ADVISORY COUNCIL ON BLOOD STEM CELL TRANSPLANTATION (ACBSCT)

U.S. Department of Health and Human Services (HHS)

Virtual Meeting

Friday, September 13, 2013

Welcome and Opening Remarks

Edgar Milford, Jr., MD, Chair, ACBSCT

Dr. Milford called the meeting to order at approximately 10:10 a.m., welcomed Council members and participants to the meeting, and reviewed the agenda.

Program Report

Shelley Grant, MHSA, Chief, Blood Stem Cell Transplantation Branch, Division of Transplantation (DoT), Health Resources and Services Administration (HRSA)

Ms. Grant reviewed the legislative authority for the C. W. Bill Young Cell Transplantation Program (the Program) and the National Cord Blood Inventory (NCBI). The Program was authorized by the Stem Cell Therapeutic and Research Act of 2005, which was reauthorized in October 2010. The goals of the program are to: increase the number of unrelated-donor transplants; conduct recruitment of potential marrow donors; provide patient and donor advocacy services; engage in public and professional education regarding transplantation; and collect and analyze data on transplant outcomes. The overarching goal is to provide opportunities to help more patients obtain transplants and other therapies using blood stem cells.

Ms. Grant provided a status update on the Program, based on fiscal year (FY) 2012 data. As of September 30, 2012, the Program's registry included approximately 10.5 million potential adult donors, 28% of whom were from minority populations. In FY 2012, 508,716 adult potential donors were added to the Program's registry, 47% of whom self-identified as belonging to a racial/ethnic minority group. The total number of cord blood units (CBU) available through the Program exceeded 163,000. Transplants overall increased to 5,833 (a 4.7% increase over FY 2011), and transplants for minority patients increased to 1,021 (a 6.9% increase). Transplants facilitated by the Program for minority patients represented 17.5% of the total, and minority adult donor transplants increased by 15.1% over FY 2011. The patient survival rate one-year post transplant has increased significantly over the past 10 years.

Ms. Grant stated that the Program is on track to meet or exceed its performance goals for FY 2013. Those goals are to: increase the number of adult volunteer donors of minority race or ethnicity listed on the Program's registry to 2.85 million; increase the number of blood stem cell transplants facilitated annually by the Program to 5,513; and increase the number of blood stem cell transplants facilitated annually for minority patients to 845.

Ms. Grant provided FY 2012 data for the NCBI. As of September 30, 2012, 53,609 NCBI CBU were available through the Program. A total of 714 CBU were distributed for transplant in 2012, compared to 690 in FY 2011. NCBI appropriations for FY 2013 will support the addition of approximately 9,500 CBU annually.

Ms. Grant stated that the final appropriation levels for FY 2013 were $21,877,000 for the Program, and $11,147,000 for the NCBI. This represents a reduction of about 6% from FY 2012, but it still provides sufficient funding to continue the important work of the Program. The President has requested the same amounts for FY 2013.

Ms. Grant shared the status of follow-up items for HRSA's Blood Stem Cell Transplantation Branch from the Council's previous meeting (May 2013), as follows:

- Provide the Advisory Council with data on transplants by indication:
  - The information packet for this meeting included the number of transplants facilitated by the Program by broad categories of disease
  - A link on the Program's website provides a tool to search transplant data by disease, age, race, cell sources, and more http://bloodcell.transplant.hrsa.gov/transplant/understanding_tx/index.html#Diseases
  - Transplant data can be obtained through the website for the National Marrow Donor Program (NMDP) (https://bethematchclinical.org/Transplant-Indications-and-Outcomes/).
- Work with the Realizing the Potential of Cord Blood Work Group and the Scientific Factors Necessary to Define Cord Blood Units as High-Quality Units Work Group to ensure that HRSA considers all possibilities for addressing cord blood bank financing:
  - HRSA issued a Request for Information (ROI), with responses due on September 27 and will share the information it receives through that process with both work groups.
- Provide the Advisory Council with information regarding progress on educational/outreach efforts to the sickle cell disease (SCD) patient and provider community:
  - Ms. Grant and the new Director of the DoT (Robert Walsh) met with Dr. Donnell Ivy, Medical Officer at the Genetics Services Branch of HRSA's Maternal and Child Health Bureau to discuss how to best coordinate common areas of interest. Dr. Ivy informed them of a Federal hemaglobinopathies work group that includes many agencies within HHS. He will keep the Division of Transplantation informed of the activities of that group.
  - NMDP included SCD in their clinical guidelines for referring physicians.
  - NMDP exhibited and provided educational materials at a 2012 conference of the Sickle Cell Association of America and will also have an exhibit at the 2013 conference.
  - NMDP promoted SCD during African American Bone Marrow Awareness month in July 2012 and 2013.
  - NMDP reviewed and updated the family information brochure for the Blood and Marrow Transplant Clinical Trials Network (BMT CTN) protocol 0601, The SCURT Study (Evaluating the Safety and Effectiveness of Bone Marrow Transplant in Children with Sickle Cell Disease) in June 2012.

Ms. Grant shared preliminary information about HRSA's Request for Information (RFI) for the NCBI, which was released on July 8, 2013. The purpose of the RFI is to provide the public with a description of, and an opportunity to submit comments on, HRSA's current approach to obtaining CBU for the NCBI; provide the public with an opportunity to propose demonstration and outreach projects that HRSA may consider implementing through new or existing contract(s) as a means of increasing donations of CBU from diverse populations; and identify additional organizations interested in and capable of providing CBU to the NCBI. To date, HRSA has received 10 responses from public and private cord blood banks (CBBs), HRSA contractors, private CBB foundations, and private information technology companies. The following themes have emerged from those responses:

- Fund Caucasian blood bank units
- Increase the total nucleated count (TNC) for qualification of NCBI funding
- Provide funding for maternal sample typing projects
- Provide more support for the Food and Drug Administration (FDA) licensure process and ISBT 128 requirements
- Provide more educational outreach and a call center for all uses of umbilical cord blood (i.e., public donation, family banking, research, discarded as medical waste)
- Simplify the cord blood donor consent process
- Provide up-front financial support to CBBs
- Increase partnerships between public and private CBBs

- Provide more financial reimbursement for NCBI CBU in general, and specifically for African American/Black and Asian/Pacific Islander ethnicity
- Integrate the remote kit collection program with a private information technology system to increase diverse cord blood unit collections.

Responses also included several capability statements to increase the diversity of cord blood donations and consideration for a single point of access infrastructure contract for searching for CBUs.

The RFI is available at https://www.fbo.gov/index?s=opportunity&mode=form&id=4a25be8a3cb7d01a3f5a5f1df281c218&tab=core&_cview=1. Responses are due September 27, 2013.

Discussion

At the request of a Council member, Ms. Grant stated that she would provide the Council with copies of the brochures that the NMDP developed for the Sickle Cell Association of America.

> **Action Item**
> Ms. Grant will provide the Council with the brochures developed by NMDP for the Sickle Cell Association of America.

Responding to a request from Dr. Milford, Ms. Grant stated that she would provide the Council and the work groups addressing cord blood financing with detailed information on responses to the RFI.

> **Action Item**
> Ms. Grant will provide the Council and the work groups addressing cord blood financing with detailed information on responses to the RFI.

Advancement in Cellular Therapies Work Group

Claudio Anasetti, MD, Chair

Dr. Anasetti noted that the purview of this new work group is to collect data on the outcome of stem cell therapies for purposes other than hematopoietic reconstitution. HRSA's contract with the Center for International Blood and Marrow Transplant Research (CIBMTR) had been instrumental in collecting data on stem cell transplant for hematopoietic reconstitution and moving the field forward, but it encountered difficulties in getting into regenerative medicine. Dr. Milford asked Dr. Anasetti to chair a work group to define the scope of the problem and provide a recommendation to HRSA to address the issue. Work group members have been identified and will hold their first meeting in the near future.

Dr. Anasetti asked Adrian Gee to provide the Council with an overview of the issues in this area.

Non-Hematopoietic Applications for Stem Cells

Adrian P. Gee, PhD, Director, Center for Cell and Gene Therapy, Baylor College of Medicine

Dr. Gee noted that Council members were familiar with traditional clinical practice, which uses hematopoietic stem cells from bone marrow, apheresis products, or cord blood for patients who have received high dose therapies for malignant diseases. The purpose of those stem cells is to restore hematopoiesis and immune functions in the patient.

Dr. Gee presented an overview of the blood stem cell differentiation process and numerous potential stem cell therapies, which involve nearly every major system in the body. Most of those therapies were unknown eight years ago. The number of applications has grown rapidly in a very short time.

Dr. Gee reviewed the variety of somatic stem cells in adults (eye, pancreatic, gut, mesenchymal, neuronal, epidermal, hepatic, and hematopoietic) and the types of cells into which they can differentiate. He explained that mesenchymal stem cells (MSCs) are adherent cells derived from stroma in bone marrow, cord blood, and fat. MSCs are a potential source for many clinical therapies because they can be

expanded in vitro, they do not express human leukocyte antigens (HLA), and they can differentiate into bone, cartilage, muscle, tendon, and fat. More than 352 studies using MSCs can be found on www.clinicaltrials.gov. MSCs appear to have an immunosuppressive effect and can be used to condition recipients for transplant.

Dr. Gee outlined ongoing and future directions for stem cell research. He noted that the most widely used cell populations are mixtures of committed and non-committed cells (e.g., whole bone marrow, marrow mononuclear cells, MSC). In many cases, it would be preferable to generate a multipotent population that could be driven to produce a pure population of the required cells. One way to do this would be to isolate embryonic stem cells and differentiate them in vitro. However, the process of making embryonic stem cells raises ethical concerns because it results in the destruction of human blastocysts, and U.S. government funding is restricted to the use of existing embryonic stem cell lines. An alternative to using embryonic stem cells would be to "regress" adult stem cells into stem cells. This has been done, resulting in a population of induced pluripotent stem cells (iPS cells) that can be used for disease modeling, drug screening, and transplantation studies and are not limited to therapeutic applications.

Dr. Gee outlined the major issues related to iPS cells:

- Are they really equivalent to embryonic stem cells?
- Use of viral vectors to reprogram cells
- Risk of teratoma/tumor formation upon administration
- Control of differentiation
- Cost
- Time required to generate the cells
- Ethical issues, including how to ensure it is done in controlled and responsible manner.

Dr. Gee noted that the first iPS clinical trial was approved in Japan in July 2013. The study uses retinal pigment epithelial cells derived from autologous iPS cells to treat macular degeneration. The trial involves six patients. It takes about 10 months to generate the cells for each patient.

Dr. Gee stated that issues in regenerative medicine include the difficulty of obtaining definitive proof of efficacy; the lack of understanding regarding how the cells work (i.e., direct, indirect, or both); and the question of whether it is better to use pure or mixed cell populations.

Dr. Gee noted that consumers are obtaining a great deal of information online. Much of the information is questionable, which is a source of concern for the FDA. The level of interest in the general population is demonstrated by the publication of *Stem Cells for Dummies* and the fact that a Google search for "regenerative medicine companies" generated 656,000 results.

Dr. Gee presented the following conclusions regarding non-hematopoietic applications:

- Potential non-hematopoietic applications for stem cells are almost limitless, but most are still in the early stages
- Controlled clinical trials will help determine the true value of these applications
- In the meantime, patients cannot differentiate between hype and hope
- Many additional ethical, scientific, regulatory and practical issues must be resolved
- Even if fewer than 10% are of value, this represents a major advance in treatment option.

Discussion

Dr. Milford asked what the Council, if any, would be in providing information and advice in this area.

Richard McQuellon, PhD, stated that one role would be to help separate the hype from the hope in public education. Dr. Gee noted that several cell therapy organizations had developed an educational brochure on medical tourism and how to evaluate the scientific merit of a proposed therapy. He agreed that finding

authoritative sources might be difficult for a patient who is searching on the Web.

Jeffrey McCullough, MD, stated that another role would be to help ensure that this work is done with proper quality and safeguards for patients. If the work is done under Investigational New Drug (IND) guidance, the Council could interact with the Food and Drug Administration (FDA) to get a sense of whether existing mechanisms are adequate.

Naynesh Kamani, MD, stated that a number of trials are being conducted at academic institutions under INDs to ensure due process of the application. But hundreds of clinics are using hematopoietic cells, often collected from bone marrow and given in an autologous manner without FDA oversight or review. Those are the ones of greatest concern.

Dr. Milford stated that it would be helpful to have data regarding how much of what kind of work is currently being done in order to get a sense of the landscape. Without this information, it is too early to counsel patients.

Susan Stewart stated that the issue reminded her of the various complementary and alternative treatments that are available, some of which are useful while others are not. The Federal government created an Institute that has synthesized information about various therapies and provided it in a coherent form to the public. This issue might need a similar treatment.

Dr. Milford asked the Council what the role of the work group should be.

Joanne Kurtzberg, MD, suggested that the work group could help to define the appropriate regulatory road map for preclinical testing and clinical implementation of these types of products. Guidelines could define the kinds of proof of concept would be needed. The work group could work with the FDA to streamline pathways for promising therapies, especially those developed at academic centers, and develop entry level criteria that would weed out those that are less promising. The work group could work on those issues and report back to the Council next year.

Responding to a question from Dr. Milford regarding the role of the FDA, CAPT Ellen Lazarus, MD, stated that the FDA has regulations that apply to biologic drugs that are subject to IND and Biologics License Applications (BLA) requirements. The FDA works directly with investigators and sponsors; it also interacts with professional organizations and offers workshops and other opportunities to engage the public regarding the development of standards.

Dr. Milford asked how quickly this would occur and noted that many naturopathic practitioners are under the impression that they do not have to deal with IND as long as their work is autologous. CAPT Lazarus stated that the FDA looks into instances of inappropriate marketing of investigative products. When individuals identify such circumstances, they can bring them to the attention of the agency.

Dr. Milford asked what the threshold is for requiring FDA approval or review. CAPT Lazarus replied that most Council members are probably familiar with the regulatory criteria in the Code of Federal Regulations, part 1271 that describes products that are not subject to the IND licensure requirements. Manufacturers can submit information describing their product and its use to the Tissue Reference Group, which would make a recommendation as to whether the product meets the criteria to be regulated solely as tissue. Most of what Dr. Gee described would be regulated as biologic drugs. CAPT Lazarus encouraged anyone who observed marketing in which firms do not appear to be following the rules to bring the situation to the attention of the FDA so the claims can be investigated.

Referencing the definition of “more than minimally manipulated,” Dr. Milford asked if the FDA had summarized the INDs related to the kind of cell products and therapeutic directions that Dr. Gee described and whether there had been any surprises. CAPT Lazarus replied that FDA’s role is to ensure

that products have the appropriate safety, purity, and potency. The FDA reviews questions submitted to the Tissue Reference Group and information shared at liaison meetings to determine the types of questions that investigators and stakeholders have about the definitions. The FDA continually reviews those questions to determine which could be best addressed through additional guidance. It publishes its intentions regarding development of guidance each year, and it works with professional organizations and liaison groups to identify new areas to be addressed by regulatory criteria. The FDA is looking into ways to enhance communications so this process can be conducted in the most transparent manner.

Dr. Milford noted that the number of people who are using these infusions therapeutically is unknown, because contacting the FDA is voluntary. The question is what the whole landscape looks like: how many things are being done, what is being done, and who is doing it. That information is essential to determine what the issues will be going forward.

Dr. Kamani clarified that the main concern is people who are infusing bone marrow cells into other organs of the same patient. The cells are not being more than minimally manipulated, and the individuals skirt the FDA regulations by assuming that it is for homologous use. The question is whether this is really homologous use. The FDA has no knowledge of many of these treatments, and there is tremendous concern about their safety and efficacy. CAPT Lazarus stated that the FDA takes strong legal action when such situations come to light. Information on legal cases is available on the FDA website.

Jeffrey Schriber, MD, expressed concern that recent high profile examples of politicians and sports figures who received injections of their own cells could lead to a "wild, wild West" atmosphere very quickly. Dr. Gee agreed that the explosive growth of this industry presents a challenge for any regulatory agency. Dr. Schriber pointed out that current regulations do not apply for autologous use because there is no risk of infection.

Dr. Kurtzberg stated that she gets 20-50 emails each week from desperate parents who are considering stem cell therapies that are not under the purview of the FDA. The work group could help to create a public awareness campaign about safety issues, factors to consider, and questions to ask when considering that type of therapy.

Dr. Milford asked Dr. Anasetti to formulate suggested charges to the new work group and present them to the Council by the end of the day. Dr. Anasetti agreed to do that.

Advisory Committee on Blood and Tissue Safety and Availability (ACBTSA)

James Berger, MS MT (ASCP) SBB, Executive Secretary, ACBTSA, Office of the Assistant Secretary for Health, HHS

Mr. Berger reported on the June 2013 meeting of the ACBTSA. The topic of the meeting was whether the current blood center system in the U.S. is designed for optimal service delivery. The topic was chosen to coincide with the publication of the most recent National Blood Collection and Utilization Survey, which is sponsored by numerous HHS agencies. The survey found a 9.1% decrease in the number of blood units collected in the U.S. between 2008 and 2011, and an 8.2% decrease in the number of blood units that were transfused. The ACBTSA attributed these findings to good patient blood management (PBM) education. Many blood centers are downsizing or being reorganized due to the decrease in productivity.

In light of these trends, the ACBTSA meeting addressed the following questions:

- What services performed by blood centers currently are considered essential to the U.S. health care system? Evaluate their successes and areas of improvement.
- How do anticipated changes in health care (business models, i.e., economic forces, or advancements in medical care, i.e., PBM) affect blood centers and the provision of essential services?

- How should the transfusion medicine field be defined in the next decade with regard to population health, better patient outcomes, and reduced costs?

Due to intense discussions and the need for further research, no recommendations were made at the meeting. A subcommittee that includes representatives of industry and the leading blood centers is meeting on regular basis and will present recommendations at the December meeting. The agenda will include presentations by other subcommittees that are discussing informed consent and identifying contingency plans for disasters to ensure adequate supplies of blood and tissue.

Discussion

Liana Harvath, PhD, asked if the December meeting would discuss contingency planning for horrific events such as the Boston marathon bombing, where the need for a significant blood supply could not have been anticipated in advance. Mr. Berger stated that the Committee discussed those issues in June 2013 and December 2012. Presentations and recommendations from those meetings are available on the Committee's website (http://www.hhs.gov/ash/bloodsafety/advisorycommittee/index.html). The purpose of the December 2013 meeting is to review the subcommittee's proposals to ensure the availability of adequate supplies to meet future contingencies. The availability of tissue is of particular concern.

FDA Licensure

CAPT Ellen F. Lazarus, MD, Director, Division of Human Tissues, Center for Biologics Evaluation and Research (CBER), FDA

CAPT Lazarus provided an overview of updates to the 2009 guidance for cord blood IND and BLA. The draft guidance was published in June and is available on the CBER website (http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/ Guidances/ CellularandGene Therapy/default.htm) and through the Federal Record. The comment period ends September 16, 2013.

CAPT Lazarus explained the rationale for updating the guidance. Since 2009, CBER has gained experience through pre-IND and pre-BLA meetings and ongoing review of BLAs, and scientific knowledge on cord blood banking and clinical use has advanced. The proposed revisions are intended to maintain consistency with current FDA policy and current practice in the field of cord banking, and improve usability of the guidance.

The draft IND guidance updates the terminology, expands the clinical indication based on review of docket data and considerations of the September 2011 meeting of the Cellular, Tissue, and Gene Therapy Advisory Committee, and clarifies the Table of Contents requirement.

The draft BLA guidance updates the terminology and expands the clinical indication, as noted for the IND guidance, clarifies the types of clinical information that should be submitted for review, and adds a reference to additional guidance documents on process validation and methods validation.

CAPT Lazarus noted that CBER had received more than 80 comments to date and would take them into consideration in preparing the final guidance documents. She thanked the Council members who submitted comments and had been involved in the licensure process.

Discussion

Responding to a question from Dr. Milford, CAPT Lazarus clarified the fundamental difference between BLA and IND. She stated that the IND is applicable when the product is in the investigational phase. The sponsor engages in the BLA process after the IND has been performed, because the product must be licensed in order to be marketed. Using the example of minimally manipulated cord blood, CAPT Lazarus noted that CBBs do not have to conduct their own clinical trials. They can follow the instructions in the BLA guidance and rely on data in the docket to support their BLA. However, cord blood products that do not meet the criteria of the guidance (e.g., cord blood that has been collected in the past and is still

available for use) must be used under IND. CBBs that do not have their own IND can transplant those products under the NMDP's umbrella IND.

Transplant Center Laboratory Work Group

Jeffrey McCullough, M.D., Chair

Dr. McCullough noted that the work group was formerly known as the "Wash/No Wash" group. The name was changed because the issues are now broader than whether or not to wash the cord blood as it is thawed and prepared for transplant.

Dr. McCullough provided an update on the work group's activities, as follows:

- Persuaded Dr. Salem Akel of St. Louis to review the literature on thawing methods and related experience. Several Council members provided input for the article, which is ready for submission. The work group endorsed the article as an important contribution to the literature.
- The CIBMTR conducted a study of clinical outcomes in relation to cord blood processing methods, led by Karen Ballen, Mary Horowitz, and Doug Rizzo. The investigators presented a preliminary discussion at the 2012 meeting of the American Society of Hematology (ASH).
- Began to review the staffing and management of transplant center laboratories to develop a better understanding of their operations and began to interact with the AABB and the Foundation for the Accreditation of Cellular Therapy (FACT), who are involved in accreditation. The work group is in the process of determining what actions, if any, it would recommend to the Council.

Dr. McCullough turned the floor over to Willis Navarro, MD, for an update on the National Marrow Donor Program's (NMDP) adverse event reporting system, which serves as a comprehensive, single point of entry to gather information about adverse events during the infusion process.

Tracking and Trending Adverse Events and Quality Issues

Willis H. Navarro, MD

Dr. Navarro provided an overview of the NMDP's processes for tracking and trending recipient adverse events (AEs), donor AEs, and product-related quality issues.

Dr. Navarro described the process for tracking recipient AEs. The NMDP asks transplant centers (TCs) to report all serious recipient AEs, independent of attribution, that are associated temporally with product infusion or that result in transmission of infectious diseases. For the last reporting quarter, eight recipient AE reports were received and reviewed by the medical monitor. All eight were expected, and six were serious. Two of the eight were not serious, and there were no infections. This pattern was consistent throughout the quarter. The only AE of interest in the past year was a CB transplant that resulted in cardiomyopathy syndrome. This case was of interest because it involved no red-cell depleted CB units, whereas prior cases involved at least one red-cell depleted unit.

Dr. Navarro noted that the NMDP retired the Quality Investigation Database (QID) in 2011 and moved to the FDA-compliant Master Control (MC) system, for which it is still establishing a baseline rate. Each reviewed AE that is serious or associated with transmission of infection results in an MC query to look for similar events.

Dr. Navarro described the process for tracking donor AEs. Donor centers are asked to report any AE that is Grade 3 or greater, or any serious or unexpected AE that occurs in the donor. The Transplant Medical Services (TMS) team and medical monitor review each AE report. Serious and/or unexpected AEs result in a CIBMTR data pull, as needed. Fortunately, serious donor AEs are rare, and most are expected. In the previous quarter, no serious and unexpected events were reported. Two events were reported to HRSA, both of which were serious and expected.

Dr. Navarro described the process for tracking product-related quality issues. The NMDP generates annual reports for apheresis centers (ACs) and collection centers (CCs), looking for important trends that may indicate performance issues. ACs are monitored for their central line placement rate, citrate toxicity, and product issues. CCs are monitored for nucleated cell concentration, marrow volume per donor weight, collection duration, and product issues.

Dr. Navarro stated that future directions include the development of additional reports using MC incident management system data and QI Macros software to enhance tracking and trending functionality for AEs and quality incidents. The NMDP is in the process of prioritizing what sorts of incident types would be monitored for tracking and trending. Implementation of the software is currently underway.

Dr. Navarro stated that the AE reporting system continues to work well, and TCs have a good understanding of how to properly report events through the system.

Discussion

Dr. Milford noted that this system would be the central, primary reporting mechanism for CBBs and TCs, and that information would be transferred to the FDA. He asked whether there was one reporting mechanisms for both types of facilities, or two separate mechanisms. Dr. Navarro replied that when an AE event occurs for a recipient, it is entered into the system. His staff reviews the event to determine whether the NMDP is the regulatory stakeholder. If so, they take the lead and conduct an investigation. If not, they pass the details of the event to the appropriate regulatory stakeholder to conduct the investigation according to their responsibilities. It is a single, unified system that allows centers to report recipient AEs or product complaints to a centralized system so they do not have to determine which regulatory agency is responsible for that particular event. If the NMDP is the regulatory stakeholder for the event, they pass the information to the appropriate CB facility.

A Council member asked if the Council could make any recommendations about how to do infusions that would help to reduce AEs. Dr. Navarro replied that the NMDP's goal is to provide information about events in order to minimize the likelihood of those incidents happening again. If it can identify a reason, then it can mitigate. The NMDP knows about deviations from its recommended processes for CB thawing and for administration. Fortunately, those events are relatively rare; there has been only one in the past six months to one year.

Dr. Milford asked Dr. Navarro if anything could be recommended to further reduce AEs that are considered "expected." Dr. Navarro replied that of the eight events over the last quarter, three were hypertension; two were Grade 3, and one was Grade 4. There were two infusion reactions, one was Grade 4. There was one grade 4 sepsis, one Grade 4 myocardial infarction, and one systolic dysfunction. Not all of those events were directly associated with the transfusion, but they were temporally associated. For example, the systolic dysfunction happened in a woman who had a lot of prior therapy with anthrocyclines and known cardiac disease going into the transplant. The TC ultimately felt that the transfusion was unlikely to have been associated with the event, but they reported it nonetheless.

Patricia A. Stroup, MBA, MPA, Executive Secretary of the Council, introduced Robert Walsh, the new director of HRSA's Division of Transplantation, as a new ex officio member of the Council. Mr. Walsh thanked the Council for including him in the meeting and noted that his prior position was with the solid organ transplantation program.

Overview of the Foundation for the Accreditation of Cellular Therapy

Phyllis Warkentin, MD, Chief Medical Officer, Foundation for the Accreditation of Cellular Therapy (FACT)

Dr. Warkentin began by summarizing the history, mission, and goals of FACT. She noted that FACT is an organization of practicing professionals, encompassing all aspects of cellular therapy. It was co-

founded in 1996 by the American Society for Blood and Marrow Transplant (ASBMT) and the International Society for Cellular Therapy (ISCT). Its mission is to promote quality medical and laboratory practice of cellular therapy through its peer-developed standards and voluntary inspection and accreditation program.

Dr. Warkentin stated that the goals of FACT are to promote quality patient care and laboratory practice; improve treatment outcomes; and foster continued development of cellular therapies. FACT pursues these goals through three core services: standards, accreditation, and education. It works in partnership with ASBMT, ISCT, the Joint Accreditation Committee in Europe (JACIE), and the International NetCord Foundation (NetCord).

Dr. Warkentin noted that FACT standards are minimal requirements for quality practice; they are not intended to establish best practices. All FACT standards are evidence based and are developed by consensus of experts in the field. The standards are subject to legal review, regulatory review, and a public comment period. Interim standards may be proposed by the Standards Committee, a Board member, or any participant to address urgent situations. Interim standards are approved and adopted by the FACT Board of Directors and the NetCord or JACIE Board of Directors. Once they are approved, interim standards are published and distributed for immediate implementation.

Dr. Warkentin reported that cellular therapy standards were first published in 1996, combining the ASBMT clinical guidelines and ISCT laboratory standards. They covered all phases of collection, processing, and administration of hematopoietic progenitor or therapeutic cells.

Dr. Warkentin described FACT's collaboration with JACIE, which was established in 1998 to assess and accredit programs in hematopoietic cellular standards in Europe. JACIE adopted the FACT standards and participated in a joint review of the second edition of the Standards in 2002. All subsequent editions have been international standards developed jointly by FACT and JACIE. The fifth edition of the *FACT-JACIE Cellular Therapy Standards* was published in March 2012.

Dr. Warkentin outlined the key changes in the fifth edition of the Standards:

- Clarify the scope to cover all phases of collection, transportation, processing, storage, and clinical administration of cellular therapy products (hematopoietic progenitor cells; therapeutic cells) derived from marrow or peripheral blood
- Include clinical administration of cord blood cells, not collection or banking
- Include a separate section for bone marrow collection services
- Explicitly include extracorporeal phopheresis
- New standards for donors
- Require an implementation plan for ISBT 2018 labeling
- Detailed standards for cord blood administration.

Dr. Warkentin noted that the first edition of the FACT Standards included a few standards for CB banking. When it became apparent that the complexity of CB banking required separate standards, FACT collaborated with NetCord to develop the *NetCord-FACT International Standards for Cord Blood Collection, Processing, and Release for Administration.* The fifth edition of the Standards was published in 2013. The Standards were established by consensus by experts in CB banking under the direction of the chair of the FACT Standards Committee. They address all aspects of CB banking, including donor recruitment, screening, testing, consents, collection, transport, processing, storage, search and matching, and clinical outcome. The Standards are inclusive of unrelated donor units and directed or family units. They do not cover clinical uses of CB or transportation. CBBs are responsible for following clinical outcomes in sufficient detail to assess the quality of the product.

Dr. Warkentin described the FACT inspection and accreditation process and noted that it is voluntary, educational, and collegial. Accreditation is based on documented compliance with all NetCord-FACT Standards. Inspections are conducted by volunteer inspectors who are experts in the field. The FACT Accreditation Committee reviews each report to determine next steps and accreditation status. Facilities may appeal the accreditation decision to the Board of Directors. Inspections are audited periodically.

Dr. Warkentin noted that FACT conducts accreditation for CBBs worldwide, and there are now FACT accredited banks in 19 countries. Eligibility for FACT accreditation extends to hematopoietic progenitor cell facilities, including clinical transplantation programs, hematopoietic cell (HPC) collection facilities, and HPC processing facilities. CBBs may be accredited for unrelated or related donors. The only requirement is that they must have at least 500 units and must be actively banking at the time of accreditation. Banks must assume responsibility for meeting all of the standards. All steps in the accreditation process are now available at www.factwebsite.org.

Dr. Warkentin stated that applicants and inspectors plan the on-site inspection and work closely with the FACT coordinators in the national office. Since many CBBs have numerous non-fixed collection sites, it is not feasible to visit every site that has patients or products. FACT has developed an algorithm to determine the number of sites to be inspected, based on the organization's total number of fixed collection sites. On-site inspections for fixed collection sites consider the following variables:

- Individual facility Medical Director
- Type of unit (related donor, unrelated, both)
- Method of collection (in utero, ex utero)
- Collection personnel (bank staff, hospital staff, physician/midwife)
- Transport to bank
- Distance from bank
- Number of units collected on average per week.

Dr. Warkentin stated that applicants have one year from self-identifying to complete their initial application. FACT generally allows about one year for a renewal, including three months to plan the inspection, three months to complete the inspection and report to the Accreditation Committee, three months for the program to make any corrections or improvements in response to the report and document compliance, and an additional three months to correct any remaining deficiencies. Accreditation is valid for three years, which reduces the burden on organizations and ensures continuous improvement and adaptation to the evolving field. Facilities are expected to complete the renewal process by the time their prior accreditation expires.

Dr. Warkentin noted that there are four potential outcomes of FACT-NetCord inspections: No Deficiencies, Few and Scattered Deficiencies, Major and Systemic Deficiencies, and Non-accreditation.

Dr. Warkentin reported that there are currently 199 accredited HPC programs around the world (177 in the U.S., 15 in Canada, four in Australia, and one each in New Zealand, Brazil, and Singapore) and 44 accredited CBBs (9 in the U.S., and 35 outside the U.S.).

Dr. Warkentin shared the results of a survey of HPC programs with 10 years continuous accreditation. Respondents reported that accreditation had a positive impact in the number of transplants, ability to obtain reimbursement, peer perception, institutional attitude, quality enhancement, research funding, and participation in clinical trials.

Dr. Warkentin noted that FACT requires all accredited banks and programs to submit an annual report that includes any significant personnel changes; new collection sites or other facility changes or moves; significant process changes; number of transplants; and CB inventory. Individualized submissions may include specific follow-up reports related to prior deficiencies, FDA citations, or other issues. Facilities

that were not inspected under the current edition of the Standards may be asked to document compliance with any significant new standard.

Dr. Warkentin outlined new initiatives, including the FACTWeb online accreditation portal; international accreditation, including the FACT International Task Force; and new accreditation goals and core standards that will enable FACT to reach out to regenerative medicine and other disciplines.

Dr. Warkentin described accomplishments in international accreditation. The FACT International Task Force is a global initiative that establishes key contacts in other regions of the world, identifies barriers to accreditation, and educates members or regional BMT societies. The Task Force has found significant interest in accreditation outside the U.S. International programs are able to meet the FACT Standards without variances or relaxed versions. The Task Force also identified opportunities for education.

Dr. Warkentin noted that FACT convened a regenerative medicine task force to develop and promote standards and accreditation for non-hematopoiesis cell therapy products. The task force drafted two new accreditation goals. The first new accreditation goal is related to collection for research and IND products only. Traditionally, collection accreditation by FACT requires the collection facility to utilize a processing laboratory that meets FACT Standards. Some facilities that only collect cell products for research use third-party manufacturers and have no control over where the manufacturing takes place, but they still want to perform collections according to established standards. FACT supports research that follows good scientific research principles, required regulatory pathways, and IRB oversight, and it supports facilities' interest in wanting to be accredited. The second new goal extends FACT accreditation to laboratories that process cellular products for regenerative medicine by broadening the terminology of the fourth edition of the Standards to include therapeutic cells. The working title is "accreditation for more than minimal manipulation," because that terminology is used by the FDA and is understood in the field. Processing facilities can now apply to be accredited for minimal or more than minimal manipulation, or both, depending on what is required for their program.

Dr. Warkentin provided an overview of the new core standards for regenerative medicine for cellular therapy products intended for human administration. They are based on the Cellular Therapy Standards and the Cord Blood Standards and will be broad enough to include most types of cellular therapy products, although they do not include all of the requirements that are necessary to determine quality processes. The new core standards illustrate that the FACT Standards are relevant to other cell therapies and will be useful in assessing complex laboratories for regenerative medicine products. The core standards will be a starting point for discussions with other fields, such as cardiology.

Dr. Warkentin noted that the FACT Professional Relations Committee was conducting an inter-organizational survey on practices for testing cord blood units and preparing them for administration. The primary focus of the survey is to develop consensus regarding standards for viability and other characteristics and for confirming identity. The survey also includes questions regarding processes for thawing, washing, and dilution. The survey would be open until the end of September and should provide good information for the Committee.

Discussion

Dr. Milford opened the floor for discussion. There were no questions or comments.

Access to Transplantation Work Group – Next Steps

Richard Champlin, MD, Chair
Michael Boo, JD, Chief Strategy Officer, Administration and Business Development, NMDP

Dr. Champlin reported on the NMDP Payor Policy Forum that addressed issues of quality, transparency, and value that impact patient access for hematopoietic transplants. Individual presentations from the meeting are available at http://www.dropbox.com/ sh/mmyyt61wqicayfy/q_QFXRITxz.

Dr. Champlin summarized a presentation by T. Scott Bentley on issues related to cost and insurance. Mr. Bentley presented figures showing that the average one-year costs of allogeneic and autologous SCT ($902,000 and $368,000, respectively) are in the mid-range of transplantation costs, compared to heart and kidney transplants ($1,136,000 and $306,000, respectively). Allogeneic cost is related to greater use of unrelated donor transplants and CB transplants, which are more complicated procedures, have more supportive care needs, and cost more in terms of services provided.

Dr. Champlin noted that four organizations are looking at quality and cost-effectiveness of SCT. ASBMT is developing treatment guidelines; CIBMTR is developing center-specific outcomes, as mandated by the legislation; FACT is developing standards for accreditation; and the NMDP sponsored the payor forum.

Dr. Champlin summarized Mr. Boo's presentation on NMDP donor costs and the process they use to find an unrelated donor for a patient if there is no match within the family. The preliminary search for potential donors is free and can be done by anyone through the NMDP online database. If the patient's physician wishes to look for unrelated donors, a formal search is conducted. The fee to activate a formal search is $1,650. Donor testing and management, including HLA typing and high resolution screening, ranges from $5,000 to $15,000, depending on the number of donors to be tested. The more complex or less common the HLA type is, the harder it is to find the donor. Roughly half of the patients are unable to find a perfectly matched donor, even though the international system of registries includes approximately 14 million people from around the world. The cost of procuring the product ranges from $30,000 to $60,000. The cost is lower for a U.S. adult PBSC or marrow. The cost for an international adult PBSC or marrow with a single CB unit is in the intermediate range because it involves travel expenses. Higher costs are associated with two CB units, particularly if they are sourced from international registries. All CBBs and registries set their own pricing. These costs do not include hospital charges or supportive care, which are part of the total cost of a transplant. The charges are highest for CB transplantation due to the cost of the unit and slower recovery of the blood count after the transplant because of the relatively small numbers of cells in the CB unit. The lowest cost is in a matched related donor transplant for blood, where patients recover more quickly and are out of the hospital sooner

Dr. Champlin summarized a presentation on insurance benefit design by Liz Danielson of the National Cancer Center Network (NCCN) and the National Business Group for Health (NGBH), which are trying to develop guidelines in this area. The NCCN guidelines are widely used by physicians, nurses, pharmacists, billing staff, managed care organizations, and patients. The NCCN clinical practice guidelines for each type of disease include the indications that should be considered for transplant. The NCCN drugs and biologics compendia determine which drugs are used in what setting. These compendia provide a rationale for the standard of care for metabolic transplantation, which frequently entail off-label use of drugs. The NCCN recommends that benefit plans should include access to a "centers of excellence" program for bone marrow/stem cell transplants, with a rigorous process for both adult and pediatric programs. The plans should cover the entire cost of the transplant, including the cost of finding a donor, collecting cells from the donor, and doing the HLA typing, which are intrinsic to the transplant process. The NNCN recommends that benefit plans cover the cost of nutritional counseling, medical nutritional therapy, and dental care for individuals diagnosed with cancer, as well as fertility preservation treatments when a medically necessary treatment may cause infertility. Stop-loss insurance should cover clinical trials and off-label use of drugs. Out-of-pocket thresholds should not create a barrier for patients. Medical plans, pharmacy benefit plans, and specialty pharmacy benefit plans should cover evidence-based cancer treatment, including off-label uses of drugs and biologics, as appropriate. Travel and housing costs should also be covered.

Dr. Champlin presented a table developed by the NMDP that presents recommended benefits for various categories (donor search, cell procurement, cell infusion/HCT, travel and lodging, length of stay, medications, and clinical trials), the rationale for each, and administrative guidance.

Dr. Champlin discussed the impact of self-funded and stop-loss provisions on transplant decisions. Sixty percent of plans are self-funded, with insurers as contracted administrators of plans developed by employers. Reinsurance provisions often restrict coverage decisions, which can make it more difficult to get coverage for patients in clinical trials.

Dr. Champlin discussed how to measure the value of transplants. He noted that although a transplant is a high-risk procedure, it may be the only treatment that can enable the patient to survive more than five years. The value of transplant should be measured using long-term metrics, because the benefits in terms of survival do not emerge until three or four years after the procedure and transplantation prevents ongoing catastrophic care.

Dr. Champlin summarized center-specific reporting results that were presented by the CIBMTR, which rates each center on its survival versus expected survival, given the risk stratification of the patients. Only two of the 17 centers on the chart were not performing as well as expected, within a 95 percent confidence interval. The results need to be interpreted in terms of the types of patients that are being treated and the types of treatments that are being performed. Dr. Champlin noted that the CIBMTR report meets the Congressional mandate to conduct center-specific analysis and reporting. Consumer Reports and other groups are conducting their own analyses. Objective assessments of outcomes and cost-effectiveness are a good thing for the field.

Dr. Champlin noted that the Affordable Care Act (ACA) mandates clinical trial coverage for all plans beginning January 1, 2014. The mandate requires coverage for routine patient costs for treatment of cancer or life-threatening disease. This is vital to improve medical care, overall, as well as care for individual patients. The question is how it will be rolled out and enforced.

Mr. Boo stressed the importance of developing strategies to address three issues in order to preserve and advance reimbursement and continue this model of care:

- The issue of quality measurement will become more important. Today, quality tends to be measured by either gross outcomes statistics or by specific evidence of good care. We need to be moving toward more specific, results-oriented outcomes data. CIBMTR may play a critical factor in helping this part of the healthcare community move in that direction.
- Value translates to cost-effectiveness. How do we demonstrate the best use of dollars for patients, given their condition, versus other therapies? The CIBMTR and NMDP research departments are working on comparative evidence studies to determine value beyond simply looking at outcomes.
- Clinical trials will continue to be a complex issue for reimbursement. Insurers want to know the point of care that is being researched, compared to the current standard of care. If insurers take a narrow view, they will continue a struggle with TCs around this issue.

Discussion

Dr. Milford asked how long center-specific data had been available in the SCT arena, and how insurance companies were using that information. Dr. Champlin replied that the C.W. Bill Young program requires center-specific outcomes data. It has only become possible to refine the data in the past few years, since CIBMTR took over responsibility and additional data points were added. Payors want an outcomes-based cost rate approach to reimbursement. The question of how insurance companies should or would use the data is still being defined.

Dr. Milford noted that in a number of arenas, there is a focus on new therapies and treating new categories of patients for whom we may not have the basis for establishing risk variables that could be easily used to normalize the outcomes. Robert Hartzman, MD, replied that this model had been used for about 20 years. It has been refined recently and modified for higher-risk procedures. Dr. Champlin added that the main difference is that TCs are treating cancer, not just replacing an organ. There is tremendous

variability in the potential outcome, with statistical bounds for treatment ranging from 30% to 70%. It is difficult to determine good or bad centers, based on their outcomes, because the outcome depends on the cancer more than on the transplant. The transplant could be perfect, but the patient could die from a relapse of the disease.

Rebecca Haley, MD noted that FACT, the American Academy of Pediatrics (AAP), and centers of independent donors now require an independent health care team for the donor and asked if that would present a problem for payors. Dr. Champlin replied that this was not a problem for TCs. The idea behind the standard is to avoid a conflict of interest for the physician between the needs of the patient and the needs of the donor. Dr. McCullough stated that there was a long history to substantiate this standard, and it was one of the first principles that the NMDP adopted when it was established. Dr. Warkentin stated that the AAP was primarily concerned about family donors who are related to the patient. Insurance companies are likely to absorb this as part of good practice. The cost differential should be small, because the work is the same.

Dr. Kamani asked about the basis for the costs that Mr. Bentley quoted for autologous and allogeneic transplants and what the rate of inflation for healthcare was between 2002 and 2013. Dr. Champlin replied that Mr. Bentley presented aggregate data from the reinsurance company where he works. The rate of inflation averaged well above 5% over the past 11 years, and possibly close to 10%.

Jeffrey Schriber, MD, noted that when the requirement to collect center-based outcomes data was proposed there was concern that centers would stop doing higher-risk transplants, and he asked whether there was any evidence that this had occurred. Dr. Champlin said he did not believe that centers had changed their practices to improve their case mix. In solid organs transplants, some centers have closed because of poor outcomes. Hematopoietic transplant is more complicated because it treats malignancies.

Ms. Stroup commented on the statutory language of the ACA and implementation of the clinical trial provision. Information at www.cms.gov states that this provision will take effect in January 2014. HRSA will be tracking the ACA implementation carefully and will keep Council members informed.

> **Action Item**
> Ms. Stroup will provide the Council with updates regarding implementation of the clinical trial provision of the ACA.

Responding to a question from a Council member, Dr. Champlin stated that Employee Retirement Income Security Act (ERISA) plans were not excluded from the clinical trials provision, but grandfathered plans would be. He believed that the grandfathered plans would be phased out by 2019.

J. Douglas Rizzo, MD, MS noted that center-based outcomes reports were part of the Program before it was called the C.W. Bill Young Program. The methodology has been relatively stable since about 1996, with some changes made in 2004. It included unrelated transplants only for U.S. transplant centers only until 2009, when related transplants performed at U.S. centers were incorporated. The CIBMTR acknowledges the importance of understanding whether TC practices have changed regarding the risk-level of patients now that there is increased surveillance of outcomes, and an active research study addressing that issue is on the agenda. The CIBMTR would like to advance that issue, perhaps as part of its outcomes forum with transplant community payers, patients, and others.

Advancing Hematopoietic Stem Cell Transplantation for Hemoglobinopathies – Work **Group Report**
Naynesh Kamani, MD, Chair

Dr. Kamani provided a follow-up to the recommendations that the work group presented at the previous Council meeting to determine whether there was a need for the work group to continue.

Dr. Kamani reviewed the two-fold charge to the work group: 1) Identify barriers to transplantation and opportunities to more fully realize its potential for individuals with SCD and thalassemia, and 2) Submit for consideration and adoption by ACBSCT recommendations regarding high priority actions.

Dr. Kamani reported that the work group had not met since the May 2013 Council meeting. At that meeting, the Council engaged in extensive discussion and made a decision to send a recommendation to the Secretary of HHS regarding the inclusion of the curative option of HCT for SCD in the National Heart, Lung, and Blood Institute (NHLBI) guidelines for management of SCD.

Dr. Kamani noted that the NHLBI has managed clinical guidelines for SCD for over 20 years. An expert panel was established in 2009 to develop the fifth edition of the guidelines. The draft guidelines that are currently under review refer to five major topics as they pertain to the management of SCD: overall health maintenance, acute complications, chronic complications, hydroxyurea therapy, and transfusions. There is little to no mention of HSCT as a potential option for patients with SCD. NHLBI has not yet published the final version of the updated guidelines.

Dr. Kamani presented the recommendation that was approved by the Council in May and submitted to the Secretary:

- We recommend that the Secretary consider appropriate mechanisms to assure that the revised NHLBI publication, "Management and Therapy of Sickle Cell Disease," include expert opinion about the curative option of hematopoietic cell transplantation for this disorder."

Dr. Kamani noted that the Council also discussed an action item for HRSA to report back to the Council about progress on outreach efforts to the SCD patient and provider community. He noted that Ms. Grant's presentation to this meeting included a report on HRSA and NMDP's activities in that area.

Dr. Kamani reminded the Council of discussion topics that the work group presented for consideration by the Council at the May meeting:

- Improve access to HSCT
    - Study current status of third-party coverage for HSCT as a therapeutic modality for all SCD patients
    - Remove insurance barriers where they exist
    - Continue and strongly encourage current efforts to increase minority representation in volunteer donor registries and the diversity of public CBB inventory
- Increase and sustain National Institutes of Health (NIH) funding to identify laboratory/genomic predictors of poor prognosis that might facilitate early referral to HSCT
- Funding of clinical trial in HSCT for SCD that target gaps in knowledge that might broaden access: reduce transplant-related toxicity, evaluate risks and improve outcomes of alternative donor BMT, overcome immunological barriers to engraftment after unrelated CB transplantation.

Dr. Kamani asked the Council whether there was a need for the work group to continue to look at barriers and develop additional recommendations. He noted that some of the issues that the work group presented in May were determined to be outside the purview of HRSA and therefore were not considered for recommendations to the Secretary.

Dr. Milford stated that this was an area where there was a potential to illuminate the disease. It could be a significant opportunity for the Council.

Andrew Campbell, MD, noted the increasing number of patients getting transplants, including older populations. Two studies are currently looking at patients being transplanted beyond age 16, with increased morbidity and mortality. There is a need for continued monitoring, increasing the donor pool, and continuing to reevaluate therapies that might improve the outcomes of HSCT. Some studies are

looking at gene therapy, which involves SCT, as an alternative to traditional SCT for SCD. A work group might not be needed, but there is a need for advice from the Council for this population.

Dr. Milford noted that many of these issues related to the NIH and asked Nancy DiFronzo, PhD whether it was useful for the Council to have a continuing work group to advance the agenda of finding a cure for hemoglobinopathies. Dr. DiFronzo replied that the blood division of NHLBI has a branch that is dedicated to supporting this area of science. The Blood and Marrow Transplant Clinical Trials Network (BMTCTN) is supporting a national clinical trial for pediatrics with a small number of patients. NHLBI is also supporting other Phase 1 or Phase 2 trials that come through the regular investigator-initiated grant mechanism. The blood diseases group is trying to support the advancement of sickle cell research. Recruitment has been a problem in some of the trials. SCD is a rare disease, with a small number of patients who are located across the U.S. Many trials do not reach completion. NHLBI is committed to completing the Sickle Cell Unrelated Transplant (SCURT) study.

Dr. Kamani noted a number of factors that could make it difficult to enroll SCD patients in clinical trials, one of which is that they are not likely to die if they do not receive a transplant. Hopefully, the SCURT trial will be fully subscribed by the end of this year or early next year.

Dr. Campbell noted that the study of hydroxyurea treatment in babies between nine and 18 months had just been published. More people are using hydroxyurea at an early age, which would decrease morbidity as they get older. Parents must decide whether to continue hydroxyurea treatment for their child or to pursue a more definitive treatment such as BMT.

A Council member stated that the long-term goal is to be able to do the replacement therapy, whether by transplant or gene therapy, as early as possible—perhaps even in the first year of life. Survivor rates have to be extremely high to advance that goal, and it will need government support.

Ms. Stroup noted that the Council's recommendations are made to the Secretary and do not have to be limited to issues that are under the purview of HRSA. Recommendations that pertain to NIH funding would be appropriate for consideration by the Council.

Dr. McCullough stated that one of the Council's responsibilities is to promote making these therapies available. It would be appropriate for the Council to continue to monitor this technology as it develops, make recommendations, and look for opportunities to help make it available.

Dr. Kamani requested that the work group be allowed to continue to meet so that it could look at these issues in more detail and perhaps draft some recommendations for discussion at the next meeting.

Dr. Milford approved Dr. Kamani's request.

Update on the Evidence Based Management of Sickle Cell Disease: Expert Panel Report 2013

Nancy DiFronzo, Ph.D., Program Director, BMTCN, NHLBI
Joylene John-Sowah, MD, Medical Officer, Division for Application of Research Discovery, NHLBI

Dr. DiFronzo provided an update on a document that NHLBI facilitated, entitled, "Evidence Based Management of Sickle Cell Disease: Expert Panel Report 2013." The expert panel was convened in 2009 and was charged with developing a comprehensive set of systematically reviewed, evidence-based SCD guidelines for both children and adults that target primary care providers to enhance management of the disease across the lifespan.

Dr. DiFronzo noted that the process for developing the guidelines was consistent with the approach recommended by the Institute of Medicine (IOM). NHLBI identified the topic area and selected the members of the expert panel. The panel developed a set of critical topics to be evaluated, as outlined by Dr. Kamani. An independent methodology team from the Mayo Clinic in New York conducted a

literature review. The methodology team evaluated the literature for quality and strength of evidence, developed an evidence table, and summarized the tables. The expert panel reviewed the evidence, developed consensus recommendations on each of the topics, and prepared a draft report in June 2012. The draft report was reviewed internally and externally was released for public comment in 2012. NHLBI staff collated the 1,300 comments received from the public for evaluation by the expert panel. The draft report was modified as needed, and the revised draft was sent to several outside organizations for their consideration in May 2013. At the time of this meeting, the near-final version of the report was being reviewed by NHLBI and relevant Federal agencies and was expected to be released in Fall 2013.

Discussion

Dr. Kamani asked if the final report was significantly different from the draft that was released for public comment with respect to references to HSCT. Dr. John-Sowah stated that the report mentioned that HSCT is potentially curative, but it did not make a specific recommendation. Transplantation was not among the key questions identified by the panel, because it is outside the purview of the primary care providers who are the target audience for the document. In response to comments received through the public comment period, the panel reevaluated what it said about SCT and decided that it was comfortable stating that transplantation is potentially curative but not yet widely available. Dr. Kamani stated that the Council would await the publication of the final report and would review it at that time.

Responding to a question from Dr. Milford, Dr. John-Sowah stated that the expert panel did not include transplant specialists. The report is close to publication. Once the document is released, the panel will be disbanded.

Dr. Milford stated that this document would serve as a blueprint for years to come and expressed concern that the document was missing an important piece. He posed a hypothetical case of a new study providing evidence of a drug that would provide a cure with no complications and asked how such a study would be incorporated in the document. Dr. John-Sowah replied that it was essential to define up front where the review would end, because there is a constant stream of new studies. Roughly speaking, the panel did not consider studies that were published after 2011. Studies coming out now would not have gone through the same type of rigorous review as the studies that were evaluated by the panel.

Dr. Kamani expressed concern that the guidelines reflected a missed opportunity and a step backwards. Previous editions of the guidelines made more reference to transplantation. The guidelines would not serve the public or primary care and specialty physicians if they do not provide information about the options that are available.

Dr. Campbell noted that the focus of the guidelines was to provide general guidelines of standard of care practices for primary care physicians, without going into too much detail about therapies. He asked whether NHLBI would publish another guideline focused on treatment strategies, such as hydroxyurea and SCT. Dr. John-Sowah confirmed that this report was specifically targeted toward primary care physicians. Previous books were considered the domain of specialists and were not developed using the same process of systematic review.

A Council member expressed concern that the panel did not include a transplant expert, which was a blind spot. Primary care physicians need to know about transplantation so they can inform their patients early on, when it is most effective. If physicians do not inform their patients, they won't see a specialist.

Dr. Kamani felt it was not appropriate to focus on primary care physicians, because they do not order blood transfusions or prescribe hydroxyurea. Empowerment of patients and primary care physicians would be improved by informing them about the role of transplantation at a very early stage.

Dr. DiFronzo asked if that was the role of patient advocacy groups. Dr. Kamani replied that patient advocacy groups take their cue from documents like the NIH guidelines. If the document does not

mention transplantation, they are less likely to trust a physician who recommends the treatment. There is no reason why primary care physicians should not know about the role of transplantation in treatment of this disease.

Dr. Campbell proposed that the Council work in partnership with NHLBI to develop a document that would discuss SCT as a treatment of choice for SCD and thalassemia, based on certain criteria.

Rebecca Pentz, PhD, stated that, from an ethical perspective, it is very important that the primary care physician is well informed early on, especially as we move toward a health care system that relies on them. She would strongly support an additional document if the guidelines are already set in stone.

Dr. Kamani supported Dr. Campbell's suggestion to develop an evidence-based document that could serve as an addendum to the guidelines. Dr. DiFronzo and Dr. John-Sowah noted that they were not in a position to authorize such a project.

Dr. Kamani state that once the guidelines are released,. the Council would have a better understanding of what additional information would need to be made available to patients and primary care physicians.

A Council member expressed concern that insurance companies might cite the guidelines as a reason not to fund transplants. Dr. Kamani responded that there had been quite a few problems with the adult population, but he was not aware of any significant issues with insurance coverage for the SCURT trial.

Dr. Campbell noted that preliminary data from current studies could potentially provide an evidence base to support transplants. Dr. Kamani noted that there is a lot of data in the literature showing that donor transplantation for SCD is a very effective therapy, including strong evidence regarding outcomes, long-term safety, and long-term potential complications. The Council should push for a document that would review the role of this therapeutic modality, for wide dissemination among the medical community and the SCD community.

Dr. Kurtzberg supported developing a document and expressed strong concerns that the SCT was not included in the guidelines. The general public and pediatricians need to know about it, because it involves family-planning and decisions about sibling cord blood banking, even within families of affected children.

A Council member supported Dr. Kurtzberg's point and noted that information showing the effectiveness of SCT could help to increase CB banking in minority populations. African Americans are still underrepresented in the registry and could potentially support SCT if they see that it is effective.

Dr. Campbell noted that in Europe, patients with thalassemia are receiving transplants very early. Although these patients represent a smaller cohort, they have lifelong blood transfusions. The Council should have an open net in terms of the hemaglobinopathies. Other Council members agreed. Dr. DiFronzo noted that NHLBI supported a small trial. The last patients had been enrolled, and preliminary results would be presented at an upcoming meeting.

Advancement in Cellular Therapies Work Group – Proposed Charge

Dr. Milford asked Dr. Anasetti to present his proposed charge for the work group.

Dr. Anasetti noted that he posted a draft motion for the Council's consideration on the chat function for the meeting. The motion included background information, followed by four questions:

1. What is the current use of cellular therapies in areas other than hematopoietic reconstitution?
2. Which of such cellular therapies are in the purview of the FDA?

3. Should HRSA monitor cellular therapy activities for non-hematopoietic reconstitution as part of the SCTOD Program? If so, the workgroup should provide guidance to the SCTOD contractor.
4. Is public education needed in these areas of cellular therapies? If so, should the responsibility fall onto entities such as FACT and AABB and professional societies such as ASH, ASBMT, ISCT or ISSCR, or HRSA?

Discussion

Dr. Champlin stated that it would be difficult for the Council to take on non-hematopoietic transplant cell therapies. The current system is built upon a voluntary CIBMTR process that was already in place for hematopoietic transplants. The criteria for success and failure and standard outcomes of hematopoietic transplant are known. Cellular therapy for regenerative medicine treats a broad range of non-malignant diseases, with no clear criteria for response and success, and totally different people are involved. Recruiting those people into the community and developing a reporting system and database would be a monumental task that is not currently feasible without significant funding or effort.

Dr. Milford suggested it was premature to make recommendations before seeing what the landscape is. He was not sure the Council had a good understanding of what is happening in the field.

Dr. Champlin supported the idea of conducting a survey. However, finding a way to communicate with people who are not part of a hematopoietic transplant program could present a challenge.

Dr. Milford requested feedback from HRSA as to whether the Council should gather information in this area. Ms. Stroup replied that the charge should be fairly broad. As outlined, it would involve a significant amount of work. She expressed concern about how the task would get done, since Council members are very busy. Gathering information would be a good idea, and the work group members who were proposed at the last meeting have some idea about the current environment.

Dr. Milford urged the Council to be humble in terms of expectations. The first step would be to collect information and get the appropriate people together to discuss how that could be done. Decisions about what to do based on that information would be made down the line.

Dr. McCullough stated that the Council needs to determine where this could go, which requires data. One possible approach could be to look at how many are affiliated with clinical transplant programs and consider recommending that type of affiliation, to avoid the problems associated with the proliferation of "mom and pop shops."

Dr. Milford suggested that the Council give the work group Chair the authority to circumscribe the charges so they are more limited and focused.

A Council member asked if any other HHS advisory committees were addressing this issue. Ms. Stroup said she would look into that and get back to the Council. CAPT Lazarus noted that the FDA works with many groups that are involved in advanced cell therapies and regenerative medicine, usually in collaboration with NIH. She offered to help Ms. Stroup collect information.

Action Item
Ms. Stroup and CAPT Lazarus will collect information on other HHS advisory committees that are addressing advanced cell therapies and regenerative medicine, and Ms. Stroup will provide the information to the Council.

A Council member noted that many of the advanced cell therapies are far beyond the scope of what SCT clinicians normally do.

Dr. Kamani noted that the practice of using hematopoietic cells for non-hematopoietic applications is complicated because it involves multiple disciplines. Traditionally, the hematopoietic cell community has been fairly uniform. It challenging to set standards for non-hematopoietic applications or monitor for outcomes, because it is difficult to go beyond the traditional pathways that those in the field are accustomed to using.

Dr. McCullough stated that the important distinction was between the non-hematopoietic uses that are being conducted under IND in a structured way to generate decent data, versus other autologous uses in physicians' offices that are not controlled at all. The FDA will have a fair amount of data about those uses that are under IND, which could help to define the landscape.

Dr. Anasetti noted that this discussion was very different from the one following Dr. Gee's presentation. The earlier discussion focused on FDA purview and public education; Council members now seemed to be questioning whether any of this was feasible. He proposed that the work group focus on questions 1 and 3.

A Council member noted that nearly all investigational therapies are under IND; the information is proprietary and closely guarded. Public reporting of information about these trials is complicated both legally and practically.

A Council member stated that, as a patient advocate, she would like to see some information to determine whether the Council should proceed further. This is a confusing landscape for patients to navigate. They are desperate for a cure and will jump on the bandwagon of any practitioner who says they can cure them. Determining the scope of the problem would be the first step in being able to provide helpful information.

Dr. Milford stated that even if it was impossible to get a clear picture of what is going on, the Council needs to make a good effort to gather information so it can inform the Secretary of what it attempted to do and what it learned.

Dr. Anasetti suggested that bringing together the stakeholders would help the Council define the problem and provide a recommendation to HRSA or the Secretary or both as to whether a dedicated effort should be made. He expressed concern about the legal status of studies that are not conducted under IND.

CAPT Lazarus clarified that not all of that activity falls under FDA jurisdiction, because some of the cell transfers may not meet the criteria for regulation as biologic drugs. She did not want to give the impression that every transfer of material that is referred to as a non-hematopoietic stem cell would automatically be illegal.

Dr. Anasetti asked CAPT Lazarus if she had sense of what proportion of the overall activity would be considered less than minimal manipulation. CAPT Lazarus stated that there is a lot of advertising, and she has the same information as everyone else. As Dr. Gee mentioned, the FDA has taken action against some establishments whose activities clearly fall under the scope of FDA regulation. That information is available to the public.

Dr. McCullough suggested that it would be well worth the effort if the Council could determine what percent of the activity falls under the IND and percent is unregulated. That could lead to a recommendation that these types of things should be linked with an academic institution.

Dr. Kamani doubted that it would be possible to determine those percentages, because there is no way to identify what goes on in private clinics. A Council member suggested starting with an Internet search. It might not be an exhaustive search, but the magnitude of what can be found is surprising.

Dr. Milford stated that the work group would have a fair amount of leeway in what it would do. He volunteered to join the group and be actively involved in formulating a more clear set of goals.

Dr. Anasetti said he would convene the group.

Action Item
Dr. Anasetti will convene the Advancement in Cellular Therapies work group.

Dr. McCullough noted that one of his junior faculty members was preparing a review article for *Transfusion* on activities that are non FDA-eligible and may be able to provide information. He would ask her to call Dr. Anasetti.

Action Item
Dr. McCullough will ask the junior faculty member who is preparing an article on activities that are nonFDA-eligible to call Dr. Anasetti.

National Cord Blood Inventory: Cord Blood Bank Accreditation Specifications
Shelley Grant

Ms. Grant provided an overview of the accreditation specifications for CBBs that participate in the NCBI. The specifications are mandated by PL 109-129 to establish the minimum criteria for accreditation of CBBs.

Ms. Grant outlined the history of the specifications:

- Prior to the formation of the ACBSCT, HRSA gave interim recognition to the AABB and FACT for the initial NCBI competitions. All NCBI CBBs are currently accredited by AABB or FACT, or both. This interim decision was followed by a recognition process that allowed for input by the Council and the public. Currently AABB and FACT are the only accreditation organizations for CBs in the U.S.
- In January 2008, HRSA charged the Council to formulate a plan for developing recommendations with regard to accreditation. The Council formed a separate work group to deal specifically with this issue.
- In May 2009, the Council recommended that the Secretary recognize both AABB and FACT as accreditation organizations for the NCBI. The recommendation specified that both organizations were expected to adhere to HRSA's specifications for accreditation organizations, and their continued recognition was based on ongoing adherence to those specifications. The recommendation also stated that, three years from the time of the recognition decision by the Secretary, ACBSCT would review HRSA's experience with the accreditation organizations with regard to their adherence to the specifications.

Ms. Grant stated that the Council was due to review HRSA's experience with the accreditation organizations at the May 2013 meeting, but the information was not included in the materials for that meeting.

Ms. Grant reported that the current specifications work very well, and HRSA has a good relationship with both of the current accreditation organizations.

Discussion

Dr. Milford asked if the Council was expected to rule on this issue. Ms. Grant replied that the Council could rule now, if it felt it had adequate time to review the background materials, or it could rule at the next meeting.

Dr. Milford asked if Ms. Grant recommended that HRSA continue with these two organizations as accrediting organizations. Ms. Grant replied that the current specifications work very well and HRSA has a good working relationship with both organizations.

A Council member asked if there had been any substantive changes in the requirements. Ms. Grant replied that the requirements initially specified that the accrediting organizations would visit each CBB every two years. That requirement was changed to every three years. Dr. Milford replied that the Council discussed that change at a previous meeting. Ms. Grant confirmed that there had been no additional changes.

Dr. Milford noted that the Council had reviewed the criteria in detail previously and was aware of the change in terms of the timing of the visit.

A motion to endorse the current accreditation organizations was made and seconded. The motion carried on voice vote.

New Business

Dr. Milford asked if Ms. Stroup or any of the ex officio members had any new business. Hearing none, ne opened the floor for public comment.

Public Comment Period

Dr. Milford asked the operator to open the phone lines for public comment and invited any member of public to identify themselves and their institutional affiliation, if any.

Hearing no individuals with public comments, Dr. Milford closed the public comment period.

Dr. Milford asked Ms. Stroup about the timing of the next meeting. Ms. Stroup stated that the next meeting would be held in approximately six months. She noted that several Council members would be rotating off in the next six months. HRSA has published a solicitation to nominate new members. She encouraged Council members to identify individuals who would satisfy the requirements of the statute, which she would send to all members.

> **Action Item**
> Ms. Stroup will send all Council members a copy of the solicitation to assist them in identifying and nominating new members.

Dr. Milford stated that it would be important to make sure that the Council has certain skill sets. He asked Ms. Stroup to send information regarding the skill sets of current members, including those who will be rotating off the Council and those who will continue to serve.

> **Action Item**
> Ms. Stroup will prepare a list of the skill sets of current Council members and will distribute it to all members.

Dr. Milford called for a motion to adjourn. The motion was made and seconded and carried on voice vote.

Dr. Milford adjourned the meeting at 3:20 p.m.