ADVISORY COUNCIL ON BLOOD
STEM CELL TRANSPLANTATION
U.S. Department of Health and Human Services

Bethesda North Marriott Hotel and Convention Center
5701 Marinelli Road
Bethesda, Maryland 20852

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Karl G. Blume, MD, Chair of the Advisory Council on Blood Stem Cell Transplantation (ACBSCT), called the meeting to order at 8:30 a.m. He asked members to review the Council's charter and consider and prioritize which topics to address next. Remy Aronoff, Executive Secretary of the ACBSCT, noted that three Council members sit on the boards of accrediting bodies that could be affected by the recommendation on accreditation (Claudio Anasetti, MD; Joanne Kurtzberg, MD; and Donna M. Regan). They will be asked to leave the room when the Council votes on the recommendation.

Cord Blood Bank Accreditation Organization and Recognition Process
E. J. Read, MD, Work Group Chair

Dr. Read reiterated the charge to the Council to develop recommendations to the Secretary of the Department of Health and Human Services (HHS) for accreditation of cord blood banks. She described the steps the Work Group had taken to date[1],including review and revision of the document, *Draft Health Resources and Services Administration (HRSA) Specifications for National Cord Blood Inventory (NCBI) Cord Blood Bank Accreditation Organizations*, which was approved by the Council at its December 2008 meeting.

The Work Group reviewed the standards, tools, policies, and procedures of the American Association of Blood Banks (AABB) and the Foundation for the Accreditation of Cellular Therapy (FACT) and found that they are compatible. The standards of the two groups vary in format, style, and level of detail; but the differences do not impede the ability of either organization to comply with the HRSA specifications. Dr. Read noted that the HRSA specifications indicate that additional requirements may be added and AABB and FACT must include any additional requirements in their inspection of NCBI facilities. In March 2009, HRSA sent the final specifications to AABB and FACT and both confirmed that they are willing and able to meet the specifications. Dr. Read said nearly all public cord blood banks are accredited by either AABB or FACT, and some are accredited by both.

On the basis of its deliberations and review of all materials, the Work Group recommends that HHS recognize both AABB and FACT as accrediting organizations for NCBI cord blood banks.

[1]The Work Group examined and refined HRSA specifications for CBB accreditation, sought and received input from the AABB and FACT regarding each organization's approach to CBB accreditation and ability to comply with HRSA specifications

Discussion
(The three members identified earlier as sitting on the board of an accrediting organization left the room prior to the discussion. Also leaving prior to discussion was Pablo Rubinstein, M.D. who informed the Chair that he is on the board of NETCord, which develops accreditation standards jointly with FACT.

Robertson Parkman, MD, asked about the ramifications of a cord blood bank achieving accreditation by one organization while failing to do so by the other organization's standards. Mr. Aronoff said the issue has never come up. Dr. Read pointed out that HRSA receives the accreditation inspection reports and therefore would know why a bank failed accreditation. Robert Baitty, Director of the Blood Stem Cell Transplantation Program, Division of Transplantation, HRSA, said that if a bank did seek dual accreditation and failed to achieve one, his office would talk with the bank about the nature of the deficiency and how to rectify it. Dr. Kurtzberg felt that such a situation would be unlikely; and Dr. Read noted that although the standards are compatible across the two organizations, individual inspectors may have different approaches or interpretations of standards. An audience member said that dual accreditation is expensive and time-consuming, so banks are strongly motivated to meet the standards if they seek dual accreditation. She added that AABB communicates with other organizations, such as The Joint Commission, to address deficiencies.

Rebecca Pentz, Ph.D., suggested HRSA establish guidelines for addressing deficiencies. Dr. Read responded that HRSA reviews inspection reports and has the power to cut funding should a bank fail to meet accreditation standards, but the banks establish their own procedures for correcting deficiencies. Dr. Read suggested that more transparency about deficiencies and how they are corrected may be helpful.

Dr. Read noted that the Council cannot review the results of individual inspection reports (for confidentiality reasons) but suggested that HRSA seek input from the Council if the inspections reveal system-wide problems, and Mr. Aronoff agreed. Richard Champlin, MD, distinguished accreditation standards from oversight issues and said no organization provides ongoing quality supervision of blood banks. The HRSA specifications require on-site inspection every 2 years and some form of evaluation every year. Mr. Baitty pointed out that his office and the accrediting body both receive notification of adverse events. Dr. Read added that reporting requirements are clear for blood banks and more guidance is anticipated about the Food and Drug Administration's (FDA's) inspection process.

Dr. Blume and Dr. Parkman suggested the Council evaluate at some predetermined interval whether its recommendation was appropriate and effective. While Dr. Read felt the Council would have ample opportunities to review accreditation issues as they arise, Dr. Parkman argued for setting a specific time in which some of the current members of the Council would still be serving and could provide that perspective to new members. Some members were concerned about the extent of reevaluation required, and others felt data on which to draw conclusions would be insufficient. Dr. Blume clarified that Council's future deliberations should be viewed not as revisiting the accreditation decision and process, but as reviewing progress on accreditation activities. There was consensus that a 3 year period would be appropriate for the

Council to revisit the accreditation specifications and HRSA staff's experience interacting with the recognized accreditation organizations.

The Council voted unanimously to make the following recommendation to the Secretary:

> **Recommendation**
>
> ACBSCT recommends the Secretary recognize both the American Association of Blood Banks (AABB) and the Foundation for the Accreditation of Cellular Therapy (FACT) as Accreditation Organizations for the National Cord Blood Inventory (NCBI). Both organizations are expected to adhere to the Health Resources and Services Administration's (HRSA) Specifications for Accreditation Organizations, and their continued recognition is based on ongoing adherence to HRSA specifications.

A majority of the Council voted in favor of adding the following language to the recommendation:

> ACBSCT will review, three years from the time of the recognition decision by the Secretary, HRSA's experience with the Accreditation Organizations with regard to meeting the HRSA specifications.

Informed Consent
Rebecca Pentz, PhD, Work Group Chair

Dr. Pentz said the Work Group began by reviewing the literature to identify significant issues around cord blood donation. She noted that the key difference between consent for cord blood donation and organ donation is that the birth mother, the biological mother, the newborn, and the intended parents can all be affected by the donation of cord blood. Informed consent is based on the principle of personal autonomy. The Work Group put forth seven draft recommendations for consideration:

1. Who should consent? The Work Group recommends that the birth mother should always consent for the donation of cord blood. When the birth mother is not the intended parent, then both the birth mother, who will have to be tested for infectious disease, and the intended parent, who will be responsible for providing the bank with information about the child and who will be responsible for the child, should consent. When the birth mother is neither the intended parent nor the biological parent, the birth mother and one intended parent should consent. For other cases, the same principles should apply—namely, that the person undergoing testing should consent as well as one guardian of the child.

Dr. Parkman was concerned that fathers were being excluded, but Dr. Pentz pointed out that the intended parent can be either the mother or father. The Work Group discussed the issue and decided that requiring both intended parents to consent could be excessively complicated in some situations. Dr. Pentz added that the proposed recommendations would translate into minimum requirements, so banks could require consent from both intended parents if desired.

Dr. Kurtzberg added that in some cases, mothers may be more apt to disclose sensitive information when the father, partner, or husband is not in the room. Robert Hartzman, MD, said that requiring both parents to consent is a nice idea but adds enormous costs relative to the value it would provide. Ideally, said Mutsuko Holiman, the intended parents would discuss the issue and come to a mutual decision, then choose which parent gives or does not give formal consent (if at all). Charles Sims, MD, added that for most medical procedures involving children, only one parent is required to give consent.

Ms. Regan wondered whether, for example, in the case of a closed adoption, a birth mother can provide fully informed consent if she does not know who the intended parent(s) would be. Dr. Pentz pointed out that if that lack of knowledge is a concern, the birth mother can refuse to consent. Dr. Sims said guidelines can never encompass every situation; instead, they should provide principles that organizations should take into account in crafting their informed consent procedures, which include providing individuals with information and an opportunity to discuss the procedure and ask questions before signing a consent form.

Dr. Pentz asked whether the intended parent in a closed adoption must provide consent or merely be informed that cord blood was donated. Dr. Parkman felt informing only was sufficient, but Dr. Kurtzberg and Susan Stewart argued that the intended parents must consent because they are responsible for providing information on the child's health over time that might affect the use of the donated cord blood.

2. Information obtained from the testing of the birth mother should be provided to the birth mother if it may impact her health and medical care and to the child's intended parent if it may impact the child's health and medical management.

Dr. Parkman questioned whether the recommendation is too broad and supported the idea that it be limited to so-called reportable diseases (as defined by the Centers for Disease Control and Prevention and FDA, for example). Edgar Milford Jr., MD, felt the institution should determine what to report. Dr. Pentz suggested the Work Group discuss how to narrow the recommendation's scope.

3. When should the consent take place? Ideally, the first discussion of cord blood banking should occur at a regular office visit well before labor and delivery. However, if the woman has not preregistered, the information about cord blood banking can be given on presentation to the hospital for delivery and during labor. Each bank should have a policy about how consent is offered during delivery that addresses the following issues: the stage of delivery and stress of the mother, the amount of precounseling that has taken place, and the amount of time available for an adequate discussion of the consent. The banks also should consider offering a "preconsent" for collection only, with the consent for banking completed after delivery.

Council members discussed the feasibility of the various options. An audience member noted that the full consent procedure can take as long as 45 minutes, so having the option for a brief preconsent process for collection only is helpful and allows more time for the mother to make a

decision about banking after delivery.

4. The Work Group does not recommend that hospital staff be required to offer banking to all birth mothers.

Dr. Parkman questioned the potential for bias when individual health care workers make the decision of who is an appropriate donor. Dr. Kurtzberg said many banks have criteria to identify good candidates; she added that, for example, women in active labor are excluded to alleviate concerns that they might be coerced. Dr. Kurtzberg said some States require that mothers be informed about all types of blood banking options. Some participants suggested clarifying to whom "hospital staff" refers. Ms. Regan said she saw the pragmatic reasons for this recommendation—for example, if the hospital has no cord blood bank, it's not reasonable to require staff to offer cord blood banking. Dr. Milford said institutional review boards (IRBs) require studies to have clearly defined target populations; in such cases, it would be necessary to establish criteria for selecting candidates for cord blood donation. Dr. Pentz suggested the Work Group revise the language to include some ideas to guide organizations.

5. Because public banking is based on altruism, the Work Group recommends that the consenters surrender all rights to the donated cord blood and that they not be allowed to direct the unit's use, so that it may be used most optimally for either clinical care or research. The consent should inform the donors of the following:
    a) There is no guarantee that the donated unit of cord blood will be available or suitable if their child or a sibling needs cord blood in the future, but the normal process of searching the public registry will be available to them. The bank does request that the parent notify it if the donating child develops a serious illness because this information may impact the usefulness of the cord blood.
    b) The unit may not be used at all; but if it is, it may be used either for clinical care or research.
    c) Any research using the cord blood will have to be reviewed by an ethics board, called an IRB, so that only ethical and important research is conducted.
    d) The donors can discuss with the banking team what kind of cord blood research is presently being done.
    e) The donors will not have any rights to any commercial product produced by the cord blood. (This recommendation was not unanimously supported by the Work Group.)

Liana Harvath, Ph.D., said the National Heart, Lung, and Blood Institute explicitly states that cord blood units (CBUs) obtained by and for federally-funded efforts will not be used for commercial purposes. She asked whether the Work Group had considered the role of Federal tax dollars in its deliberations. Ms. Stewart questioned the legality of asking donors to give up their rights should their donation result in commercial use. Mark McGinnis, JD, explained that courts generally agree that individuals do not have a property interest in their bodies (e.g., donated blood or tissues), although in one case a court found that a man who had been asked repeatedly to donate blood did have a fiduciary interest in the commercial use of his blood because the donation process was costing him time and money.

Dr. Read said the recommendations would take away the mother's right to refuse the use of her donated cord blood for research. Dr. Pentz said the consensus of the Work Group was to keep the process simple for those collecting and banking the cord blood, recognizing that even if research on de-identified cord blood samples does not undergo review by a full IRB panel, it is reviewed by an IRB process, so protections against misuse remain.

Dr. Harvath wondered whether families who did seek out the cord blood the mother had donated for a later medical need had to pay for it. Dr. Kurtzberg said that situation has come up four times at her blood bank; and each time, the bank still had the blood and provided it to the family at no charge. (An audience member said her bank did the same.)

There was some discussion about identifying priorities for use of cord blood and stating that clinical care would always come before research. Dr. Milford advised against such specificity because clinical research can blur the distinction.

6. Alternatives to public banking, namely, discarding the cord blood or private banking, should be described in the informed consent document.

7. The cord blood bank should have procedures that will allow the donating parents to provide relevant health information about the donor-child in the event of the onset of serious diseases, such as childhood leukemia or an inherited disorder, which could adversely affect the well-being of a recipient of that cord blood. Procedures should also be in place for relevant health information to be offered to the donor-child's guardian if the recipient-child develops a serious disease that may be linked to the cord blood.

Dr. Parkman said "linked to cord blood" was too broad a term, and Dr. Kurtzberg suggested replacing it with "transmitted by cord blood." Also, "recipient-child" should be replaced with "recipient." Dr. Pentz said the Work Group would refine the recommendations according to the discussion with the Council.

Scientific Factors Necessary to Define a CBU as High Quality
Joanne Kurtzberg, MD, Work Group Chair

Dr. Kurtzberg gave an overview of the procedure of processing, preserving, storing, shipping, and thawing cord blood. The end-product of cord blood collection depends on the type of processing and may or may not include plasma, leukocytes, red blood cells, or mononuclear cells. Once processed, cord blood must be stored in a container at a constant temperature of -150° C or colder. The shelf life of cryopreserved cord blood is not known, said Dr. Kurtzberg, although she knows of samples that are 13 years old.

The cryopreserved units remain frozen until they are requested for transplant, when they are shipped in special dry shipping containers. Dr. Kurtzberg showed some containers with self-monitoring equipment that records the temperature throughout storage. Once the units reach the transplant center, they are stored there for as long as 3 weeks in some cases until the infusion procedure is started. Dr. Kurtzberg said there are no clear guidelines for storage at the transplant

center. When needed, the cord blood units (CBUs) are thawed and infused; depending on the transplant center's approach, the units may be diluted or washed or both. Dr. Kurtzberg described various washing methods and the complications associated with infusions.

Dr. Kurtzberg emphasized that CBUs pass through many stages between collection and infusion, and most of those stages are outside and beyond control of the cord blood bank and its stringent guidelines. When the bank receives a unit, the bank evaluates each CBU before cryopreservation. According to draft FDA guidelines, CBUs must meet the following potency criteria (on the basis of a 20-kg recipient):

≥500 x 10e6 total nucleated cell count (TNC)
≥1.5 x 10e6 viable CD34 cells
≥85-percent viability

HRSA National Cord Blood Inventory reimbursement criteria set a higher bar for potency, Dr. Kurtzberg said. The FDA guidelines do not specify the processes to be used for matching. Many banks check CBUs for cell count viability at the time of release for transplant. However, there is no standard approach; and there may be other, more sensitive assays of potency.

Dr. Kurtzberg explained that when her bank analyzed samples both before cryopreservation and after thawing for infusion, it found good correlation between CD34 counts before and after thawing; but poor correlation between the number of colony-forming units (CFUs) of a given sample before and after thawing. CFUs are a good indicator of potency (i.e., viability of the units). Dr. Kurtzberg posited that some cord blood may lose potency during shipping or while in storage at the transplant center. She added that CBUs with 50-percent viability may be sufficient for infusion in a small child but not for a larger recipient.

Through further testing of random samples from her own blood bank, Dr. Kurtzberg and colleagues demonstrated that the viability of thawed cord blood varies widely, and that variation is not reflected when measurements are taken before cryopreservation. Further evaluation showed that CFUs are a better indicator of cord blood viability than TNC or CD34 and are more strongly correlated with engraftment. However, it is difficult to standardize CFU assays across laboratories; and the assays take a long time (about 2 weeks).

Therefore, Dr. Kurtzberg and colleagues are seeking a rapid assay that correlates with CFUs in CBUs to determine viability. They believe that aldehyde dehydrogenase (ALDH) bright cells, which are markers of stem and progenitor cells, correlate well with CFUs and may be predictive of engraftment. On the basis of these results, Dr. Kurtzberg and colleagues are proposing a multicenter, prospective study to determine which studies on thawed segments can predict engraftment (potency) of a CBU. Dr. Kurtzberg noted that neutrophil engraftment is reported to the Center for International Blood and Marrow Transplant Research (CIBMTR), so the study will focus on that parameter for data. She described the proposed study in some detail, pointing out that samples will be analyzed by two reference laboratories. Dr. Kurtzberg concluded that she hoped the study would ultimately help banks assess potency before releasing a unit to a transplant center.

Discussion

Hal Broxmeyer, Ph.D., pointed out that the best results from laboratory analysis come when only one reference laboratory is used. He said the lack of good markers for hematopoietic stem cells is a barrier. Dr. Broxmeyer added that the potency of a CBU at the time of collection affects the potency at the time of release, that is, even under the best cryopreservation and storage conditions, you can only get back what you put in. Some research has addressed how to get more cells during collection, but it's challenging and has not been a priority.

Dr. Read asked whether the segments that would be analyzed could be considered representative of the whole unit because the segment, once transported, could be warmer than the rest of the unit. Dr. Kurtzberg said the study would validate findings at multiple points and with multiple segments from the same unit. If storage during transportation seems to affect the segments, she said, that issue could be addressed, although at a significant financial cost.

Dr. Hartzman asked if a follow-up study would address what is transplantable. Dr. Kurtzberg agreed such a study would be useful but could not be completed in the time allotted for the proposed study. She added that most NCBI cord blood banks indicated their support for the study and have agreed to provide samples. Other participants commented on details of the execution of Dr. Kurtzberg's proposed study.

Overview of Recent Clinical Developments and Current Issues
Richard Champlin, MD, ACBSCT Member

Dr. Champlin described the research priorities for allogeneic hematopoietic stem cell transplantation (alloHSCT) and the related barriers and challenges. Research priorities fall into three major categories:

- Improving the safety and effectiveness of alloHSCT
- Determining indications for alloHSCT
- Improving access to and delivery of alloHSCT

<u>Improving the Safety and Effectiveness of alloHSCT</u>
Improving safety and effectiveness requires more basic research to understand and control alloreactivity, specifically the immune system's reaction to transplantation. Translational and clinical research is needed to address the major clinical problem areas: engraftment, graft-versus-host disease (GVHD), immune reconstitution, and disease relapse.

In transplantation, the patient receives a regimen that eradicates abnormal cells and depresses the immune system so that the body will not reject the implanted cells. Donor cells are infused, go into the bone marrow and grow, thereby reproducing the donor's immunity in the blood of the host. Over about a year, donor T-cells begin to regenerate in the recipient.

Hematopoietic transplantation holds great promise for treating a number of conditions but remains risky. It replaces defective cells, restoring hematopoiesis and immunity to the recipient. AlloHSCT is the definitive treatment for hemoglobinopathies. Transplantation could "reboot"

the immune system of individuals with autoimmune disorders, said Dr. Champlin, and could induce tolerance in the body, enabling transplant of organs from the same donor. For metabolic disorders, alloHSCT could replace defective proteins that are produced by hematopoietic cells. For cancer patients, transplantation serves as an adjunctive therapy that supports the use of high-dose chemotherapy and induces an immune antitumor effect.

Hematopoietic cells have limited capacity to differentiate. For example, very few of the recipient's epithelial cells reflect the donor's cells. While embryonic stem cells can differentiate into any kind of organ, research has been limited by ethical concerns. Dr. Champlin described "enormous interest" in induced pluripotent stem cells, which can reprogram adult cells with the characteristics of embryonic stem cells. The potential for tissue regeneration is of particular interest in cardiology. Studies have demonstrated that blood and bone marrow cells injected into damaged myocardial tissue do not generate muscle cells but do promote healing. More basic science is needed to address whether stem cells could regenerate myocardial muscle cells.

AlloHSCT is most commonly used to treat cancer. Current cancer treatments (chemotherapy and radiation) suppress bone marrow. However, they can be used in high doses to eradicate cancer cells, followed by alloHSCT to rescue bone marrow. Dr. Champlin points out that the immune system of a cancer patient is defective, having become tolerant of the cancer. The donor's immune cells mediate a graft-versus-malignancy (GVM) effect—the recognition of residual cancer cells by the T-cells of the donor. Donation between identical twins has a higher rate of disease relapse because twins' cells may have the same tolerance to cancer.

As we better understand the GVM effect, said Dr. Champlin, researchers have begun developing nonablative transplantation approaches. The next step is to restore immunity to cancer patients through transplantation while eradicating cancer with more tolerable doses of chemotherapy and radiation. Researchers also are seeking to decrease graft rejection rates, GVHD, post-transplant immunodeficiency, and infections.

Dr. Champlin described some of the conditions that researchers believe would benefit from a targeted GVM effect. Some research seeks to engineer T-cells that could target only cancer cells.

About two thirds of the population does not have a good family match to serve as a donor, although about one third of those could find a good match through a registry. That leaves about one third of the population with no donor source, and that's where cord blood plays a key role, said Dr. Champlin. The better the match, the more likely a transplant will be a success, so researchers are looking at improving compatibility by addressing alloreactivity, for example, by developing nonalloreactive immune cells for reconstitution and antitumor effects. Mismatch of human leukocyte antigen (HLA) increases the rate of rejection and GVHD. Some mismatches may be acceptable, and others may be minor but have a cumulative effect. Researchers are seeking to identify which loci and combinations result in GVHD and GVM effect.

Comparison of various sources of hematopoietic stem cells will help to determine which has the most value. Using bone marrow treatment as a baseline, peripheral blood progenitor cells (PBPCs) engraft more rapidly but carry a higher risk of chronic GVHD and possibly acute

GVHD. Dr. Champlin anticipated the results of a large study comparing the two may offer some clarity. Cord blood results in slower engraftment and more complications than bone marrow but lower risk of acute GVHD. Researchers hope to reduce the risk of GVHD and are interested in learning how to get as many cells as possible from sources and accelerate engraftment.

The use of both cord blood and PBPCs over bone marrow transplants is increasing every year. Cord blood is a rich source of hematopoietic stem cells that are immunologically immature and therefore less prone to produce GVHD. Cord blood transplantation provides better results in children than adults, and researchers are seeking ways to improve outcomes among adults.

It was long believed that an identical twin was the best donor source, but, as stated, that may not be the case. A matched, nonidentical sibling is the best match for an allogeneic transplant. The GVM effect increases with some mismatches, and there is debate about whether an intentional mismatch could result in a beneficial antitumor effect. In the absence of a sibling, what is the best alternative donor source? Transplantation from a matched, unrelated adult donor increases the risk of rejection and GVHD, but success increases when HLA typing is used to minimize HLA mismatches. Cord blood transplantation is most successful in children when HLA-matched blood is used. Whether cord blood transplantation would be more successful in adults with similar HLA types has yet to be fully explored.

At present, it is not known which of the various, competing donor sources and technologies will surface as the best approach for patients who do not have a matched sibling donor. Dr. Champlin said the optimal size and composition of donor registries and cord blood banks depends on which approaches/technologies yield the best results.

Dr. Champlin noted that research must focus on reducing complications of alloHSCT: graft rejection, acute and chronic GVHD, and treatment-related mortality. For acute GVHD, research is centered on better understanding the pathogenesis, creating better immunosuppressive drugs for treatment, and replacing alloreactive with nonalloreactive cells. Chronic GVHD is the most common complication of transplantation, affecting as many as half of patients. Research is seeking effective strategies to prevent and treat GVHD.

Graft manipulation involves combining or engineering cells to achieve better results, such as directing T-cells to turn off the immune system or using natural killer (NK) cells to achieve an antitumor effect. NK cells could be used to kill leukemia and decrease GVHD; they are being studied for use as adjuncts to transplantation. Ideally, researchers could determine how to "customize" transplants by manipulating cells on the basis of individual need.

<u>Determining Indications for alloHSCT</u>

A number of cancers have been shown to respond to alloHSCT, but the procedures are complex and carry the risk of complications that must be weighed against standard treatment options for each patient. For acute myelogenous leukemia, for example, patients with early-stage leukemia had better results with alloHSCT than those who were not treated until they had advanced disease; but the overall survival rate compared with standard chemotherapy is only modestly better with alloHSCT. Therefore, it is difficult to determine which patients would benefit; and

investigators are trying to identify which groups are most at risk from chemotherapy to help guide decision-making.

For most indications for alloHSCT, alternative therapies are available; and research must determine the safest and most cost-effective treatments. Results vary depending on diagnosis, prognosis, and disease stage. Because alternative therapies are also improving, the target is constantly moving, said Dr. Champlin. The goal of treatment is usually survival or quality of life (which can be subjective), and balancing the two requires consideration of the toxicities and complications of treatments.

The timing of alloHSCT remains a question. Treatment at the time of diagnosis involves risks that the patient can avoid by using alternative therapies. Waiting longer, however, reduces the chances of success. Treating patients identified at an early stage of disease who are at high risk and for whom at least one treatment method has failed still requires weighing the risks and benefits, which vary by patient.

Most research is being conducted in small trials involving single centers, so the results represent enormous variations in practice. Recently, a multicenter group was formed that included cooperatives, the Blood and Marrow Transplant Clinical Trials Network (BMTCTN), and CIBMTR. Dr. Champlin listed some of the studies planned as a result of the multicenter group's efforts.

Improving Access to and Delivery of alloHSCT

Dr. Champlin said more people could benefit from transplantation even given the current limitations. Addressing access and delivery requires attention to broader health care delivery issues (e.g., workforce limitations, facility capacity). Registries must be sufficient in size and function to identify donors rapidly. Financial barriers, such as no or limited insurance coverage, delay or prevent people from getting transplants. Medicare is considering a National Coverage Determination for transplantation for Myelodysplastic Syndromes, but it would not become effective for a year and would not apply to lymphoma. Candidates face logistical barriers, such as the availability of home care. Some physicians have a financial incentive to continue treating patients and thus do not refer them for transplantation when appropriate. More research is needed to identify and rectify these and other barriers.

Other challenges include the expense of research weighed against the small market for treatment, the difficulty of protecting intellectual property in cell research, and the complexities of FDA approval. (Dr. Champlin noted that none of the treatments currently used for immunosuppression with alloHSCT are approved by the FDA for that indication.) With limited funding and infrastructure to support such research, large companies are reluctant to pursue it.

Conclusion

Dr. Champlin concluded that although alloHSCT can be an effective or even definitive treatment for a broad range of hematologic, immunologic, metabolic, and neoplastic diseases, the risks remain high. We must reduce the risks and make procedures more attractive to patients, he said. In addition, we should seek to provide access to alloHSCT for patients who are good candidates.

Discussion
Dr. Broxmeyer agreed with Dr. Champlin's assessment of the research priorities but added that engraftment should become a higher priority for research. More funding is needed to characterize stem cells and enhance engraftment, he said. The National Institutes of Health (NIH), which funds most of the research in this area, tends to support mechanistic research. Dr. Broxmeyer hoped the Council would support research focusing on the practicality of engraftment. Dr. Champlin agreed that there are many areas beyond discovery that merit more study.

Adult Donor Recruitment: Strategies and Challenges
Jeffrey Chell, MD, Chief Executive Officer, National Marrow Donor Program (NMDP)
(The NMDP holds the HRSA contracts for the three components of the C.W. Bill Young Cell Transplantation Program, including the Bone Marrow Coordinating Center.)

Dr. Chell noted that by the end of 2009, NMDP will have facilitated 40,000 transplants since the organization began in 1987. To better meet the need for transplants, NMDP set a goal of facilitating 10,000 transplants per year by 2015 (on the basis of two studies of the likelihood that an individual in need of a transplant would benefit from an unrelated donor). The organization facilitated 4,350 in 2008. It developed a strategic plan to meet the 2015 goal, which requires organization-wide transformation. The number-one objective in the strategic goal is to successfully serve all patients in need of a transplant. As advocates for patients, Dr. Chell said, NMDP will go beyond identifying sources to addressing other barriers, such a geography, language, literacy, health care economics, and family support.

Dr. Chell described some milestones recently achieved by NMDP:

- >100,000 CBUs in the NMDP registry
- >3,000 cord blood transplants facilitated
- 7.6 million donors in the NMDP, representing about one third of the world's donors

The NMDP network involves 76 donor centers, seven of which are international; and NMDP is the coordinating center for over 500 organizations around the world. The network includes 24 cooperative registries and 21 cord blood banks. International collaboration is critical, said Dr. Chell. Notably, 40–50 percent of transplants cross international boundaries, and 25 percent of transplants in the United States involve non-U.S. donors. Therefore, standards and regulations must be harmonized. Policy changes made in the United States can have a significant impact on other countries.

Historically, NMDP has recruited donors through other organizations, such as the American Red Cross. The Red Cross decided to focus on blood donation in 2004 so NMDP took on the management of a number of former Red Cross donor centers. Dr. Chell explained that NMDP has increased staff and funding substantially to recruit donors. To achieve its ambitious recruitment goals, the organization has become more performance-oriented, setting specific performance measures and implementing tools to evaluate not just recruitment but also retention of donors, including more education of potential donors. Donor management is handled separately from donor recruitment, and NMDP recently hired new leaders for both areas.

Among its new tools, NMDP has established an online recruitment center, where users can give their health information and receive a home cheek swab kit, which they use and return to NMDP for tissue typing. The online approach allows NMDP to conduct virtual donor drives, for example, via employers who have a small number of employees per site. The organization also has put in place a more comprehensive training curriculum that includes orientation.

Donor retention remains a significant concern. NMDP measures retention at the time of confirmatory typing, when a formal application is made and more information about the donor is needed. Among those potential donors willing to go to a center and have their blood drawn and who are confirmed as appropriate matches, 98 percent will donate. However, the overall retention rate is 61 percent for 2009 to date and varies by ethnicity, ranging from 46–72 percent. Of those who are not available when NMDP seeks them, 11.7 percent say they are no longer interested in donating. Another 5.2 percent are unable to donate because of a medical problem, and 15.6 percent are temporarily unable to donate for any number of reasons. Despite applying a wide range of tools to maintain contact with potential donors, NMDP is unable to contact 6.6 percent of those registered.

To improve retention, NMDP is targeting those most likely to follow through with donation, improving education of potential donors at the time of recruitment, and following up with new donors 2 months after joining to ensure that contact information remains valid and to answer additional questions. More contact with registrants via e-mail and an improved website are intended to create a stronger sense of membership among potential donors. The e-mails and website encourage potential donors to get involved and volunteer as well as to keep their contact information up to date.

To increase the number of registrants who respond to requests to undergo a confirmatory blood typing test, NMDP has improved the tools it uses to locate donors who may have moved and helps coordinate activities between local donor management staff and transplant centers. The growing registry and the ability to use cord blood increases the number of donors from which to choose and the number of backup donors.

Donor residency and immigration status affect donor management, as undocumented residents can be difficult to locate and can be more difficult to protect with insurance. NMDP offers wage replacement and health care to manage complications to protect donors, but undocumented residents often are reluctant to take advantage of those benefits, because they could be exposed to Government scrutiny as a result. Sometimes, undocumented residents are unwilling to travel outside their own city to complete the donation. Dr. Chell said NMDP is considering how to revise its policies in keeping with the Government's immigration policies.

The registry maintains a list of donors from age 18 to 61 years old. The upper age limit was established mainly to protect donors, and few people age 60 and older are chosen to be donors. Dr. Hartzman added that programs are very cautious about using older donors because of the risk of complications, no matter how small the risk. An audience member said an NIH-funded study is planned to assess outcomes by age of donors. At the other end of the spectrum, NMDP

requires donors to be at least 18 years old, which is consistent with the policies of all other countries (although two U.S. States permit younger people to register).

People ages 18–24 who register have the lowest retention rate and also the highest likelihood of being chosen to donate. In terms of selection of donors, Dr. Chell said transplant centers tend to select younger male donors (although there is not strong evidence of better outcomes). Younger registrants represent more ethnic diversity than older registrants. In its recruitment efforts, NMDP is targeting younger donors by using online social networking, recruitment center incentives, do-it-yourself recruitment via the website, and aiming efforts at universities.

"Be the Match" is NMDP's new initiative to raise awareness and funds. It is underway through web and social media, as well as traditional media, in Houston, Texas, and Charlotte, North Carolina and NMDP plans to expand it nationally. Dr. Parkman noted that NMDP's advertising on the dashboard of a NASCAR race car was very impressive and attention-getting. Dr. Chell said the advertising space—worth $1 million—was donated by the Rick Hendrick team and garnered a lot of response. NMDP no longer has the dashboard but does have free advertising space behind the wheels.

Through evaluation of donors, NMDP identified groups it labeled as the "Socially Connected" and the "Living My Faith" group as those most likely to join the registry and remain in it. The Living My Faith group represents people who feel they have a "higher purpose." The Socially Connected group is likely to include blood donors and people who join clubs and participate in social activities. "Be the Match" will focus media efforts on these two groups.

Discussion
Dr. Chell pointed out that if everyone who would benefit from a transplant received one, the number of transplants would increase by about 5,500 per year. He believes that in the future, about half of all transplants will involve cord blood, and the rest will involve an adult donor. As noted, the goal of 10,000 transplantations per year is beyond the current capacity of the health care system, and NMDP is partnering with the American Society for Blood and Marrow Transplantation to consider workforce and other issues.

Dr. Anasetti said research showed that, once the number of donors reached 5 million, the benefit of expanding the size of the donor pool disappears; and he would prefer to see more funding aimed at cord blood transplantation rather than increasing donor registries. Dr. Hartzman countered that he believes the studies on which that finding was based were flawed. He added that the target number of transplants would change dramatically if survival rates improved, for example, for children with sickle cell anemia or thalassemia.

In response to an audience member's question, Dr. Chell said the cost of international donations varies, but the goal is to keep the costs reasonable so that decisions are made on the basis of what's best for the patient. An audience member suggested NMDP could increase cord blood donations by improving access to collection centers for women about to deliver and providing more education to women earlier in pregnancy. Dr. Kurtzberg commented that HRSA is considering a kit that could be used by any hospital to collect cord blood, even if it doesn't have an affiliated cord blood bank.

Future Council Activities
Karl Blume, MD, ACBSCT Chair

Dr. Blume identified seven topics suggested in the ACBSCT's charter but not yet addressed:

- The necessary size and composition of the adult donor pool available through the C. W. Bill Young Cell Transplantation Program and the composition of the NCBI;
- Public and professional education to encourage the ethical recruitment of genetically diverse donors and ethical donation practices;
- Criteria for selecting the appropriate blood stem source for transplantation;
- Program priorities, research priorities, and the scope and design of the Stem Cell Therapeutic Outcomes Database;
- Regulatory policy, including compatibility of international regulations;
- Potential actions by State and Federal Government and public and private insurers to increase donation and access to transplantation; and
- Research on emerging therapies using cells from bone marrow and cord blood.

Members noted the following areas of interest:

- Enhancing engraftment.
- Access to transplantation: Access among minority populations, Medicare coverage, support for patients enrolled in clinical trials, increased public education (especially among minority populations), and attention to workforce issues that pose a barrier to access.
- Cellular therapy: Criteria for clinical trials, criteria for licensing products, standardized shipping practices, and embryonic stem cell therapy (group should include FDA representation).
- Collections: Education to encourage cord blood donation, research on increasing the amount of usable cells from cord blood.
- Research portfolio: Who is using cord blood, for what, and how much? Who is funding cord blood research? Are enough cord blood units available for research?

For a future agenda, Dr. Read suggested a presentation on the California Stem Cell Research and Cures Initiative from the California Institute of Regenerative Medicine (suggested speaker: Marie Csete, MD, PhD, Chief Scientific Officer) focusing on induced pluripotent stem cells.

The Council decided to form two new work groups, one with a broader, more policy-focused charge, and one to look at more pragmatic, immediate concerns:

The Access to Transplantation Work Group will consist of the following members:

- Claudio Anasetti, MD
- Deborah Banker, PhD
- Clive Callendar, MD

- Richard Champlin, MD
- Mustuko Holiman, RN
- Robertson Parkman, MD
- Rebecca Pentz, PhD
- Susan Stewart

The Cord Blood Collections Work Group will consist of the following members:

- Nancy DiFronzo, PhD
- Liana Harvath, PhD
- Joanne Kurtzberg, MD
- Donna Regan
- Pablo Rubinstein, MD
- Stephen Sprague
- Susan Stewart

Public Comment

There were no public comments. Dr. Blume adjourned the meeting at 3:15 p.m.