U.S. Department of Health and Human Services
Advisory Council on Blood Stem Cell Transplantation (ACBSCT)
January 28-29, 2008
Rockville, MD

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After all of the council members were sworn in, they returned to the meeting room.

Welcome

Health Resources and Services Administration (HRSA) Associate Administrator for Healthcare Systems, Joyce Somsak, welcomed the council members and commented this has been a long process and she is happy the members are here. She introduced Dr. Betty Duke, who has led HRSA since 2001.

HRSA provides direct health care to 20 million people in the U.S. Through the Ryan White CARE Act, HRSA helps provide medications and treatment to help people living with HIV/AIDS. HRSA's health centers deliver preventive and primary health care to patients, 40 percent of whom have no health insurance. HRSA's Maternal and Child Health grants fight infant illness and mortality by supporting health care. HRSA also trains health care workers, places them where there is a lack of providers, encourages organ and tissue donations, and oversees the transplantation field.

As Administrator of HRSA, Dr. Duke has made HRSA a more cohesive organization; and she has streamlined the way that HRSA communicates with both the public and Congress. In 2006, she was awarded the Presidential Rank Award, which is the most prestigious award given to Federal employees. Ms. Somsak closed by saying that it's wonderful to work for someone who knows how to get things done.

Dr. Duke opened by saying she was thrilled to see the Advisory Council members here, ready and eager to begin their work. It has been, she noted, a long process; but this meeting is a great step forward. Dr. Duke expressed her delight that the members are all here. The Advisory Council represents an enormous contribution of talent to the Nation. This contribution of time comes out of the members' lives and personal time. She said that HRSA cannot thank the members enough and, on behalf of HHS Secretary Leavitt, Dr. Duke expressed her appreciation for the Council members' work.

Dr. Duke also recognized that this Advisory Council meeting is a huge step forward for the program and that it has been 2 years in the making. "Good things take a while to get going," she said. Still, she has been excited about the pace at which HRSA has been able to move in implementing the new programs overall. President Bush, HHS Secretary Leavitt, and members of Congress have all been very supportive of this work. HRSA is blessed to have fabulous bi-partisan support for its programs. This Program brings together opportunities to serve both the field and the patients in most need of care. Advisory Council members have an opportunity to

influence policy as well as to make information available so that patients know what their choices are, resulting in more informed decision-making.

Even though HRSA is not as well known as some sister agencies such as NIH and CDC, Dr. Duke outlined some of the valuable work done by HRSA. HRSA tries to deliver complex programs in the simplest way possible. It takes the tax money given to it by the American people and turns it into programs for the public as Congress and the President have dictated through laws that have been passed and signed. HRSA performs a considerable amount of work in HIV/AIDS. In fact, the Ryan White CARE Act has been reauthorized several times, becoming more complex each time. The Ryan White CARE Act now includes many partners, which is the key to every HRSA program's success. The Administration does not see itself as the be-all and end-all, but rather as the means to bring partners together to benefit the public. Through Ryan White, HRSA has relationships with the biggest cities where the AIDS epidemic has had the biggest impact. HRSA also works with the States and, through them, provides support for HIV/AIDS drugs for 500,000 people living with the disease. In addition, HRSA supports community-based organizations, for which the goal is prevention or provision of early intervention and treatment; and it supports oral health care and family services.

To better address all of the needs of these programs, Dr. Duke said that HRSA has a series of partnerships. It also works with universities to provide education. Ryan White provides a good example of partnerships, and the hope is that this new Program will work in a similar manner as well. HRSA also works with over 4,000 community health clinics, which have been expanding rapidly. The number of clinics has been increased by 1,200 in recent years. The goal is to serve isolated, rural, and underserved populations. This overview gives some of the sense of HRSA's work and approach.

Dr. Duke went on to explain that this Advisory Council, as with many others with which HRSA works, exists to give members the opportunity to provide the best possible advice to the Secretary. HRSA has a number of Advisory Councils, which are considered vital to the partnership approach of its work. HRSA is used to working with these Councils and, through each of them; the Administration learns new things and gains new opportunities to work more effectively. The agency wants members' feedback on how to affect national policy and how HRSA can work to ensure that the gift they are giving, by their service, is backed up by bureaucratic support in order to make their contribution as effective as possible.

Dr. Duke mentioned that the Advisory Council members would hear more later about the Act that created this new Program, as well as more about what has been accomplished so far. For the C.W. Bill Young Cell Transplantation Program, HRSA used competitive contracts to get it up and running. Four contracts were awarded in September 2006 to set up the bone marrow and cord blood coordinating centers, patient advocacy office, and data collection system for transplant outcomes. Three contracts are held by the National Marrow Donor Program (NMDP) and the other award was to the Center for International Blood and Marrow Transplant Research (CIBMTR). The transition to the new structure was accomplished without any reduction in services to patients. Adult donors are being recruited at a good pace from all populations and the programs are on target to reach their stated goals. Data collection has begun. Most importantly,

record numbers of transplants have been facilitated: 4,000 occurred in 2007, which is a record high.

Regarding the National Cord Blood Inventory, Dr. Duke said that six banks were awarded contracts in November 2006 through a competitive process (HRSA is very committed to clear and open competition for all of its programs). The six banks are: Puget Sound Blood Center, New York Blood Center, Duke University, MD Anderson Cancer Center, the University of Colorado, and StemCyte. Two more were recently added: the South Texas Cord Blood Bank and the St. Louis Cord Blood Bank. More than 10,000 cord blood units have been collected, over half of which are from minority donors, including 12 percent African American donors.

Many challenges remain, Dr. Duke noted, and in these areas HRSA seeks the Advisory Council's help. Each year the number of patients who are unable to find a suitable donor or cord blood unit exceeds the number who are able to do so. HRSA needs help in finding ways to change this situation. Also, minority patients have a poorer chance than Caucasian patients of finding a suitable donor; a better job needs to be done to decrease disparities in access to this life-saving therapy. Gratifyingly, survival rates have been improving and, in some cases, are almost as high as with a related transplant, but still are well short of what is needed. HRSA is well aware of the challenges and does not think this will be easy. Dr. Duke said she knows that if everyone works together and puts their shoulders to the grindstone, it will work.

Dr. Duke closed by saying she was eager to hear what the members will do as they work through the ambitious agenda which, she was sure, would engage everyone. She asked members to let HRSA know about any agenda deficiencies they perceive, and HRSA will try to do better. She thanked the members for being part of this enormous work and for being present today.

Opening Remarks & Introduction of Members

Dr. Karl Blume, Chair of the Advisory Council on Blood Stem Cell Transplantation (ACBSCT), invited members to briefly introduce themselves and describe their relationships with transplantation and with the Council's work. After members introduced themselves, Mr. Remy Aronoff, Executive Secretary of the ACBSCT, thanked everyone for participating in the Advisory Council.

Mr. Aronoff described how the Council works. It is most similar to the Advisory Council on Organ Transplantation (ACOT), of which Dr. Edgar Milford was a member. The meeting agenda is based on any suggestions the members have, a summary of what occurred during the previous meeting, and anything else that is current and/or potentially interesting. Agenda items may be something about which the Council might make a recommendation, or just something of particular interest to members. Recommendations can be made and agreed upon at the meeting, or they can be refined through subject-specific workgroups held in between Council meetings. Council workgroups tend to meet once or twice between Council meetings. Recusal and waiver memos have not yet been collected from all members, but it's still possible to draft a recommendation and discuss it a work group for a vote at the next meeting, to be held on April 28-29, 2008.

Mr. Aronoff explained that a member can be on as many workgroups as desired. The ACOT has not had permanent workgroups, just issue-specific workgroups that are disbanded when a resolution is reached. When the Council approves a recommendation, it is sent to the Secretary of the Health and Human Services Department (HHS). Usually, 2 or 3 months elapse before the Council hears whether the recommendation has been approved or not. Then, if approved, the recommendation is sent to HRSA's Division of Transplantation staff and entities that are addressed by the recommendation (and sometimes to Council members, too), to collaborate on implementation. ACOT has had a number of recommendations related to the Organ Procurement and Transplantation Network (OPTN), for example, and has had a lot of success in getting policies altered or changed based on its work.

Members of the public who want to make comments or remarks were asked to hold them until the end of each day during the public comment period. If anyone wished to make a comment, they were told to let the staff know; and they would be put on the schedule to speak during the public comment period.

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Dr. Jim Burdick added his welcome to Mr. Aronoff's, stating this is an exciting time in this field and in the field of medicine. Then Dr. Burdick said he would speak about the Advisory Council's role and purpose and what the group might be called upon to do, or might wish to do, as part of its service.

The Role of the Advisory Council on Blood Stem Cell Transplantation, Dr. Burdick, Division of Transplantation

Dr. Burdick began by describing the Council's role and purpose, which is to discuss and make recommendations regarding the Program and matters related to it, including both the National Cord Blood Inventory (NCBI) and the C.W. Bill Young Cell Transplantation Program. The Council is to: "Provide a consolidated, comprehensive source of expert, unbiased analysis and recommendations to the Secretary on the latest advances in the science of blood stem cell transplantation," and to: "Advise, assist and consult on broad Program Policy" as described in the Charter for the ACBSCT.

Dr. Burdick noted that establishment of an Advisory Council can be intellectually far-reaching, but has a structured place in government language and Federal law. The steps taken towards establishment of the ACBSCT under the Federal Advisory Committee Act (FACA) included:

- Draft and final establishment packages sent to HHS;
- Charter and call for nominations published in the *Federal Register;*
- Draft and final nomination packages sent to HHS;
- Members appointed by the Secretary of HHS; and
- First meeting scheduled and published in the *Federal Register.*

HRSA started work on this Advisory Council as soon as the Law was signed because it recognized that establishing an Advisory Council takes a long time. Since there was urgency from Congress to move ahead, HRSA opted for parallel implementation of the Program components, including the Advisory Council, with the recognition (and expectation) that many of the interim policies would be revisited by the Council and Program at a later date.

In terms of the Council's composition, the Law lists 15 required categories for membership. There is a large variety in these categories including voting and non-voting ex officio members (this is also all noted in the *Federal Register* notice). Some members have expertise in several of the required categories.
Additional categories were recommended to HRSA in the Request for Information (RFI) responses and through consultation with other stakeholders. The categories specified in the *Federal Register* are:

Voting members:

- Representatives of marrow donor centers and marrow transplant centers
- Representatives of cord blood banks and participating birthing hospitals
- Recipients of bone marrow transplant
- Recipients of cord blood transplant
- Persons who require such transplants
- Family members of a recipient or a patient who has requested the assistance of the Program in searching for an unrelated donor of bone marrow or cord blood
- Persons with expertise in bone marrow and cord blood transplantation
- Persons with expertise in typing, matching, and transplant outcome data analysis
- Persons with expertise in the social sciences
- Basic scientists with expertise in the biology of adult stem cells
- Ethicists
- Hematology and transfusion medicine researchers
- Persons with expertise in cord blood processing
- Members of the general public

Non-voting, ex officio members include representatives from HRSA, the Food and Drug Administration (FDA), National Institutes of Health (NIH), Department of Defense (DoD), Centers for Medicare and Medicaid Services (CMS), and the Centers for Disease Control and Prevention (CDC).

Dr. Burdick stopped for a second to talk about "marrow," noting that the more technical terms are "adult blood stem cell donor" and "cord blood." These are two frequent sources of cells from adult donors: the bone marrow literally and blood stem cells released from the marrow into the circulating blood, with the circulating blood being the more frequent source today. He noted that the group will likely talk about marrow, however, so he asked the members to please specify if he or she means marrow specifically; otherwise, it will be assumed that the speaker is referring to "adult blood stem cell donation."

Dr. Richard Champlin noted that transplants from marrow have some clinical differences from those from circulating blood and cautioned against dismissing the term "marrow," because it is a different tissue and preferred in some clinical settings.

Regarding possible topics for ACBSCT discussion, Dr. Burdick said that speakers have already mentioned minority access; and HRSA wants to emphasize the importance of this issue. Overall, there are millions of donors available but, sadly, many patients from all populations are unable to

identify an appropriate match. So one critical question is: "How can the public be more engaged in donation of adult donor cells and cord blood?" Another key issue is informed consent, particularly regarding the situation of the pregnant mother and child-to-be. HRSA also welcomes input on our interim definition of high-quality cord blood units eligible for reimbursement through the National cord Blood Inventory. Dr. Burdick also noted that about forty percent of the transplants facilitated by the program each year involve either a unit from outside coming in, or U.S. material leaving the country, so there is a huge international component to this field.

Dr. Burdick showed a summary of possible topics for ACBSCT discussion:

- Targets for National Cord Blood Inventory (NCBI) and the Adult Registry, including size and composition
- Requirements about informed consent for cord blood donation
- Accreditation requirements for cord blood banks
- Scientific factors defining a high-quality cord blood unit (CBU)
- Public and professional education related to donation
- Criteria for choosing appropriate stem cell sources for transplantation
- Priorities for the Program
- Research priorities, including emerging therapies using blood stem cells from all sources
- The scope and design of the Stem Cell Therapeutic Outcomes Database
- Regulatory policy including the compatibility of international regulations
- Public and private insurers, including actions to increase donation and access to transplant
- State and Federal Government actions (other than as insurers) to increase donation and access

In this meeting, the Department asks the members to specifically discuss three issues:

(1) Cord Blood accreditation for the NCBI;
(2) Confidentiality policies for cord blood donors; and
(3) Scientific factors necessary to define a CBU as high-quality.

Dr. Burdick closed by saying he was very excited to be part of the beginning of this process, a great moment in science and policy; and he wished all of the members well in this endeavor.

Status of Implementation of the Stem Cell Therapeutic and Research Act, Robert Baitty, Division of Transplantation

Mr. Aronoff announced that the group is ahead of schedule, so the agenda was adjusted. Specifically, the overview of the Act was moved up from the afternoon.

Mr. Baitty, Director of the Division's Blood Stem Cell Transplantation Program, discussed the components of the Stem Cell Therapeutic and Research Act, and noted the group would hear more about the Act later, as well. He said he would provide background and an overview of the Act; describe HRSA's implementation approach; describe the program components; and address

the current status of implementation. From the outset, HRSA saw this Act as an exciting opportunity to extend access to transplants to more of those who need them.

The Stem Cell Therapeutic and Research Act of 2005 (P.L. 109-129) is the authorizing law, and was preceded by efforts to enact authorizing legislation for collection and distribution of cord blood units (CBU) and to re-authorize the National Bone Marrow Donor Registry. Appropriations for a National Cord Blood Stem Cell Bank Program occurred in fiscal years (FY) 2004-2006. Other relevant activities include a 2004 Conference Report for the Appropriations law that required an Institute of Medicine (IOM) study about the best ways to implement a national cord blood program, the report for which was issued on April 14, 2005. Appropriations for these 3 years totaled nearly $24 million ($1 million was specified for the IOM study).

The aims of the Stem Cell Therapeutic and Research Act of 2005 (signed December 20, 2005) are to increase (1) the number of unrelated-donor transplants; (2) the public inventory of high-quality CBU from diverse populations; and (3) the number of CBU available for research. The Act has four sections: (1) a short title, (2) the National Cord Blood Inventory (NCBI), (3) the C.W. Bill Young Cell Transplantation Program (the Program), and (4) a requirement for a report on the status of FDA licensure of cord blood.

Section Two concerns the National Cord Blood Inventory (NCBI). Federal funding is intended to be temporary, with funding of individual banks limited to 3 years, after which point the banks are expected to achieve self-sufficiency. Making units available for research also is very important. While banks are collecting units suitable for transplantation they also will collect other units that can be used for internal quality improvement and for research. This section provides HRSA funding for high-quality, diverse CBU with a target of garnering 150,000 new units. It authorizes appropriations of $15 million per year from FY 2007-FY 2010. The funding structure is via one-time contracts. Cord blood banks (CBB) must participate in the C.W. Bill Young Cell Transplantation Program for at least 10 years, and the NCBI CBUs must be available through the Program in perpetuity. A related cord blood donor demonstration project is to be funded from a small portion (up to 5%) of the appropriations for FY 2007-FY 2009.

For the NCBI, HRSA reimburses at a fixed rate per unit. HRSA also negotiates discounted prices, which are necessary to make progress toward the goal of having 150,000 units. CBB eligibility requirements include accreditation by organization(s) recognized by the HHS Secretary (pending this recognition, accreditation by FACT or AABB) and a minimum public inventory of 500 CBU collected and banked by the applicant bank.

HRSA plans to have annual competitions for new cohorts of banks, if funds permit. The goals are to add banks in new geographic areas in order to fine-tune the diversity of CBU; to broaden opportunities for Federal support; to encourage quality improvement across the “industry”; and to permit timely adjustments based on the bank’s performance. The current (FY 2008) appropriation is for about $8.8 million, which is less than needed for continuation of current banks, so future funding cycles may be impacted.

Section Three addresses the C.W. Bill Young Cell Transplantation Program (the Program), which is the successor to the National Bone Marrow Donor Registry (NBMDR). The Program is

intended to facilitate transplants and collection of outcomes data. Up to five different infrastructure components were to be separately (and competitively) awarded by HRSA. In addition, the Act specified the creation of an Advisory Council at the HHS level, which is this Advisory Council. The Act includes Program provisions about accrediting organization(s) for Cord Blood Banks (CBB), informed consent for those donating CBU, and continued planning for marrow-toxic emergencies. Federal funding of the Program is intended to be on-going and the Act authorized $38 million per year for FY 2007-FY 2010 (the FY 2008 appropriation was about $23.5 million).

Mr. Baitty showed a diagram of the Program components and described them. On the left, the accrediting organization(s) indicate new HRSA relationships. Also, new is this Advisory Council. The ovals to the right of the accrediting organizations represented possible new contract structures for the Program. Public cord blood banks (CBB) collect, process, store, and make available the cord blood units contained in the banks. The Cord Blood Coordinating Center and the Bone Marrow Coordinating Center facilitate transplants with cord blood and adult donor cells, respectively, conduct recruiting, and tissue-types the adult donors. Additional ovals represented the Single Point of Access to cells from both cord blood and adult donors and the Office of Patient Advocacy which assists patients in overcoming a variety of barriers to transplant. The bottom of the graph showed the "users," which are the transplant centers, patients, and referring physicians.

HRSA's approach to implementation is guided by three goals: (1) creation of a single point of access for patients and physicians to all sources of blood stem cells; (2) expeditious collection of high-quality diverse CBU; and (3) collection of comprehensive data on transplants' clinical outcomes. HRSA recognizes that the field is evolving rapidly and has been cognizant of that in implementation.

Implementation was also informed by extensive consultation, specifically:

- RFI was published in August 2005
- Teleconferences with transplant physicians
- Consultation with American Society for Blood and Marrow Transplantation (ASBMT) representatives
- Teleconferences with public and private CBB
- Site visits to public and private CBB
- Teleconferences on informed consent
- Correspondence with accrediting organizations and participation in inspector training
- Teleconferences on accreditation (announced in *Federal Register*)
- Discussions with experts in CBU processing
- Consultation with other Federal agencies (e.g., NIH, FDA, CDC, Navy)
- Many Congressional briefings

HRSA engaged in the initial implementation process parallel with the creation of the Advisory Council because it knew the latter process was going to take considerable time due to the Federal Advisory Committee Act (FACA) process. In the interim, HRSA needed to address the practical imperatives of creating the program structure and of spending time-limited Federal funds directed to this Program. HRSA also was aware of the many patients each year who are unable

to obtain an unrelated-donor transplant, and so felt an urgent need to begin collection of the National Cord Blood Inventory as quickly as was consistent with ensuring high quality.

The parallel establishment of components included competitive contracts, contracts with CBB to collect for the NCBI, and four contracts for the C.W. Bill Young Cell Transplantation Program (the Cord Blood Coordinating Center, Bone Marrow Coordinating Center, the combined Office of Patient Advocacy and the Single Point of Access, and the Stem Cell Therapeutic Outcomes Database), this Advisory Council, and recognition of the accrediting organization(s). Per congressional direction, requests for proposals (RFP) did not prescribe or prohibit a particular model or technology, and the RFPs allowed for subcontracting and consortia arrangements.

During this transition, HRSA extended the contract for National Bone Marrow Donor Registry and established several working groups to coordinate among the component agencies. Making contract awards by September 2006 (when the FY 2006 appropriations for the Program would expire) required interim approaches in many areas, including the technical requirements for NCBI CBB and HRSA-reimbursed CBU; recognition of the accrediting organization(s); and requirements for informed consent. These interim provisions will be revisited with the input of both this Advisory Council and the public.

Mr. Baitty showed an updated version of the graphic shared earlier, illustrating the contracting structure for the Program. This graphic, however, does not show the complex relationships among Program components for facilitating transplants and reporting outcomes data. The graphic indicated how funding flows from HRSA to the contract organizations. The horizontal dotted line near the bottom of the graphic indicated the differences in what the external communities (patients and doctors) deal with (these are below the dotted line), and the infrastructure components (above the dotted line). Also note, as indicated, that the Office of Patient Advocacy and the Single Point of Access, the main organizations with which patients and physicians will interact, have been combined.

Turning to the status of implementation, Mr. Baitty noted that contracts were competed for, and awarded, in September 2006, for the Outcomes Database, the Cord Blood Coordinating Center, the Bone Marrow Coordinating Center, and the (combined) Office of Patient Advocacy and Single Point of Access. For the NCBI, HRSA awarded contracts to the first cohort of 6 cord blood banks in November, 2006, and to a second cohort of 2 banks in September 2007. HRSA announced interim recognition of accrediting organization(s), and issued several announcements in the Federal Register leading to the first Advisory Council meeting held on January 28-29, 2008. An interim report on the definition of a "high-quality cord blood unit," required by the Act, was submitted to Congress on October 23, 2006.

Mr. Baitty showed a slide illustrating that the National Marrow Donor Program (NMDP) was awarded the contract for the Bone Marrow Coordinating Center, the (combined) Blood Stem Cell Single Point of Access and Office of Patient Advocacy, and the Cord Blood Coordinating Center. The Center for International Blood and Marrow Transplant Research (CIBMTR) at the Medical College of Wisconsin received the contract for the Stem Cell Therapeutic Outcomes Database. The first cohort of NCBI banks was: Puget Sound Blood Center, New York Blood

Center, Duke University, MD Anderson Cancer Center, the University of Colorado, and StemCyte. The second cohort was the South Texas CBB and the St. Louis CBB.

Funding for the initial year of collections under the HRSA contracts will enable the six NCBI CBU to acquire about 10,500 new cord blood units, with good representation from populations with historical difficulties in finding and recruiting adult donors. The percentages of new units by racial/ethnic group are: Caucasian (37.4%), Hispanic (28.8%), African-American (19.8%), Asian (7.1%), Multi-Race (6.3%), and Other Minorities (1%). For Year 2, the eight NCBI CBU banks are expected to add another 11,800 cord blood units with the following representation: Caucasian (33.8%), Hispanic (29.7%), African-American (21.6%), Multi-Race (7.7%), Asian (6.8%), and Other Minorities (1%).

As of January, 2008, the first cohort of banks is collecting units at a good pace. Approximately 10,000 CBU that meet NCBI criteria have been banked, over half of which come from minority individuals. The number of collection sites has been increased (e.g., birthing hospitals), and there has been targeted selection of collection sites in order to complement HRSA's diversity goals. Thirteen NCBI CBU had been shipped for transplant as of December 31, 2007.

All of the banks experienced delays in the beginning, largely expected, , as they made some changes in technical processing of units to comply with HRSA's requirements and obtained IRB approval for modifications in their informed consent processes and forms. Banks needed between 2 and 4 months to complete this preliminary work and begin collecting units in full compliance with the contracts. More discussion of these and other challenges faced by the banks will occur on the second day of the Advisory Council meeting.

In conclusion, the status of the Program is that all four contracts are fully operational. The transition to the new Program was completed without any interruption in service to patients or physicians. The National Bone Marrow Donor Registry contract has been completed. Recruitment of adult donors, overall, and minority donors, specifically, is meeting HRSA targets. Cord Blood collections for the National Cord Blood Inventory are solidly underway. The outcomes data collection process began in December 2007. And most importantly, a record of nearly 4,000 transplants were facilitated in 2007.

Discussion

Dr. Bertram Lubin asked about the number of patients who cannot find donors. Mr. Baitty said estimates made in different ways converge on between 10,000-12,000 individuals each year in the U.S. needing an unrelated donor transplant, with fewer than 4,000 receiving one. This is very sobering, as patients who need an unrelated donor transplant have no good alternative therapies, and the prognosis for these individuals without transplant is poor. Factors, other than lack of an adequate donor or cord blood unit also often impede patients from getting a transplant, such as late referrals to transplant centers, and financial barriers.

Ms. Susan Stewart asked if there are areas in which this Council touches on related donors. The response was that, in general, this program is about *unrelated* donor transplants. The data

collection requirements for this law are broader, however, covering unrelated and related allogeneic transplants, as well as on emerging therapies involving "stem cells from a donor."

Dr. Robertson Parkman asked about the units to be used for research rather than transplantation, and whether those guidelines had been established. The answer was that they have not yet been established. In fact, HRSA would very much welcome the Council's help in determining whether guidelines are needed to supplement the policies of individual banks, and establishing such guidelines regarding the types of units that can (or should be) used for research.

Dr. Blume asked about 4,000 transplants performed in 2007, and what the sources were for those grafts. Mr. Baitty responded that National Marrow Donor Program (NMDP) staff would present a detailed breakdown later. In general, peripheral blood transplants are the majority (about 60 percent) and the bone marrow and cord blood are roughly equal at about 20 percent, with cord blood growing rapidly.

Related Cord Blood Donor Demonstration Project, Randy Gale, Division of Transplantation

Since the meeting was running significantly ahead of time, Mr. Aronoff asked Mr. Randy Gale to do his presentation early. Mr. Gale is a Public Health Analyst in the Division of Transplantation.

Mr. Gale described the Related Cord Blood Donor Program Demonstration Project, which was authorized by Public Law 109-129 as part of the larger National Cord Blood Inventory (NCBI) initiative. He mentioned that these units do not count toward NCBI goals, however, and no more than five percent of funds appropriated for NCBI (FY 2007-FY 2009) can be used for this project. Several public and private banks are already engaged in these activities, including Children's Hospital Oakland Research Institute, which for several years received NIH funding for this activity.

Mr. Gale said that the project is a 3-year demonstration under which qualified banks collect and store cord blood for families in which a first-degree relative has a diagnosis that may be treatable through blood stem cell transplantation. The cord blood units are to be collected and stored at no charge to the eligible families. At the demonstration's conclusion, the Secretary is to report to Congress on the utility and feasibility of continuing such a program.

Mr. Gale went on to explain that the law does not specify goals or study questions, although it requires the report to Congress to include the number of cord blood banks participating; the number of cord blood units banked; the number of units used for transplantation; the results of any research; and the amount of money spent by the banks in support of this project. The law (and the accompanying Senate Report) indicates that qualifying unused units should revert to the Program's public inventory. A CBU initially intended for use in a first-degree or second-degree blood relative but later intended for use in an unrelated allogeneic recipient would need to be licensed or under an Investigational New Drug (IND) application. HRSA will have to carefully consider all implications of cross-over, working with FDA and the banks.

The status of the project is that a *Federal Register* notice (May 2007) proposed several key study questions and invited comment from the public on HRSA's approach. One idea suggested in the

Federal Register notice was that, based on the limited funds and potential demand far in excess of what the funding can support, HRSA might limit participation in the demonstration to those populations that have the most difficult time finding matched-unrelated donors, i.e., African Americans. The respondents urged HRSA not to limit eligibility to any one population. Respondents also suggested additional key questions for the project.

Mr. Gale said that in the fall of 2007, the first and second cohort of NCBI banks were invited to submit proposals for participation (five out of eight banks are participating: Carolinas Cord Blood Bank at Duke, MD Anderson Cord Blood Bank, Puget Sound Blood Center, StemCyte, Inc., Texas Cord Blood Bank). HRSA provided very modest reimbursement for collection and maintenance of these units. In FY 2007, there were funds to cover about 765 CBU. The CBCC contract (with NMDP) also was modified to include assisting in coordination and implementation of this project. HRSA has considered ways in which the remaining NCBI banks and other banks might contribute, as well. In December 2007, a planning meeting was held in Washington, D.C. Participants included public and private (family) banks; physicians; representatives from the Cord Blood Coordinating Center, FDA, NIH, and other entities with relevant experience.

The basic components of the Project design are to:

1. Create ways in which the service can be offered to and reach the maximum number of eligible families;
2. Assess the program's effectiveness in reaching and serving eligible underserved and underrepresented populations (e.g., African Americans);
3. Enable access to better treatment options (transplant) for eligible families; and
4. Determine the Program's financial impact relative to the benefits for affected families.

Key questions that would be studied are:

- What is the demand in the U.S.?
- What are the clinical indications for which related CBU are used for transplantation?
- Can the program be designed to gather the necessary data regarding the possible safety and utility of cross-over of family-banked CBU to the public inventory?
- Do units collected through this Project represent unique HLA types?
- How can public and private (family) banks collaborate?
- Can this Project demonstrate the effectiveness and efficiency of a remote (kit) collections model that meets accreditation requirements and allows selectively targeting and increasing minority donations to the public inventory?
- Can sufficient outcomes data be collected, reported, and analyzed by the Stem Cell Therapeutic Outcomes Database?

Mr. Gale then mentioned that work groups are being established to refine the program design, specifically around: (1) Education and outreach for families; (2) Collections; and (3) Clinical Indications and Demand.

HRSA expects to begin collections and banking based on the finalized program design in the spring/summer of 2008. HRSA will monitor the project and provide updates to this Council at future meetings.

Discussion

Dr. Parkman asked about a case involving a family in which there had been a patient, but the patient died, so there was no living patient who needed a transplant. In this case, would the family be able to use the program? Mr. Gale responded that there has to be a documented need on the part of the living patients. Dr. Lubin commented that, when getting into autoimmune diseases, there will be a larger demand for innovative therapies. Mr. Gale agreed and said that this would be brought up in the Clinical Demand Working Group. Dr. Joanne Kurtzberg added that the concept has been similar to that of sickle cell, where the intent is to save the units for the family if it has had a death already. Although this question had not been raised, the working groups would address it.

Dr. Lubin stated that this is a small amount of money and a minor component of the law. In his experience, twenty percent of the sibling units collected and HLA-matched with the patient have gone to transplant. "That's huge and," he said, "if one could HLA type the babies' cord blood type from the mother's blood, and collect units matched, it would be a remarkable project." Dr. Lubin suggested being mindful of the fact that the pilot program would generate much interest, but there are very limited resources to support such an effort. Also, HRSA provides newborn genetic programs in the U.S. (through partnerships with genetic services); and there is a need to help doctors know that there is a resource for collecting this information. The word needs to get out and there should be implementation, through State policies, so that obstetricians could ask if there is a child with a disease. If so, they'd be able to tell them so that they could consider utilizing this resource.

Dr. Pablo Rubinstein agreed to the importance of this and stated that his bank's experience was quite different. He has had 92 donations that were originally intended for the donor's sibling since 1994. This is a small number but none of them have been transfused to the intended recipient. The donations remain in the freezers without being used. The main reason that they are not used, based on surveys, seems to be that the families do not know what can be achieved and what can be expected. Families need help taking advantage of this program. His organization's approach is that the family donates to the bank. If there is a full match to the individual, then the unit is permanently reserved for that individual until the patient is transplanted or a different mode of operation is reached. Otherwise, the unit belongs to the bank or is available for research. Some have been made available for research, another aspect of these donations. There may be genetic or other causes of concern that the sibling of the patient may be at increased risk of disease.

Ms. Stewart wanted to know which questions were different from those in Dr. Lubin's program. Mr. Gale said that the NMDP Working Groups would bring up these issues and everyone would work together. He wanted to encourage the broad collection of data. Cross-over data are the most needed, as with sickle cell. When they went back and asked families who had not used the units yet to put them in the public bank, a fair number were not interested because they thought that they might have another child.

Dr. Champlin asked about the feasibility of Dr. Lubin's pilot program. Dr. Lubin responded that it took a long time to get support for this program; a supporter convened a special NIH study session that recommended it for funding. When families are highly motivated (e.g., sickle cell families), the mother takes the key role in informing the obstetrician about it. Less than two percent of the units collected were insufficient and/or contaminated. Furthermore, cell recovery ***is*** exceptionally good for families who are motivated by having a child that could benefit from transplant.

Dr. Kurtzberg commented that Dr. Lubin's program was wonderful but that it is no longer supported by the Federal Government. This was taken over by Viacord, a private CBB, which may continue the effort. She noted that private banks' practices differ from those of public banks and the NMDP policies. She suggested getting public support for units with a high probability of being used to be collected in a highly standardized way, and for families to know how to access the program. Quality is not standardized across other banks, and that's the mission. If Dr. Lubin's program was still being supported by the Federal Government, she said there would be no need for this. However, this is not the case – so there is a need.

Dr. Milford noted that there are a lot of collections and transplantations going on and asked what data collection has been mandated by the Federal Government, as well as how it is being enforced. Specifically, he wanted to know what the universe of data would be in the next year. Mr. Gale responded that outcomes data are to be reported on both related and unrelated allogeneic transplants: transplants with a U.S. recipient even if involving a foreign donor source, and products that leave the U.S. for an international patient. All types of blood stem cell transplants except autologous must be reported, but the leaders in the field have also recommended using the same mechanism to collect data on autologous transplants.

Dr. Lubin commented on the funding question, stating that the National Heart, Lung, and Blood Institute ceased funding the program because it was no longer research. "It's now seen as service," he said, "although the CDC didn't fund it, either." Dr. Lubin said that he cannot speak to the rest of the banks, but he believes that the quality of his bank is comparable to public banks. He went on to say that this may not be a long-term plan, so in terms of funding opportunities, he felt that one should think in terms of the growth and utility of cord blood as a source of stem cells in the future. Hopefully this can be addressed by the Advisory Council.

Dr. Kurtzberg said she wanted to inject a dose of reality and noted that she had an Adrenoleukodystrophy (**ALD**) family that had prospectively saved cord blood, yet it could not be used. She said that she has had 15 transplants from private banks, of which 6 had contaminations and 3 had other problems. These are real safety issues. The program should be federally controlled and monitored for the benefit of families. Dr. Lubin added that they are entering all of the data into the national registry, so it will all be evaluated using the same parameters. Any problems can be identified, and then procedural changes implemented.

FDA Draft Guidance on Cord Blood Bank Licensure, Ellen Lazarus, FDA

Dr. Lazarus noted that this Guidance ("Minimally Manipulated, Unrelated Allogeneic Placental/Umbilical Cord Blood Intended for Hematopoietic Reconstitution in Patients with

Hematological Malignancies") describes how the FDA believes it can help industry submit biological license applications for cord blood. Dr. Lazarus thanked the participants for participating in this meeting and said that the FDA is looking forward to a very interesting discussion, and she is very grateful for the Council members' willingness to participate and share their expertise. She gave an overview of content of draft guidance and discussed the steps the FDA is taking to finalize the guidance and move ahead with licensure of these regulated products.

In 1997, the FDA proposed a tiered, risk-based regulatory framework for human cellular and tissue-based products (also known as HCTPs), including hematopoietic stem/progenitor cells. The framework was implemented by promulgating three final rules that comprise *21 CFR Part 1271* (Registration and Listing, Donor Eligibility, and Current Good Tissue Practices). These rules became effective on May 25, 2005. Under the tiered regulatory approach to HCTP, more complex cells/tissues had more regulations, and less complex ones had fewer regulations. As described in the Registration rule, HCTPs with a systemic effect or dependent on the metabolic activity of living cells, and that are not intended for autologous or family-related use such as unrelated donor cord blood, are also regulated as biological products under Section 351 of the Public Health Service Act, and are subject to both IND and BLA requirements.

Dr. Lazarus said that in 1998, the FDA issued a notice in the *Federal Register* explaining that it may be possible to develop product standards and establishment and processing controls for minimally manipulated, unrelated donor cord blood and peripheral blood progenitor cells based on clinical trial data submitted to a public docket. The *Federal Register* notice requested comments on the establishment controls; manufacturing controls (processing), and product standards for minimally manipulated unrelated allogeneic cord blood and PBSC intended for hematopoietic reconstitution. If adequate information was submitted to show safety and efficacy, the FDA would issue guidance containing controls and standards. Most of the comments received concerned cord blood.

In 2003, a meeting was held of the (then-titled) Biologic Response Modifiers Advisory Committee (BRMAC) to discuss scientific issues relating to cord blood transplant. Many of those attending today's Advisory Council meeting also attended that meeting, during which the FDA provided an analysis of clinical outcome data submitted to the docket. The Committee discussed safety and efficacy issues that the FDA should take into consideration. Afterwards, a CBER task force determined that the data submitted to the docket, presented at the BRMAC meeting, and available in the published literature were sufficient to permit development of recommendations for applying for licensure for unrelated allogeneic cord blood. This led to the publication of the Draft Guidance in January 2007, which is under discussion today.

According to Dr. Lazarus, this guidance presents one approach to licensure of minimally manipulated allogeneic unrelated cord blood for homologous use. Manufacturers can also use alternative approaches, if they show that the alternative satisfies the applicable regulatory requirements. The draft guidance reflected the current FDA thinking on this issue, but it does not establish any legally enforceable responsibilities. The draft guidance comment period ended on April 17, 2007, and the FDA is currently considering the comments made and the information presented at the CTGTAC Meeting held on March 30, 2007. The final guidance will include an

implementation date that will end the period of delayed implementation of IND/BLA requirements for these products, at which time manufacturers would have to submit INDs or Biologics Licensure Applications (BLA).

Dr. Lazarus stated that the purpose of the draft guidance is to provide recommendations of ways for cord banks to apply for licensure for specified indications and explain the applicable regulations in Title 21 of the Code of Federal Regulations. The draft guidance covers cord blood products that are minimally manipulated and are intended to be used in recipients unrelated to the donor and intended for specific clinical indications supported by data in the public docket (e.g. hematopoietic reconstitution in patients with hematological malignancies). It does not cover PBSC (HPC, apheresis); other cord blood products such as those that are more than minimally manipulated, or have intended uses other than those proposed in the guidance; or cord blood for autologous/family-related use (although the FDA encourages following the manufacturing recommendations).

The reason for the clinical indication for cord blood considered to fall within the scope of the draft guidance is that the preponderance of data (about 65%) submitted to docket described cord blood transplant outcomes in patients with hematologic malignancies. There were many fewer data from patients in other disease categories, such as genetic diseases or aplastic anemia. However, subsequent information submitted to FDA and available in more recent literature allows the Agency to consider expanding the clinical indications.

In terms of using the guidance to apply for a Biologics License, the manufacturer would demonstrate in the application that it followed the guidance recommendations. The manufacturer may modify any procedure in the guidance so long as it provides evidence that this modification will provide similar assurances of safety, purity, potency, and effectiveness. The FDA recommends consultation with CBER about alternative approaches to licensure. The guidance provides specific recommendations if the manufacturer wishes to rely on data in the docket rather than submit clinical data obtained from their own studies. The biologics license would apply to HPC-C manufactured at the time of and after approval of the license application. For cord blood entities with banked inventory (collected before the licensure application was approved), the guidance explains that the license would also apply to HPC-C previously manufactured in accordance with the information provided in the application, where documentation is provided to demonstrate their comparability.

Dr. Lazarus described the recommended contents of a BLA and noted that the attachments should include a citation to the data in the public docket and an indication that the manufacturer is ready for inspection. The guidance also reminds manufacturers that they may submit to FDA a validation plan for review prior to submitting their application, or request a pre-BLA meeting. She explained that the FDA will review the application and schedule a pre-license inspection as soon as possible after receiving the completed application. If an application is not complete, the FDA will identify this fact and advise the establishment of the additional information that must be submitted.

As previously stated, for HPC-C that were previously manufactured using the same procedures as described in the application, the license would apply to HPC-C in the inventory when

documentation is provided to demonstrate the comparability to products manufactured after approval of the license application. For HPC-C previously manufactured using different procedures, the license could apply provided that the manufacturer submits a separate validation summary, including specific data.These data must demonstrate the comparability of the previously manufactured HPC-C to the currently manufactured HPC-C. The data must also provide evidence that the methods, facilities, and controls used for manufacture conformed to CGMP and other applicable regulatory requirements. The FDA is considering the regulatory approach for previously manufactured HPC-C that cannot be demonstrated to be comparable, or manufactured in accordance with CGMP, but that are still deemed important to be retained in inventories for public use.

Discussion

Dr. Broxmeyer commented that collections used to occur under imperfect manufacturing procedures and that some collected 20 years ago are still around. He asked if this would relate to such collections, most of which cannot be used for public banks. He also noted that he still gets emails from people asking if he still has the cord blood, and whether it is still good. "If they were to be used, would they fit here or would they be a separate issue?" The response was that cord blood products for autologous use or among first- and second-degree blood relatives, are not regulated as biological drugs and are not subject to licensure.

Dr. Milford asked what the relationship is between the licenser and the IND, and the next step after that. He also asked Dr. Lazarus to discuss the cord blood units that are collected elsewhere (e.g., by obstetricians in private offices) and then handed over to a bank. "Would the person collecting not have to be registered?" The answer was that, under the regulatory approach, unrelated donor cord blood is regulated as a HCT/P and a biological drug. Under the Section 351 of the Public Health Act (and in the Food, Drugs and Cosmetics Act), these products require licenses to be distributed to treat patients in the U.S. While developing the proposed approach the FDA has not required BLA and INDs for these products, although some cord banks and the NMDP have voluntarily submitted them. When this guidance is finalized, it will end this period of delayed implementation and, at that point, in accordance with the applicable regulations and statutes, manufacturers will have to obtain a license. Under the approach described in the draft guidance, cord blood manufacturers may proceed to BLA without getting an IND.

Sometimes collection is performed by someone other than cord blood manufacturing staff (such as by obstetricians or nurse practitioners) who may have an agreement or contract with the manufacturer. Note that this is still considered to be manufacturing, however. Those who engage in these collection procedures need to do them under the appropriate regulations (good manufacturing practices), but they may not be required to register with the FDA. The license applicant would have to provide the FDA with information about how they or their contractors (those individuals with whom they have agreements) meet the specifications.

Dr. Hartzman said that the previously collected cord blood is going to be an issue and that there is a lot of material that is being used successfully that was collected in the past. Dr. Lazarus agreed that there is a need to maintain the safe and effective cord blood that is in the system

already. The FDA does not want the ones that are in the market already to be discarded unnecessarily. This is a tremendously important consideration.

Dr. Read asked if a cord blood product were initially collected for a family and then the family decided to make the units available for unrelated use, would the bank need to prepare itself up-front to follow the guidance for non-related banks? Dr. Lazarus said that the question of crossovers is one that is under consideration, but that there is no position at this time. She said that, indeed, the cord blood would have to meet all of the requirements explained in the guidance, but that there are other issues, too. Donor eligibility is one such issue. In the unrelated donor setting, the donor eligibility determination is made and the cord blood is made available for public use. When cord blood is donated for specific family member's use, however, the donor eligibility determination is different. Another issue is that cord blood manufactured for autologous and family-related use may not conform to all of the CGTP and CGMP requirements (e.g. sterility).

Dr. Bowman asked if the scope of this guidance applies to imported cord blood units. The answer was that FDA is aware that a significant proportion of transplantation involves cord blood in international exchange that are either coming into or going out of the U.S. Distributors of biological products to be transplanted in patients in the US have to comply with the FDA regulations. Licensure of cord blood establishments that list their products in international registries poses unique challenges because cord blood is not manufactured for U.S. use alone and most of the non-US cord bank products would not be used in the U.S. This is a major issue and there is a need for mechanisms to ensure the safety, purity, and potency of the non-US cord blood establishment products distributed in the US.

Ms. Holiman asked how the products coming in are regulated. She said that she wants to clarify that the regulation does not regulate family-stored cord blood because that is not considered to be a "manufactured product." There seems to be a lack of understanding in the public mind about cord blood. In New England, very few hospitals collect cord blood for public use. Mothers who even think about it cannot really donate, but all obstetric departments are advertising private banks. There is a huge need for public education about this issue. Dr. Lazarus agreed, stating that the FDA sends staff like herself to public meetings as well as to the meetings of professional organizations, specifically to explain the regulations around family and non-family use. The hope is that this outreach will help providers and manufacturers learn what regulations apply to them.

Dr. Appelbaum asked, since the new rules are coming into play soon, whether there was any concern about accessing cord units from other countries. He asked whether there is a possibility that they will not be available for use in the future. The response was that the FDA has no intent for the implementation of this guidance to impede the international exchange of safe cord blood products. There is a need to create a mechanism for the legal importation of safe products so that it happens in a timely manner and that the products meet applicable regulations. "It's a solvable problem" said Dr. Lazarus. She explained that much FDA activity is directed to addressing this issue. Dr. Lazarus provided assurances that FDA is aware of the extent of stakeholder concern regarding this issue and is working on a regulatory approach to address it.

Dr. Milford asked if the FDA licenses foreign manufacturers. The answer was yes [for those foreign manufacturers distributing biologic drugs in the US].

Dr. Lubin suggested that there are places that have very different standards. There is no desire to use a unit to cure one disease and end up causing another one. The response was that the FDA agrees that the international cord blood issue needs to be addressed where the products could not be licensed but were still needed to treat a patient. For example, the FDA does recommend specific safety tests and non-US cord establishments that do not use the recommended donor screening tests may need to address this under a BLA or IND.

Dr. Blume thanked the speaker.

ACBSCT Ethics Training, Louise Wagner, HRSA

Ms. Wagner, a HRSA Ethics and Personnel Specialist, described the ethics rules for HRSA and showed a 20-minute video about the system. She noted that bylaws are being created, but they are not yet completed. HRSA has reviewed all of the Council member's financial disclosure reports, which are due by May 31 of each year.

The ethics requirements address the prohibition of participation by any member with an employer that may benefit from his or her participation. There are potential conflicts for some members, and HRSA is generating recusals (e.g. for those associated with AABB or FACT) and developing a recusal letter that members can use when necessary. The Ethics Office is also looking at members' investments, such as with health care industries or device manufacturers. If a member does not have a recusal in place yet, it does not mean that there's no issue or that one won't develop. Therefore, members need to be aware of this possibility.

In terms of political activities, under the Hatch Act, one cannot solicit, accept, or receive political contributions, or have position of authority intended to influence an election. This only applies when one is on duty working for the Advisory Council so, at other times, the rules would not apply to Council members.

Ms. Wagner showed a video about ethics to the Council members.

Discussion

Dr. Appelbaum said that he had served on a previous Council and had been prohibited from accepting invitations to talk in other countries. He asked if this applies here. The response was that U.S. Federal employees may not accept money from a foreign government. If it's a private organization like a university, that's acceptable; however, one cannot be paid by a foreign government. Dr. Appelbaum asked about a situation in which the university is funded by the government. The response was that, if the funder is a government-controlled university, it would not be acceptable to have the university pay for, or reimburse, the expenses.

Dr. Milford noted that he had this problem when serving on the ACOT. When he spoke at or visited universities that were publicly funded, it was a problem. He followed up by asking

whether the Council members who are from donor centers are, in effect, representing those private organizations on the Council. Ms. Wagner said this would be a concern if a matter came before the Council that involved that specific donor center, but the situation is not entirely clear-cut. Mr. Aronoff clarified that no member was selected because of his or her employment but all members were chosen for their individual expertise and accomplishments. Ms. Wagner's contact information was available in the handouts if anyone had further questions.

Dr. Read asked for clarification on paid and unpaid activities outside the Council. The answer was that it depends on the person's involvement, including appearance and finances.

Overview of C.W. Bill Young Cell Transplantation Program, Jeffrey Chell and Dennis Confer, NMDP; Mary Horowitz, CIBMTR

National Marrow Donor Program (NMDP), Jeff Chell

Dr. Chell began by thanking the Advisory Council members for their willingness to serve and to assist patients in need of cellular transplant therapy. The NMDP has served as the contractor for the C.W. Bill Young Cell Transplantation Program and its predecessors since the Program's inception 20 years ago. NMDP is a non-profit corporation governed by an independent board composed of transplant physicians, transfusion medicine physicians, patients and family members, donors, and other members of the community.

NMDP's mission statement is: "We save lives through cellular transplantation, science, service, and support." The NMDP vision is that cellular transplant therapies are readily accessible to all; cellular transplant therapies result in successful outcomes for a broad range of medical conditions; and that cell therapy donations are safe, convenient and widely accepted. The organization's core values are:

- Commitment: We share a passion for saving and improving lives.
- Resourcefulness: We are dedicated to delivering the best solution to each person in need.
- Compassion: We treat each individual with understanding, sensitivity and respect.
- Collaboration: We actively pursue and value cooperative relationships in support of our mission.
- Excellence: We achieve results through continuous improvement, innovation and quality.
- Integrity: We conduct ourselves with honesty, accountability and ethical behavior.

NMDP is part of a worldwide network of organizations. The Coordinating Center is at the Minnesota headquarters, but there are many other organizations involved. Dr. Chell showed a slide listing all of the following network members.

- 26 HLA typing laboratories
- 166 Transplant Centers (43 international)
- 90 Apheresis centers (7 international) – collection
- 99 Collection centers (16 international) – collection
- 2 Sample repositories
- 11 Recruitment Groups -- acquisition

- 21 Cord Blood Banks (2 international) -- acquisition
- 24 Cooperative Registries -- acquisition
- 76 Donor Centers (7 international) – acquisition

Dr. Chell showed another slide illustrating the growth in number of donors since the inception of the program in 1988. There are now almost seven million donors in the NMDP registry. Cord blood came later, in 1998, and now NMDP has 73,000 units of cord blood. When looking at the Registry by race, it's clear that a person's likelihood of finding a match is associated with the raw number of people who are likely to match the individual in the Registry. On the cord blood side, the percentages are continuing to improve with respect to racial and ethnic minorities.

In terms of the number of transplants performed for different cell sources, Dr. Chell showed a slide illustrating NMDP transplants alone. After 1999, peripheral blood stem cells showed rapid growth and now account for 60 percent of transplants. Rapid growth has also occurred among cord blood transplants, which are now 22 percent of the total. Recently, cord blood transplants have been larger in number than bone marrow transplants and are the second biggest source of stem cells, including all of the cord blood units in U.S., not only those made available through NMDP.

Dr. Chell explained that looking at transplant recipients by diagnosis, chronic myelogenous leukemia (CML) cases have been decreasing markedly. CML is now the seventh most common reason for such a transplant, down from number one in 1999. The most common indications now are acute leukemais, myelodysplastic syndrome, and lymphoma. A slide on transplants by race indicates that the number of minority transplants is growing more rapidly than are overall transplants. The field is far from having achieved equal access, but the increase in minority access to care is heartening. Cord blood is a big percentage of this and has a profound impact.

Looking at transplants by age, the groups with the most growth are those over age 50, and, now, among those in the first decade of life (0-10), which is driven by access for minorities. NMDP is starting to look at over-65 data, which is a growing group.

Dr. Chell said that he could spend a half-day on the search algorithms but decided to simplify to give the group an idea of the access to different databases of donors worldwide. The system requests a search through the TRAXIS software and four reports emerge. Two of the databases are searched in real time and results appear in less than one minute. Another two are searched overnight and results are provided the next business day. In total, 6.8 million donors are searched. Results can be manipulated to get more data about donors.

Dr. Clive Callender commented that he has been involved in and has observed the growth of this field for over 20 years. He thought the global perspective was wonderful. He said that he wants to see one issue changed, however. In 2000, the human genome project made it clear there is just one race. Race is a social construct that involves putting one group down when compared to another group. Dr. Callender expressed the hope that the field can get away from race and talk about ethnicity instead. Dr. Chell responded that he appreciated that perspective. The color of a person's skin is used as a surrogate for the true diversity that exists in the U.S. and internationally; and it's a poor surrogate, at best. As there is greater understanding of how

diversity is manifested and how it can be maximized, this can change. Dr. Chell appreciated the comments about NMDP's work and how this is communicated.

Dr. Kurtzberg asked if Dr. Chell could elaborate between reported race and HLA. The response was that the process is based on self-reporting, by both donor recruitment and patient. HLA typing and population genetics show that people have perceptions about their ethnicity which might not be "accurate." From an HLA standpoint, there are more multicultural or multi-ethnic people than the number who self-report as being multicultural. It impacts the data's ability to communicate accurate information.

Dr. Claudio Anasetti noted there has been a stunning growth of acute myelogenous leukemia (AML), especially among the elderly. He proposed that the Advisory Council deal with Medicaid coverage and the role in covering myeloma or non-Hodgkin's lymphoma, as well as the lack of coverage for clinical trials. Mr. Chell commented that those issues will be clearly addressed when Dr. Confer describes the work of the Single Point of Access Office of Patient Advocacy. As these therapies are being made available to everyone, cell source is just one thing that can affect access. In addition, financial issues have a significant impact on people's access to care. Only 40 percent of those for whom an unrelated donor is the only hope even get into the system. They may lack a referral into the system, but it can also result from a person's financial wherewithal to participate in the system at all. Once there is a search, NMDP can track the person and determine why they did not get a transplant, whether it was due to cell source or finances.

Continuing the talk, Dr. Chell showed a slide of international cooperation in this area. There is a need for harmonization, as all other countries have their own regulations as well. Safety, efficacy, and harmony are all issues. The search for bone marrow donors occurs worldwide. The NMDP is a partner and sponsor of the World Marrow Donor Association (headquartered in the Netherlands), which contains 67 member registries from 49 countries. There are 12 million potential donors in these registries (6.8 million of which are from NMDP). In 40 percent of transplants, the donor and recipient are from different countries. Without international collaboration, these patients would have received a less-matched donation and their survival would have been significantly affected.

The most common "trading partners" for U.S. imports are Germany (633), the UK (35), the Netherlands (17), France (13), Canada (12), Israel (12), and Italy (12). Biggest partners for exports are Germany (133), France (84), the UK (72), Italy (71), Canada (65), Spain (37), and Australia (15). Over 2,000 (2,086) of these transplants were conducted in 2006, and that year the U.S. exported 326 cord blood units and imported 166 cord blood units.

NMDP will soon be able to make NetCord available in real time as part of NMDP's real time search of seven million donors and up to 200,000 cord blood units. NMDP is working to continue the development and use of tools to communicate better and faster internationally. There are over 850 cord blood transplants projected for 2008 and 25 percent of the transplants will use dual cord blood. This speaks to increasing access to care for adults, as dual-cord transplants are performed more often in adults than in pediatrics.

The NMDP goal is to reach 10,000 transplants by 2015 (a figure based on estimated need). NMDP intends to accomplish this by increasing access to transplants (by both expanding the stem cell supply from adult donors and cords, and by limiting non-match barriers to transplant), and by improving outcomes (through earlier diagnosis and referral, and expanded research on post-transplant complications). Speaking specifically on non-match barriers to transplant, as noted, upwards of 40 percent of those who need a transplant do not have transplantation health care coverage or are not searching for pre-transplantation needs. If the goal of access is met, therefore, transplant centers would have to be able to expand volume by two and a half times their current volume. Many centers are not ready to do this. NMDP hopes to help ensure that there are the donors needed, and that non-match barriers have been removed.

Dr. Broxmeyer asked if there was ever a case in which someone in the U.S. needed a unit that was also needed/requested outside the U.S. He went on to ask: "If so, what happens? Does the U.S. patient get the unit?" Dr. Chell responded that the Cord Blood Council and others have looked at allocation issues. It occurs on a first-come, first-served basis, regardless of where the person is. Whoever reserves the unit gets it first. Dr. Chell has not heard of cases where this sort of conflict has arisen. Dr. Broxmeyer asked what the timing is for reserving a unit. Dr. Confer responded that the unit is reserved when there is a request for further typing, so it's instantaneous.

Dr. Champlin asked why Germany has so many imports and exports. Dr. Chell responded that it was the second largest registry in the world, so it's reasonable that the U.S. would deal the most with them. Many people in the U.S. also came from Northern Europe, so they are likely to find a match for that reason. In addition, Germany is in the first search stream; so if a donor is located there, the system does not search further.

Dr. Read asked if NMDP was thinking of using geo-coding to increase diversity in recruitment. Dr. Confer responded that geo-coding is an effort to improve on race and ethnicity as indicators of diversity. One project is to map HLA types to see what locations in the U.S. are likely to represent unique output types and then conduct recruitment there. NMDP is still trying to see if it works and whether it allows identification of genetic hotspots where, if there is target recruitment, it would increase diversity.

Overview of the Contracts, Dr Confer, NMDP

Dr. Confer began by showing the same slide that had been projected before, indicating the four major contracting areas under the Act. NMDP was awarded the contracts for the Bone Marrow Coordinating Center, the Cord Blood Coordinating Center, and the Office of Patient Advocacy/Single Point of Access. These were competed as part of an RFP process, which includes specification of the tasks to be completed under the contract. The tasks range from very simple to very complicated. Because they were separate contracts and because multiple contracts are held by NMDP, there has been some consolidation of tasks, such as communication and collaboration.

Dr. Confer explained that the first contract is for the Bone Marrow Coordinating Center. One task under this contract was to "make data regarding potential adult bone marrow donors

available through a single point of access." To do this, NMDP created a new system called "TRAXIS," which replaces the older system. It is a major improvement. The biggest change is that it is browser-based; and one can use any computer with Internet access to get into it. (In the old system, special software called Translink had to be installed on the user's desktop). There still is strict security though. A team of 12 transplant centers helped to design and beta-test the new product, which is scheduled to launch in early 2008. New application goals and features include improved and secure access from any Internet connection; a faster, more reliable, and easier to use system; electronic work up (request donor work-up and order CBUs on-line); a multi-cord selection tool (conduct multi-cord searches and request CBUs); and work flow management tools (receive work flow management actions on the home page). The goal is to provide everything one needs in one intuitive, web-based application.

Another task under this contract, explained Dr. Confer, is to "recruit and retain volunteer potential donors." NMDP has been undergoing a sea of change to establish the next generation system for recruitment. This is a strategic initiative that aims to take the recruitment capabilities to the next level by building on strengths and transforming weaknesses. The goal is to create a high performance organization based on strong fundamentals and to execute the tasks with excellence. NMDP has clear performance metrics that include percentages for minority recruitment and availability. The highlights of last year's accomplishments include a 23 percent growth in total recruitment in 2007; a 26 percent increase in minority recruitment; a 20 percent increase in Caucasian recruitment; and increases in African American and Asian recruitment by 23 and 71 percent, respectively.

Key programs around recruitment include: the Volunteer Program (under which the expectation is that 500 trained volunteers will contribute an aggregate of more than 5,000 hours of service); proactive patient family recruitment, which is a program to identify patient families with a desire to participate in recruitment; fundraising and media relations in partnership with the NMDP; and a program to integrate recruitment with fundraising via successful partnerships. One example of a successful partnership is the one with the U.S. Postal Service. The 2007 "Delivering the Gift of Life Employee Campaign," resulted in 5,545 new additions to the Registry. The "*Thanks Mom 2007"* campaign, another example, added over 42,000 donors via live drives and Do it Yourself enrollment kits (DIY).

However, according to Dr. Confer, recruiting is not enough if the donors are not retained and available when needed. NMDP has a goal, therefore, to also improve retention and availability. NMDP will build on its experience and insights gathered through previous NBMD contracts to produce a comprehensive plan for donor retention. This plan includes the Recruitment Group (RG) Search Contact Program, in which four minority-focused RGs apply their language skills and cultural competency to manage daily search-related activities for donors recruited by their organizations. Also, through the Centralized Preliminary Donor Contact, representatives make contact with donors identified on patient preliminary search reports. The goal is to re-educate, screen and remove donors who are deemed unavailable prior to a subsequent stage. (This also expedites the process for searching patients at the time of donor activation.) Also, in the spring, NMDP is implementing a Post Recruitment Survey, to survey approximately 1,000 donors each month for 9 months. The survey's primary objectives are measuring individual recruiter and center performance and improving donor retention.

The last task described by Dr. Confer was creating a "plan for increasing operational efficiencies." In order to meet this goal, NMDP is implementing an electronic workup request process and expanding customized search support to non-network and affiliated centers. The cost savings benefit is expected to be over $500,000 for the volunteer courier program alone.

The second contract is for the Cord Blood Coordinating Center (CBCC). Dr. Confer stated that there were 17 tasks in the CBCC contact, of which four would be discussed. There are different types of cord blood units in NCBI inventory and non-NCBI inventories. Data on these need to be synched so an efficient and balanced search can be conducted by transplant centers. In addition, the Advisory Council's definition of a "high-quality unit" would be very important.

The first contract task was to "coordinate a national network linking transplant centers and cord blood banks," meaning, essentially, to operate a network of domestic and international cord blood banks. Some of these banks will have NCBI contracts, while others will not. NMDP will develop and maintain unit and banking processes as consistently across this network as possible and there will be total access to all units through NMDP. There are more than 40 banks in the network, and more than 200,000 units. NMDP is working to improve access to units from the NetCord Registry through an integration agreement.

The second contract task was to "establish and maintain an information system to facilitate searches and transplants." NMDP will provide an inter-bank technical proficiency program (offered through StemCell Technologies) with the goal of reducing inter-bank variation in TNC, viability, CFU and CD 34+ counts. The program is free to banks participating in the CBCC.

The third contract task was to "collaborate with the Stem Cell Therapeutic Outcomes Database (SCTOD) to obtain outcomes data, determine optimal composition of cord blood inventory." According to Dr. Confer, NMDP has worked with SCTOD to develop new adverse event reporting forms and recipient outcome content; to integrate reporting by extracting the available data in CORD Link® to populate appropriate forms; and to assure outcomes data are returned to banks for accreditation and quality assurance purposes.

The last contract task that was discussed was to "support public and professional education and recruitment activities." NMDP has developed and is implementing public and professional education plans with a continued focus on minority recruitment. There is a collection DVD for professional staff, as well as "print on demand" capability to assist banks. Dr. Confer showed a screenshot of the multi-chord tool that will be integrated into TRAXIS. Users can select NMDP cord blood, international cord blood, or both. One can specify the HLA match and supply the patient weight.

Dr. Broxmeyer noted that NMDP is no longer national, and no longer just about the bone marrow program. Dr. Confer replied that it's true. The organization has an effort, called *Project Brand*, to explain who it is and what it does, and to figure out what it should be called. Dr. Broxmeyer suggested "the national adult stem cell program."

Dr. Callender asked if NMDP engaged in public education. The answer was it is going to do this, and it's very important. There was not time to go into the details but there is an overview in the PowerPoint handout. The Office of Patient Advocacy and CBCC contracts include tasks on education.

Center for International Blood and Marrow Transplant Research (CIBMTR), Mary Horowitz, CIBMTR

Dr. Horowitz said that, while NMDP won three contacts for the work described previously, CIBMTR was awarded the Stem Cell Therapeutic Outcomes Database (SCTOD). It's important for everyone to understand the history of the CIBMTR in order to understand what the organization is building upon and what changes were necessary to fulfill the HRSA contract requirements, which had 13 tasks.

Dr. Horowitz showed a slide which illustrated the Program components' interactions with the Office of Patient Advocacy/Single Point of Access (OPA/SPA). The slide showed that the Coordinating Centers will establish membership agreements with transplant centers, cord blood banks, donor centers, Hematopoietic Stem Cell (HSC) collection sites, and international registries, as appropriate. Cord blood banks, donor centers, and registries will report listing data for CBUs and donors. Searches will be initiated through the OPA/SPA, and will be forwarded to the Coordinating Centers and results returned through the OPA/SPA to the requestors. Transplant centers will select CBUs/donors for further testing that must include the cord blood banks, donor centers, and registries. Collected HSC products will be shipped to the transplant centers. Outcome results will be reported from the transplant centers to the SCTOD with subsequent distribution of relevant results to OPA/SPA, patients, physicians, Coordinating Centers, and member banks and centers.

Under the HRSA contract, SCTOD tasks are to:

1. Collect data (and specimens):
    - All allogeneic hematopoietic cell transplants (HCTs) with a recipient or donor from the U.S.
    - Related donor-recipient repository
    - Other cellular therapies
    - Quality of life data
    - Secure, efficient electronic data capture system.
2. Analyze data
    - Center-specific outcomes for U.S. transplant centers
    - Perform analyses of optimal size for the adult donor registry and cord blood unit inventory
    - Conduct and support other research using the data collected under the contract.
3. Disseminate data
    - Within the Program
    - To the scientific and medical community
    - To patients, families and the public

The CIBMTR itself grew out of two important BMT collaborations, the International Bone

Marrow Transplant Registry (IBMTR) and the National Marrow Donor Program (NMDP). The IBMTR was established in 1972 to monitor and study outcomes of bone marrow transplants (just 4 years after the first allogeneic transplant was performed). It is an academic division of the Medical College of Wisconsin. It maintains a database of clinical information on recipients of autologous and allogeneic hematopoietic stem cell transplants in about 450 centers in 47 countries. It also provided scientific and statistical support for analyzing those data. NMDP was established in 1986 when U.S. Government appropriated funds to establish the National Bone Marrow Donor Registry (Donor Panel). In 1988, the U.S. Organ Transplant Amendments Act mandated collecting outcome data (Recipient Registry). The NMDP also collects donor outcomes (mandated since 1988). It is the unrelated donor-recipient research repository of DNA and cells, involving about 150 transplant centers and 90 donor centers.

She explained that the Center for International Blood and Marrow Transplant Research is a research affiliation between the IBMTR and the NMDP to support clinical research in BMT and related fields. It was established July 2004 in recognition of the common mission and complementary strengths of the two organizations. This collaboration allows us to take advantage of complimentary strengths of the two entities. Dr. Horowitz showed a slide of all the centers participating in the CIBMTR and noted that, with the research affiliation between IBMTR/ABMTR and NMDP, the CIBMTR has expanded its representation to more than 500 centers from 54 countries worldwide. It has a lot of data on more than 250,000 transplant recipients, and has coordinated clinical trials, as well.

Added value includes the NMDP Research Repository, which was established in 1988 and includes specimens for more than 12,000 unrelated donor-recipient pairs. It has shipped more than 10,000 samples to investigators over the past two years. Another added value is the statistical support led by Dr. John Klein, a fellow of the American Statistical Association and elected member of the International Statistical Society. Dr. Klein works with four other PhD statisticians, ten Master's-level statisticians, and seven medical/master's level faculty. This is an active program of statistical methodology research specifically focused on transplant outcomes in addition to support for clinical studies.

Dr. Horowitz showed a slide indicating data flow prior to the new HRSA contract. There used to be two separate data collection mechanisms, one that came through NMDP (this was a long form with a lot of information) for mandatory reporting purposes. On the IBMTR, there is voluntary data reporting for all donors (autologous, related, unrelated) using both a short form for all patients and a long form for a subset of patients. European basic data are also included. For CIBMTR observational data, the extent of the data collected resembled a Ven diagram in which the research report forms was a large circle, and the Transplant Essential Data (TED) form was a nested, smaller circle.

Dr. Horowitz noted that it was important that, regardless of other changes, CIBMTR's productivity was maintained. For example, CIBMTR has more than 200 approved studies (20 of which involve specimens from the repository). It had 20 peer-reviewed publications in 2006 and 30 publications in 2007 and ten that are currently under review. More than 2,000 patients have been enrolled on clinical trials since 2003.

"What's new here," said Dr. Horowitz, "is the mandatory data reporting of all allogeneic transplants and having to have data collection approved by the OMB." The challenge was to accommodate the many demands for data in a way that meets the needs of SCTOD and all other users (including the research programs of CIBMTR), ensures quality, is maximally efficient, and minimizes demands on transplant centers. The approach has been to (1) build on existing infrastructure and preserve the things that work, while transforming the others; (2) build consensus both in the U.S. and internationally; (3) expand existing partnerships and develop new ones; and (4) to provide informatics resources that fundamentally change how data are shared.

New data collection processes are in place, and now the system looks different. Dr. Horowitz showed an update of the previous data flow slide. The future data flow system builds the existing structure. Two important notes are that there is a plan to assess quality of life being created by CIBMTR's Late Effects and Health Policy Working Committees, and that the related donor-recipient repository has been added to the existing unrelated donor-recipient repository.

Non-U.S. and U.S.-auto data (which are voluntary) and U.S.-related and -unrelated data (which are mandatory) both flow to an expanded TED. The organization spent a year with its international colleagues to try to develop a consensus on an expanded TED form that would fulfill the necessary requirements without being onerous. Others have adopted this form now. CIBMTR report forms are also voluntary. The expanded TED flows to a single CIBMTR database and there is a single set of CIBMTR forms, going into one database, through the new data capture system. CIBMTR will continue to select cases from the larger group on whom more data will be gathered. Between 200 and 300 centers have agreed to provide more detailed information about their patients. It is collecting and sharing data on transplants that use U.S. donors but are performed outside of the U.S., and also collaborating with EBMT, Eurocord/ NetCord, Asian-Pacific BMT Group, and Japanese BMT Groups.

CIBMTR can offer the transplant community new and improved informatics resources. Data are still collected on paper, but can also now be done electronically as well. In the future, the system that will be used is called AGNIS, which will be described later by Doug Rizzo. Creating this new system has consumed a lot of time and resources.

Doug Rizzo, CIBMTR

Dr. Rizzo noted that one of the contract deliverables was the creation of an electronic system to collect and disseminate data. FormsNet2, the system used to collect data, grew out of the existent NMDP data collection system. It is a web-based system that was launched in December 2007. FormsNet is used to collect all of the data from TED and research forms. It features web-based data entry with multiple features for data staff. It offers real-time forms due reports and error/range checking upon entry. Forms can be printed by the centers and eventually will also include downloadable data. It offers a very high level of security in order to protect data integrity that includes Secure ID cards and designated staff. It will be gradually implemented across the centers.

Dr. Rizzo also mentioned another system called AGNIS, (A Growable Network Information System) to exchange data. AGNIS was an NIH-funded project of NMDP and CIBMTR

collaborating with the European Bone Marrow Transplant (EBMT) program and other international organizations to facilitate sharing of BMT outcomes data. AGNIS is a sophisticated tool that can be used to communicate data between and among centers, registries, and other providers and users of data. It offers secure communication protocols and is based upon data standards established by the NCI. AGNIS allows any transplant center to put its data into the system, and then anyone else within AGNIS can access those data. When implemented, it should provide a pathway for data flowing and being used, although the data only have to be entered once. The goal is to collect data once and use them often. NIH funding for AGNIS is ending, and identifying funds to complete the work is important to reducing the reporting burden on transplant centers.

Discussion

Dr. Appelbaum noted that TED, which is the short form, is both mandated and also unfunded. At the Fred Hutchinson Cancer Research Center, a large center, they do 450-500 transplants a year and have to report about 350 of them, for which they are not reimbursed. The long form, on the other hand, comes with some reimbursement, but not enough to really pay for it. It is not clear what percentage of the consented patients will be requested for the long form, but a total of up to four FTEs will be required to process them. This goes to the hospital, which charges more for care. It is one more reason why health care costs so much in the U.S. Patients are paying for research, but they do not know they are doing so. This is where the money comes from to collect the data, and this group should talk about this.

Dr. Horowitz concurred that this is an unfunded mandate. On the other hand, it's the same kind of data that insurers ask for in their requests for information and could reasonably be considered to be a cost of business. It is also a reasonable topic for consideration by the Council. The NIH grant covers some costs of collecting data; thus, technically, these forms are paid for by the NIH and NMDP. Dr**.** Blume added that there is a significant discrepancy in the bottom line with the numbers. Dr. Horowitz stated that she did not disagree. AGNIS was placed on a high priority because it's a way for institutions to connect local database to CIBMTR and share their data.

Dr. Parkman added that there's a difference between what one has to do because it is the law, and what one wants to do to make a good product. He has been reading the law and felt that it would be helpful to clarify what was required in the RFP. Dr. Horowitz said she would be happy to share this. Dr. Parkman suggested that long-term follow up appears to be the big issue and reads like the gene therapy trials, in which one is committed to life-long follow up. Informed consent forms should, therefore, say one is expected to provide lifelong follow up. Dr. Parkman asked if this was the intent. Dr. Horowitz thought it was. There are compelling reasons to do long-term follow up and patients can opt out. They are not so reluctant to do this, however. The issue is to make it easy for this to happen, especially for the transplant centers. Dr. Horowitz commented that, as a transplant physician, she knows how hard this is. CIBMTR is trying to find ways to make it easier because there are benefits to having long-term follow up of patients for things not obvious up-front. Dr. Rizzo stated they are also mandated to include quality of life. One idea is to try to collect data on ways to follow patients and see how the patients prefer to do this. Maybe the patients want to be more involved, although it is important not to eliminate the centers. Dr. Kurtzberg is interested in a long follow-up period for the pediatric patients.

Overview of Federal Advisory Council Act, Patricia Mantoan, J.D., Office of the General Counsel

Ms. Mantoan discussed the Federal Advisory Committee Act (FACA). The General Law Division of the Office of General Counsel for HHS provides legal advice relating to the FACA and the General Services Administration's regulations that implement the statute. The FACA is a statute (5 U.S.C. Appendix 2) that controls the circumstances by which agencies or officers of the Federal Government can establish or control committees or groups to obtain advice or recommendations when one or more members of the group are not Federal employees.

"Its purpose was to ensure that new advisory committees be established only when essential and that their number be minimized, that they be terminated when they have outlived their usefulness; that their creation, operation, and duration be subject to uniform standards and procedures; that Congress and the public remain apprized of their existence, activities, and cost; and that their work be exclusively advisory in nature." (Public Citizen, 491 U.S. at 446.)

Ms. Mantoan explained that FACA requires the Advisory Council to meet in public in a space that is reasonably accessible for members of the public. An announcement is placed in the *Federal Register* when the meetings will occur and where they will be held. This is usually done several days beforehand and is a procedural requirement. This notice is intended to permit interested persons to attend, appear before, or file statements. The public is permitted to file a written statement with the committee, and members of the public may speak at advisory committee meeting if the agency's guidelines so permit.

There are exceptions to these requirements, noted Ms. Mantoan. Portions of meetings may be closed for reasons stated in the Sunshine Act (5 U.S.C. § 552b). This determination must be made in advance and in writing by the agency. At HHS, the most common reasons for closing a meeting are to discuss confidential, commercial, or financial information. A meeting may also be closed if the group is discussing information that might cause an individual's privacy to be violated. The reason *why* a meeting has been closed must be announced.

There are two types of meetings that do not have to be formally closed. The first is a meeting of two or more committee or subcommittee members convened solely to gather information, conduct research, or analyze relevant issues and facts in preparation for a meeting of the advisory committee or to draft position papers for deliberation by the advisory committee. The second type is a meeting convened solely to discuss administrative matters of the committee or to receive administrative information from a Federal officer or agency (administrative meetings).

Ms. Mantoan went on to say the first of these two relates to Advisory Council subcommittees, which do not invoke the FACA. The subcommittee must, however, report to the parent committee; and the parent committee must deliberate on any recommendations made by the subcommittee. Subcommittees would implicate the FACA if they make recommendations directly to the agency or Federal official rather than for consideration by the chartered advisory committee, or if the parent committee adopts the subcommittee's recommendations without further deliberation. Along the same lines, preparatory meetings also are not required to be open

because advice is not given to the Federal Government at that time. Instead, the subcommittee is advising the parent committee and that advice will be publicly deliberated upon at a later time.

When meetings are not substantive, i.e., the ethics presentation, they are not required either to be open or to be formally closed. This relates to administrative matters, personnel, and ethics.

According to Ms. Mantoan, other requirements are that the Committee's records be made available to the public in a timely manner (i.e., by the day of the meeting). These are the records made available to and prepared for or by the advisory committee. These records are subject to redaction or withholding pursuant to the Freedom of Information Act exemptions. Detailed minutes must be taken and transcripts made available. Meetings must be attended, or chaired, by designated Federal officials, who must approve or call the meeting, approve the meeting agenda (although this requirement does not apply to presidential advisory committees), and adjourn the meeting when this in the public interest. There is also a requirement to file eight copies of the committee's report with the Library of Congress.

FACA requires that advisory committees be utilized solely for advisory functions, unless a statute or presidential directive specifically provides otherwise. It also requires determinations of action to be taken and policy to be expressed with respect to matters upon which an advisory committee reports or makes recommendations to be made solely by the President or an officer of the Federal Government (Section 9[b]).

Ms. Mantoan noted that this information is presented to advisory councils because it is a Federal law to do so; and if FACA is not followed, there is a risk of legal challenges. HRSA could be ordered by a court not to implement recommendations made if the rules are not followed when the recommendations are made or forced to start over, which might result in abandonment of a project.

Cord Blood Accreditation Programs for the NCBI, Robert Baitty, HRSA

Mr. Baitty noted this is the first topic about which HRSA is specifically asking the Council to make recommendations. He discussed the relevant statutory requirements. He provided some general background on cord blood bank accreditation. He noted he would not describe or characterize specific standards and procedures of the cord blood bank accrediting organizations. Finally, he updated the group on HRSA's activities to date with respect to accreditation and describe the role of the Advisory Council.

The statutory requirements are that "The Secretary shall, through a public process, recognize one or more accreditation entities for the accreditation of cord blood banks." NCBI banks must be accredited by the organization(s) so recognized. The Senate Report notes that Congress feels that accreditation is vital for ensuring high-quality, along with the establishment of FDA requirements for licensure of cord blood, and continued regulation by the FDA and States. Neither the law nor the report specify criteria to guide the recognition process, define the envisioned "public process," or specify a contract or award of Federal funds to the accrediting organization(s). Right now, banks pay application and inspection fees, but HRSA cannot assume these costs so the NCBI Requests for Proposals (RFP) noted that banks are responsible for

expenses associated with accreditation.

Mr. Baitty explained that, as background, nearly all public cord blood banks are accredited by one or both of the cord blood accrediting bodies in the U.S. All 8 NCBI banks are accredited by either the AABB (four banks), FACT (three banks), or both (one bank). The choice is generally correlated with whether the parent institution is a blood center or a transplant center. Standards and procedures for both bodies are evolving.

The AABB was formerly known as the American Association of Blood Banks. It is an international association representing individuals and institutions that are involved in activities related to transfusion and cellular therapies, including transplantation medicine. It accredits Donor Centers (that perform collection, processing, testing and distribution); Transfusion Services (e.g., pre-transfusion and compatibility testing, blood administration); Cellular Therapy (e.g., hematopoietic progenitor cells, cord blood, somatic cells); Immunohematology Reference Laboratories; Relationship/Parentage Testing; Perioperative Services; and Specialist in Blood Banking (SBB) Schools.

FACT was co-founded by the International Society for Cellular Therapy and the American Society of Blood and Marrow Transplantation for the purposes of voluntary inspection and accreditation in the field of cellular therapy. It accredits Cellular Therapy Product Facilities (clinical transplantation programs, cellular therapy product collection, cellular therapy processing lab) and Cord Blood Banks. FACT partnered with NetCord (an international network of non-profit public cord blood banks) to develop international standards for cord blood collection, processing, testing, banking, selection, and release.

The FY 2004 appropriations for a National Cord Blood Stem Cell Bank Program required an Institute of Medicine (IOM) study, which was published in April 2005 (entitled *Cord Blood: Establishing a National Hematopoietic Blood Stem Cell Bank Program*). This report emphasized the role of accreditation in ensuring quality. The IOM made specific recommendations about accreditation (italics in the first recommendation are important because they were <u>not</u> carried forward in the statute). The following are the recommendations:

- IOM Recommendation 4.1: HRSA should identify *a* Cord Blood Accrediting Organization by means of an open, competitive request for proposal process. This organization should be charged with the delineation of standards for any cord blood bank, collection center, *or transplant center* desiring to participate in the National Cord Blood Stem Cell Bank Program.
- IOM Recommendations 4.2: Uniform standards for the collection of cord blood units without alteration of safe obstetrical practice should be established by the Cord Blood Accrediting Organization suggested in Recommendation 4.1 and should be required of all banks participating in the National Cord Blood Stem Cell Bank Program.
- IOM Recommendation 4.3: Uniform quality assurance standards and criteria should be established by the proposed Cord Blood Accrediting Organization for the collection, processing, and storage of cord blood, and adherence to these standards should be required of all banks participating in the National Cord Blood Stem Cell Bank Program. In addition, a system for the frequent performance of compliance reviews should be established.
- IOM Recommendation 4.5: The committee strongly recommends that all cord blood banks,

regardless of public or private status or participation in the national program, adhere to the established quality standards.

HRSA actions to date on the IOM recommendations include the following. First, it engaged in information gathering and consultation. HRSA published a Request for Information in August 2005 on the National Cord Blood Stem Cell Bank Program and held calls with transplant physicians in October 2005. It also reviewed AABB and FACT Standards and sent letters to the organizations requesting specific information on standards and procedures in February 2006. Public conference calls on accreditation were announced in the *Federal Register* in May 2006, and HRSA staff attended AABB and FACT assessor/inspector trainings in May and October 2006.

Second, HRSA has as interim measure required accreditation by AABB or FACT prior to NCBI awards. This interim decision will be followed by a recognition process that allows for input by the Advisory Council and the public.

Third, HRSA developed draft specifications as the possible basis for a competition among accrediting organizations. These specifications addressed the following three areas:
(1) Standards and Procedures (including the rigor of standards and relation to HRSA NCBI requirements; inspector selection, training, and ongoing monitoring of inspectorate; how inspection and review process ensures consistency and objectivity; and how all aspects of the banking process are evaluated).
(2) Compliance Monitoring (including re-inspection interval and procedures; assurance of ongoing compliance; action, e.g., revocation, for banks that fail to comply; HRSA notification of NCBI banks that fail to comply; and requirements for reporting of adverse events).
(3) Inspection/Assessment against HRSA Requirement (how the organization would evaluate NCBI banks against NCBI program-specific requirements and provide reports to HRSA).

Finally, when it became clear the Advisory Council soon would be in place, HRSA decided to revisit the interim recognition decision with Advisory Council before proceeding with specifications. HRSA requests the Council to: Formulate a plan for developing recommendations to the Secretary and HRSA about accreditation. The desire is that the plan would cover the recommended "recognition" process, the criteria for "recognition," and the expertise and backgrounds of individuals to be involved in HRSA's recognition decision. HRSA also would like the Council to execute the plan for developing recommendations by engaging in information gathering (including presentations by the accrediting organizations) and developing proposed recommendations for Council deliberations at future meetings. This could be done, for example, in a working group that would bring deliberations and recommendations to the full group for a vote.

Discussion

Dr. Broxmeyer asked if the goal was to have one accrediting unit and, if so, whether it would be one or the other of those organizations. Mr. Baitty responded that this was why he had contrasted the IOM language with the statutory requirement. The law says *one or more*, so it is

not necessary to choose. The IOM advice should be kept in mind, although it is not legally binding. Dr. Broxmeyer suggested it would be possible to use them both and link them somehow. Dr. Blume interjected that he felt this would be a huge challenge.

Then Dr. Liana Harvath asked if the Federal Government is put in a difficult position by having to select one, in terms of restraint of trade issues. Having both organizations might speed up the selection and the Federal Government could involve both organizations. Mr. Baitty noted that a number of people who have commented to HRSA on this issue suggested making the two processes more similar. Others suggested that the two organizations are very different in terms of processes and perhaps rigor, so making them more equivalent might be difficult to do. Mr. Mark McGinnis with the HHS Office of General Counsel commented that Council members should not worry about making the Federal staff's job harder or easier. Instead, he asked them to think about which is the best organization for the job and make a selection based on the best assessment of which one to choose. He noted that the Federal Government can defend the decision if it should come to that. It would not be a restraint of trade issue because the State action doctrine covers this and, therefore, monopoly issues do not come into play.

Dr. Parkman suggested that the Council not take on more work than what is needed. The organizations could harmonize their criteria, such as by having joint training of inspectors. Dr. Blume stated that, in view of the last slide, the Council should hear presentations from both organizations. He suggested that the Council might want to pursue this as an issue on which more discussion can occur and a work group can be established. In April, the Council members can hear from the groups, and then make their decision.

Dr. Milford mentioned the solid organ aspects of accreditation. For example, issues arise about the accrediting organizations doing accreditation for general baseline criteria and not for reasons relevant to the Program. There are a fair number of issues that may be unique to participation in this Program. As the members deliberate, they should keep in mind what is being discussed.

Dr. Lubin noted that, of the eight banks in the NCBI, four are accredited by AABB, three by FACT, and one by both. He asked if there was any evidence that one of these is better from a quality standpoint. Dr. Read commented that, if there are one or two accreditation organizations, then HRSA can force the issue of their having uniform and robust standards. Mr. Baitty clarified that the FDA and accrediting organizations have standards, whereas HRSA has reimbursement criteria for units under the NCBI program.

Dr. Kurtzberg commented that it's not clear whether there is a need for accreditation, if the FDA licensed the cord blood organization. Mr. Baitty responded that the law requires it. Dr. Read added that the FDA licenses blood banks, but they still also have accreditation.

Dr. Rubinstein stated that accreditation has to be targeted to achieving a set of conditions. It has to be meaningful in terms of a "high-quality unit." One must be able to distinguish banks that can produce these high-quality units consistently from banks that cannot, and help the latter to increase their abilities in this area. The process has to be geared to identifying the organization that can help select the desired units. The first step in the procedure should be the definition of the units. Dr. Burdick agreed and said the Council would be asked to do this the next day of the

meeting. Mr. Baitty said the HRSA reimbursement requirements, in some aspects, exceed what the FDA is contemplating. The goal of ensuring high quality is the same, however. The accrediting organization must be relied upon to ensure certain things which need to occur.

Dr. Parkman said that it is intellectually satisfying to create the optimal unit size; but if doing so eliminates ones that have been successfully used in the past, it hurts the patient. Clinical evidence must be used in order to avoid doing a disservice to patients. Dr. Champlin suggested the organizations have to comply with the FDA and also to adopt what is considered to be best practices. In an emerging field, there are two groups with different approaches to accreditation. Dr. Burdick responded to Dr. Parkman by noting that HRSA will specify what constitutes a reimbursable unit to be put into the HRSA inventory. This is designed to be a high-quality unit, but it is also designed to get the field moving. It was not intended to provide the majority of the financial assistance to the banks, just an additional assist. It is expected there will be a large volume of additional units that might not make this cut but would still be considered to be perfectly good. All units should be available for searching and use. It's not inconsistent with HRSA-reimbursable units and the rest of the field.

Dr. Milford raised another parallel with organs, in which UNOS set its own guidelines, and accrediting organizations have a checklist that complied with these components of the HRSA-accredited program. Dr. Burdick stated that solid organs are a little different, however. HRSA/OPTN is about the best use of the gifted organs, and there are other players, like CMS. It's not exactly the same.

Dr. Parkman expressed a concern that third-party payors are going to say they will only pay for a HRSA-accredited unit and will not pay for a non-HRSA unit. Patients may get a less-than-optimal unit in the view of the physician. As soon as there are criteria, someone will limit what they pay for based on such criteria. Dr. Appelbaum commented that, if the Council does not specify which accrediting agencies are sufficient, the agencies will multiply and that will increase costs. The Council should pick one, or make clear that the two can be harmonized in some way. Dr. Blume agreed that, if there are multiple entities, there will be one accrediting organization coming through after another. Having more than one standard would burden the system unnecessarily.

Dr. Harvath asked if the Council could have representatives from the two organizations make a presentation to the Council in which they would highlight the differences between the standards, and describe how they meet the HRSA criteria that have already been set.

Dr. Read asked what expertise the inspectors have, and whether any one set of people has the expertise to make one sweeping inspection. Dr. Parkman said there should be one, joint training of the inspectors. Mr. Charles Sims added that he runs two banks, and they are accredited by one of the organizations and are also inspected by the State. Through years of experience, it is clear that the inspectors differ from one another; and they also differ from year to year within the same organization. Some come and spend three weeks at the bank while some only spend three days, even if they are inspectors within the same organization. The State inspection was the toughest of them all. One has to develop a philosophical attitude that multiple inspections are painful and time-consuming; however, they add to the robustness of the system.

Dr. Parkman suggested that, in the interest of saving time, the Council should challenge the organizations to develop and present a harmonized plan to the Council. Mr. Aronoff sought input about whether the Council members wanted a harmonized plan. He noted that this is an issue for which the Council could form a workgroup, so it would be appropriate to have deeper discussion in that group. Mr. Baitty added that HRSA is requesting the Council establish a workgroup, talk with the organizations, and make a recommendation. Dr. Blume asked if it would be better to have the organizations come in April and then have the Council work on it, or whether the workgroups should start now. Mr. Baitty recommend that a Council workgroup be formed, to include transplant doctors and banks, and start working right away.

Dr. Champlin asked if there was a conflict of interest preventing him from being on the workgroup. Mr. McGinnis clarified that he can be on the workgroup; but he cannot vote on the recommendation, pending approval by the HRSA ethics office. His service on the Board of FACT, however, would be an issue.

Dr. Milford said that funding lasts until 2010 only. If the Council approves one organization rather than the other, then banks currently not accredited by the one that's picked will have to apply for new accreditation. The process takes 3 years; therefore, there may not be any funding for the program (or its requirements either).

Dr. Read added that it is likely that HRSA will want the banks to have a license and asked if there was a role for including the FDA in the accreditation goals, as there will be overlap. Mr. Baitty said HRSA would welcome the inclusion of FDA if the FDA would find it helpful.

Public Comment

No public comments were offered.

Areas for Discussion

Dr. Blume summarized the problem areas which had arisen in the course of the day and asked for four to six members to serve on each workgroup. He added that the workgroup can recruit one or two non-members as advisors. Proceedings of the workgroups will occur by email and conference call, and it is expected they would be reported on at the April 2008 meeting.

The issues are: (1) quality control requirements for grafts from international providers (this is the most important because lives depend on it); (2) cord blood bank accreditation and the recognition process (FACT, AABB); (3) funding for data documentation to meet new requirements as spelled out; and (4) a process for accessing cord blood units for research purposes. The Council discussed them in turn.

(1) Quality control requirements for grafts from international providers

Dr. Kurtzberg asked if the group can talk about this without addressing quality for domestic procedures. Dr. Appelbaum said that it's necessary to talk about access to foreign cord units.

Dr. Lazarus said she cannot guarantee the actions the FDA may take, but she can say the FDA is fully apprised of the need to maintain the international cord units from unrelated donors. The FDA is actively working on mechanisms to allow this to happen under the current regulatory approach. There is no reason to expect a cessation of international cord blood units due to FDA regulations.

Dr. Sims asked how the FDA squared this with the import ban on Creutzfeldt-Jakob Disease (CJD). Dr. Lazarus said the donor eligibility rule specifies this must be screened for as a communicable disease. There are provisions for the use of products with communicable disease agents. It's an important issue and is linked with international exchange; it is currently being addressed.

Dr. Parkman said many questions are answered by data. If the question can be framed by data, and answered by data, it's easier. Is it possible to tease out U.S. recipients who receive cord blood from overseas and have a contaminated graft? Then, if there's no difference, the answer is the sources are equivalent. Dr. Horowitz said there were data on some, but not all, cord blood transplant recipients. In any event, CJD occurs 30 years down the road.

Dr. Appelbaum commented that, if it is not a danger, then there is no need for a workgroup on this issue. Dr. Blume agreed that this issue can go on the shelf, and the group will wait to see what Dr. Horowitz comes back with.

(2) Cord blood bank accreditation and recognition process

Workgroup members:
- Elizabeth Read
- Charles Sims
- Robyn Yim
- Pablo Rubinstein
- Bertram Lubin
- Donna Regan

(3) Funding for data documentation

Workgroup members:
- Frederick Appelbaum
- Joanne Kurtzberg
- Susan Stewart
- Karl Blume
- Doug Rizzo (ex officio)

The group has heard very good information, but getting from A to B is not just one step. The costs of moving to computerized systems have to come from somewhere. The question is, "who pays for it?"

(4) Process for access of cord blood units for research

Workgroup members:

- Robertson Parkman
- Liana Harvath
- Hal Broxmeyer
- Donna Regan
- Edgar Miford

Dr. Rubinstein noted that his bank's practice is to make available, free of charge, the cord blood units that cannot be used because they do not meet the bank's minimum standards. The researcher just has to apply and briefly describe the project. This could be done on a central level also. Dr. Blume agreed and said that what is needed is for people to know that the samples are there, as well as which samples are located in which repository. Most of the requests address fresh cord blood units. It is rare for groups to need frozen units, of which Dr. Rubinstein's bank has a small number.

Dr. Broxmeyer addressed the issue of placental tissue and cord samples. The State of Indiana now has a bill to establish a State cord blood bank and will probably store cord blood and also obtain a placental and cord sample. There is currently a lot of ongoing research surrounding this issue. It is outside the Council's purview, perhaps, but it is on the horizon and folks are starting to do it. Dr. Sims suggested deferring this topic and recommending that the accrediting units establish a mechanism for providing units for research. Dr. Kurtzberg said that many banks have policies which can be shared with one another in order to learn about best practices. It's necessary to know what is happening before acting, or even assuming, there is a problem.

Dr. Blume stated that the work group can look into this, and he thanked the members for their participation. The meeting was adjourned for the day.

January 29, 2008

Registry Policy Models and Center-Specific Survival Analysis

Models Regarding Composition and Size of Adult Donor and Cord Blood Registries, Dennis Confer, NMDP

Dr. Confer, the NMDP's Chief Medical Officer, began by asking: "Why do we need models? What's their value?" He answered that models serve many purposes. They extend knowledge about HLA, teach about populations, predict matching rates for patients, determine the optimal registry size and composition, and provide an analysis of cost versus benefits. It should be possible to tell a patient his or her percentage chance of finding someone in the different registries.

Dr. Confer said HLA genes are clustered on the short arm of chromosome 6. Multi-genes are DP, DQ, and DR; and because they are close together, they are inherited together. They are a haplotype (a string of genes that are inherited as a group). In a family, the likelihood of matching siblings is 25 percent. If one child needs a transplant, his siblings are good places to look first. Fifty percent of the siblings will be half-matched and 25 percent of them will have no match.

Family genetics are pretty well understood, but population genetics are harder. The NMDP has HLA information on all of its 6.8 million donors, but the information is incomplete. Buying the highest-quality typing for new donors costs $1,000 each and is prohibitive, so NMDP types at an intermediate level, which lacks some information. Technology also changes. Earlier donors were typed by serology, which had an error rate of 25 percent, while newer DNA typing has lower error rate. Newly recruited donors are typed by DNA-based technologies, with an error rate of less than one percent. Cord blood uses DNA typing, too, but not at highest resolution. "How does one know, for the next set of donors, what their HLA type will be?" asked Dr. Confer. Modeling is useful for that question.

What is sought in a desired match, explained Dr. Confer, has changed over time. It used to be A, B and DR by serology. Then it was A, B by serology, and DRB1 by DNA. Then, A, B by DNA, but not at the allele-level. Next was DRB1 by allele-level DNA , and now C and maybe DQ are both added. The field is considering the importance of DP, too (for adult, unrelated donors). Originally, it wasn't known that one had to type to the allele level. Cord blood products are a subset of adult matching allele-level DNA (it's AB by DNA with intermediate resolution, and DRB1 at the allele level). If the modeling problems for adults can be solved, the modeling problems for cord blood will be solved too. The size of the cord blood is a critical factor, too.

Dr. Confer discussed adult donor modeling, and he included the questions: "What's the chance that a patient has a well-matched donor in the Registry? As the Registry expands, does that chance increase and, if so, how quickly. Finally, what's the cost-benefit?"

In terms of methods for registry modeling, Dr. Confer explained that haplotypes and their frequencies are calculated with the Expectation-Maximization (E-M) algorithm. The HLA phenotypes of "new donors" are predicted by combining haplotypes according to their defined frequencies. The impact on matching for patients can be estimated by running searches against the expanded registry. Dr. Confer showed a slide that illustrated the algorithm in which the bars show the haplotype frequency in the population. It is clear that some are more common than others. The full frequency consists of thousands of ever-decreasing numbers of haplotypes. (Which patients to run against the Registry is a complicated issue that would not be discussed at this meeting.)

Dr. Confer referred to an article by Craig Kollman, included in the handouts, and showed several slides of matching scenarios from the 2004 registry. The article explains that the match rate for African Americans is just 40 percent. If recruitment remains at the current rate, it will increase to 47 percent from 2004 to 2007. Toning down White enrollment would not help African Americans, however. Doubling African Americans recruitment would increase the match rate to 51 percent. Increasing Hispanic recruitment would help African Americans a bit, but increasing Asian/Pacific Islander recruitment does not. If recruitment were increased for African Americans by 10 times, the match rate would increase to 64 percent, which would be better, but would still be well below the White match rate (which would be at 84 percent on that basis).

Dr. Confer said what this earlier analysis indicates is that massive recruitment does not have dramatic results. However, it's also not correct. Problems with this analysis include that the resolution of matching is too low (A, B low resolution and DRB1 high); that HLA-C was not included; that populations are broad racial/ethnic groups; that there is a need to consider donor availability; that there is donor attrition (donors are estimated to stay on the registry for 25 years, but 10 years is more likely); and that there is a lack of validation of the predictions.

Dr. Confer showed an analysis at higher resolution, using donors in four groups at all allele level types. In this analysis, the donors were either part of the donor-recipient pair project; typed for the EM algorithm validation project; from CT/HR requests; or from other prospective high-resolution typing projects. Looking at the HEGL cohort, it is clear this is an overestimate for Whites as well as for African Americans. This probably occurred because there were too few high-resolution phenotypes for the E-M algorithm and because broad racial and ethnic categories are inadequate for estimation and recombination.

As a next step, NMDP held a Population Genetics Summit in December 2007 and invited five well-known experts. They discussed the best approach to dealing with limited high-resolution HLA typing data; issues of racial and ethnic grouping; models for increasing the registry size; and the best approach for a validation study. The best approaches to dealing with limited high-resolution HLA typing data were to perform more high-resolution typing; to obtain HLA-data from other sources; to predict additional haplotypes using recombinations existing haplotypes; to look at algorithms other than E-M; and to collect pedigree information.

The notion is that, if one can go back to the grandparent level for pedigree, it might help create populations where recombination frequencies are predictable. Introducing the F-statistic (an adjustment to define structured subpopulations and indicate the likelihood that two alleles descended from same ancestor) makes it possible to use "whole genome markers" (e.g., HapMap) to better define populations and to perform genotype clustering before haplotype estimation.

Dr. Confer said that half of all searches are cancelled, so one idea was to continue typing donors to see if there would have been a match. The Swiss have done something similar and published the results. This is very costly to do because this sort of typing is very complicated and expensive. NDMP will keep working on it and evaluating informed consent issues. The best approaches suggested for a validation study included to accumulate consecutive real-patient search submissions and pursue them all to completion; to run complete searches on a randomly selected set of donors; or to estimate the true match probability with selective typing for a subset of pseudo-patients.

By the end of the Population Genetics Summit, it was clear that the geneticists found the problems intellectually challenging. NMDP promised to reconvene the group by calls and meetings to continue with next steps.

In summary, Dr. Confer said accurate models are necessary to evaluate registry functionality and plans for growth. Accurate models should optimize the allocation of limited resources. Development and validation of accurate models is complex, computationally intensive, and expensive.

Discussion

Dr. Blume thanked Dr. Confer.

Dr. Appelbaum noted that Dr. Horowitz may talk about this, but this presentation indicates that HLA is the end-all and be-all. It's important, but there are two issues. The first is dangerous donors and safe donors, based on inflammatory genes, and thus the potential need for many more donors. The second is that, with unrelated donors and a haplotype match, there might be only one haplotype. Thus, the question that arises is whether one should be looking at the haplotype level. The model is built on HLA, so how would one think about a model with these considerations. Dr. Confer said that Dr. Appelbaum was absolutely correct, and this point underscores the fact that knowledge is constantly changing. The modeling does not consider the immune response genes, for example. It doesn't consider whether there are some HLA

mismatches that are permissive or that must absolutely be avoided. Not enough is known yet. For example, does haplotype matching, by itself, overcome mismatching at other loci? This is complicated and changes all the time. Dr. Blume added that one cannot separate this from the outcomes, either.

Dr. Lubin noted that the data and the characterization do not take mixed ethnicities into account. In California, and throughout the U.S., it is a major change which has to be considered. "Many people are concerned and are calling us about it," said Dr. Lubin. The group should consider private business partnerships to improve screening so more can be done. Perhaps there are other funding sources for partnering as the field advances technologically. Additionally, there are things that are not known about cord blood because it is a new playing field. Dr. Milford responded to the multi-race issue by stating that the NMDP Summit looked at data for people who did not find a match. This describes the unmet need and those who fail to get transplanted because they are not matched. Mixed race people comprise a high proportion of non-matched people.

Ms. Holiman asked, on the recruitment side of the unmet need, why not fully investigate patients who, over many years, have not been able to find a matched donor? In Japan, where she has been involved with recruitment, it is very regional in terms of antigen types and diversity. The idea of using regional approaches to get at the diversity is a good one. Dr. Confer noted that Dr. Milford is also doing this. An analysis of patients with no matches is very important to do, and they are very common. Geographic distribution is another factor and NMDP is working on this with geo-coding to identify hot spots.

Dr. Parkman commented about the sobering fact that minorities are underrepresented compared to Whites. The question is whether the goal should be for the distribution to match the general U.S. population, or for all groups have an equal probability of finding a donor. In order for this to happen for African Americans, all of the people in the U.S. would have to be typed. Dr. Confer agreed there is a problem with sheer numbers. In order to match the percentage for Whites, it would involve recruiting a significant proportion of all the African American people in the country. It is necessary to figure out how to do successful transplants with less perfect matches and cord blood is one strategy for this to be successful. Dr. Champlin said that if everyone in the world were typed there would still be people who lacked matches. There is a need to figure out how to create more effective tolerance, to improve resource allocation, and to add more resources into researching this issue. Finding donors alone will not do it.

Dr. Sims interjected that "African American" is a political construct rather than an ethnic group. To assume it is one group is inaccurate. There is great diversity in Africa and no scientific basis for using "African American" as an ethnic group. There should be a better way to describe those who need transplants if there is no predictive value to saying they are African American.

Dr. Anasetti asked how cost effective it is to expand the registry and if doing so would be cheaper than some of the other things being done in medicine. The answer was that it is very important to conduct cost effectiveness analysis. HLA typing costs are declining and the resolution is increasing and yielding a lot more for the amount of money expended.

Analysis of Transplant Center-Specific Outcomes, Mary Horowitz, CIBMTR

Under the contract, SCTOD is obligated to collect and analyze data and disseminate data on a wide variety of issues and outcomes. Meaningful analysis of transplant outcomes requires a very large number of patients and a lot of data. The difficulties in analysis at individual transplant centers include: the heterogeneity of patients, small sample sizes, conveying complex data analysis to the non-statisticians, acceptance by the medical community, unintended consequences, and translating results into improvement. There are many features of disease and of the patient that predict a good or bad outcome. Dr. Horowitz discussed each of these difficulties.

A person's prognosis is determined by many factors. Patients are heterogeneous, and they vary by center (e.g., center case mix) as well, which can lead to different outcomes. It is hard to adjust for that, but efforts are made to do so.

According to Dr. Horowitz, small sample sizes create a large problem with imprecision, and with varying sample sizes, the 95 percent confidence level varies tremendously. With 10 patients, the confidence interval may range from a 70 percent to a 30 percent survival rate. Showing a slide on HLA-identical sibling transplants, she noted that there are only about 10,000 allogeneic transplants per year (vs. 200,000 cases of breast cancer). To do an analysis by center yields problems stemming from small samples sizes. Only a few centers have as many as several hundred cases, and most have many fewer cases per year.

Dr. Horowitz showed a slide of center-specific survival analysis done in 2006 showing risk-adjusted survival rates for transplants done from 2000-2004.

Dr. Horowitz asked how we can help consumers better understand this complex analysis. Studies show that consumers have a hard time interpreting this sort of thing and end up with misperceptions. "How can consumers (who have widely varying levels of scientific and medical backgrounds) be aided to personalize these statistics to their own situation?" This requires conveying information that is imprecise and uncertain, addressing disease-specific experience and competences, assessing other outcomes (e.g., quality of life), factoring in the time lag before data is collected and ready to analyze, and weighing issues such as accessibility and other available services.

The NMDP Web site includes information on survival after unrelated-donor transplants at individual transplant centers which seems perfectly clear to a statistician but may not be clear to the general public. It is necessary to test how things should be explained to ensure the public and patients understand as fully as possible. Dr. Horowitz said that a study on how to present information might be useful.

This RFP and its resulting activities have made centers more aware of outcomes evaluation, including related and unrelated donors. One of the challenges noted earlier is the medical community's acceptance. Centers may be more reluctant to treat patients who are sicker, or to participate in trials, if it hurts their reported outcomes. There may be a time lag between

reporting results that may affect the outcomes, too. Data collection and publication may have unintended consequences. Patients may risk spending time and money to go to a center far away, when doing so may not help them, said Dr. Horowitz.

Dr. Horowitz went on to explain that the final challenge is translating results into improvement. Accomplishing this involves assessing the goal of ensuring that every patient who needs a transplant can get one without being able to travel too far and be ensured of getting the best possible care and outcomes. The choice of center should not put a patient at a disadvantage. It is not enough to just put out the results and let patients go wherever they would like. The results have to be used, rather, to increase the quality of care at all transplant centers.

Dr. Horowitz showed a slide from Berwick et al, illustrating pathways to quality improvement. In Pathway 1 ("Selection"), findings are published, which influences where patients are referred and choose to go. Pathway 2 is about "change" and it is equally important. For both, it is important to know what the performance is, and what the process/results are, to be able to tell what may cause one center to have better outcomes than another. The information can (and should) be used by providers to change their practices. Center-specific outcomes are needed, as are center-specific processes, to identify and disseminate best practices and improve care.

Dr. Horowitz went on to explain that the approach consists of building on the existing infrastructure in order to preserve the things that work, and transform the others. It is necessary to build consensus (both in the U.S. and internationally) on this and to expand existing partnerships and develop new ones. Finally, CIBMTR will provide informatics resources that fundamentally change how data are shared. The plan is to continue the annual assessment of center-specific outcomes of unrelated donor transplants and adding related donor transplants in 2010. CIBMTR will engage the transplant community through the ASBMT Quality Outcomes Committee and a forum on assessing center-specific outcomes. CIBMTR also will engage the public, for example through the CIBMTR Consumer Advocacy Committee. In addition, CIBMTR will engage in an active research program into the processes and resources that determine performance.

Discussion

Dr. Lubin asked how third-party payers look at this and how they decide who and what they pay for. Dr. Confer responded that they are very interested in this and do ask the transplant centers for their outcomes data. It seems likely that insurers might wish to use these data and analyses, once available, rather than collecting and doing their own. The insurers will try to get information out to their stakeholders (both their employer partners and the patients) to help them make their decisions. Dr. Horowitz added that insurers have been looking at this themselves and that they have a different bottom line. The CIBMTR analysis is only going to be allotransplants, though. The intention is to build into the data collection system an ability to generate the common RFI for the insurers.

Dr. Kurtzberg said that she would like the Council to tackle the disconnect between what the patient may want and what the insurer may desire. Often, insurers have a contract with one center, but the family may want to go to another center and are not able to do so. Center

experience in rare disorders should be known and families should be able to access those centers without penalty. Dr. Horowitz agreed that both disease- and population-specific expertise are factors. She cautioned against raising expectations, however, because it will not be possible to fix the U.S. health care system this way.

Dr. Appelbaum asked whether CIBMTR had studied how patients make decisions. If no one uses the information that is available, it would be important to know. The response was that the Office of Patient Advocacy has case managers who talk with patients about how to select a center, working with their physician. However, the data are technical and hard to explain to families. It is as user-friendly as possible, but it is still very complex. The OPA encourages the patients to talk with physicians as a starting point. What is important is the centers' experience around the patient's disease, the patient's age group, and insurance coverage. NMDP has conducted focus groups with patients to look at what is presented on the Web site and publish the information in an annual directory. NMDP would like to conduct a study specifically on how people make decisions, so it is possible to evaluate drivers of transplant center choice.

Ms. Stewart said that her facility has a directory which does not list outcome but does list the number preformed by transplant type. The directory gets 600,000-1,000,000 hits a month. It is a subset though, of people who will use this information, because it involves a lot of interpretation. As a result, her organization spends a lot of time talking with patients about how to compare and contrast their options. Dr. Confer noted there is a lot of information on the NMDP site, but it's all about unrelated donors.

Dr. Burdick said he wanted to say something, but he wanted to issue a disclaimer that his remarks do not come from the Federal point of view. He continued that organ transplantation has a lot of experience with this question. There was a lot of concern 10 years ago about the risk-adjusted, center-specific data, but the system is working well now. There is a standardized RFI for insurers that has been created and has been very helpful. To speak to Ms. Stewart's point, patients look at a lot of things when deciding. If a center has a great idea and gets good results then, for a given risk index, that center will look better than everyone else. This sort of data collection has not inhibited progress in organ transplantation. Finally, one should look at the risk risk-adjusted comers to all programs.

Dr. Champlin noted that the difference with solid organs is that this field is primarily treating cancer, so one must consider the patient's status in terms of remission. It is more complex than just organ failure. Dr. Burdick agreed there are differences but said that, when one talks to solid organ transplanters, they say they have their own complexities. Engaging the medical community is important because the goal is for them to take the results and do a better job.

Dr. Appelbaum said he is a strong advocate for providing information to patients, and asked about the patient satisfaction outcomes and suggested there is a lot going on in the transplant field beyond its medical aspects. Dr. Horowitz said that this analysis is looking at survival rates, but there are other important outcomes as well. Satisfaction is part of the Quality of Life measures. Survival can be obtained pretty easily without a lot of variability, but measuring other things is more complicated. This will probably be done for a subset of patients.

Dr. Kurtzberg said that one impact is disease status at time of transplant. The field does not do well enough in encouraging those who make referrals to do so earlier (like oncologists). Dr. Horowitz agreed but said that this analysis will not help with that, necessarily. CIBMTR is working with the NMDP to alter referral patterns. Dr. Anasetti asked if survival is the most important thing, in terms of outcome. The answer was that there are 200 studies currently looking at best approaches to curing patients. This analysis focuses on what centers control in terms of delivery of care, not processes about transplantation as a whole.

Ms. Stewart asked if this takes into account Graft vs Host Disease (GVHD) prophylaxis. The answer was that it does for the prophylactic regimen, but not for the treatment.

Scientific Factors Necessary to Define a CBU as High Quality Unit, Robert Baitty, HRSA

Mr. Baitty began by telling the group that he would go over the legislative requirement for defining a high quality cord blood unit; describe HRSA's interim report to Congress; and make a specific request to the Council.

He explained that the law requires the Secretary, acting through the Advisory Council, to submit to Congress a report of "recommendations on the scientific factors necessary to define a cord blood unit as a high-quality unit." The report is to be submitted no later than six months after enactment of P.L. 109-129. The corresponding Senate Report stated that: "The committee thinks it is of preeminent importance that the Secretary promptly develops a scientifically sound definition of a 'high-quality cord blood unit' and anticipates that the Advisory Council will play a prominent role in this process." The Senate Report suggested that the definition include quantitative measures of cell counts and viability, HLA typing resolution, Match algorithms, and an agreement on outcomes measurements, and said it is also likely to address quality testing, selection criteria, collection and transportation standards, confidentiality and integration of files, searches and general procedures.

The statutory deadline required an interim report, to be revisited with the assistance of the Advisory Council, which was submitted to Congress by the Secretary on October 23, 2006. The report described HRSA's interim requirements for NCBI banks and reimbursable cord blood units, as well as HRSA consultations that occurred on those requirements. The report noted that the interim requirements were, in some respects, more rigorous than current banking practice and accreditation requirements (e.g., minimum cell counts). This was done because higher counts are associated with better clinical outcomes and preferred by transplant physicians. The report did not describe the roles played by the FDA and accrediting organizations in assuring quality and safety.

Mr. Baitty noted that HRSA's interim requirements were based on extensive consultation with the field and interested public, including the following:

- IOM recommendations of April 2005
- HRSA Request for Information, August 2005
- Teleconferences with blood stem cell transplant physicians and scientists, and public and private (family) cord blood banks
- Site visits to CBB, birthing hospitals, and cell processing facilities

- Consultation with accrediting organizations
- Consultation with experts within the Federal Government
- Review of relevant literature.

The report listed HRSA's requirements of the NCBI banks, in areas including regulation, accreditation, licenses; testing of units and maternal samples; SOPs and quality management; storage temperatures; and proficiency testing programs. The report also listed CBU characteristics required for NCBI reimbursement. These required CBU characteristics include:

- Total nucleated cell count $\geq 90 \times 10^7$ (without subtraction of nucleated red blood cells)
- CFU-GM assay must show growth
- TNC Viability $\geq 85\%$
- Content of viable CD34+ cells measured, no minimum value specified
- ≥ 2 attached segments
- Negative for infectious disease markers, bacteria and fungi, clinically significant hemoglobinopathies
- Minimum human leukocyte antigen typing: low/intermediate resolution at the A, B loci, high resolution at the DR locus; all by DNA methods.

Mr. Baitty went on to say that NCBI banks have had challenges with respect to meeting these requirements. These include the minimum TNC of greater than or equal to 90×10^7, particularly for minority populations. HRSA has been asked whether, for some populations, a lower level of TNC should be accepted. However, this might be seen as accepting lower quality care for some populations. HRSA welcomes the Advisory Council's input on that issue. The biggest challenge has been reaching goals for African American units. The minimum donor age (18) has been a problem for some.

Also, there are issued associated with some automated processing methods regarding the HRSA minimum TNC requirement, and the role of TNC in ranking of CBU on search reports. TNC counts may not have the same implications for potency from one bank to another because of their varying processing methods. More reliable measures are needed.

HRSA requests that the Council review the interim report and make recommendations for a final report to Congress, particularly regarding the scientific specification of a high-quality CBU, which could be broader than HRSA NCBI requirements. The Council is asked to focus on unit characteristics, not the systems or the process through which the units are made available and selected for patients. The Council's report will help guide HRSA in the development of future criteria for NCBI funding.

Discussion

Dr. Blume began by reiterating that this is an area where the Advisory Council has specifically been asked for a recommendation. There will be a workgroup dedicated to this issue, and he encouraged those members who have not already signed onto a workgroup to participate in this one.

Dr. Parkman asked about the dose and the nucleated cell dose per kg. HRSA minimum cell count requirements might eliminate some units that might work well with small persons. This could be disadvantageous for them. The response was that these requirements concern only which units HRSA may reimburse under the NCBI program; they do not limit what is banked or used for transplant. HRSA wants units suitable for a wide range of patients and for good outcomes. Banks collect many units that might not meet the HRSA criteria but would still be good for transplant. Dr. Parkman cautioned against the development of two tiers of units and the danger that third party payers may replicate the HRSA payment scheme. Mr. Baitty noted that there are already many tiers of reimbursement. He is not aware this is an issue presently, but he agreed it might become one.

Dr. Kurtzberg added that, even for small babies, there is an advantage to getting bigger units. She said it was an economic question about which units HRSA finds it most cost-effective to encourage, and did not think a HRSA reimbursement requirement for larger units disadvantaged anyone. Dr. Hartzman stated that doctors are asking for the larger units anyway, and the cost of the unit is only a small part of the cost of a transplant. He also noted that the data are not very good on assays and on what constitutes a good unit. The first task should be to develop better analytic systems to determine what is in a unit.

Dr. Champlin said that it would be useful to know the distribution of cells in units collected by NCBI banks. This could suggest liberalizing the criteria. Mr. Baitty agreed to obtain this data for the workgroup.

Dr. Anasetti said that one can be very precise for adults. He suggested that the workgroup look at using viable C34 instead. Mr. Baitty stated that the TNC is used so widely in cord blood selection because it is repeatable and there is a need for improvements in the inter-bank reliability of CD34 and especially CFU measures. Dr. Lubin added the importance of not applying the criteria for siblings. Mr. Baitty said that the HRSA criteria apply only to reimbursement of units collected by public banks under the NCBI program; they do not address desirable counts for family banks.

Dr. Rubinstein suggested that the issue might be related to the terms which are used. There are high-quality units that might not qualify for HRSA reimbursement for many reasons. Perhaps it makes sense not to use the phrase "high-quality" unit, which suggests that others are of lower quality. He suggested using a more neutral term instead, like "HRSA-reimbursable." Mr. Baitty noted that Congress wanted to help guide the field, but this suggestion should be considered as the Council looks at the issue. Dr. Rubinstein concluded that the HRSA definition is helpful but creates a tiered system in which usable and good units may be considered to be second-class.

Dr. Kurtzberg spoke to Dr. Ansaetti's point, noting there is not a standard with cord blood banks and there are efforts to improve correlation of measures from bank to bank. Now with CD34, there are 109-fold differences based on measurements of CD34, and CFU, are potentially a good marker, but the inventory is so mixed that they cannot alone be used now for unit selection. They could work going forward, however, if more reliable measurement systems are developed. Dr. Anasetti responded that there are a small number of banks in the U.S., so one could develop

and use tables comparing test results across banks. Dr. Kurtzberg noted that one goal is to unify the field, to be able to compare with products from Germany, for example.

Dr. Rebecca Pentz said the workgroup may want to reconsider having the minimal maternal age of the donor be 18 years of age. Research shows that adolescents between the ages of 14-17 are perfectly competent to make complex decisions and are, in fact, as good as adults are at doing so.

Dr. Parkman returned to the earlier discussion and said that the HIV population shows it is viable to use CD34. Dr. Kurtzberg responded that CD34 is more complicated. Dr. Parkman disagreed, stating that it was better to use a biological basis than use something else just because the latter was more easily measured. Dr. Blume added that it is a different kind of problem. Dr. Hartzman weighed in that people have tried and failed for years to standardize this. In his view, it is a technical problem. Dr. Blume summarized by saying there are all sorts of problems, technically, including the concentration that is analyzed versus suspensions. The structure will differ.

Dr. Read said that the CD34 problem is that most labs are doing multiple platforms and calculating the CD34 percentage, so it has to be multiplied by TNC anyway to get a CD34 count. The workgroup should think about whether it is possible to come up with a standardized CD34, and whether the transplanters would prefer it in the future. If so, "should this be built into specifications at some point in time?" She hears from transplanters that a biological marker is better. Dr. Kurtzberg said to look at the studies with clinical outcomes. Dr. Read responded that these data are based on TNC. Dr. Kurtzberg said she had data on thousands of transplants and has not even established what correlates best with clinical outcomes. Dr. Read asked that if one could get a reliable CD34, would it be preferred. Dr. Kurtzberg answered that she did not know which was better.

The following Council members volunteered to be on this workgroup:

- Joanne Kurtzberg (workgroup leader)
- Donna Regan
- Pablo Rubinstein
- Hal Broxmeyer
- Robert Hartzman
- Bertram Lubin

Mr. Aronoff stated that, by February 4, HRSA will provide dates and times for conference calls for the workgroups. He asked members to let HRSA staff know when they are available, and the staff will gather useful information on each of the topics. If members have ideas about that information, Mr. Aronoff asked them to let him know.

Confidentiality Policies for Adult & Cord Blood Donors, Shelley Tims, HRSA, and Kathy Welte, NMDP

Federal Overview

Ms. Tims described the law's statutory requirements about confidentiality for bone marrow donors versus cord blood donors. Her talk covered HRSA's recommendations to the Cord Blood

Coordinating Center (CBCC) and issues around defining confidentiality requirements for cord blood. HRSA is specifically requesting the Advisory Council's input on this subject. She asked members to hold their questions until the end of the presentations.

P.L. 109-129 carries forward confidentiality language regarding adult donors that has been in place since the 1990's for the National Bone Marrow Donor Registry. The section of the law pertaining to bone marrow functions specifies information that cannot be disclosed. The law states that: "The Secretary shall enforce for participating entities, including the Program, individual marrow donor centers, marrow donor registries, marrow collection centers, and marrow transplant centers…standards that require the establishment of a system of strict confidentiality of records relating to the identity, address, HLA type, and managing marrow donor center for marrow donors and potential marrow donors." The law also requires maintaining with respect to confidentiality for cord blood donors but does not provide detail about what must not be disclosed.

The term "qualified cord blood bank" means a cord blood bank that has established a system of strict confidentiality to protect the identity and privacy of patients and donors in accordance with existing Federal and State law. The law specifies civil penalties (e.g., fines) and criminal penalties (e.g., prison terms) for the unauthorized disclosures about adult donors or cord blood donors.

The Senate Report on P.L. 109-129 noted that it is of preeminent importance that a "high-quality cord blood unit" be defined by the Secretary in consultation with the Advisory Council, and specified that this definition was to include many factors, including confidentiality.

Ms. Tims said HRSA is mindful that cord blood donor babies do not consent to donation of their umbilical cord blood—the mother provides the consent for her baby. Therefore, HRSA recommends a level of protection for donor babies equivalent to or greater than that required for adult donors. HRSA believes that confidentiality breaches could occur if certain information were used to solicit a response from an individual with matching demographics and history, including: allele level HLA typing data, the cord blood bank where the CBU was stored, and the collection date (e.g., the donor's birthday) and, for this reason, discourages sharing this information with patients or their families.

HRSA asked that the Advisory Council review the current practices related to confidentiality and cord blood donation; consider the differences in legislative requirements around confidentiality for bone marrow donors and cord blood donors; and make a recommendation about safeguarding the confidentiality of cord blood donors.

Cord Blood Confidentiality, Kathy Welte, NMDP Center for Cord Blood

Ms. Welte stated that she will provide some background about protecting donor and recipient confidentiality. The original requirements and directions applied by NMDP around confidentiality were developed to protect the identity and privacy of adult donors who provide cells for transplants. They evolved from the requirements of Federal law for the National Bone Marrow Donor Registry preceding P.L. 109-129 and other documents, and are well-established

today. While a number of those provisions are clearly applicable to cord blood donors, several items are more challenging and may not fit as well in the cord blood arena. These were highlighted.

NMDP takes confidentiality protection very seriously throughout the network because the impact of breaches can be severe both for the donor and for the public's confidence in the whole system and in the NMDP. Donors could see their name in the newspaper and what may have been a private, altruistic act for that person now becomes a public event. This could also have a chilling affect on other people's willingness to become a donor, and could even encourage other families to try to identify their donor.

For cord blood, the actual donor is the baby; but the mother consents to the collection of the unit and it is her information (on about health status, transmissible disease risk factor assessment, and infectious disease marker testing) that is obtained and reviewed at the time of donation. The questions asked are extensive and cover sensitive topics for the mother, as well as many questions about the baby's family medical history. For this reason, the identity of the maternal donor and baby are protected.

Ms. Welte explained that the possibility of donor and recipient meeting each other is a key difference between adult donors and cord blood donors. Many registries, including the NMDP, permit donor and recipient to meet each other a year after transplant, if both parties wish. A request by either party to meet is brokered by the registry to assure that both parties really want to meet. For cord blood donors, however, general bank practice and current bank and registry policy do not allow the possibility for the recipient to meet the baby or mother. This is specified up-front for both the donor family and the recipient. Cord blood banks and the NMDP have been asked if a recipient can contact the donor to thank him/her for donating cord blood, and the answer is always "no."

Ms. Welte explained that most meetings flow from the recipient's great interest in being able to personally thank the donor and feeling a real bond with this person. But, the major risk in such meetings is that, once the donor's identity is known, if the recipient later needs more cells the donor may feel pressure to supply them or the recipient may directly contact the donor. The recipient may even ask for another organ, such as a kidney. This has happened. While some donors welcome such a request, others may not. In any event, adult donors are able to make that decision for themselves. NMDP wanted to avoid any such possibility for cord blood donors. Unlike marrow or PBSC, cord blood is collected to be part of a general program with the hope that it may be used at a future point in time. An inherent limitation of the cell source is that what's in the bag is all there is from that donor. In contrast, marrow and PBSC are donated for a unique recipient who is known at the time of donation.

NMDP started discussing confidentiality specific to cord blood donors, explained Ms. Welte, because there were a few instances in which recipient families wanted to contact and thank the cord blood donor. They either contacted the cord blood bank directly because they knew the source of the unit, or they contacted the NMDP. There had also been several newspaper articles about cord blood transplant recipients that mentioned the specific bank and location. This made NMDP uneasy because many cord blood banks only collect units from a few hospitals and

deliberately make it easy for the general public to identify individual hospitals so they can become donors if they choose. In this electronic age, NMDP was nervous that it might not be difficult for an enterprising person to identify the baby donor based on date of birth and location of the bank. NMDP started talking about this with banks and realized there were nuances to protecting confidentiality that seem to clearly apply to adult donors but are not as clear here.

Ms. Welte said that the list of documents on confidentiality that NMDP used as discussion background include the legislation for the C.W. Bill Young Transplantation Program, the Privacy Act of 1974, the NMDP's Standards, HRSA contracts with NMDP, and NMDP Donor and Patient Confidentiality Guidelines. There is considerable overlap in the requirements among these documents as would be expected. Since its founding, NMDP has thought about these issues and has had confidentiality procedures in place for many years. NMDP employees also sign a statement acknowledging that one risks fines and imprisonment if confidentiality is violated.

The primary discussion of how confidentiality should be upheld for cord blood donors and recipients has occurred through the venue of the NMDP Cord Blood Committee, which was created in 2004 as a Committee of the Board of Directors. It has several primary functions in its work to advise management and the Board of Directors on issues related to cord blood. A significant part of the work has been to develop uniform standards that each bank agrees to follow. The NMDP Cord Blood Committee advises management and Board on issues related to cord blood as a cell source; assists NMDP, in partnership with government agencies, to improve ability to provide oversight to cord blood activities; and develops uniform standards for donor screening, cord blood processing, storing, testing, thawing and use for the Network. The Committee includes representatives from each participating cord blood bank, transplant physicians and staff, obstetricians, researchers, regulatory experts, government agencies, and NMDP staff. It is co-chaired by Dr. Rubinstein and Dr. Kurtzberg and other Advisory Committee members are members (Hal Broxmeyer, Bertram Lubin, and Donna Regan).

Key considerations in the NMDP guidelines include the search process, stem cell transport, donor-recipient contact after transplant, and other special considerations. The NMDP confidentiality guidelines address specific information that can be shared during specific activities and what to do when confidentiality guidelines are breached. This is a useful way to look at the issues to be sure all aspects of the work are addressed. It also recognizes that participants in the network (like transplant centers and their processing labs) have different needs for specific information as part of their clinical work and compliance with regulatory issues.

There have been several committee meetings on this issue. Ms. Welte proceeded by giving a picture of the evolution of the discussion. The committee began by describing what is traditionally shared by adults and what probably make sense to be shared for cord blood units, too.

As a result of the first sets of discussion, the committee proposed the following fields as acceptable to share with patients: donor's sex, degree of match, age of CBU in years, ABO/Rh, CBB name and location, responses to MRQ/FMHQ if hospital policy requires this; and the recipient's sex, age, and diagnosis. The group felt it was important for the recipient to know the sex and ABO/Rh, as these will be evident as the unit engrafts after transplant and may be used to

determine chimerism. The degree of match may have an impact on outcome and is also important for the family to know.

Ms. Welte said that the CBB name and location was thought to be important, in part, because it is on the label of the unit. There was a big discussion on this issue. Cord blood units are subject to much more manufacturing than adult donor products, and may be stored for years before being used. Banks have different processes and procedures that may be of interest to transplant centers and patients. In addition, the ISBT-128 numbering system that is being adopted by a number of banks internationally includes a two-digit facility number, which would probably be fairly easy for a motivated recipient to tie to a bank. The equivalent donor center identity would not be shared with families receiving marrow or peripheral blood stem cells, but these products are minimally manipulated by the collecting facility. The final item recognizes that, if there are some unusual findings in the medical history of the maternal donor or baby's family, the transplant center may inform the family of that information in advance. Opponents were concerned that this information is not shared with adult donor cases and may breach confidentiality. It has been the tradition not to share that information, and it has worked well with adult donor populations.

Ms. Welte explained that the discussion has really focused on the degree of match, the CBB name and location, and detailed HLA type. A number of committee members believed that the patient has a right to know the allele level, the very specific typing of the unit. They have said that patients often come to the transplant center with search reports from specific banks that include this information. Many patients do a lot of research and are very knowledgeable. They want as much detail as possible about the product and are not satisfied just knowing the loci of mismatch. They want to be sure that what they receive is what they are expecting, which includes everything from the medications to the stem cells. Committee members also noted several practical considerations: the HLA type of the unit will become the recipients HLA type after transplantation. Thus, a person will know the HLA type after transplant. Another practical consideration is that this information is part of the recipient's hospital chart, which is open to them. Some transplant centers may keep a separate chart for the donation information, in practical terms, that families could access.

HRSA sent letter to NMDP on July 20, 2007, to assist in these deliberations. The letter included the following recommendations:

(1) Cord blood donor babies did not have an opportunity to consent to the donation; their parents consented for them. Therefore, the level of protection for these babies should be equivalent to, or greater than, that required for adult donors.
(2) The Internet increases the risk that a public appeal could result in identifying a baby donor and resulting in a request for more cells based on family knowledge of the date of collection, the HLA type, and the cord blood bank. (Increasing numbers of people know their HLA type through National Geographic, etc.)
(3) NMDP should carefully assess whether the patient needs to know the allele level HLA typing, the date or month of the CBU collection, and/or the identity of the CBB.
(4) The year of collection could potentially affect the unit's potency and degree, and the location of a mismatch could affect the outcome.

The HRSA letter was discussed with the full committee at its most recent meeting. There was a division between those who felt that knowing allele level typing and cord blood bank identity was really a patient's right that overrides current confidentiality protection guidelines, and those who felt that this information should not be shared with the recipient. This is an important issue for the HRSA Advisory Council to consider.

Ms. Welte explained that the main challenges are notifying families of allele-level typing and sharing the name and/or identification of the bank. In addition, there are questions about whether the transplant center should be able to ask the bank to contact the maternal donor to assess whether the baby has developed conditions that appear in the recipient and that could be related to the cord blood. Today, there is no contact between the recipient and the baby donor; however, what if the now-adult donor wanted to meet his or her recipient and the recipient has expressed interest in doing so. There are units that date back to the early 1990s, so this could happen in the near future. Finally, should the Program have limits about how frequently a donor family can be contacted; if so, for how many years?

These are the types of concerns that will need to be addressed for this newer source of cells for transplantation.

Discussion

Ms. Holiman said that, in the adult registry world, one would accept a second request for additional cells if the patient needs them and asked if that situation had arisen. The answer was that the limitation is that what's in the bag is what one gets. NMDP does not request second cells because the donor is a baby. People do worry about this problem, however; someone could try to find the baby and make a request later on.

Dr. Anasetti commented that people do meet and, because of that, some have recommended confidentiality be established for perpetuity. He asked if the NMDP had studied the adverse potential effects of this. Dr. Confer responded that, surprisingly, there have not been too many problems developing between recipients and donors when they meet. Problems tend to stem from subsequent requests for cells, as well as the NMDP's fear that donors may not feel they can decline the request. NMDP works with ethicists in these cases. Otherwise, other potential problems, such as request for money, seem not to have occurred. Dr. Kurtzberg said there was a published focus group of mothers both before and after pregnancy and donation. One showstopper for the mothers was that if the identity of the baby was to be released, they might be approached again for donation later.

Dr. Appelbaum suggested that this would be an interesting study to conduct. Banks or NMDP should look at the experience of recipient and donor meetings. There are many reports that this was the peak experience in the donor's entire life. Meeting the recipient is incredibly important to the donor. Ms. Welte added that NMDP has researched donors and concurs. Donation is a highly significant act and people feel extremely positive about making the donation. Dr. Hartzman agreed, and said that, while there have been some negative experiences, we should not rule by exception. In most of cases, it's a very important and positive experience.

Dr. Milford stated that it's a different thought process for saying it *will* be confidential, or that it *can* be confidential. Confidentiality must be maintained for those who want it, while allowing those who want to break it voluntarily to do so.

Dr. Champlin added that clerical errors are a factor. It is important to be able to identify where the unit came from so it can be checked. There are an alarming number of errors, and the transplant centers have to be able to identify where the units come from. Dr. Blume said that it was scary that Dr. Champlin said "frequently." Dr. Champlin responded that it happens a couple of times a year. While the number on the bag should match the number on the order, people make mistakes, so the system needs checks. The speaker noted that there is a difference, however, between what is shared with the center and what is shared with the recipient.

Dr. Kurtzberg expressed her belief that patients are ahead of this curve. They already know the bank and have talked with its employees about specific units at that specific bank. There is a whole network of communication before the final interaction with a center occurs. Patients come in with the unit report in hand, know what unit that they want, and have written recommendation about the "best" unit from the bank director. Dr. Kurtzberg also believes it is the family's right to know as much as possible. They are going to want to know the HLA type, for example.

Dr. Blume asked why it is important to know the bank a unit comes from, and Dr. Kurtzberg answered that families know that certain banks have good reputations. The families want to know that all of the banks were used in the search. Families are very data-oriented. They do not just believe something simply because their providers say it.

Dr. Rubinstein said his facility's policy is that it is not possible to meet the donor. The baby donor is unaware of the donation, and thus there is no sense of accomplishment that can reasonably be derived from this act for the baby. But, patients have a need to relate in some way to the donor as member of a group that has helped the patient overcome disease. So, the facility provides a substitute when the need arises. At random, another mother is selected who has consented to be a substitute for all of the mothers in the registry; and she communicates with the recipient. It has been very calming and useful for the patients. It does not completely accomplish what the patient wants, but it does provide a feeling of having connected. Mr. Sprague agreed that it's hard to describe how important it is, unless one is a recipient, to know who gave the patient back his or her life. There is a 10- or 11-year-old girl somewhere in New York he thinks about every day and he would love to tell her what she had done. Mr. Sprague was also sure she would love to know what she did. He felt there was a way to accommodate both.

Ms. Stewart asked, if parents have the right to make the donation decision for their children to donate to their siblings, as well as for all sort of other things, why do they not have the right in this case? The response was that it goes back to not wanting to put the donor in a position to be asked for more cells later. Dr. Rubinstein described his policy, which is that the person can contact the facility. He has had five patients whose donors have developed leukemia and who

wanted to know if another unit is available. So far, there has been uniform consensus that the units should not be used. Of course, this requires the public to contact the bank.

Ms. Holiman asked where the group goes from here because it is very different from adults. Her first thought was that this was like that of blood donations, where no one would know. She said she had not known there was any further contact with the mothers. Ms. Regan explained that her group tells the mothers they will be contacted, and they all have cards that ask the facility to contact them. There is a lot of contact, but the mothers are not told if the unit has been banked or used. Ms. Holiman said the group could spend hours on this, and suggested forming a workgroup. Dr. Blume agreed that this was the goal.

Dr. Sims said there is an important difference between donation and information sharing. If parties wish to share information, this can be done without breaching confidentiality. With a minor child, the question is whether they can consent to surrender their autonomy just because someone else requests it, even if that person is their mother. The child may become the victim of the parent. The recipient's health is tied into the donor and their genetic make up. The Council members should be cautious yet open.

Dr. Kurtzberg added that it is very expensive to follow people to age 18 years, to get their consent as adults for this. Secondly, this is a great opportunity for genetic screening and follow-up, if there were funding for it. And, "how can the system ensure that an autologous unit isn't given back, too?" she asked.

Dr. Blume commented that there are clearly a lot of opinions. Volunteers for this workgroup are:

- Mutsuko Holiman
- Joanne Kurtzberg
- Susan Stewart
- Stephen Sprague
- Rebecca Pentz
- Claudio Anasetti

Public Comments

There were no public comments.

Closing Remarks

Federal staff described the reimbursement process for Advisory Council members.

Dr. Blume recognized an audience member, Dr. Paul McCurdy**,** a physician who has, for decades, been instrumental in advancing the field of transplantation and donor registries, graft availability, and legal process. (The members and public applauded Dr. McCurdy.)

Dr. Blume thanked the members for attending and for being so active. He also thanked the NMDP staff for their participation, as well as the others who have provided data and reviewed the status of the field for the Council. The organizing group at HRSA did a great job. They are

looking to the Advisory Council to provide distinct advice to them. Problem areas have been identified, and workgroups formed to provide feedback to the Secretary. There are five groups, not in order of importance:

(1) The process of access of cord blood units for research
   a. Robertson Parkman -- leader
   b. Hal Broxmeyer
   c. Donna Regan
   d. Edgar Milford
   e. Liana Harvath
   f. Robert Baitty
   g. Remy Aronoff
   h. Karl Blume

(2) Public funding for data documentation
   a. Frederick Appelbaum – leader
   b. Doug Rizzo (ex officio)
   c. Joanna Kurtzberg
   d. Susan Steward
   e. Robert Baitty
   f. Remy Aronoff
   g. Karl Blume

(3) Accreditation of cord blood banks
   a. Elizabeth Read -- leader
   b. Charles Sims
   c. Bertram Lubin
   d. Donna Regan
   e. Pablo Rubenstein
   f. Robyn Yim
   g. Robert Baitty
   h. Remy Aronoff
   i. Karl Blume

(4) High-quality cord blood
   a. Joanne Kurtzberg -- leader
   b. Pablo Rubinstein
   c. Hal Broxmeyer
   d. Bertram Lubin
   e. Edgar Milford
   f. Robert Hartzman
   g. Robert Baitty
   h. Remy Aronoff
   i. Karl Blume

(5) Confidentiality issues

a. Michelle Bishop -- leader
b. Mutsuko Holiman
c. Rebecca Pentz
d. Susan Stewart
e. Stephen Sprague
f. Robert Baitty
g. Remy Aronoff
h. Karl Blume

The meeting was adjourned.