



2010

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Via Electronic Submission to: nilsenwj@od.nih.gov

May 25, 2010.

Re: Response to RFI (NOT-OD-10-078) on the Priorities for the NIH Adherence Research Network.

Dear Dr. Nilsen:

The American Society of Hematology (ASH) appreciates this opportunity to respond to the National Institutes of Health's April 20, 2010 Request for Information on the Priorities for the NIH Adherence Research Network (NOT-OD-10-078).

ASH represents over 16,000 clinicians and scientists committed to the study and treatment of blood and blood-related diseases. These areas include anemia (including sickle cell and thalassemia), thrombosis (including venous thrombosis, heart attack and stroke), bleeding disorders, transfusion medicine, and gene therapy, as well as the malignant hematologic leukemia, lymphoma, and myeloma. In addition, hematologists have been pioneers in the fields of bone marrow transplantation and stem cell research.

The priorities for adherence research listed below are consistent with the mission of the NIH Adherence Network, and refer to scientific research of at least 3-5 years duration.

PRIORITY #1: ADHERENCE RESEARCH IN PATIENTS WITH SICKLE CELL DISEASE (SCD).

Challenge 1a: Neurocognitive Challenges. There is a need to understand issues that affect adherence to treatment of SCD. Strategies to improve adherence must incorporate potential neurocognitive challenges such as poor memory and executive functioning.

Potential Solutions: There is a need for correlation of neurocognitive testing and adherence followed by evaluation of an intervention, such as studying an effect of a cognitive remedial training program on adherence outcome.

Challenge 1b: Lack of Education and Employment. Chronic illness, particularly in SCD, is dramatically worsened by the lack of education opportunities and employment. Under-employment and lack of education leads to non-compliance to treatment and negatively affects adherence.

Potential Solutions: Systematic interventions need to be implemented on the level of improving education and employment experiences as a means of improving overall quality of life for people with SCD. There is a great need for development and implementation of programs to address the barriers to adherence imposed by low health literacy. Research projects in SCD risk communication to enable patients to understand risks of sickle cell disease *vs.* benefits of disease-modifying interventions (stem cell transplantation, hydroxyurea, transfusions) are greatly needed. Previous pilot studies found that education of an extended person of significance for the patient and including them in visits had a significant impact on compliance with medication and appointments. In addition, evaluating a pilot program that incorporates paid employment as an intervention could shed light on how under-employment affects adherence.

Challenge 1c: Depression and Adherence. There is a great need to understand how depression affects treatment outcomes and adherence to treatment.

Potential Solutions: A pilot program should be developed with the help of the NIH where patients are initially analyzed by the MINI Mental State Exam or other screening tests for depression followed by adherence correlated with depression. Depression would then be treated with counseling, medication, and adherence compliance can be compared.

Challenge 1d: Cultural Competence. There is growing evidence that compliance correlates with cultural competence of the provider^{1,2}. Many health care providers lack cultural competence in diseases prevalent in ethnically diverse populations.

Potential Solution: The NIH should aid in establishing a pilot program that trains the provider in cultural competence and then reassesses its impact on patient adherence.

Challenge 1e: Pediatric to Adult Transition. Numerous factors contribute to the difficulties in providing comprehensive care to adults with SCD. The problem is particularly challenging not only because of the severity of the underlying chronic disease but also because of the many associated problems that require substantial care coordination and the input of numerous subspecialists. Adherence research into effective programs of transition from pediatric to adult-centered care and enhancing the effectiveness of both pediatric and adult-centered care delivery systems is a critical need recognized in all SCD centers nationally and internationally.

Potential Solution: The NIH should make the development of techniques to improve adherence to recommended treatment a major focus of pediatric to adult-oriented care transition programs.

Challenge 1f: Adherence to Hydroxyurea Therapy. Although hydroxyurea can be an effective treatment for SCD, adherence to hydroxyurea therapy remains an issue due to concerns about the overall safety and effectiveness, as well as a lack of providers expert in the treatment of patients with SCD.

Potential Solution: The NIH should aid in developing physician tools and patient education materials to specifically address adherence to hydroxyurea therapy.

¹ Gozu A, Beach MC, Price EG, Gary TL, Robinson K, Palacio A, Smarth C, Jenckes M, Feuerstein C, Bass EB, Powe NR, Cooper LA. Self-Administered Instruments to Measure Cultural Competence of Health Professionals: A Systematic Review. *Teach Learn Med.* 2007 Spring;19(2):180-90.

² Thom DH and Tirado MD. Development and Validation of a Patient-Reported Measure of Physician Cultural Competency. *Med Care Res Rev.* 2006 Oct;63(5):636-55.

PRIORITY # 2: RESEARCH INTO ADHERENCE TO IRON CHELATION THERAPY IN PATIENTS WITH THALASSEMIA.

Challenge: Data from numerous studies demonstrate that the regular use of iron chelation therapy delays or prevents the accumulation of transfusional iron and the onset of iron-induced cardiac failure or arrhythmias. As a result, patients with thalassemia who regularly use iron chelation therapy have the potential for a vastly improved quality of life and normal or nearly normal lifespan. However, the development of these effective chelators, even those that are orally active, has not been matched by a rate of adherence that is necessary to achieve the long-sought benefits. The issue of adherence was felt by many to be one that would disappear as the oral chelators replaced the parenteral agent deferoxamine that required nightly infusions. Adherence, however, remains a major problem which, perhaps, should not be so surprising given the known problems of adherence with medication for hypertension, chronic renal disease and other disorders in which no immediate clinical benefits (*i.e.*, relief of symptoms) are visible to the patient. Thus, patients with thalassemia, particularly adolescents and young adults, continue to accumulate iron, to develop heart disease and to die prematurely despite drugs that are capable of preventing all of these unfavorable outcomes.

Potential Solutions: Research on the behavioral and social aspects of adherence to treatment, as well as research into compliance measures, is urgently needed for the patients with thalassemia. Focus groups are currently underway to characterize further the barriers to adherence, and these should be completed or expanded as necessary. Strategies that have been applied to other disorders, including regular contact between care providers or the medical home and the patient, development of electronic reminders, electronic reporting of medication use, patient to patient communication and others should be studied in thalassemia. In light of the growing ethnic diversity among patients with thalassemia in the United States, there is a concomitant need to develop interventions that account for cultural differences.

PRIORITY # 3: ADHERENCE RESEARCH IN CHILDHOOD LEUKEMIA.

Challenge: In single-parent households, the overall burden of earning a living and taking care of multiple children can be especially stressful, especially if the parent (typically a young mother) is having family members care for the child with leukemia. Often the participating family members do not know how to give the medications, tend to illnesses, and are unprepared to care for a child on acute therapy. Moreover, for teens and young adults undergoing transition to adulthood, many are expected to take their own medications. In patients who are in remission, have doubts about the need for the medications, or have toxicities related to the medications, the decision not to take the medicine is an easy one.

Potential Solutions: For single parent households, there is a need to identify the perceived gaps in information, family structure, or availability of medicines to caretakers in young households. Once these barriers to compliance have been identified, finding individualized care plans would help such families cope with a prolonged medication course. In addition, the guidelines on how to dose these medications can be very confusing to healthcare professionals, so efforts by the Pediatric Central Institutional Review Board (PedCIRB) or other IRBs to make dosing parameters clear would be very helpful.

There is a general lack of knowledge about increasing compliance to medication of adolescents and young adults. The recent web-based programs called "Remission" seem to have been successful, but may miss many segments of the population (such as girls who do not play video games). Current research on teen motivators (such as money, popularity, freedom), does not provide insights on improving adolescent compliance with chemotherapy. Gender differences also play an important role, as, for example, teenage girls are very reluctant to comply with steroid treatment.

ASH will be happy to provide further information and discuss these priorities with you. Please contact ASH Scientific Affairs Manager, Ulyana Desiderio, Ph.D., at (202) 776-0544 or udesiderio@hematology.org for any additional information.

Sincerely,

A handwritten signature in black ink that reads "Hal E. Broxmeyer". The signature is written in a cursive style with a long, sweeping underline.

Hal E. Broxmeyer, PhD

President