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

Hyatt Regency Bethesda
Bethesda, MD

September 21, 2009

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. Remy Aronoff, Executive Secretary of the ACBSCT, noted that several members would complete their terms of service in January 2010: Deborah Banker, PhD; Karl Blume, MD; Hal Broxmeyer, PhD; Robertson Parkman, MD; Elizabeth Read, MD; Charles Sims, MD; and Robyn Yim, MD. Michelle Bishop, PhD, will resign from the Council following this meeting. Mr. Aronoff expressed his appreciation to those members for their service. He especially thanked Dr. Blume for his leadership as chair. Edgar Milford, Jr., MD, will take on the role of Chair of the ACBSCT beginning in January 2010.

Informed Consent Work Group Recommendations
Rebecca Pentz, PhD, Work Group Chair

Dr. Pentz described changes the Work Group had made in response to input from the Council to the draft recommendations for informed consent for cord blood banking:

- **Introduction**: Added the statement, "We intend these recommendations to allow individual banks the flexibility to adopt their own procedures consistent with the recommendations."
- **Recommendation 1**: Reduced the number of examples of who should consent to one.
- **Recommendation 2**: Regarding who should receive information about an event related to cord blood donation, the Work Group revised the wording from "the person for whom it may have medical impact" to "the person for whom it *is likely to* have medical impact" (emphasis added) in the principle and similarly in the example.
- **Recommendation 3**: Regarding when consent should be obtained, the Work Group clarified that it is reasonable in some situations to seek informed consent when the pregnant woman presents for delivery; it removed the phrase "and during labor."
- **Recommendation 4**: Revised as follows regarding the issue of requiring hospitals to offer cord blood banking: "Although the Work Group does not recommend that hospital staff be required to offer banking to all birth mothers, *we encourage banks to develop procedures to approach all eligible mothers, with particular attention to mothers from underrepresented demographic categories*" (emphasis added).
- **Recommendation 5**: Removed the phrase "surrender all rights to the donated cord blood" and revised as follows: "Because public banking is based on altruism, the Work Group recommends that donors not be allowed to direct the unit's use, so that it may be used most optimally for either clinical care or research."

  Dr. Pentz pointed out that only a small percentage of donors refuse consent to use the

donations for research, and rather than distinguishing and tracking units on the basis of donor preference, it would be easier and less expensive to forego collection from such donors. She added that the Work Group agreed that institutional review boards (IRBs) and others are better informed and capable of making decisions on the appropriate use of donated cord blood.

Banks are encouraged to accommodate families by stating, "If, however, a child from a donating family needs a unit, we encourage banks to offer the unit, if available."

Dr. Pentz said the Work Group retained the statement (in Recommendation 5); "The donors will not have any rights to any commercial product produced by the cord blood" because private partnerships are already part of the cord blood research enterprise, and such research should not be discouraged from commercial development. No substantial changes were made to recommendations numbers 6 and 7.

Discussion
Dr. Joanne Kurtzberg said that IRBs sometimes impose their own parameters on informed consent.

Action Item

Dr. Pentz agreed to add to the introduction that recommendations should be interpreted in light of State and Federal laws and regulations, "as well as Institutional Review Board requirements."

Council members differed on the time and expense involved when donors are permitted to choose whether their donation is used for research or clinical treatment or both. Dr. Pentz emphasized that individual banks may offer such a choice to donors, but the Work Group agreed that it is impractical. Several Council members suggested the wording of the statement be clarified to distinguish clinical research from laboratory research. Others asked that it be softened slightly.

Action Item

Dr. Pentz will revise Recommendation 5 as follows: "Because public banking is based on altruism, the Work Group *suggests* that donors not be allowed to direct the unit's use, so that it may be used most optimally for either clinical *use* or *laboratory* research" (emphasis added).

Dr. Pablo Rubinstein suggested adding that some donated cord blood may be used for quality assurance, but Dr. Pentz and others felt that would be adding too much detail and raise other potential questions.

Recommendation

The Council approved the recommendations of the Informed Consent Work Group with the changes described above (see attachment 1). The recommendations will be revised as indicated and forwarded to the Secretary for consideration.

Access to Transplantation Work Group Findings and Recommendations
Richard Champlin, MD, Work Group Chair

Dr. Champlin summarized the findings of the Work Group, noting that only about 15% of patients under the age of 70 years with hematologic malignancies considered treatable by hematopoietic stem cell transplantation (HCT) go on to have a transplant, and fewer than 10% of those with a disease (e.g., acute leukemia) for which allogeneic HCT is considered the best approach will have such a transplant. He said African Americans are less likely than Caucasians to get transplants, citing socioeconomic barriers as the key reason. Dr. Champlin categorized the main barriers to access for all people:

- **Lack of insurance or inadequate coverage**. Medicare, Medicaid, and private insurers may not cover transplantation, even when it has been demonstrated to be effective, or may underpay for transplantation, resulting in cost-shifting. Some insurers restrict certain HCT sources. Many insurance plans do not cover the ancillary costs of donor HLA typing or donor searching.
- **Lack of access to clinical trials**. Many insurers don't cover the cost of participation in clinical trials. More than half of States require insurers to cover such costs, but those laws apply only to State plans.
- **Lack of physician referral**: Misinformation and controversy about appropriate indications for HCT prevent doctors from referring patients. Community physicians have a financial incentive not to refer patients to a transplant center, or to refer too late in the disease process.
- **Lack of adequate facilities and staff**: Current resources are insufficient to meet the needs.
- **Lack of education**: Health care providers and patients would benefit from more and better information about HCT.
- **Logistic and socioeconomic factors**: Distance to a transplant center, time required for the procedure, and post-procedure needs all pose significant challenges to patients.
- **Lack of donors**: Larger inventories of cord blood are needed to meet demand. It is difficult to maintain donor registries and to keep up donor enthusiasm.
- **Inefficient search processes**. The Institute of Medicine's recommendations recognized that searching for a suitable match requires time and expertise, but most centers still have inadequate resources and volunteer-driven search mechanisms remain slow and cumbersome.

The Work Group presented preliminary recommendations for consideration:

- Medicare and Medicaid should cover allogeneic hematopoietic transplantation for the

following conditions:
    - Myelodysplastic syndrome
    - Lymphoma
    - Myeloproliferative diseases
    - Inborn errors of metabolism involving hematopoietic tissues
    - Hemoglobinopathies
- Allogeneic hematopoietic transplants should be approved for indications listed in the National Comprehensive Cancer Network's guidelines or other generally accepted compendia.
- The Health Resources and Services Administration (HRSA) should convene a panel of experts to recommend guidelines for insurance coverage.
- Insurance plans should be required to cover costs of treatment of catastrophic illness, such as cancer and HCT, to provide adequate coverage to cover realistic costs for HCT and cancer treatment, and to eliminate caps.
- Insurance plans should be required to cover the costs of human leukocyte antigen (HLA) typing, donor search, and donor transplant acquisition.
- Insurance companies should be required to cover standard medical charges incurred with patient participation in clinical trials.
- HRSA should work with the National Marrow Donor Program (NMDP) to improve the search process:
    - Develop information systems for one-stop shopping.
    - Speed turnaround time for each step in search-to-transplant process.
    - Perform an efficiency review of current system involving efficiency experts, rather than blood bankers.

Although not a formal motion, Dr. Champlin suggested convening transplant experts and disease experts to develop a consensus document that provides disease-specific algorithms for identifying good candidates for HCT. Such an effort could use the National Comprehensive Cancer Network's guidelines as a starting point.

Discussion

J. Douglas Rizzo, MD, of the Center for International Blood and Marrow Transplant Research, underscored that African Americans are less than half as likely to get transplants as Caucasians, even when donor issues are not a complicating factor. Dr. Bertram Lubin said cost data can help make the argument for earlier transplantation. Dr. Champlin agreed, saying research supports that transplantation can be more cost-effective than other treatments.

Following discussion of whether autoimmune diseases and multiple sclerosis should be added to the list of conditions Medicare and Medicaid should cover, Dr. Robertson Parkman suggested the recommendation be revised to include a process for ongoing reassessment of conditions amenable to transplantation that Medicare and Medicaid should cover.

In response to Dr. Kurtzberg's suggestion to consider including cell therapy in the recommendations, Dr. Champlin said that insurers' refusal to cover cell therapy outside of transplantation has been a major barrier to the development in this field.

Mark McGinnis with the HHS Office of General Counsel pointed out that the Secretary of HHS only has authority over Medicare and Medicaid, although the Department of Defense and the Department of Veterans Affairs often follow suit in their own programs. Regulation of private insurers requires congressional legislation, for which the Secretary can advocate. He noted that Medicare is in the process of considering coverage for HCT for myelodysplastic syndrome. Dr. Champlin said the Medicare coverage process is opaque, and coverage of myelodysplastic syndrome has been under consideration for over a year. Dr. Parkman suggested focusing the Council's efforts on Medicare and Medicaid coverage, as that would provide political and psychological leverage to compel other insurers to provide coverage. Robert Baitty, Director of HRSA's Blood Stem Cell Transplantation Program, said the Secretary also may be able to influence coverage determinations for the Federal Employees Health Benefits Plan. Requiring the participating insurers to cover HCT would go a long way toward expanding and standardizing coverage, he said.

Mr. Aronoff said it would be feasible to convene a group focused on insurance coverage for HCT. He asked the Council to provide more specific direction and indicate who should take part. Dr. Blume said insurers should be represented. Dr. Pentz suggested representation from patient advocacy organizations, and Dr. Kurtzberg said rare disease groups should have a voice. Dr. Blume cautioned against creating too large a committee.

Action Item

Dr. Champlin will work with Mr. Aronoff to develop a list of stakeholders to include on a committee focused on expanding insurance coverage for HCT, with the goal of establishing workable guidelines, similar to California's Medi-Cal selection criteria for bone marrow transplantation.

Dr. Blume said California's clear Medicaid guidelines for transplant coverage improved access and simplified the work of health care providers. Dr. Claudio Anasetti said such guidelines would help in Florida.

Regarding the recommendation to require insurers to cover the costs of treatment, Dr. Blume suggested specifying HCT for life-threatening conditions. From the floor, Dr. Rizzo suggested adding post-procedure costs, which Ms. Mutsuko Holiman strongly supported; and Dr. Kurtzberg suggested including coverage for pre-existing conditions. Dr. Charles Sims felt the recommendation aimed too broadly and exceeded the charge of the Council. Dr. Parkman said the recommendation highlights a significant barrier to access that translates into inequitable use of publicly-funded banks; therefore, it is important information to provide the Secretary, which she may use to advocate for change.

Dr. Blume called the discussion to a close, saying the Work Group should further deliberate on all of the recommendations and present them for additional discussion at the next Council meeting.

Cord Blood Collections
Human Term Placenta as a Source of Hematopoietic Cells
Bertram Lubin, MD, ACBSCT Member

Dr. Lubin asked the Council to consider making a strong recommendation and provide guidelines about the value of cord blood therapy for treatment of hemoglobinopathies. He summarized case studies on pediatric patients with sickle cell anemia and thalassemia cured by cord blood transplantation but said hematologists remain hesitant to refer patients.

Dr. Lubin summarized the results of research demonstrating that the placenta appears to be a good source of hematopoietic stem cells ("Human Term Placenta as a Source of Hematopoietic Stem Cells," by Serikov, V., Hounshell, C., Learkin, S., Green, W., Ikeda, H., Walters, M.C., et al. *Experimental Biology and Medicine*, 2009 Jul;234(7):813–23). Research in mice demonstrated that the placenta is rich in hematopoietic and pluripotent stem cells. The work of Serikov, et al. demonstrated that "human placenta contains large numbers of CD34-expressing hematopoietic cells, with the potential to provide a cellular yield several fold greater than that of a typical umbilical cord blood harvest."

Mozobil breaks the adherence of stem cells to epithelial cells, said Dr. Lubin, thus releasing those stem cells "stuck" in the placenta. The potential to harvest stem cells from placenta raises other questions:

- Will the effort required to collect and store placenta pay off in the amount of usable stem cells harvested?
- Will the use of placental stem cells fill the gap in usable stem cells for currently underserved populations? (Dr. Lubin is seeking funding for research to assess the amount of cells collected from the placentas of African American mothers.)
- When and how often should placental stem cells be harvested?
- Would it be cost-effective to cryopreserve placentas? (Research shows cells can be recovered effectively from fresh or frozen placentas.)
- Should consideration be given to establishing placental stem cell banks? If so, would placental stem cells be used as an alternative or adjunct to cord blood stem cells?

Dr. Lubin concluded that human placenta stem cells should be considered for human stem cell transplantation in the future.

Discussion
Dr. Hal Broxmeyer concurred that placenta may be a useful source of stem cells and research is likely to find methods for getting more cells more quickly. He worried about the potential for maternal contamination; Dr. Lubin said earlier studies did not find maternal contamination. Dr. Broxmeyer and Dr. Lubin agreed that there is no way to confirm that Mozobil actually enhances the yield of stem cells. Dr. Kurtzberg was skeptical about the amount of usable end-product that could be generated, but Dr. Robert Hartzman said the potential is significant and the approach worth exploring. Dr. Rubinstein said studies in the late 1960s and early 1970s reported similar results but they were not reproducible. He added that outcomes vary tremendously depending on technical factors that affect the results.

Meeting with Department of Commerce Secretary
Liana Harvath, PhD

Dr. Harvath explained that Commerce Secretary Gary Locke requested a meeting with representatives of the Council and various Federal agencies to discuss cord blood banking and research. Secretary Locke raised several questions, and Dr. Harvath summarized the responses:

- **Why does it cost $2,000–$3,000 per cord blood unit to collect and store it in a public bank? What can be done to lower the cost of cord blood collection and storage?** Participants emphasized the cost of processing, administration, and typing, noting that, contrary to Secretary Locke's and others' perceptions, infectious disease testing is not the main cost driver.

- **To reduce costs, can cord blood units be collected without upfront testing and instead be tested just before release for transplantation?** Participants explained the importance of not banking tissue that may not be dispensed for use.

- **Why do mothers need to consent to have cord blood collected for research purposes?** Participants said patients believe they should be informed of and have some control over the use of their biological materials for research. Secretary Locke asked for more in-depth evaluation of the question.

- **Can the ACBSCT discuss and develop recommendations to reduce the cost of cord blood banking?** Participants said the Council's Cord Blood Collections Work Group will discuss cost reduction strategies.

Dr. Harvath said that after the meeting, HRSA prepared a two-page letter with written responses to the questions. She added that the National Institute of Standards and Technologies, which falls within the Department of Commerce, has a strong biophysics research program that could support cellular research of interest to Council members.

Work Group Preliminary Findings
Donna Regan, MT (ASCP), SBB, Work Group Chair

Ms. Regan described the objectives established by the newly-formed Cord Blood Collection Work Group:

- Encourage a remote site collection model.
- Develop physician education tools aimed at proper collection technique to optimize cell recovery.
- Develop educational tools for maternal donors, stressing the importance of early registration, proper coordination, and recipient safety.
- Deliberate about collection methods to optimize cell recovery.

Remote collection requires considerable education to ensure proper technique, kits that meet storage and transportation standards, and mechanisms for transport. HRSA is funding a remote collection pilot program involving the National Marrow Donor Program (NMDP) and three institutions which will begin October 1, 2009. Ms. Regan suggested that legislators could demonstrate their support for cord blood transplantation by encouraging their States to invest in remote collection programs similar to the pilot program if it is successful. She felt that this approach, if successful, could be used by states to start or expand collections without the cost of creating a physical cord blood bank.

Ms. Regan said that some physician education materials already exist. Additional education should stress the importance of early education about cord blood donation so that mothers can provide truly informed consent and to ensure that accurate information about the donor is gathered, which helps protect the recipient's safety. Planned and coordinated education and collection efforts result in a higher-quality donated product.

Among the factors that motivate physicians to spend more time promoting cord blood donation are the mother's enthusiasm and altruism, success stories, and compensation, reimbursement, and incentives. Providing financial incentives to physicians raises ethical and cost considerations that must be addressed.

Physicians play a key role in how mothers and families feel about cord blood donation. Educational materials exist that target new mothers, including a pregnancy passport. The Work Group determined that additional, updated information should be added to the passport document so that it can be disseminated more widely. States could be encouraged to post the document, once it is customized and purchased, along with other educational material on their public health websites.

Communication is greatly complicated, Ms. Regan noted, by the fact that the health care system lacks the resources to collect, process, and store all the potential cord blood donations. Public-private partnerships offer education, but Ms. Regan advocated for focusing on government-funded programs, such as HRSA and NMDP, that provide clear information about remote collection sites and public banks.

The Work Group has not yet addressed how to optimize collections. It hopes to look at ways to improve collections among specific racial/ethnic groups and to educate and motivate more obstetricians to collect cord blood. The Work Group also plans to:

- evaluate the results of the pilot project on remote collections,
- assess continuing education for physicians on cord blood collection,
- promote reliable sources of information (e.g., websites) to the public, and
- draft new consumer-friendly language on donation to add to patient pamphlets and public health websites.

Discussion

In response to questions, Ms. Regan estimated that about 25% of the products collected are usable and stored in a bank. Dr. Sims said the amount varies on the basis of the donor pool for a

given bank. Private banks that focus on donors of higher socioeconomic status may bank about one third of the blood they collect, he estimated.

Ms. Regan clarified that in the pilot program, at the remote sites outside of the three centers involved; the mother initiates the conversation about cord blood donation (as opposed to the staff). Dr. Kurtzberg said her organization is involved in the pilot and provides training and certification to those who will collect cord blood.

Dr. Lubin expressed enthusiasm that remote collection efforts could improve the amount of cord blood donated by minority populations. He stressed that taking the time to educate mothers is key to success; a remote kit with generic educational materials would not be sufficient. Dr. Lubin also suggested obstetric training include cord blood collection and said medical schools, professional societies, and State genetic disease programs should all be targets for improving education about cord blood collection.

Several Council members suggested that facilitating collaboration among collection sites within and across States could maximize resources and improve the efficiency of collecting and storing cord blood.

Dr. Sims pointed out that obstetric delivery is poorly compensated, so serious consideration should be given to paying staff to take on the additional burden of cord blood collection. Dr. Parkman added that facilities that serve diverse populations tend to be the most resource-challenged, and efforts to increase collections would amount to an unfunded mandate. Dr. Sims noted that some private banks pay physicians for collection, but most public banks don't.

Stephen Sprague stated that communication is further complicated by the implied message that "good" parents store cord blood donations in private banks, and public banks lack the resources to counter that message. Kathy Welte of NMDP said that evaluation criteria provide information that may be useful to the Work Group.

Dr. Blume asked the Work Group to update the Council on its progress at the next meeting.

Induced Pluripotent Stem Cells (iPS) and Adult Stem Cells
Marie Csete, MD, PhD, Chief Scientific Officer, California Institute of Regenerative Medicine

Dr. Csete provided an overview of the science, explaining the advantages of embryonic stem cells over adult stem cells. She described how stem cells are derived and the promise of therapeutic cloning seen in animal studies.

Recent research suggests that iPS are equivalent to embryonic stem cells, which has spurred a flood of research on human iPS. Ideally, iPS could be reprogrammed to the embryonic stem cell state. Virtually any cell can be reprogrammed, said Dr. Csete, but progenitor and stem cells are easier to reprogram; therefore, cord blood may become more popular as a source of stem cells. She described some of the scientific challenges researchers face and their efforts to address them.

While iPS hold promise as an alternative to hematopoietic stem cells, Dr. Csete cautioned that concerns about immune response and differentiation have yet to be addressed fully. However, iPS have immediate utility for developing disease models for laboratory research, and Dr. Csete described numerous examples of research underway.

Cord blood is being used more often for hematologic indications, and bone marrow is being used more often for non-hematologic indications, Dr. Csete noted. She anticipated an increased demand for cord blood as research progresses.

Finally, Dr. Csete summarized the major themes in stem cell research:

- iPS are increasingly easy to generate and manipulate, but research is costly and the business model difficult.
- True regenerative therapies using hematopoietic stem cells are not limited to hematopoietic diseases.
- An explosion in research on nonregenerative therapies is likely.
- Head-to-head comparisons of stem cell sources that generate hematopoietic stems cells are needed, but funding is unlikely.
- It is possible that millions of cord blood samples could be stored around the world.

Discussion
In response to a question from Dr. Parkman, Dr. Csete said she hoped to study more markers of cell senescence. Dr. Broxmeyer said iPS research is moving fast and could potentially be a boon for private banks that focus on autologous use. If iPS live up to their promise in humans, he added, every stored unit of cord blood potentially could be used for clinical purposes. Dr. Csete added that researchers are looking into a number of possible sources of iPS, including hair and skin.

NMDP Infrastructure Summit
Jeffrey Chell, MD, Chief Executive Officer, NMDP

NMDP has set a goal of facilitating 10,000 transplants per year by 2015, and the goal has proven to be an effective tool for communicating to stakeholders about the need to prepare for a substantial increase in transplants. It has also helped staff identify and focus on priorities and imparts a sense of urgency to the NMDP's mission. Since establishing the goal, NMDP has:

- significantly increased the number and diversity of cord blood units searchable through the NMDP, with the National Cord Blood Inventory contributing heavily in recent years,
- significantly increased adult donor recruitment, increased international partnerships,
- improved the matching algorithm,
- increased patient advocacy and assistance, and
- initiated a project to re-engineer the donor management process.

Dr. Chell said the major obstacles to meeting the 2015 goal are the lack of suitable donors, barriers not related to HLA matching (e.g., lack of adequate insurance coverage, lack of timely referral, and negative attitudes about transplantation, as described by Dr. Champlin), and

mortality and morbidity rates. Research is essential to improving access, survival, and quality of life, he added.

A number of barriers can be categorized as health care system issues, specifically money (e.g., financing, investment in capacity), staff (trained physicians, nurses, and other health care providers), and attitudes about the effectiveness and cost-effectiveness of transplantation. NMDP, in partnership with the American Society of Blood and Marrow Transplantation (ASBMT), is proposing a summit on hematopoietic stem cells that would bring together key stakeholders to delve into the systemic barriers and propose solutions. Dr. Chell said the summit might address issues such as how to encourage students to choose a career in transplantation or what factors influence an organization's decision to invest in transplantation capacity and resources.

The Oncology Nursing Society has agreed to serve on the core committee for the summit, said Dr. Chell. The core committee develops a case statement and organizes topic-specific working groups that meet in advance of the summit and present their findings at the summit for discussion. Following the summit, participants review a white paper summarizing the event that eventually is translated into recommendations or priorities for NMDP. Dr. Chell asked the Council for advice on who should be invited to participate.

Discussion
Dr. Clive Callender suggested involving representatives of the National Medical Association and the Student National Medical Association for insight on addressing the disparity in the number of transplantations among African Americans. Dr. Parkman suggested contacting the National Association of Children's Hospitals and Related Institutions, which represents all of the major children's hospitals.

Radiation Injury Treatment Network (RITN)
Nelson J. Chao, MD, MBA, Chief, Division of Cellular Therapy/Bone Marrow Transplantation, Duke University

Dr. Chao presented an overview of radiation syndrome, which can occur with transplantation or as a result of accidental exposure to industrial products containing radiation. Following the end of the Cold War and until the terrorist attacks of September 11, 2001, concern about mass radiation exposure dissipated, and much of the infrastructure for addressing such a threat was dismantled. Dr. Chao described the types of radiation, mechanisms of contamination, and the pathology and symptoms of acute radiation syndrome.

In patients being treated for cancer, Dr. Chao said, determining the amount of radiation exposure would be straightforward. However, biodosimetry tools are needed to assess victims of an attack. Current tools would not provide rapid results, so health care providers would rely on clinical symptoms to determine exposure. (To learn more about biodosimetry tools, Dr. Chao recommended the Armed Forces Radiobiology Research Institute's downloadable software that facilitates biodosimetric assessment [http://www.afrri.usuhs.mil/outreach/biodostools.htm] and the National Library of Medicine's website Radiation Event Medical Management

[http://www.remm.nlm.gov], which includes web-based software and other resources for providers.)

Following September 11, 2001, RITN was formed by NMDP and the American Society for Blood and Marrow Transplantation (ASBMT). According to its charter, "RITN provides comprehensive evaluation and treatment for victims of radiation exposure or other marrow toxic injuries. RITN develops treatment guidelines, educates health care professionals, works to expand the network, and coordinates situation response." Centers performing blood stem cell transplants have extensive experience caring for patients with bone marrow damage caused by the patient's disease or by pre-transplant radiation or chemotherapy.

From an operational standpoint, RITN provides facilities and staff to care for victims in the aftermath of a radiologic event resulting in mass casualties. It also educates hematologists, oncologists, and stem cell transplant practitioners about their potential roles in responding to such an incident. In 2006, RITN established its first formal agreements with 13 transplant centers; in 2007, RITN expanded to include 52 donor centers and cord blood banks.

RITN focuses on preparation for possible events such as radiologic or chemical attacks by educating and training potential responders, encouraging development of standard operating procedures and standard admitting and treatment protocols, supporting standardized data collection, and coordinating with international entities. Dr. Chao said that RITN is governed by the Office of the Assistant Secretary for Preparedness and Response, but he emphasized that RITN participants are not first responders. In most scenarios, RITN would provide support to tertiary care facilities to which victims of an event are transferred for ongoing treatment following stabilization.

Dr. Chao concluded by stating some of the challenges RITN faces, including funding for treating patients, lack of capacity to respond to a large event, and the need for more international coordination.

Discussion

Dr. Hartzman pointed out that some planning scenarios postulate a large number of casualties, but the number of people needing treatment may not be as overwhelming as feared. Council members discussed the role of stem cell therapy in treating radiation victims. Dennis Confer, MD, Chief Medical Officer, NMDP, said it may be necessary to prepare for a lot of transplants, although ultimately only a small number might be needed. Dr. Chao noted that some of those exposed to radiation recover without transplantation. In response, Dr. Broxmeyer suggested that it may be appropriate for research to focus on agents that can accelerate recovery in the absence of transplantation. Dr. Chao said Project Bioshield, the National Institute of Allergy and Infectious Diseases, and the Biomedical Advanced Research and Development Authority are all potential Federal sources of research funding in this field.

Dr. Hartzman said that in addition to the possibility of a mass casualty event, accidental exposure is more common than many people realize. He hoped RITN training would prove useful to those who treat small or rare events.

Dr. Chao added that RITN provides a small stipend to facilities that participate. To earn the stipend, the centers must demonstrate active engagement each year—for example, by training staff, presenting grand rounds, or taking part in exercises.

Trends in Post-Transplant Survival
Dennis Confer, MD, Chief Medical Officer, NMDP

Dr. Confer presented NMDP data from a recent analysis prepared for the NMDP Donor and Patient Safety Monitoring Committee. The report covered more than 29,000 transplants performed since 1987. The overall proportion of transplants by type (about 55% bone marrow, 40% peripheral blood stem cells, and about 5% umbilical cord blood) is quite different from the current distribution of transplants being facilitated through NMDP(60% from peripheral blood stem cells, 20% from bone marrow and 20% from cord blood).

Dr. Confer offered data demonstrating not only the increasing use of transplants to treat older adults but also consistent improvements in post-transplant survival rates within the past decade among all cohorts. He summarized the methodology used to analyze the data, which come from outcomes reported by centers. For all transplant recipients (since 1988), 1-year survival rates have been improving particularly since 2002. The data also show decreases in transplant-related mortality since 2002 for many populations, with especially notable decreases among pediatric patients for several indications. Survival rates for those receiving transplants from an unrelated donor are approaching those of sibling donor transplants.

In various transplant populations, Dr. Confer pointed to 3-year survival rates that changed little from 1987 to 2002 but improved noticeably beginning in 2002. (In some of the groups described, survival rates began improving between 1999 and 2002.)

The number of racial/ethnic minority patients receiving transplants is growing, which attests to the value of cord blood, said Dr. Confer, because it does not require as precise matching as other sources. Data on umbilical cord blood transplantation are insufficient to assess survival over time; but when recipients are categorized by the precision of the match and the cell dose, those with better matches and high doses had better survival rates than those with poor matches and low doses

Dr. Confer said the reasons for the improvements are not entirely clear. The quality and timeliness of matching has been improving since the late 1990s, he noted, and the number of mismatched transplantations has declined from about 70% in 1988 to less than 5% in 2008. Dramatic changes in the quality of care for transplant patients, including advances in treating infections and complications, also play a role. Outcomes involving unrelated donors are improving, which may fuel growth in unrelated donor transplantations. Dr. Confer asked Council members for their opinions on factors affecting the improved outcomes overall.

Discussion
Ms. Holiman suggested that the increased use of prophylaxis before transplantation may play a role. Susan Stewart recommended that NMDP evaluate the incidence and severity of graft-versus-host disease (GVHD) over the past decade. Dr. Confer noted that NMDP is working on

an algorithm that would help standardize outcomes reporting to distinguish, for example, GVHD from infection. Dr. Anasetti said his institution has looked at the effects of better HLA typing, but the level of improvement in survival rates demonstrated by the NMDP data cannot be explained by better matching alone. Two other factors that have become more prominent in the past decade are less intensive conditioning therapy and better antifungal treatments.

Discussion
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Dr. Anasetti said his institution has looked at the effects of better HLA typing, but the level of improvement in survival rates demonstrated by the NMDP data cannot be explained by better matching alone. Two other factors that have become more prominent in the past decade are less intensive conditioning therapy and better antifungal treatments.

Public Comment
There were no public comments.

Conclusion and Adjournment
Karl Blume, MD, ACBSCT Chair

Dr. Blume thanked the HRSA staff and the Council members for working so hard to move forward on important issues. He congratulated the Council on coming to consensus on recommendations that were submitted to the Secretary. Dr. Blume adjourned the meeting at approximately 3:40 p.m.

ATTACHMENTS
- Recommendations to the Secretary on informed consent

Advisory Council on Blood Stem Cell Transplantation (ACBSCT)

Recommendation 6

ACBSCT recommends to the Secretary that the following informed consent principles and standards be implemented for public cord blood banking.

Background

Informed consent for clinical care, research, donation of tissue and organs is based on the ethical principle of personal autonomy – a person has the right to make decisions about what shall be done to and with his or her body. Although informed consent for public cord blood banking is akin to donation of organs, it is complicated by the fact that the birth mother, the biological mother, the newborn child and the intended parents can all be affected by the choice. Cognizant of these relationships, the ACBSCT sets forth the following recommendations. ACBSCT intends these recommendations to allow individual banks the flexibility to adopt their own procedures consistent with the recommendations. These recommendations should be interpreted in light of State and Federal laws and regulations, as well as Institutional Review Board requirements.

- ACBSCT recommends one basic principle to guide the decision about who should consent for cord blood banking: the birth mother and, if applicable, one legal parent or guardian of the child should consent for donation.

  Rationale: The birth mother should consent because she needs to undergo testing prior to donation. The legal guardian needs to consent because he or she is responsible for providing the bank with information about the child and will be responsible for the child. For example, when the birth mother is not the intended parent, whether she is the biological mother or not, then both the birth mother, who will have to be tested for infectious disease, and one 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.

- Information should be provided to the person for whom it is likely to have medical impact.

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

- 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 pre-registered, the information about cord blood banking can be given on presentation to the hospital for delivery. Each bank should have a policy about how consent is offered, which addresses the following issues: the stage of labor and stress of the mother, the amount of pre-counseling that has taken place and the amount of time available for an adequate

discussion of the consent. The banks should also consider offering a "pre-consent" for collection only, with the consent for banking completed after delivery.

- ACBSCT encourages banks to develop procedures so that all eligible mothers are consistently approached with particular attention to approaching mothers from underrepresented demographic categories. (ACBSCT does not recommend that hospital staff be required to offer banking to all birth mothers.)

- Because public banking is based on altruism, ACBSCT suggests that donors not be allowed to direct the unit's use, so that it may be used most optimally for either clinical use or laboratory research.

  The consent should inform the donors that:

  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 that the normal process of searching the public registry will be available to them. If, however, a child from a donating family needs a unit, the ACBSCT encourages banks to offer the unit to him/her, if available. 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 use or laboratory research.

  c) Any human subjects research using the cord blood will be reviewed by an ethics board, called an Institutional Review Board, so that only ethical 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.

- Alternatives to public banking, namely, private banking, research or discard should be included in the informed consent document.

- 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 also should be in place for relevant health information to be offered to the donor-child's guardian if the recipient develops a serious disease that may have been transmitted by the cord blood.