disease, kidney failure, or chronic anemia) and cancer types. Traditionally, drug manufacturers have conducted research focused on whether or not ESAs worked in a variety of clinical settings. Now, the medical community has a wealth of data about these medicines, but little knowledge about how to use them to improve the health and productivity of every individual. CMS would play an instrumental role in closing this gap.

Part of CMS's strategy should be finding a model, such as the FDA's Critical Path Initiative, which applied 21st century science to accelerate the development of personalized medicine. CMS should create a similar enterprise to apply new approaches to data analysis and clinical reviews, thereby promoting patient-centric insurance and healthcare. For example, CMS should consider the practice guidelines that are developed by professional medical societies or other respected organizations because they constitute important recommendations that

are derived from evidence reviews. Also, when clinical evidence is generated through the most rigorous of clinical trials, CMS should rely on that evidence and issue a Medicare coverage determination consistent with that evidence, in a timely fashion. Coverage policies may be revised, as additional evidence becomes available.

Prompt coverage permits the maximum contribution of medical therapies to society. It enables the improvement of patient health outcomes, while facilitating continued clinical research in routine, real-world practice settings, under a wide variety of circumstances, and in patients with various coexisting conditions. This generates the kind of practical clinical knowledge and experience that is useful in gaining a clear understanding of long-term effectiveness and clinical value. Further, it provides prompt access to medical therapies for patients and providers. Access should be based on what combination of genetic, clinical, and demographic factors would keep people healthy, improve their health, or prevent disease. HHS has invested in electronic patient records and genomics. Encouraging CMS to cover services based on patient-level needs and value would complement such efforts.

CMS has the ability to start such an initiative and no excuse not to. It funds many demonstration projects designed to manage disease and improve outcomes. Medicare Advantage is migrating towards a prevention-and-risk-adjustment payment model that will be able to access patient data, as outlined by several initiatives to now underway building electronic-record resources. Under the authority of Section 1862(a)(1)(E), the NCD process may cover an item or service if there is a pre-specified process for gathering additional data about that item or service, and if the safety and well-being of the beneficiaries, such as those who participate in certain clinical trials, are protected under the terms of and during this process. With such authority, CMS, in the absence of its own evidence, has ample leeway to request and obtain additional data without radically disrupting clinical practice.

Recommendations

Although the value-based approach to an evidence-based review coverage is still, but achieving it is not difficult. It requires personalized evidence about what works. CMS could take the following steps to obtain such information and improve the transparency and scientific integrity of its decision-making activities:

CMS should initiate a Critical Path for comparative effectiveness, similar to that which the FDA developed for drug approval and development. "The Critical Path Initiative is FDA's effort to stimulate and facilitate a national effort to

modernize the sciences through which FDA-regulated products are developed, evaluated and manufactured.” CMS needs to initiate, in a manner that is as transparent and as collaborative as that undertaken by the FDA, a national effort to modernize the scientific information used to determine the clinical value of treatments. Just as the key scientific insights guiding the FDA Critical Path are genetic variations and biomedical informatics that predict and inform individual responses to treatment, CMS needs to establish a process to incorporate knowledge and tools that personalize evidence of response in its decisions.

CMS should consider, to the fullest extent possible, using its authority with regard to the consideration, collection, and review of evidence related to medical treatment, when making coverage determinations. This includes consideration of research grants and partnerships with industry, as well as communication with the FDA, NIH, and the new Reagan-Udall Critical Path Institute to “harness the potential of bioinformation used to evaluate and predict safety, effectiveness, and value of treatments for each patient.” Instead of focusing on coverage decisions, CMS should identify opportunities and develop tools that foster clinical decision-making based on new science.

CMS should in cooperation with the Agency for Healthcare Research and Quality ([HYPERLINK "http://www.ahrq.gov" www.ahrq.gov](http://www.ahrq.gov)) should bring together all stakeholders to create a list of approaches to promote the development of patient-centric information on outcomes. This effort can draw on the example of the FDA which has put together a “Critical Path Opportunities List” ([HYPERLINK "fda.gov/oc/initiatives/criticalpath" fda.gov/oc/initiatives/criticalpath](http://fda.gov/oc/initiatives/criticalpath)) in cooperation with many interested parties. The opportunities list provides 76 concrete examples of how new scientific discoveries – in fields such as genomics and proteomics, imaging and bioinformatics – could be applied during medical product development to improve the accuracy of the tests used to predict the safety and efficacy of investigational medical products.

CMS should develop a similar list that shows how tools, such as electronic patient records, could improve the predictive and prospective nature of medicine. For instance, the Dosing and Outcomes Study of Erythropoiesis-Stimulating Therapies (D.O.S.E.) Registry provides data on outcomes of cancer patients in hospital and community based cancer centers. Such data can be used by physicians to improve patient outcomes and reduce adverse events. Further, use of observational cohort studies – so-called practical clinical trials – can help to improve patient outcomes in highly specific settings, as opposed to efforts to use average findings from randomized trials that exclude patient differences to make a dosing decision that affects millions without regard to such variations. CMS has changed reimbursement policy in response to such practical trials.

As a first step, CMS could use the reopening of the ESA coverage decision as example of how to achieve a more targeted and patient-centered protocol for ESAs in treating chemotherapy-induced anemia. A list of opportunities may be generated around this particular issue, with continued coverage of an investigational medical product being dependent on the developers' participation in Critical Path activities.

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