

**ADVISORY COUNCIL ON BLOOD  
STEM CELL TRANSPLANTATION (ACBSCT)  
U.S. Department of Health and Human Services (HHS)**

Hyatt Regency Bethesda  
Bethesda, Maryland

**November 15, 2010**

**Welcome and Introductions**

Edgar Milford, Jr., MD, ACBSCT Chair, called the meeting to order at 8:00 a.m. He noted that the Council had addressed most of the issues assigned to it by statute and asked members to consider additional areas on which it would like to advise the HHS Secretary. Patricia Stroup announced that she will take over as the Executive Secretary for the Council. Ms. Stroup welcomed the members and thanked them for their participation.

**Cord Blood Bank Collections Work Group Update**

*Donna Regan, MT (ASCP), SBB, Work Group Chair*

Ms. Regan reiterated the purpose, objectives, and membership of the Work Group and described progress to date. A pilot project underway on remote collection (involving the National Marrow Donor Program [NMDP] and three collection centers) is already facing challenges. The collection process is slower (and thus volume is lower) than anticipated, probably because collectors need more practice and training. Also, the cost of transporting product from remote areas is high.

*Optimizing Cord Blood Collections*

The Work Group continues to evaluate other means for optimizing cord blood collections. Recent publications describe a new approach that uses pulsatile machines and seems promising for getting more immature cells from the placenta, but this approach may be difficult to scale up. Combining in utero and ex utero methods (and engaging both obstetricians and obstetric staff members) may be effective in collecting more cord blood.

*Improving Medical Professional Education*

The Work Group continues to seek support from medical boards and professional associations to incorporate cord blood collection into residency training and to include it in board examinations. Ms. Regan suggested that, as a first step, cord blood collection could be taught alongside blood transfusion [transfusion medicine]. The NMDP has developed a flip-chart for obstetricians to use in counseling patients; it should be available in 2011, so the Work Group believes no further initiatives are needed by the Council at present on educating obstetricians.

*Educating Potential Donors*

As recommended by the Council, language on cord blood donation was included in a Federally funded document known as the *Pregnancy Passport*; 100,000 copies were purchased and distributed. The Maternal and Child Health Bureau of the Health Resources and Services Administration (HRSA) has expressed interest in using the *Pregnancy Passport*. The NMDP created two short videos suitable for doctors' offices and other health care settings promoting

donation. Ms. Regan said hospitals should be prepared to refer potential donors who are inspired by these outreach efforts but do not live near collection sites. She added that legislation on raising donor awareness exists on which the Council can build.

#### *Reauthorization*

The Stem Cell Therapeutic and Research Reauthorization Act of 2010 was signed into law, which will have a great impact on cord blood banks, said Ms. Regan. It directs cord blood banks to increase collections, for example, by using new technology and establishing new collection sites. It also requires cord blood bank to demonstrate measurable progress toward self-sufficiency but does not define the requirement further.

#### *Work Group Plans*

In summarizing the Work Group's action items, Ms. Regan noted that, in the service of the remote collection pilot project, the group should solicit best practices for transportation from colleagues in the private sector. It is hoped the results of the project can be used to build confidence within the U.S. Food and Drug Administration (FDA) that remote collection sites can develop and employ science-based safety precautions and provide high-quality products, even though they are not monitored the same way that cord blood banks are.

The Work Group will continue to investigate innovative collection approaches, forge relationships with other organizations to encourage residency training, make contacts related to crafting donor awareness legislation, and work with the NMDP and other organizations to further the Work Group's goals.

#### *Discussion*

Clive Callender, MD, said cord blood donation does not seem to be accessible to patients. Dr. Milford noted that the Council has been charged with providing advice on how to increase collections and accessibility, given the limited number of collection sites for public banks.

Joanne Kurtzberg, MD, pointed out that cord blood collection kits are one mechanism for expanding collections, but it is not clear how the FDA would license such kits unless hospitals accept some of the responsibility for their distribution and use. Robert Baitty of HRSA noted that several NCBI banks have HRSA funding to cover the costs of collecting cord blood from a newborn for the purpose of helping another child in the same family. He agreed with Dr. Callender about the need to raise awareness among providers about cord blood donation options. Bertram Lubin, MD, added that pediatricians should be educated as well, because evidence shows they are not aware of the value of cord blood banking. Dr. Lubin said California has proposed funding for cord blood banks, and he suggested the Council support that legislation. Dr. Milford noted that HRSA recognizes the need to ensure that cord blood collections reflect the needs of minority populations.

#### **Action Item**

The Covered Diagnosis and Costs Work Group will evaluate proposed legislation in California on funding for cord blood banks and consider how the Council can express support.

Dr. Kurtzberg said the high cost of collection and storage limits even private banks from substantially increasing capacity. Only one of the States that supports cord blood banking actually provides funding. With no additional money, Dr. Kurtzberg asked, how can you ask cord blood banks to increase their inventory 10-fold and become self-sufficient? Robert Hartzman, MD, agreed that the current financial model does not work. He called for an assessment of how much cord blood is needed serve the population. He suggested seeking funding from charities and charging more for cord blood. Richard Champlin, MD, noted that the start-up costs for a cord blood bank at his institution was \$3 million. Ms. Regan suggested that as clinical use of cord blood develops, banks may be better able to recoup their costs.

Ellen Lazarus, MD, said that companies have an opportunity to talk with the FDA before they submit their biologic license applications (BLAs). She noted that collectors who have a formal agreement with a cord blood bank do not have to register with the FDA. Dr. Lazarus said cord blood banks can develop their own procedures for meeting FDA requirements.

### **Access to Transplantation Work Group Update**

*Richard Champlin, MD, Work Group Chair*

Dr. Champlin pointed out that the indications for hematopoietic stem cell transplantation (HSCT) are evolving and public and private insurers are inconsistent in their coverage. He noted that another expert panel, the European Group for Blood and Marrow Transplantation, developed a list of indications for HSCT, categorized according to acceptable settings or uses (ranging from “standard of care” to “generally not recommended”) and distinguished by the level of evidence that supports the indication. Dr. Champlin said the European system provides a good framework but may be too specific; the Work Group would prefer to see treatment guidelines that emerge more naturally.

Some issues that affect insurance coverage are treatment decisions based on prognosis, which is a moving target, and coverage of imperfect matches or cord blood sources, which can be effective in adults. The Work Group believes all sources and type of matches should be covered.

To increase access to transplantation in the United States, the Work Group believes that insurers would benefit from more guidance on indications. However, such guidance would be more credible if developed by the greater medical community rather than the Advisory Council alone, with input from the American Society of Clinical Oncology and the American Society of Hematology, for example. The Work Group plans to convene a small panel of experts to develop a short list of effective transplantation options with some detail on genetic and metabolic diseases for which transplantation has been shown to be effective.

### *Discussion*

Dr. Champlin proposed that, once approved by the Advisory Council, the Work Group would seek to publish its expert panel findings in a medical journal, then send subsequent conclusions or recommendations to the Secretary. Dr. Lubin pointed out that published guidelines can quickly become the basis for care, so findings should be carefully considered. He suggested involving relevant companies; he also asked how such guidelines would relate to health care reform legislation. Dr. Champlin replied that an expert panel would strive to be inclusive, yet practical. He noted that California developed a list of indications that it updates annually. A

process would need to be developed for determining when an indication should be included on the list.

Claudio Anasetti, MD, noted that an advisory panel in Florida is publishing a list of indications shortly. That panel addressed the need to cover clinical research trials for rare diseases. Dr. Milford noted that States are moving forward in their coverage decisions, even without Federal funding.

#### **Action Item**

Dr. Anasetti will provide the Access to Transplantation Work Group with the guidelines from the Florida advisory panel.

### **Realizing the Potential of Cord Blood Work Group Update and Recommendations**

*Liana Harvath, PhD, Work Group Chair*

*Michael Boo, JD, Strategic Development Officer, NMDP*

Dr. Harvath presented the first update from the group, which was formed following the May 2010 Council meeting. She presented the Work Group's charge, which includes, "identify[ing] important gaps and strategic opportunities with regard to more fully realizing the potential of cord blood in such areas as clinical research, technology development, and the economics of public cord blood banking," and described its process and membership. The Work Group has already identified a list of high-priority research questions:

- How can the concentration of cord blood stem cells be increased during collection?
- What automated processes improve cord blood transplant outcomes?
- What criteria define the best cord blood unit for a patient?
- Are transplant outcomes equivalent for ex vivo expanded cord blood and multiple-unit cord blood stem cell grafts?
- What are the most efficient approaches to increase the current inventory of high-quality cord blood units?

Dr. Harvath asked for Council members' input on some research funding opportunities through the National Institutes of Health. Some of the research questions may already be reflected in existing or planned funding applications.

#### *Financial Self-Sufficiency*

In response to the Reauthorization Act, HRSA asked the Work Group to recommend measures for cord blood banks to achieve financial self-sufficiency and benchmarks toward that goal. As a starting point, the Work Group evaluated a financial analysis from NMDP, which Mr. Boo reiterated for the Council.

Mr. Boo presented an analysis of NMDP data describing a selective depletion of the inventory: cord blood bank inventories tend to contain a lot of smaller cord blood units (total nucleated cell [TNC] count  $< 125 \times 10^7$ ), while transplant physicians tend to select the largest units (i.e., TNC  $> 125 \times 10^7$ , which is even larger than the minimum for NCBI units). The pattern holds when the inventory is sorted by race. Beginning in 2009, recruitment focused on getting more larger units, but the inventory still leans heavily toward smaller units.

Increasing use of multiple-cord transplantation is driving the overall growth of cord blood transplantation (up 21% in 2009). The selection of TNC is biased toward multiple-cord units, but it does not appear that transplant centers are combining smaller multiple-cord units to achieve a larger dose. Mr. Boo said centers don't know which units will work, so they try to have on hand enough of each type of unit to complete the transplant. Banks are working harder to increase the number of units with high TNC counts and disqualifying smaller units.

Starting in 2005, adult patients have comprised an ever-growing percentage of total cord transplant recipients, representing 54% of all patients in both 2008 and 2009. Increasing use of double cords for adult patients is driving demand for larger units.

In the United States, more than 30 percent of cord blood transplants occur in minority patients, so cord blood is increasing access to transplantation, as promised, Mr. Boo noted. In 2008 and 2009, more than half of all recipients were Hispanic.

As the inventory includes more large cord blood units, fewer transplant centers select smaller units. Mr. Boo said that over the past five years, use of larger units is significant, although there is some diminution over time as units are selected by human leukocyte antigen (HLA) status. Half of the adult transplantation population is served by cord blood units with TNC counts in the  $170\text{--}180 \times 10^7$  range, and the average unit selected has a TNC count of  $177 \times 10^7$ . All of these data combine demonstrate the economic inefficiency of storing smaller cord blood units that are not used very often.

Mr. Boo presented a chart comparing the amount of cord blood units collected and distributed beginning in 2009 alongside average costs per unit of recruiting, processing, storing, distributing, etc. He noted that 33% of all units collected will be banked. The chart showed that the bank in question generated about \$51 million in revenue—\$12 million less than needed to cover costs.

However, if the TNC cutoff were raised—that is, if the bank processed and stored less of the smaller units—the bank could be profitable. The downside of such an approach is that banks may not collect the kind of units that could be needed in the future, because they would be focused on the current bias toward larger units. The approach implies banking a smaller number of units, particularly in some minority populations, but increasing the likelihood that a banked unit will be selected for transplant.

Mr. Boo concluded that the current inventory does not serve patients well. Banks are storing units that do not reflect the selection preferences of the users. Federal funding is not being used efficiently. There is variation in the conversion ratio from collected to banked units. Cord blood units in the inventory that have TNC counts less than  $90 \times 10^7$  and are more than 5 years old are unlikely to be used. In light of these conclusions, further analysis is needed to answer the following questions:

- Should banks store only units with TNC counts greater than  $125 \times 10^7$ ?
- Is Federal funding being used effectively to achieve a diverse and usable inventory?

- How can the collection-to-banking ratio be improved? (Development of best practices? Development of better collection devices? Focus on high-volume and diverse hospitals?)

Dr. Harvath asked the Council to consider two recommendations from the Work Group in light of Mr. Boo's presentation. The first recommendation describes the steps needed to expand NMDP's financial analysis so that the Work Group can develop further recommendations on prioritizing resources to ensure access. The second provides guidance to HRSA in defining "financial self-sufficiency."

#### *Discussion*

Dr. Milford asked whether units transplanted with lower TNCs are those with rare genotypes. He also asked how increasing the inventory on the basis of TNC counts would affect racial distribution. Mr. Boo responded that at higher TNC counts, banks save money because they recruit the same number of donors as for lower TNC counts, but the total cost of processing decreases since only the larger units are processed and stored. He added that there does not seem to be a connection between amounts when looking at rare diseases. He also noted that banks are not getting enough diversity, even at higher TNC counts.

Pablo Rubinstein, MD, said his data show that better matches can work with fewer cells. Frederick Appelbaum, MD, questioned whether a single cutoff point (e.g.,  $TNC > 125 \times 10^7$ ) would be optimal. Dr. Rubinstein agreed, saying reducing the cutoff and increasing the number of smaller units would have a small benefit.

Dr. Kurtzberg said any outcomes analysis should include long-term results and the impact of chronic graft-vs.-host disease (GVHD). The NMDP model does not take into account distribution by the bank, which could vary. She added that some people are helped by mid-range cell doses.

Mr. Boo said NMDP will continue to analyze its data to better understand how changing the cutoff level would affect transplantations among minorities and how banks would maintain a minimum volume of units.

Dr. Lubin said the Council could have an impact by encouraging more recruiting to collect more units. He called for increased attention to improving cell counts to work toward more financial self-sufficiency. Dr. Applebaum agreed, noting the importance of addressing imminent concerns (i.e., for the next 2–5 years). However, analysis of the genetics of compatibility could dramatically change how stem cells are used in the next 5–10 years, so, he advised keeping in mind the long-term perspective.

Turning to discussion of the Work Group's proposed recommendations to continue the financial analysis and define "financial self-sufficiency," it was noted that the term "race" is probably not helpful, and the word "ethnicity" should be substituted. There was general support for the intent of the recommendations, but the specific requests were not clear. The recommendations were tabled for revision and further consideration later in the day.

## **Scientific Factors Necessary to Define a Cord Blood Unit as High Quality Work Group Update and Recommendations**

*Joanne Kurtzberg, MD, Work Group Chair*

Dr. Kurtzberg said the Work Group's deliberations integrate with those of the Realizing the Potential of Cord Blood Work Group and the financial analysis from NMDP. She described the group's process and membership. At the May 2010 Council meeting, HRSA asked the Work Group to make recommendations about criteria for National Cord Blood Inventory (NCBI) funding.

Dr. Kurtzberg said the rules excluding individuals from donating blood are applied to pregnant women who donate cord blood, which may unnecessarily exclude safe cord blood units. For example, pregnant women tend to have high false-positive rates when screened for human T-lymphotropic virus 1. In addition, the travel exclusions tend to have a higher impact on minorities than others. The Work Group suggests that it develop a report that identifies those screening tests that should not be used to exclude pregnant women from cord blood donation.

The Work Group will continue to accrue data on whether TNC is the best parameter for cord blood selection or the best predictor of cord blood potency. Because HRSA guidelines are out of synch with those of other recognized authorities (e.g., the Foundation for Accreditation of Cellular Therapies *Cellular Therapy Accreditation Manual*, 4th ed.), the Work Group suggests that HRSA harmonize its requirements, looking specifically at the issue of when cryopreservation must be initiated following collection, as explained below.

Dr. Kurtzberg said the FDA advises including an expiration date on a label affixed to a cord blood unit cryopreservation bag. She noted that not only would it be difficult to affix a label to a frozen plastic bag, but also it is not known when a cord blood unit expires (i.e., loses potency). The Work Group suggested alternatives to "affixing" such a label and recommended that banks determine the dates based on ongoing, internal stability testing. Dr. Kurtzberg described the stability evaluation that her organization uses (thawing and evaluating segments) and the results of tracking outcomes of cord blood units transplanted on the basis of the age of the units. Dr. Kurtzberg believes FDA will only accept stability data on products from individual banks, but she would like to see banks collaborate to develop collective information on cord blood stability. She offered some specific approaches that banks could use to evaluate stability and report it to the FDA for licensure.

Dr. Kurtzberg further described various evaluation methods, concluding that the most frequently used parameter—TNC count—seems to be the least predictive. She believes that experts could devise an algorithm based on various parameters that would provide transplant centers with more useful information about a cord blood unit that would improve engraftment rates.

The Work Group also discussed concerns about FDA licensure, noting that cord blood banking is more closely aligned with blood banking than tissue banking and would be better served by following facility guidelines applied to blood centers. Dr. Kurtzberg provided a number of examples to support the contention. She said there appears to be limited understanding among FDA reviewers about how cord blood banking works and perhaps inadequate consistency among those at FDA about applying regulation requirements. Dr. Kurtzberg said applying the blood

banking requirements to cord blood will raise costs beyond what the market can bear. Moreover, she noted, the requirements do not increase the safety, purity, potency, or stability of cord blood. Therefore, the Work Group asked that FDA clarify its guidelines for facility requirements for blood banks.

### *Discussion*

Council members generally agreed that the FDA requirements may not improve the safety or quality of cord blood but have the potential to very substantially raise the cost of cord blood, and that there is already pressure to reduce the costs of transplantation.

Dr. Kurtzberg clarified that the HRSA guidelines require that cryopreservation be completed within 48 hours of collection, while other authorities require that it be initiated within 48 hours. Cryopreservation only takes about 90 minutes, and no problems have been observed in the very few cases in which cryopreservation began 48 hours after collection. Mr. Baitty said HRSA might not agree to synchronizing all of its requirements with those of accrediting bodies but would be open to making specific changes such as this one. Dr. Rubinstein pointed out that, in principle, requirements should move toward decreasing, not extending, processing time.

In response to a question, Dr. Kurtzberg said she did not feel that cord blood units need to have an expiration date, but if it's required by the FDA, she believes each bank should develop its own criteria to determine an expiration date and include that information with the unit when it is released from the bank. Dr. Rubinstein pointed out that the cord blood units may maintain stability for a very long time (he has units that are stable after 18 years) but the packaging may begin to break down. Thus continuous surveillance and quality control are important. Dr. Kurtzberg said banks want more guidance from FDA about stability and potency testing.

Dr. Lazarus noted that the FDA is considering several of the points raised by Dr. Kurtzberg. The agency is learning more about cord blood banks through the BLA procedure. Dr. Lazarus said she is not aware of any regulations suggesting that good manufacturing practices (GMPs) apply differently depending on the systems that different banks employ.

Dr. Milford pointed out that cord blood banks "insisted" that cord blood be regulated as tissue, not blood. Dr. Harvath described how the current regulations came about, saying that it is difficult to go backward now that cord blood is treated as tissue. She asked whether FDA will accept that blood facilities that demonstrate compliance with GMPs can process and manufacture cord blood units effectively in the same facilities. Dr. Lazarus replied that banks should contact FDA with their specific questions. She noted that FDA probably could not say a certain facility design would be acceptable but rather provides clarification of GMPs to individual banks. Dr. Lazarus suggested the Work Group identify and articulate specific issues about which clarification is needed. Dr. Hartzman said he'd like to see a mechanism for addressing systemic issues across cord blood banks.

An audience member from the FDA's Center for Biologics Evaluation and Research responded to some of the particular examples Dr. Kurtzberg gave from her organization's experience with FDA reviewers. He stressed that licensing is a learning process, and the FDA is trying to



maintain a consistent approach. He said the FDA is not applying cellular product standards to cord blood.

The Council voted to accept the following recommendations of the Work Group:

### **Recommendations**

The Scientific Factors Necessary to Define a Cord Blood Unit as High Quality Work Group, with the help of ad hoc consultants, will review and prepare an advisory report to the FDA about false-positive tests that occur in pregnancy that should no longer be used to exclude mothers from donation.

Regarding cell count requirements, the Work Group will continue to accrue data.

Regarding the request that FDA clarify its guidelines, Ms. Regan pointed out that in March 2010, a public forum was held with representatives from FDA and various professional organizations, and she did not believe there was enough time to organize another such forum before the licensure deadline. However, opportunities for collaboration still exist, and individual cord blood banks have learned a lot about licensure since the March meeting.

The recommendations on synchronizing HRSA requirements, expiration dates and labeling, and clarification of GMP requirements were tabled for revision and further consideration later in the day.

### **Cord Blood Thawing and Washing Work Group Update**

*Jeffrey McCullough, MD, Work Group Chair*

Dr. McCullough presented the first update from the group, which was formed following the May 2010 Council meeting to address consistent, safe practices for cord blood handling by transplant centers. The group outlined all of the steps in the handling process, then began collecting information on each step:

- Bank-to-transplant center laboratory communication prior to shipment
- Receipt and inspection of unit
- Storage of unit
- Preparation prior to transplant
- Thaw/wash process
- Quality control and critical values and review
- Infusion and nursing care

For each step, Dr. McCullough described the Work Group's current thinking. For example, regarding advance communication, it may be appropriate to recommend the use of checklists, as some transplant centers already do. Further, when a transplant center opts not to follow the blood bank's directions, the transplant center should have effective, validated standard operating procedures (SOPs) in place for thawing the type of cord blood provided by the bank. It may be necessary to establish an accreditation process for such validation.

Dr. McCullough described the lack of consensus around post-thaw processing or the relative value of washing vs. diluting vs. thawing. The Work Group is reviewing the data and will consider publishing its findings and recommending further study of outcomes in relation to processes.

The Work Group also identified the lack of standard practices or recommendations for infusion-related activities and nursing care during infusion. Again, validated SOPs should be in place to address patient identification, compatible intravenous solutions, vascular access, filters, premedication, rate of infusion, and recognition and management of reactions, among others. The Work Group is considering developing sample SOPs. Transplant centers also lack standards for acceptable intervals and storage conditions between thawing and infusion. The Work Group will review data and consider whether more studies are needed to identify acceptable temperatures and concentrations of dimethyl sulfoxide.

The Work Group believes a more comprehensive system is needed for reporting serious adverse events (SAEs) that meets FDA expectations, such as FDA's short timeline for reporting and its focus on product-related SAEs and infusion-related toxicity. Transplant centers are accustomed to using the reporting mechanisms of the Center for International Blood and Marrow Transplant Research (CIBMTR), for example. The NMDP also has a reporting system and may play a role. The Work Group may recommend that another entity work on harmonizing the definitions of SAEs.

### *Discussion*

In response to questions, Dr. McCullough said that the rules and regulations for stem cell therapies do not overlap much with those for cord blood. Laboratory environments vary from large, sophisticated laboratories that process lots of types of novel cell products and have GMPs and quality control mechanisms in place to smaller laboratories run by researchers and technicians with limited experience in laboratory management. Dr. McCullough emphasized the importance of reaching some standardization to ensure that valuable products are not damaged. Dr. Kurtzberg added that distance of the laboratory from the transplant center can be an important variable; she supported the need for specific guidelines addressing all the processes involved. Dennis Gastineau, MD, felt that all organizations have some SOPs around the steps identified, and regulation should verify that SOPs are in place while recognizing that variation in practice is acceptable.

Adrian Gee, PhD, felt some of the responsibility for quality control should take place at the bank before the product is released. Dr. Kurtzberg agreed but said transplant centers should also have their own center-specific procedures for each aspect of the process. The lack of standardization or even detail about procedures is problematic, she said.

Dr. Rubinstein said banks could help by providing transplant centers with a list of specific questions that the center's laboratory should address. Dr. McCullough agreed, noting that the checklist approach would allow transplant centers to get information in advance from the bank about any particular needs for a given unit.

## **Reauthorization Overview**

*Robert Baitty, Director, Blood Stem Cell Transplantation Program, Division of Transplantation, HRSA*

Mr. Baitty described key points of the Stem Cell Therapeutic and Research Reauthorization Act, which renews program authority for five years. The NCBI continues to have its own authorization of appropriations, while a second authorization covers the C.W. Bill Young Cell Transplantation Program. Appropriations for FY 2011 are not yet finalized.

Changes to the NCBI reflect continued concern that the inventory remains short of the original goal of 150,000 units, new approaches are needed to increase collections, and banks should be working toward self-sufficiency. The legislation also defines remote collections as collections at locations without written contracts with banks for collection support.

For the C.W. Bill Young program, confidentiality requirements for bone marrow transplants now are less specific and match those for cord blood. The legislation also expands the description of what the cord blood coordinating center can do to aid collections. Within one year and annually thereafter, HHS must identify and expand at least one project that enhances cord blood collection. HHS must also set annual goals for cord blood collection, which is currently determined through the contracting process.

For the NCBI, the legislation retains the emphasis on high-quality, genetically diverse cord blood units, and more attention is given to demonstration projects. Contract durations will now be 10 years from the last award of Federal funds, and NCBI banks are required to provide an annual plan for moving toward self-sufficiency. Banks are eligible for funding extensions if they provide plans to expand collections and annual plans toward self-sufficiency, and demonstrate superior ability to meet the goals of the program.

The legislation requires three new reports, two of which require Council action. Within 180 days, in consultation with the Council, HHS must provide an Interim Report to Congress describing methods to distribute NCBI funds to banks and how banks contract with collection sites, as well as recommendations for improvements in NCBI funding methods to encourage efficient collection of high-quality, genetically diverse units. Because the report is due before the next Council meeting, HRSA staff will consider what mechanisms can be used to gather Council input, such as soliciting individual comments by e-mail.

In addition, the legislation requires that the Advisory Council provide a report to the Secretary, within one year, with recommendations regarding whether “models for remote collection of cord blood units should be allowed only with limited, scientifically justified safety precautions” and whether the “Secretary should allow for cord blood unit collection from routine deliveries without temperature or humidity monitoring of delivery rooms in hospitals approved by The Joint Commission.”

Also within one year, the Government Accountability Office must develop a report on cord blood donation and collection that 1) reviews studies, demonstrations, and outreach; 2) identifies challenges and barriers to increasing cord blood collection sites; and 3) offers recommendations to improve collections.

### *Discussion*

Emily Levine of the HHS Office of General Counsel said she believes “in consultation with the Council” means that the Council should provide its consensus opinion on the Interim Report to Congress, not individual member comments. However, a full meeting can be conducted by phone that meets all the necessary requirements of advance public notice and opportunity for public comment.

### **Action Item**

HRSA staff will organize a public meeting by telephone of the Council in the coming months to provide input on the HHS Interim Report to Congress.

Regarding the Council’s report giving recommendations on the two specific aspects of collection, members agreed with both statements in general but debated the intent of the statement “should be allowed only with limited, scientifically justified safety precautions,” as it could be interpreted in various ways. Ms. Regan asked that the second statement not specify The Joint Commission, as some hospitals are accredited by other organizations. Members were in favor of the proposed language as follows.

### **Recommendation**

The Council recommends that models for remote collection of cord blood units be allowed with only limited, scientifically justified safety precautions. The Council also recommends that the Secretary allow for cord blood unit collection from routine deliveries without temperature or humidity monitoring of delivery rooms in hospitals approved by the appropriate bodies.

Dr. Milford noted that the Council may offer additional explanatory language to accompany the recommendation.

### **Arizona Reimbursement Concerns for Medicaid Beneficiaries**

*Jeffrey Schriber, MD, ACBSCT Member*

Dr. Schriber explained the pathway to and current status of Arizona’s legislation, effective in September 2010, to deny coverage of stem cell transplantation involving unrelated donors for Medicaid patients on the basis of recommendations from private consultants. He noted that he and others have not been able to obtain the private consultants’ report that concluded that stem cell transplantation does not increase in life expectancy more than other treatments. The director of Medicaid agreed with Dr. Schriber and his colleagues when they presented their data demonstrating the benefit of stem cell transplantation, but that person had no authority to reinstate the coverage. Some limited transplantation coverage has been reinstated, Dr. Schriber.

Dr. Schriber went on to describe how, with extensive press coverage, his institution was able to get coverage for a specific patient. However, he remains extremely concerned that the Medicaid cuts were made without reliable data and in spite of appeals from practicing doctors and others. He believes Arizona’s cuts will embolden other States—almost all of which are facing budget deficits—to cut Medicaid coverage for stem cell transplantation, because Arizona’s legislators paid no political price for doing so.

Solid data alone are not enough, said Dr. Schriber, and he called for political solutions. He believes it is time to designate transplantation as an essential service, not an option, under Medicaid.

#### *Discussion*

Dr. Champlin moved to recommend that HSCT be considered an essential medical service. Mr. Boo clarified that the HHS Secretary determines essential health benefits, so the Council could ask the Secretary to designate blood and marrow transplantation as such. He added that the Secretary is currently looking at private insurance coverage as the basis for what should be covered under Federal programs. Dr. Anasetti said there is no doubt that transplantation is both effective and more beneficial than chemotherapy for certain conditions. Dr. Champlin agreed to work with other Council members to present a formal recommendation for review by the end of the day.

#### **Myelodysplastic Syndromes (MDS) Coverage**

*Jyme Schafer, MD, M.P.H., and Roya Lotfi, Health Insurance Specialist, Centers for Medicare and Medicaid Services (CMS)*

Dr. Schafer explained how CMS determines what items and services must be covered under the Social Security Act, a process known as national coverage determination (NCD). She emphasized that up to 90% of coverage decisions are made at the local level. The CMS process for finalizing an NCD includes preliminary discussions, internal review, and, sometimes, external review and takes at least nine months. Proposals for NCDs may come from external sources—for example, because local policies vary substantially—or internal sources—for example, as a result of new research, new technology, or concerns about inappropriate use.

The Social Security Act requires payment only for items and services “reasonable and necessary for the diagnosis or treatment of illness or injury or to improve the functioning of a malformed body member.” Dr. Schafer said CMS looks for evidence that gives sufficient confidence that the item or service improves health outcomes and is generalizable to the Medicare population. Standard principles of evidence-based medicine are applied. Ideally, there is “adequate evidence that a treatment strategy using the new therapeutic technology compared to alternatives leads to improved clinically meaningful health outcomes in Medicare beneficiaries,” Dr. Schafer said. Similar criteria are applied to diagnostic services.

Dr. Schafer noted in making NCDs, CMS looks for evidence that the item or service increases the lifespan while improving function and participation, improves symptoms significantly, or reduces the need for burdensome treatments and tests. Outcomes that are less impressive include increasing the lifespan without improving function or participation, improving disease-free survival without improving overall survival, better surrogate test results, better-looking diagnostic images, and doctor’s confidence. “Historically, Medicare has stated publically as a matter of policy that it does not consider cost in making NCDs,” said Dr. Schafer.

Following a review, CMS can choose any of the following designations:

- National coverage
- National noncoverage
- National coverage with conditions
- National coverage with data submission
- No national coverage decision (left to contractor discretion)

National coverage with data submission (or evidence development) is rare but has been designated, for example, for coverage of MDS.

Ms. Lofti said she has been appointed to review the request for Medicare coverage of stem cell transplantation. Currently, Medicare has different coverage policies for autologous and allogeneic transplantation. Ms. Lofti summarized the definitions of allogeneic and autologous stem cell transplantation in the 2010 NCD manual. Allogeneic stem cell transplantation is covered by Medicare for leukemia or leukemia in remission, aplastic anemia when reasonable and necessary, severe combined immunodeficiency disease, and treatment of Wiskott-Aldrich syndrome. It is not covered (nationally) for multiple myeloma. As stated, MDS is covered with data submission. All other indications for stem cell transplantation remain at local contractor discretion.

Ms. Lofti described MDS and patient classification and scoring systems. She noted that MDS is more prevalent in older people, and the median age of diagnosis is about 65 years old. While HSCT typically had been used for younger patients, the advent of nonmyeloablative chemotherapy and reduced intensity chemotherapy before transplantation allows older patients to tolerate HSCT.

Ms. Lofti noted that an external request in December 2009 for an NCD originally focused only on the high-risk MDS population, but in August 2010, CMS expanded conditional coverage to all beneficiaries with MDS. The final decision requires completion of an approved, prospective clinical study demonstrating improved outcomes.

Autologous HSCT is covered for acute leukemia in remission under certain conditions, multiple myeloma in certain patients, and amyloid light chain amyloidosis in certain patients. It is not covered for acute leukemia not in remission, chronic granulocytic leukemia, solid tumors (other than neuroblastoma), or tandem transplantation (multiple rounds of autologous stem cell transplantation) for patients with multiple myeloma.

#### *Discussion*

Ms. Lofti clarified that an NCD supplants a local determination. She said CMS is now reviewing proposals for studies on MDS and hopes to select a study protocol shortly. Asked to what extent private insurers look to Medicare or Medicaid as the basis for their own coverage decisions, Dr. Schafer declined to answer but said the question comes up frequently regarding Medicare. However, it does not come up often regarding Medicaid, and she was not sure whether that might change going forward. Dr. Schriber noted that, particularly for conditions that are less common and difficult to study, clinicians feel they cannot pursue any treatments because they are not covered. Dr. Champlin echoed the concern, saying CMS has identified a few indications out of hundreds that could be considered. He asked how to bring less common indications to the

attention of Medicare. Dr. Schafer reminded the Council that most coverage decisions are made locally. A rare condition could rise to the level of an NCD depending on the evidence, she said.

### **Medicare Reimbursement for Costs for Allogeneic or Autologous Transplants**

*Richard Champlin, MD, ACBSCT Member*

Dr. Champlin explained that the Medicare population makes up the fastest-growing population of transplant recipients, but patient access may be limited by reimbursement levels that are far below costs. Medicare reimbursement for physicians is low, and some physicians opt out of Medicare altogether as a result. Coverage of HSCT is limited to a few indications. Coverage of donor costs is complicated.

CMS categorizes inpatient procedures according to disease-related groups (DRGs) and bundles all the services related to the procedure into one code for payment. Payment is based on the average costs to deliver care. For outpatient procedures, CMS takes a similar approach but uses ambulatory payment classification (APC) codes. Dr. Champlin noted that new codes have been proposed for 2011 that distinguish allogeneic from autologous transplantation procedures.

CMS determines Medicare payment rates based on data collected from claims. However, because coverage is limited, CMS has very few claims on HSCT, and thus it is difficult to identify the true costs. Patient complexity is not considered. Dr. Champlin said CMS' outpatient rate-setting is too simplistic. Transplant centers are also part of the problem, he noted: because payment rates are poor, centers have little incentive to report fully on their costs. As a result, CMS receives misleading data. In addition, CMS sets payment rates using 2-year-old claims.

CMS pays for search and procurement costs for solid organs on a "pass-through" basis—that is, reimbursement is determined on a "reasonable cost basis." Stem cell acquisition, however, is lumped into the transplantation procedure, said Dr. Champlin, and treated like a supply. Thus, stem cell acquisition is reimbursed at a fraction of its cost, because CMS assumes that hospitals and transplant centers mark up the costs of supplies substantially. CMS pays for blood and blood products at 42% of their costs (known as the cost-to-charge ratio). Notably, if the stem cell transplantation is not completed (e.g., the patient dies prior to the stem cell infusion), the transplant center receives no payment for stem cell search and procurement costs.

Dr. Champlin gave examples of how transplant centers report costs inadequately and noted that NMDP is trying to educate centers on more complete reporting to CMS. He noted that claims that include multiple services are not included in CMS' cost calculation. After transplantation, readmissions are categorized under the same DRG and APC coding systems described, and it is critical that CMS receive complete cost data on these events as well.

Dr. Champlin concluded that the Council should recommend to the Secretary that stem cell transplantation be covered by CMS under pass-through status.

#### *Discussion*

Council members agreed to consider a formal recommendation; Dr. Champlin said he would provide a written recommendation for consideration by the Council by the end of the day.

## **System Capacity Initiative Update**

*Edward Snyder, MD, Chair, NMDP Board of Directors; Director, Blood Bank/Apheresis Service, Yale-New Haven Hospital*

Dr. Snyder gave an update on NMDP's effort to address workforce and infrastructure challenges to the use of HSCT by convening key stakeholders to identify barriers and develop recommendations. What began as a single symposium to kick off the initiative has morphed into a full-scale NMDP program, said Dr. Snyder. He noted that the NMDP bases its projections of future capacity needs on evidence that the number of transplantations will continue to increase to approach the annual need, which is two to three times the current annual number of transplants.

The System Capacity Initiative did not receive anticipated funding from the Agency for Healthcare Quality and Research but has continued with funding from NMDP. At a recent meeting, the stakeholders gathered in working groups to analyze current capacity from various perspectives. Dr. Snyder said that in many areas of medicine minorities tend to receive lower-quality care. Therefore, diversity is an over-arching consideration of the initiative, and the stakeholders sought to address diversity in a way that discourages use of solely race-based strategies in favor of other components, such as socioeconomic status, education, language, immigration status, and geography. They also hope to examine systems that may perpetuate bias or decrease access. The Diversity and Disparities Working Group developed an action plan for 2011 that focuses on expanding diversity in the workforce, increasing cultural competency, integrating culturally and linguistically appropriate services standards, assessing system bias, and identifying successful policy or program models to increase access, reduce disparities, or promote diversity.

Dr. Snyder described the 2011 work plans for each of the other working groups, noting that many of the groups identified similar needs and approaches.

### *Physician Workforce*

- Assess and validate work effort benchmarks
- Conduct a transplant-physician census to establish more precise numbers
- Create a directory of HSCT training and fellowship programs
- Establish a faculty membership training program
- Develop models for part-time positions
- Target recruitment strategies to include medical schools and residency programs

### *Nursing Workforce*

- Develop HSCT nursing clinical rotation through nursing programs
- Partner with others to identify funding sources for nurse scholarships
- Partner with transplant units to increase student exposure to HSCT nursing
- Explore successful models to address work-life balance, compassion fatigue, and moral distress

### *Advanced Practice Professionals*

- Better define the advanced practice professional role within HSCT
- Increase exposure in student programs and to practicing advanced practice professionals



- Improve quality of work life
- Engage administration group to explore compensation and benefits package options
- Partner with the American Society for Blood and Marrow Transplantation to create orientation and education standards

#### *Facility/Bed Capacity*

- Collect more data from transplant programs to determine trends and best practices
- Identify centers with high patient transplant per bed rate benchmark efficiency and effectiveness
- Engage NMDP to assist expansion planning by dissemination of success stories, partnering with program administrators, or through use of external consultants

#### *Care Delivery Model*

- Work with professional medical organizations to highlight optimal transplant timing using payer data
- Develop mechanism for patients and treating physicians to access applicable patient records
- Explore models for providing post-transplant care (e.g., telemedicine, satellite clinics)
- Partner with Medicare and other payers to structure reimbursement for care in a variety of settings
- Identify housing options near transplant centers
- Provide recommendations on staffing and design of outpatient facilities
- Develop patient and caregiver education materials and training programs

#### *Financial*

- Identify an essential set of HSCT benefits
- Develop model benefits/guidelines; campaign for adoption among payers
- Promote consistent use of HSCT terminology among providers/payers
- Establish how utilization management occurs
- Educate providers/payers on coding issues
- Advocate for inclusion of transplant within essential benefit set in health care reform initiatives

Dr. Snyder said the group has applied for funding from the National Heart, Lung, and Blood Institute. It also restructured some working groups, merging facilities and care delivery into one working group. A pharmacists' working group was added in response to requests from pharmacists that they be better represented. It will address workforce shortages and the need to update guidelines on the role of pharmaceuticals in HSCT.

The initiative seeks to generate white papers from its deliberations that will be published in various venues and presented to professional organizations of stakeholders. However, Dr. Snyder hoped the papers would be presented in other arenas as well, include financial, legal, political, and general news forums. He also hoped the initiative would evolve into an international effort. In conclusion, Dr. Snyder said he hoped to share the initiative's recommendations with the Council and solicit input and support as appropriate.

### *Discussion*

Ms. Regan suggested that the initiative include some representatives from cellular therapy laboratories, because stem cell therapy is not part of the curriculum for pathologists, for example.

### **Review of Revised Work Group Recommendations**

Dr. Champlin, Dr. Kurtzberg, and Dr. Harvath presented revised versions of recommendations proposed throughout the day to the Council for consideration.

### *Medicare Reimbursement for Costs for Allogeneic or Autologous Transplants*

Following review and discussion to determine ideal wording, the Council accepted the following recommendations:

#### **Recommendations**

The Advisory Council recommends to the Secretary of HHS that hematopoietic transplantation, including autologous and allogeneic blood, marrow and cord blood transplantation, be included in the “Essential Benefit Set” as treatment for generally accepted indications, as called for in the current health reform law. We recommend that hematopoietic transplantation be listed as a required covered therapy for all Federally funded programs, including Medicaid, to the fullest extent allowed by law.

Rationale: This is based on compelling evidence that autologous and allogeneic blood, marrow, and cord blood transplantation are effective treatments for a variety of life-threatening hematologic, immune, metabolic, and malignant diseases.

The Advisory Council recommends to the Secretary of HHS that Medicare reimburse the costs for acquisition of blood, marrow, and cord blood products for hematopoietic transplantation as a pass-through, using a “reasonable cost basis” similar to the reimbursement for graft acquisition for solid organ transplantation.

Explanation: Medicare payment seriously under-reimburses the cost of performing hematopoietic transplantation. The cost of transplant acquisition is lumped into the overall reimbursement. This is fundamentally different than reimbursement for solid organ transplantation. This recommendation is made to correct one aspect of Medicare reimbursement.

### *Scientific Factors Necessary to Define a Cord Blood Unit as High Quality Work Group*

Following some discussion about the ideal wording, the Council accepted the following recommendations:

#### **Recommendations**

The Advisory Council recommends that HRSA requirements be changed to require initiation of cryopreservation up to 48 hours from cord blood unit collection. In general cord blood units should be processed and cryopreserved as close to the time of collection as possible.

For cord blood units incapable of bearing a full label, the Advisory Council recommends that the Secretary of HHS clarify that the expiration date can be placed on an attached label provided with the unit at release to a transplant center. The Advisory Council believes that protocols for determining stability of cord blood units should be developed.

The Advisory Council is very concerned that the FDA requirements for licensure of cord blood banks might prohibitively increase the cost and decrease the availability of public cord blood units for transplantation without necessarily increasing the safety, stability, potency, or purity of the product. Therefore, the Advisory Council recommends that the Secretary require the FDA to review requirements for licensure in light of these concerns and that the FDA urgently meet together with the cohort of applicant cord blood banks to share and resolve specific concerns regarding licensure.

#### *Realizing the Potential of Cord Blood Work Group*

Following some discussion about the ideal wording, the Council accepted the following recommendations:

#### **Recommendations**

The Advisory Council recommends that a financial analysis needs to be integrated with a demand (need) analysis to determine the cost of providing access to cord blood transplantation for the United States population. The Advisory Council recognizes that additional HRSA resources will be required to complete the work outlined below, but the work is essential to develop further recommendations on prioritization of HRSA resources to assure access to a suitable cell source in the future. To complete the assessment, the work group recommends the following as next steps:

- 1) Complete financial analysis
  - a) Analyze historical use by TNC count for all broad ethnic groups.
  - b) Compare HLA match rate by TNC by broad ethnic groups of donors and recipients.
- 2) Conduct a retrospective multivariate analysis of outcomes in cord blood transplantation in adults.
  - a) The goal is to study cord blood characteristics against recipient outcomes including survival, disease-free survival, and GVHD.
  - b) Minimum variables will be pre-freeze TNC and CD34, where available; HLA match rates; colony forming units; post-thaw viability; infused TNC/kg, CD34/kg and colony forming unit/kg cell doses; and ethnicity. Other product characteristics may also be considered.
  - c) Include data from the CIBMTR, the New York Blood Center, the European Group for Blood and Marrow Transplantation (if workable), and individual banks, as needed.
- 3) Integrate registry size analysis with financial model to assess the following:
  - a) Cost of meeting access thresholds by ethnicity
  - b) Impact on self-sufficiency scenarios

The Advisory Council notes that the reauthorization for the HRSA programs includes a requirement that cord blood banks receiving NCBI funding provide a plan for, and

demonstrate measurable progress toward, financial self-sufficiency. The Council recognizes the importance of providing Federal funds to individual banks only as long as it is truly needed to achieve the statutory goal of improving patient access to transplant and transplant outcomes by rapidly increasing the inventory of high-quality, genetically diverse cord blood units. The Council also recognizes that as the use of cord blood for transplantation, and potentially for other therapies, increases, it should become possible for banks to finance appropriately high levels of collections from diverse populations through sales of cord blood units. The Council recommends that HRSA, in providing guidance to banks regarding self-sufficiency, define financial self-sufficiency in a way that incorporates continued, rapid progress in building the inventory urgently needed by patients.

### **Cord Blood Transplantation Adverse Events**

*Dennis Confer, MD, Chief Medical Officer, NMDP*

Dr. Confer described NMDP's systems for tracking adverse events involving transplantation, beginning with the working definitions of "adverse event," "incident," "serious," and "unexpected." NMDP uses the National Cancer Institute's Clinical Terminology Criteria for Adverse Events, which categorizes events according to severity. Dr. Confer noted that various types of centers have reporting requirements from different sources that govern how they report adverse events.

NMDP has three nurses, four full-time physicians, and several administrative staff who review reported adverse events, and they address donor events and patient/product events in different ways. The Donor Advocacy Group follows up on long-term issues. NMDP uses a quality improvement system that monitors and scores all reported events. The Donor and Patient Safety Monitoring Advisory Group has representatives from outside NDMP, including a donor, and provides external review, particularly for unexpected or SAEs. The advisory group assists NMDP with root cause analysis, makes recommendations for further investigation, offers clinical insight, makes recommendations for reporting to stakeholders, and suggests modifications to consent forms to alert donors about potential complications.

Donor adverse events are reported to a number of bodies, depending on the nature of the event and the setting in which it took place, including the FDA, HRSA, principal investigators, and collaborative organizations (e.g., pharmaceutical manufacturers or the World Marrow Donor Association).

The current system is imperfect, said Dr. Confer. Adverse event reporting is probably incomplete, partly because it is not always clear what to report and to whom, given multiple systems and criteria for reporting. Organizations may be reluctant to report out of liability concerns. Adverse event reports are usually channeled manually to stakeholders.

NMDP is improving reporting by creating a centralized database for events and incidents that includes built-in mechanisms for corrective and preventive action. A cord blood advisory group subcommittee is looking at definitions and options for interim reporting. Dr. Confer noted that the National Cancer Institute's Cancer Adverse Events Reporting System is free; it would enable transplant centers and cord blood banks to report to one system and can be programmed to

facilitate required notifications. The Phoenix Initiative focuses on business process improvement and could help NMDP as it develops a more robust reporting system. Dr. Confer provided a sample corrective and preventive action evaluation matrix, which allows organizations to map out adverse events according to frequency and severity so they can determine where to invest resources.

Interest in improving adverse event reporting was sparked by reporting of two cases related to cord blood infusion in 2010. With further evaluation of various systems, a total of seven such cases were identified, all involving double cord infusions. All seemed to be related to infusion of red-cell-replete cord blood units. The findings led NMDP to contact principal investigators about the circumstances surrounding the events and to develop a series of recommendations for preventing recurrence.

### *Discussion*

Dr. Milford asked how FDA reporting requirements will be met when cord blood units are licensed. Dr. Confer responded that NMDP will collect adverse event data for licensed products, which are subject to post-market surveillance regulations. For unlicensed products distributed under investigational protocols, NMDP will offer a reporting system, but cord blood banks and transplant centers may have their own. NMDP believes there should be a single adverse event reporting system for the entire field, regardless of product licensure, to ensure that information comes in unambiguously and goes to whoever should receive it. Dr. Confer added that NMDP could partner with banks and others to design and implement such a system. Dr. Lazarus said that, currently, license application holders can establish whatever mechanisms they choose, as long as they meet the FDA regulation requirements. She believes a single mechanism potentially could work to meet these needs.

Dr. Kurtzberg noted that timeliness of reporting varies depending on the institution. Dr. Confer said more education is needed, especially at transplant centers, about reporting requirements. Dr. Rubinstein added that adverse event reports should go immediately to the cord blood banks, because they are required to report them to the FDA within as little as five days. Dr. Confer agreed that the current manual system poses problems of timeliness. He said he would ask NMDP staff to ensure that transplant center policies include reporting to the cord blood bank.

Dr. Confer said NMDP would like to move toward electronic medical reporting, and the Cancer Adverse Events Reporting System may be the first step in that direction.

### **New Business**

Dr. Rubinstein raised concerns about the lack of genetic screening for disease among donors. He suggested studying a mechanism (i.e., a DNA chip) to identify the most frequently occurring genes capable of causing inheritable diseases that could be transmitted through transplantation. On a large scale, such a study could be economically feasible when compared with the current risk. Dr. Kurtzberg felt it was more economical and safer to screen patients than to evaluate stored blood. She suggested collaborating with new groups that are screening newborn and cord blood. Dr. Rubinstein felt the two approaches would achieve different ends. He suggested FDA consider screening as part of the cord blood bank's responsibility. He agreed with the suggestion to collaborate with other groups and thought a group of clinicians, geneticists, and others should

convene to discuss the risks and come up with rational suggestions. Dr. Milford noted that HRSA has done some work on genetic screening based on HSCT.

**Action Item**

HRSA staff will invite appropriate representatives from the agency to provide a presentation to the Council at a future meeting quantifying the risk of genetic disease transmission from HSCT.

**Public Comment**

Kathy Welte of NMDP said her organization could poll cord blood banks who had already met with the FDA to develop a list of common issues related to licensure. Ms. Regan said the findings from the March 2010 meeting mentioned would be a good starting point. Dr. Lazarus and Dr. Milford agreed that such an effort would be worthwhile.

**Conclusion and Adjournment**

Dr. Milford adjourned the meeting at approximately 3:30 p.m.

**ATTACHMENTS**

- Summary of recommendations to the Secretary and Council action items
- List of attendees (by type)

# ADVISORY COUNCIL ON BLOOD STEM CELL TRANSPLANTATION

## Summary of Recommendations and Action Items November 15, 2010

### RECOMMENDATIONS

#### **Realizing the Potential of Cord Blood Work Group**

**Recommendation 1:** The Advisory Council recommends that a financial analysis needs to be integrated with a demand (need) analysis to determine the cost of providing access to cord blood transplantation for the United States population. The Advisory Council recognizes that additional HRSA resources will be required to complete the work outlined below, but the work is essential to develop further recommendations on prioritization of HRSA resources to assure access to a suitable cell source in the future.

To complete the assessment, the work group recommends the following as next steps:

- 1) Complete financial analysis
  - a) Analyze historical use by TNC count for all broad ethnic groups.
  - b) Compare HLA match rate by TNC by broad ethnic groups of donors and recipients.
- 2) Conduct a retrospective multivariate analysis of outcomes in cord blood transplantation in adults.
  - a) The goal is to study cord blood characteristics against recipient outcomes including survival, disease-free survival, and GVHD.
  - b) Minimum variables will be pre-freeze TNC and CD34, where available; HLA match rates; colony forming units; post-thaw viability; infused TNC/kg, CD34/kg and colony forming unit/kg cell doses; and ethnicity. Other product characteristics may also be considered.
  - c) Include data from the CIBMTR, the New York Blood Center, the European Group for Blood and Marrow Transplantation (if workable), and individual banks, as needed.
- 3) Integrate registry size analysis with financial model to assess the following:
  - a) Cost of meeting access thresholds by ethnicity
  - b) Impact on self-sufficiency scenarios

**Recommendation 2:** The Advisory Council notes that the reauthorization for the HRSA programs includes a requirement that cord blood banks receiving NCBI funding provide a plan for, and demonstrate measurable progress toward, financial self-sufficiency. The Council recognizes the importance of providing Federal funds to individual banks only as long as it is truly needed to achieve the statutory goal of improving patient access to transplant and transplant outcomes by rapidly increasing the inventory of high-quality, genetically diverse cord blood units. The Council also recognizes that as the use of cord blood for transplantation, and potentially for other therapies, increases, it should become possible for banks to finance appropriately high levels of collections from diverse populations through sales of cord blood units. The Council recommends that HRSA, in providing guidance to banks regarding self-sufficiency, define financial self-sufficiency in a way that incorporates continued, rapid progress in building the inventory urgently needed by patients.

## **Scientific Factors Necessary to Define a Cord Blood Unit as High Quality Work Group**

**Recommendation 3:** The Scientific Factors Necessary to Define a Cord Blood Unit as High Quality Work Group, with the help of ad hoc consultants, will review and prepare an advisory report to the FDA about false-positive tests that occur in pregnancy that should no longer be used to exclude mothers from donation.

**Recommendation 4:** Regarding cell count requirements, the Work Group will continue to accrue data.

**Recommendation 5:** The Advisory Council recommends that HRSA requirements be changed to require initiation of cryopreservation up to 48 hours from cord blood unit collection. In general cord blood units should be processed and cryopreserved as close to the time of collection as possible.

**Recommendation 6:** For cord blood units incapable of bearing a full label, the Advisory Council recommends that the Secretary of HHS clarify that the expiration date can be placed on an attached label provided with the unit at release to a transplant center. The Advisory Council believes that protocols for determining stability of cord blood units should be developed.

**Recommendation 7:** The Advisory Council is very concerned that the FDA requirements for licensure of cord blood banks might prohibitively increase the cost and decrease the availability of public cord blood units for transplantation without necessarily increasing the safety, stability, potency, or purity of the product. Therefore, the Advisory Council recommends that the Secretary require the FDA to review requirements for licensure in light of these concerns and that the FDA urgently meet together with the cohort of applicant cord blood banks to share and resolve specific concerns regarding licensure.

## **Reauthorization Overview**

**Recommendation 8:** The Council recommends that models for remote collection of cord blood units be allowed with only limited, scientifically justified safety precautions. The Council also recommends that the Secretary allow for cord blood unit collection from routine deliveries without temperature or humidity monitoring of delivery rooms in hospitals approved by the appropriate bodies.

## **Medicare Reimbursement for Costs for Allogeneic or Autologous Transplants**

**Recommendation 9:** The Advisory Council recommends to the Secretary of HHS that hematopoietic transplantation, including autologous and allogeneic blood, marrow and cord blood transplantation, be included in the “Essential Benefit Set” as treatment for generally accepted indications, as called for in the current health reform law. We recommend that hematopoietic transplantation be listed as a required covered therapy for all Federally funded programs, including Medicaid, to the fullest extent allowed by law.



Rationale: This is based on compelling evidence that autologous and allogeneic blood, marrow, and cord blood transplantation are effective treatments for a variety of life-threatening hematologic, immune, metabolic, and malignant diseases.

**Recommendation 10:** The Advisory Council recommends to the Secretary of HHS that Medicare reimburse the costs for acquisition of blood, marrow, and cord blood products for hematopoietic transplantation as a pass-through, using a “reasonable cost basis” similar to the reimbursement for graft acquisition for solid organ transplantation.

Explanation: Medicare payment seriously under-reimburses the cost of performing hematopoietic transplantation. The cost of transplant acquisition is lumped into the overall reimbursement. This is fundamentally different than reimbursement for solid organ transplantation. This recommendation is made to correct one aspect of Medicare reimbursement.

### **ACTION ITEMS**

#### **Cord Blood Bank Collections Work Group**

The Covered Diagnosis and Costs Work Group will evaluate proposed legislation in California on funding for cord blood banks and consider how the Council can express support.

#### **Access to Transplantation Work Group**

Dr. Anasetti will provide the Access to Transplantation Work Group with the guidelines from the Florida advisory panel he noted when they are published.

#### **Reauthorization Overview**

HRSA staff will organize a public meeting by telephone of the Council in the coming months to provide input on the HHS Interim Report to Congress.

#### **New Business**

HRSA staff will invite appropriate representatives from the agency to provide a presentation to the Council at a future meeting quantifying the risk of genetic disease transmission from HSCT.

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