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To: Federal Coordinating Council on Comparative Effectiveness Research

June 10, 2009

Submitted electronically at <http://www.hhs.gov/recovery> and via e-mail to CoordinatingCouncil@blseamon.com

The American Society of Hematology (ASH) appreciates the opportunity to comment on Comparative Effectiveness Research (CER) to the Federal Coordinating Council (Council). ASH represents over 16,000 clinicians and scientists committed to the study and treatment of malignant and non-malignant blood and blood-related diseases such as leukemia, lymphoma, sickle cell disease, anemia and hemophilia.

ASH commends the Council for creating a public forum that underscores the importance of input from a broad range of stakeholders interested in priorities for CER. The Council's charge is consistent with ASH's mission to promote the understanding, prevention and treatment of blood disorders, and improve healthcare and patient outcomes with hematologic disease.

ASH believes that timely CER on the following topics will have the highest impact in hematology based on prevalence, disease burden, variability in outcomes in diverse populations and costs of care. Research in these areas has the potential to address the gaps in knowledge and uncertainty within the clinical and public health communities, ultimately leading to improved quality of care, outcomes and cost-effectiveness.

I. Management of Patients with Sickle Cell Disease (SCD).

The survival of children with SCD has improved with early identification of affected infants and enrollment in comprehensive pediatric hematology programs. However, there is a paucity of comparable adult-oriented programs and the growing young adult sickle cell populations face ongoing challenges in obtaining effective and comprehensive care. CER should evaluate health care transition training programs for adolescent patients. Many adult patients do not have access to physicians with expertise in sickle cell disease on an ongoing basis. There is a need to evaluate alternative medical care models for patients in the community setting. Examples include co-management with primary care physicians and utilization of telemedicine.

The few randomized clinical studies that have been performed addressing management of patients with SCD have had high impact on improving outcomes. Observational studies have also had major influence on clinical practice (*e.g.*, treatment of acute chest syndrome). There are opportunities to use CER to identify optimal approaches to encourage the adherence to proven preventive and treatment interventions. Administrative and clinical data sets such as state Medicaid claim and hospital discharge files would provide useful resources to assess current practices and measure outcomes of interventions. The following topics are examples to be considered:

- A. *Pain management.* The utility of clinical pathways in the outpatient, emergency department, and inpatient settings needs to be addressed. CER analysis of multidisciplinary and multimodality approaches to pain management for patients with SCD compared with conventional pharmacological therapies would provide opportunities to identify treatments resulting in improved patient quality of life and cost-effectiveness.
- B. *Hydroxyurea therapy.* Hydroxyurea therapy is underutilized in the management of symptomatic adult patients. CER can be employed to evaluate programmatic interventions at the patient, provider, and health care system levels to enhance appropriate use of hydroxyurea therapy.
- C. *Red blood cell transfusions.* Guidelines are available for the use of transfusions in the management of sickle cell complications but they are based on limited data. CER can be used to address questions such as the extent of phenotype matching of red cells used for chronic transfusion and techniques of transfusion administration (simple vs. exchange) for specific acute indications.
- D. *Clinical decision support tools.* Adults often receive their care from physicians with few sickle cell patients in their practices (*e.g.*, community based hematology/oncology and primary care physicians). Management of sickle cell-related issues such as hydroxyurea therapy and health maintenance (*e.g.*, screening for pulmonary hypertension, renal disease, ophthalmologic complications) can be challenging in these settings. CER can be employed to address the utility of clinical assessment tools, electronic health record reminder systems, and other approaches to optimizing receipt of appropriate intervention.

II. **Specialized Challenges in Thrombosis.**

Insertion of inferior vena cava filters (IVCF) is widely performed in patients with, or at risk of, venous thromboembolism. IVCF likely prevent pulmonary embolism (PE) in highly selected patients with acute venous thromboembolism (VTE) who have absolute contraindications to therapeutic dose anticoagulation. However, the majority of IVCF are placed in patients with either no active VTE

(“prophylactic IVCF”) or those with acute VTE who do not have an absolute contraindication to anticoagulation.

However, there is little evidence to guide the use of IVCF. Only one randomized trial has been performed in which patients with acute VTE were randomized to anticoagulation with or without IVCF. The study demonstrated an acute reduction in PE, with no impact on mortality and an increase in VTE over 8 years of follow-up, leading the authors to recommend against routine use of filters in patients who can be anticoagulated. There have been no randomized controlled trials examining the use of retrievable filters or the use of filters for the prevention of pulmonary embolism in patients who do not have acute venous thromboembolism. Evidence-based guidelines have recommended against the use of IVCF for the prevention of pulmonary embolism in patients who do not have acute DVT. Despite this guideline recommendation, the majority of IVCF in the United States are placed for this indication. For example, IVCF use is routine in some trauma centers. This practice occurs despite the fact that insertion of IVCF is expensive (estimated to cost in excess of US\$5000 per use), that IVCF cause otherwise avoidable deep vein thrombosis (at an estimated US\$5000 to US\$10,000 per event) and that IVCF may provide physicians with an excuse to neglect the administration of a pharmacologic prophylaxis, which is proven to be the most effective and cost-effective treatment for patients at high risk of VTE.

Data on insertion of IVCF should be easily accessible. Indications and complications of their use should be discernible. Comparison of event rates in patients with and without IVCF matched for other co-morbidities should also be available. Such an analysis would likely establish definitively that IVCF use is both more expensive and more toxic than alternate, effective therapies currently recommended by consensus guidelines.

III. Management of Patients with Myelodysplastic Syndrome.

Myelodysplastic syndromes (MDS) affect older adults with a rapidly rising national disease burden owing to the aging of the American population. Patients with MDS have a chronic bone marrow failure disorder often associated with other co-morbidities, and are cared for by primary care and hematology subspecialists. Patients and health care providers must address complications related to the disease process itself that include cytopenia-associated risks for infection or bleeding, the risk for evolution to acute myeloid leukemia (AML), and secondary organ complications arising from red blood cell transfusions and iron overload.

Although evidence-based guidelines provide management pathways for physicians that utilize an array of FDA approved therapeutics, the impact of these costly treatments on the disease natural history and co-morbidities remains largely undefined. Large prospectively randomized therapeutic trials represent the

benchmark to define the benefit for most interventions, but size and the ethical challenge of non-treatment arms prohibits such definitive studies. Important insight into the clinical benefit of interventions could be obtained from the analysis of large federal health claims databases such as the Medicare Standard Analytic File. Data from patients diagnosed in a given year can be mined for subsequent billings for acquired co-morbidities such as diabetes mellitus, cardiac and liver complications, survival and red blood cell transfusions.

Given the large size of the database, important insight can be gathered regarding the success of health care delivery strategies in the U.S. that is applicable to the population of patients at large, rather than to those that meet the restrictive eligibility of registration trials. CER comparing usual supportive care versus care by protocol-driven community-based, advanced health practitioners and teams may lead to a reduction of variability of care, costs, and improved quality of life. Examples of CER that would have an impact on care and provide insight as to the cost benefit of treatments include those related to current management practices for iron loading and disease modifying therapies:

1. Does the use of an iron chelator delay or prevent end-organ co-morbidities, or extend survival in lower risk transfusion-dependent patients?
2. If so, what proportion of patients that may benefit have access to such treatment?
3. Using current practice regimens for hypomethylating agents such as azacitidine or decitabine, is there a demonstrable survival benefit or difference in resource utilization in patients with higher risk disease?
4. How often is the use of an erythropoietic stimulating agent (ESA) effective in preventing the need for transfusion in the lower risk MDS population? What is the impact of ESA response on the natural history of low risk MDS?

Information from an analysis of the latter may support prior ASH recommendations to the CMS against the restriction of ESA access to those individuals with the greatest potential for benefit. Such CER analyses would provide critical information as to the best management strategy for the MDS population at large to modify disease natural history, the magnitude of benefit to patients, and cost-effectiveness.

IV. Use of Transfusions.

Transfusion therapy remains essential to the successful treatment of oncologic and hematologic disorders, many surgical procedures, and traumatic injuries. However, the appropriate threshold for transfusions in various clinical situations as well as the appropriate dose of the blood component transfused remains unclear. Modification of blood components by procedures such as irradiation or

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leukocyte reduction have an important role in improving transfusion safety; however the indications for such procedures are unclear in many patient populations and are applied heterogeneously. The risks of transfusion beyond that of transfusion-transmitted infection and transfusion reaction remain controversial. For example, there continues to be considerable debate about whether transfusion is associated with an increased rate of cardiac morbidity and multiorgan failure. CER comparing outcomes with different red blood cell transfusion thresholds in patients with cardiac disease, hematologic malignancy or surgery will help to most effectively manage a blood supply that frequently must address shortages. A better understanding of adverse outcomes related to transfusion will allow physicians to better weigh the risks and effectiveness of transfusion therapy.

Thank you for the opportunity to submit these comments. Please contact ASH Scientific Affairs Manager, Ulyana Vjugina, PhD, at (202) 776-0544 or uvjugina@hematology.org for any additional information.

Sincerely,

A handwritten signature in black ink, appearing to read "Nancy Berliner". The signature is written in a cursive, flowing style.

Nancy Berliner, MD
President