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

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Bethesda, MD

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Welcome and Introductions

Edgar Milford, Jr., MD, Chair of the Advisory Council on Blood Stem Cell Transplantation (ACBSCT), called the meeting to order at 8:30 a.m. Members of the Council introduced themselves.

Cord Blood Bank Collections Work Group Recommendations

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. The Work Group is awaiting more information from a pilot project underway on remote collection (involving the National Marrow Donor Program [NMDP] and three cord blood banks) that will inform efforts to expand collection. The Work Group has discussed practical means for optimizing collections but feels it has little additional to offer in this area. Devices exist that allow collection without cannulation, but they are not widely available. Research on perfusion of placentas to augment recovery of hematopoietic cells from cord blood is promising, but the approach may not be scalable for large cord blood banks.

Educating Potential Donors: The Pregnancy Passport

To provide more education to potential maternal donors, the Work Group has drafted language for inclusion in an existing Federally funded document, the *Pregnancy Passport*. The Work Group is seeking more details about how the *Pregnancy Passport* is distributed and the costs and procedures for revising it to include the proposed language on cord blood donation. The Work Group has asked the Centers for Disease Control and Prevention (CDC) and the Council of State and Territorial Epidemiologists to publish similar language in educational materials in States with cord blood banking services. Ms. Regan asked for volunteers from the Council to serve as contacts for these organizations.

Ms. Regan presented the draft language, noting that it appeals to the reader's spirit of philanthropy and gives basic information as concisely as possible, in keeping with the tone and length of the *Pregnancy Passport*. In response to a question about readability, Ms. Regan noted the language was borrowed from the websites of both the Health Resources and Services Administration (HRSA) and NMDP, both of which follow guidelines regarding appropriate reading levels?

Discussion

The group offered a number of suggestions for revising the language:

- ☐ Describe cord blood donation as an opportunity to give back in more dynamic terms, and place the language up front.
- ☐ Add a descriptive title.

Increasing and Improving Cord Blood Collections
Ms. Regan presented draft recommendations aimed at increasing awareness and education about cord blood donation and collection and improving mechanisms that support cord blood donation and collection. The recommendations focus on seven areas:

- ☐ Increasing awareness, particularly of public banking services
- ☐ Increasing parent education
- ☐ Improving medical professional education, both through formal curricula and collections training
- ☐ Addressing appropriate compensation for medical professionals
- ☐ Encouraging passage of State legislation that promotes dissemination of accurate, unbiased information
- ☐ Encouraging FDA approaches to cord blood bank licensure that allows for innovation and use of alternative collection methods
- ☐ Supporting best practice guidelines and cost-effective practices

Regarding the recommendations on legislation, Ms. Regan said 18 States have already passed legislation but, in some cases, that legislation is heavily influenced by lobbyists for private cord blood banks. The recommendation seeks to ensure that information provided about cord blood banking is accurate, unbiased, and firmly based in scientific evidence.

Regarding industry standards, Ms. Regan noted that a Federally sponsored workshop on cord blood bank licensing resulted in formation of 10 work groups addressing the Food and Drug Administration's (FDA's) licensing requirements that go into effect October 2011. One suggestion from the workshop was to develop templates that all cord blood banks could use to submit their licensing applications, so that FDA could focus on the content of the applications rather than format and clerical issues. Another suggestion was to look at cord blood thawing procedures, because every bank recommends different methods to transplant centers.

Ms. Regan asked the Council to consider what role it should play in influencing residency training to improve medical professional education and in crafting model legislation for States to consider.

Discussion
Council members suggested the following changes to the draft:

- ☐ Revise the term "appropriate geographic regions" to specify regions where public cord blood banking is available.
- ☐ Revise the recommendation on legislation to streamline legislative proposals, so that individual State laws do not conflict with one another.
- ☐ Consider replacing the phrase "industry standards" with terminology that more accurately reflects the intent to develop best practice guidelines.

Council members suggested targeting professional pediatric and obstetric medical societies with education about cord blood banking and formally requesting that the Accreditation Council for Graduate Medical Education's Residency Review Committee include cord blood collection as part of residency training and board certification for obstetricians. In addition, HRSA should consider new media beyond informational websites to disseminate materials to younger audiences, such as YouTube and Facebook.[1] In response to a question, Ms. Regan noted that the National Cord Blood Inventory (NCBI), funded by HRSA, targets underrepresented groups.

The recommendation about legislation could be communicated to the California Human Stem Cell Research Advisory Committee and other similar State advisory boards. There was some interest in recommending national legislation to facilitate informed consent and research, but it was noted that States have their own standards for consent and collection. Lack of funding was identified as the major obstacle to implementing legislation that improves public cord blood banking efforts; it was suggested that Federal legislation could address funding issues. In some States, private banks are aggressively pursuing legislation that primarily benefits the private banks. It was suggested that public banks be just as aggressive in their education and outreach campaigns as private banks.

Both recommendations of the Cord Blood Collection Work Group were tabled for revision and further consideration later in the day.

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

Dr. Champlin provided some background on two draft recommendations offered by the Work Group. The group is working with NMDP on more general issues around access to health care insurance.

Gaining Consensus Around Indications for Stem Cell Transplantation
Dr. Champlin explained that each health care payer has its own list of covered diagnoses and conditions. More consensus around when stem cell transplantation should be covered would improve patient access. In addition, it would take the burden off of individual payers to evaluate new stem cell sources as they become available to determine whether coverage is warranted.

Twenty years ago, California created a mechanism to gain consensus around transplantation indications for its MediCal (i.e., Medicaid) beneficiaries. A group of experts reviews the indications for each diagnosis, the type of transplantation appropriate for the indication, patient

[1] HRSA has YouTube and Facebook pages currently in place http://www.youtube.com/watch?v=roruyg-1gYU. The official Facebook Page about HRSA is at www.**facebook**.com/profile.php?id=199893476843 which offers the option to join **Facebook** to start connecting with Health Resources and Services Administration.
Several HRSA offices are using these tools. DOT is also pursuing using those venues in the near future.

selection considerations, and the strength of the evidence. The consensus of the group is summarized in a simple tabular format and is frequently updated. The Access to Transplantation Work Group believes an expert panel working at the national level could develop such a consensus document for Medicare and Medicaid that could also be used by third-party insurers.

Discussion
Dr. Champlin clarified that the proposed expert panel would meet periodically to review evidence and update the consensus list of covered indications. He added that insurance companies have been responsive to the California expert panel and generally appreciate the authoritative recommendations. Jeffrey Schriber, MD, pointed out that Arizona is poised to stop covering stem cell transplantation involving unrelated donors for Medicaid patients on the basis of recommendations from private consultants (and despite evidence provided by clinicians and medical societies). An expert panel could prevent individual States from making such inappropriate coverage decisions, Dr. Champlin noted. Jeffrey Chell of NMDP supported the idea and hoped the Council would spell out the next steps to ensure that the expert panel's recommendations would be implemented by payers.

Discussion ensued about how the expert panel would be established, and it was agreed that the Council would convene a committee to plan the expert panel. The planning committee would invite additional experts as needed to take part and publish its findings. Recommendations would be sent to the Council, which, in turn, would make recommendations to the HHS Secretary. The HHS Secretary can influence Medicare and Medicaid coverage decisions, and many third-party insurers follow those same coverage guidelines. The expert panel would establish its own criteria and procedures to guide its decision-making process. Because recent health care reform legislation will affect the entire landscape of health care, the panel would take into account changes in health care coverage over time. It was suggested the panel consider the long-term economic impact of stem cell transplantation on patients' quality of life and the long-term cost savings of such treatment; therefore, expertise in the economic and business aspects of health care coverage would be needed. The group would have broad representation, including patient advocates. Patricia Stroup, representing Remy Aronoff, the Executive Secretary of ACBSCT, said that HRSA could provide funding and support for such a group.

Some discussion surrounded when stem cell transplantation should be covered for investigational or experimental uses. Dr. Champlin explained that the Access to Transplantation Work Group has a separate recommendation addressing coverage for patients in clinical trials. Combining the list of recommended covered indications with possible investigational uses could dilute the authoritativeness of the list and thus limit patients' access to transplantation, said Dr. Champlin.

Covering Patient Participation in Clinical Trials of Stem Cell Transplantation
The Work Group agreed that patients' costs for participating in clinical trials should be covered by insurers. Dr. Champlin said that although President Clinton mandated that Medicare cover the costs of care for patients involved in clinical trials, implementation of the mandate has been ineffective. Recent health care reform legislation would cover such costs, but not until 2015. Therefore, the Work Group drafted a recommendation asking the Secretary to mandate such coverage immediately for Medicare and Medicaid patients and suggesting that other insurers do so as well.

Discussion
The Council members suggested the following specific changes:

- ☐ Specify the types of clinical trials that should be covered, using the language from the original mandate by President Clinton.
- ☐ Revise the language to recognize that the Secretary can encourage private insurers to cover clinical trials but cannot require them to do so.

Dr. Champlin noted that in some cases private insurers will pay for treatment but will not cover the same treatment if the patient is enrolled in a clinical trial and the clinician collects data on the treatment. Frederick Applebaum, MD, said an informal study at his organization found that this scenario applied to 11% of its patients. James Gajewski, MD, representing the American Society for Blood and Marrow Transplantation, said the Clinton mandate does not cover clinical trials that study the efficacy of a procedure, which poses a problem. Dr. Champlin noted that the wording of such a recommendation can be tricky, but the Work Group would like to see patient costs covered for investigations involving hematopoietic transplantation that use FDA-approved drugs and biologics.

Both recommendations of the Access to Transplantation Work Group were tabled for revision and further consideration later in the day.

FDA Final Guidance for Cord Blood Licensure
Ellen Lazarus, MD, Medical Officer, Division of Human Tissues, Office of Cellular, Tissue, and Gene Therapies, Center for Biologics Evaluation & Research, FDA

Dr. Lazarus provided an overview of guidance published by FDA on cord blood use. She explained that cord blood for autologous use and use in first- or second-degree relatives is regulated under one section of the Public Health Service Act with its own set of requirements, while cord blood from unrelated donors is a biologic and drug product that falls under three different sets of regulations. Dr. Lazarus described the history of FDA guidance on cord blood products that culminated in the final guidance on licensing for industry published in October 2009 and the companion draft guidance on investigational new drug (IND) applications. The requirements for biologic license applications (BLAs) and IND applications are being phased in; the phase-in period ends in October 2011. Dr. Lazarus encouraged sponsors to submit applications as soon as possible to allow time for FDA to complete its application review by the October 2011 deadline. She emphasized that the guidance does not apply to unrelated, allogeneic hematopoietic progenitor cells collected by apheresis.

The final guidance on licensure applies to manufacturers (usually cord blood banks). The draft guidance on INDs was published to address public and advisory committee calls to maintain access to unlicensed products. The licensure guidance includes a table summarizing the data used by FDA to determine criteria so that applicants can demonstrate that they meet the criteria using the same testing approaches and procedures. Dr. Lazarus noted that licensing may apply to cord blood already in inventory at the time of application if the manufacturer demonstrates that the same good manufacturing practices (GMPs) were used in producing the supply in inventory as it

would use for future licensed products. Dr. Lazarus described changes between the draft and final guidance on licensure, noting that the scope was revised to apply more broadly to minimally manipulated cord blood products for specified indications and detail was added on chemistry, manufacturing, and control criteria.

Dr. Lazarus noted that IND approval will be required for clinical use of unlicensed products. The scope of the IND guidance is similar to that of the licensing guidance and addresses not only access but situations in which cord blood is produced outside of the United States or in establishments that do not meet licensing criteria. The guidance describes the minimal information needed for IND application.

Finally, Dr. Lazarus encouraged cord blood banks and others to seek advice from FDA before submitting their applications. She provided contact information for those who wish to meet with FDA staff or get clarification about the guidance and regulations.

Discussion

Richard Durbin worried that the expense of obtaining an FDA license would drive up the costs of cord blood banking. He hoped FDA would take a more practical approach that treats cord blood in the same manner as other blood products and not a strict approach that treats it as a drug. Kathleen Sazama of LifeSouth Community Blood Centers asked what would happen to preexisting INDs in October 2011; Dr. Lazarus said existing INDs would not necessarily be terminated but banks and blood centers should discuss their individual circumstances with FDA. Dr. Lazarus said it may be necessary to make adjustments if an existing IND is no longer covered.

Dennis Confer, MD, of NMDP said his organization is exploring the possibility of a broad IND approval that covers an entire bank or registry, for example, and of covering cord blood units that cannot be licensed within the United States.

Dr. Lazarus explained that the indications listed in the final guidance reflect the data provided to FDA and thus cover some conditions broadly and others more narrowly. She noted that the public docket remains open and encouraged continued data submission. Dr. Lazarus conceded that it is possible that one center could receive IND approval for a specific indication because that center provided data to support the IND use while others did not. Joanne Kurtzberg, MD, called for some mechanism for expedited review—either by FDA or through the Council—to ensure coverage of additional indications once adequate data are submitted. Dr. Kurtzberg noted that some cord blood can be used off label, but she is concerned that fewer transplantations will be performed if centers are required to obtain IND approval or licensure. Dr. Lazarus said communication with FDA can elucidate which situations require IND approval.

Dr. Champlin said FDA should accept the premise that the source of stem cells does not affect the success of transplantation, and banks should not be required to document the effectiveness of each source. Dr. Lazarus emphasized that the FDA licensure of biologics requires specific data on safety and efficacy. Dr. Champlin countered that the costs could be prohibitive and asked whether FDA had conducted an economic analysis of its BLA standards. Dr. Lazarus said no economic analysis was performed, but data were provided by stakeholders, and FDA believes

most of its criteria reflect procedures and standards currently in use. She added that the FDA sets the GMP criteria but allows manufacturers flexibility in determining how to meet the criteria.

Stephen Sprague asked Dr. Lazarus whether FDA has everything in place to avoid delays in licensing and approval that would affect patient access. Dr. Lazarus replied that FDA is focused on access to safe and effective products, and the guidance documents are intended to address the requirements and systems needed. She added that direct communication with FDA will help manufacturers and centers determine what constitutes compliance with GMP. Mutsuko Holliman said she appreciated FDA's goal of ensuring access to safe and effective products but remains "scared" about potential delays or barriers to access. Dr. Milford praised FDA for making real progress with its guidance.

Models Predicting the Impact of Growth of the Cord Blood Inventory and the Adult Donor Registry

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

Mr. Baitty said HRSA contracts for the program have required modeling for over 10 years to better understand the degree to which patients of different racial and ethnic background have suitable donors or cord blood units available through the program, and to analyze and improve recruitment policy. He asked the Council to consider whether the findings of the current models presented by NMDP reflect the experience of individual members. He also asked the Council for suggestions on how to further validate the results and refinements to consider for future modeling.

Model Results—Dennis Confer, MD, Chief Medical Officer, NMDP

Dr. Confer said NMDP's modeling addresses the likelihood of locating a human leukocyte antigen (HLA)-matched adult donor or suitable cord blood unit for transplantation now and in the future. The likelihood of a match depends on various patient factors, medical standards and considerations, and the composition of the registry. Analysis of data from the Center for International Blood and Marrow Transplant Research (CIBMTR) indicates that the degree of matching affects the long-term survival of transplant recipients in the early stages of disease, but the effect on survival decreases as the stage of disease advances. Thus, in some cases, proceeding with a mismatched donor or cord blood unit may be better than waiting for a better match and allowing the disease to progress, said Dr. Confer.

Dr. Confer described the process for creating computational models from a registry. He noted that, compared with previous models, current models have better data on HLA haplotypes, more nuanced categories for race and ethnicity, conform more closely to current clinical matching criteria, more thorough consideration of cord blood, and improved incorporation of information about donor availability and cord blood cell doses. Dr. Confer described the methodology, characteristics, and findings of the NMDP report, *Modeling Effective Patient-Donor Matching for Hematopoietic Transplantation in United States Populations*. The key points are as follows:

- ☐ Caucasians of European descent have the highest match rates for both donors and cord

blood units because there are more of them in the registry than any other race or ethnicity.

- ☐ For groups other than European Caucasians, the best donor or cord blood unit available is often a slight mismatch.
- ☐ Across all races and ethnicities, the likelihood of a cord blood match is higher for children than adults because children do not need very large cord blood units, and therefore the pool is larger.
- ☐ Recruiting more donors increases the likelihood of an ideal match by about 1% per year.
- ☐ Increasing the availability of ideal matches would have a stronger effect on minority populations than it would for European Caucasians (who already have high ideal match rates).
- ☐ Validation models—one using hypothetical patients and the current registry and one using real-world experience of a large transplant center—suggest that NMDP's models are reasonably accurate.

Dr. Confer summed up the findings by pointing out that 1) many minority patients do not have access to an ideal match, 2) increasing adult donor recruitment yields modest improvements in the overall likelihood of matching, 3) increasing the cord blood inventory has a larger impact on match rates but is costly and 4) for many patients, the likelihood of a match is suboptimal. Improving the likelihood of an ideal match could be achieved by:

- ☐ recruiting more adult donors,
- ☐ increasing cord blood donation,
- ☐ increasing adult donor retention and availability, or
- ☐ expanding clinical research to improve results with less-than-ideal matches.

In addition to continued validation of the models and analysis of sensitivity, NMDP is pursuing collaborations to develop cost-effectiveness models. In its next annual report, NMDP will model match rates for multiracial recipients, simulate the effects of depleting the supply of cord blood, and consider what it would take to achieve a 90% likelihood of an ideal match for patients of every race/ethnicity.

Discussion

Dr. Confer said future models may categorize cord blood units into deciles so that they better illustrate dose availability by the weight of the potential recipient. Retention and availability of adult donors is a significant problem that NMDP is attempting to address. Dr. Confer said NMDP is piloting a method for purging unavailable donors from the registry before a transplant center makes a request, which appears to be effective.

Recent studies by CIBMTR suggest that patients who receive transplantation with ideally matched cord blood units have better survival rates than those who receive transplantation from an ideally matched donor, said Dr. Confer, and Ruben Rucoba, MD, said such findings suggest that cord blood should be an area of focus. Dr. Rucoba added that future studies should evaluate the effect of the degree of match on quality of life as well as on survival, and Dr. Confer agreed.

Dr. Applebaum pointed out that recent evidence shows a 30–40%-difference in survival rates among those who received transplantation from an ideally matched donor because of variations in patient risk factors. He said current recruitment goals are based on current science about the degree of match needed for success, which is evolving. He called for more investment into research that could improve techniques and results, which in turn would allow more effective, efficient use of the available products. Dr. Confer agreed, adding that the models can inform decisions about prioritizing the focus of recruitment. One option for improving the pool for underrepresented groups, Dr. Confer said, may be to target the types of cord blood units that provide the most potential matches.

Bertram Lubin, MD, pointed out that newborn genetic screening programs could provide data on multiracial individuals that would indicate what HLA types will be prominent in the near future. Dr. Champlin said obtaining more cord blood units is clearly more cost-effective than recruiting more adult donors and suggested that this should be the priority for Federal funding. Dr. Milford said funding comes from a complex mix of Federal and other sources, all with their own policy goals and target populations. It was noted that cost-effectiveness analysis is critical to prioritizing the recruitment goals.

Frances Verter, Ph.D., of the Parent's Guide to Cord Blood Foundation, asked why the models did not include a category for Jews, given that research has shown that Jews differ genetically from other European Caucasians. Dr. Confer said the registry only asks about race/ethnicity, not religion; however, early analysis using information from registries in Israel suggests that distinguishing Jewish HLA types accounts for a lot of variation.

Review of Revised Work Group Recommendations

Ms. Regan and Dr. Champlin presented revised versions of the recommendations of their respective Work Groups to the Council for consideration.

Access to Transplantation Work Group

Discussion

Regarding coverage of patient participation in clinical trials, Council members suggested adding to the rationale that patients who participate in clinical trials have better outcomes than those who don't. Some minor editorial clarifications were suggested. No further changes were suggested for the recommendation to convene an expert panel on indications.

> **Recommendation**
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> The Council unanimously approved the recommendations of the Access to Transplantation Work Group (Attachments 1, 2). The recommendations will be forwarded to the Secretary for consideration.

Cord Blood Collections Work Group

Discussion

Tom Carpenter of Wexler & Walker said the recommendation about legislation unfairly demonizes States that have developed initiatives on education and awareness. He added that no evidence suggests that existing legislation or initiatives are biased toward private blood banks. Ms. Regan said the recommendation calls for harmonization and does not reflect negatively on private blood banks. However, she added, in States that do have legislation but do not have

public banking options, the laws necessarily promote one option over the other. Dr. Milford suggested the Council avoid language that needlessly castigates private banks. Mr. Chell suggested the rationale explain that the information provided varies across States, which supports the need for harmonization.

Recommendation
The Council unanimously approved the recommendations of the Cord Blood Bank Collections Work Group (Attachments 3, 4). The recommendations will be forwarded to the Secretary for consideration.

Realizing the Potential of Cord Blood
Robert Baitty, Director, Blood Stem Cell Transplantation Programs, Division of Transplantation, HRSA

Although advancing the use of cord blood has been a major focus of the Council, as evidenced by the efforts of its Work Groups and its deliberations, more work is needed to realize more fully the potential of cord blood in transplantation, said Mr. Baitty. Specifically, areas in need of further development are:

- ☐ strategic clinical research, e.g., permissible HLA mismatches, including the role of non-inherited maternal antigens, and the role of race/ethnicity in matching;
- ☐ technology development, e.g., ex vivo expansion of cord blood cells, methods to improve cord blood yield at collection, and improved testing methods; and
- ☐ economic issues, e.g., financial models for cord blood banking, managing the cost of increasing cord blood regulation, and opportunities to reduce costs.

HRSA requests that the Council form a new work group to evaluate gaps and opportunities in cord blood research, technology, and economics; recommend actions to improve the therapeutic potential of cord blood; and focus at least initially on the role of cord blood in transplants for hematopoietic reconstitution. Mr. Baitty noted that the proposed scope is broad and merits refinement by the Council or the work group. Gaps and opportunities may change rapidly given the pace of cord blood research. The work group may need to add expertise in certain areas, such as financial issues. Mr. Baitty offered a draft charge for the Council to consider if it agrees to form a new work group.

Discussion
The Council agreed with the need to form such a work group. Mr. Baitty reminded the Council that U.S. Department of Commerce Secretary Gary Locke has expressed strong support for public cord blood banking and could provide technical expertise or funding from the Department of Commerce for technology development. Some Council members felt two groups might be appropriate—one focused on science and technology and the other on business and finance—but others said the issues are so intertwined that experts in both area should work together. Mr. Baitty suggested the new group perform a quick survey of the landscape (e.g., research planned and underway) to determine where to focus its efforts.

Action Item

The Council will establish a new work group to evaluate research, technology, and economics of cord blood. Dr. Milford appointed Liana Harvath, PhD, as chair of the new group. Those interested in joining the new group should contact Dr. Harvath. Before the Fall 2010 meeting of the Council, the new group will convene by phone to draft its charge and to assess what relevant efforts are already underway, and it will present the draft charge and assessment to the Council. Dr. Harvath invited transplant physicians who deal with reimbursement issues to take part in the new group. Dr. Milford invited all the meeting participants to volunteer their expertise.

Thawing and Infusion of Cord Blood for Transplantation

Joanne Kurtzberg, MD, ACBSCT Member

Dr. Kurtzberg noted that the Council and others have focused on procedures at the cord blood banks but not procedures at the transplant centers. Methods of thawing, washing, and infusing cord blood vary substantially among centers, and no randomized or controlled trials or standards address which methods are best. New staff at transplant centers are not formally trained in these procedures. Banks provide information on thawing procedures, but transplant centers implement those procedures inconsistently. Dr. Kurtzberg called for improving thawing and related processes and expanding safety monitoring.

Dr. Kurtzberg described all the factors related to thawing and infusion that vary among centers, from the type of product used and the packaging of the product to the lack of uniform numbering and identification systems. Centers do report adverse events, but more could be done to improve the completeness of tracking and support timely investigation of cord blood infusion problems. Dr. Kurtzberg summarized the procedures her organization uses, from the receipt and storage of cord blood through thawing, washing, and infusing the cord blood.

A number of factors have converged to make the issue of consistent thawing and infusion practices a concern. Over the past few months, reports have arisen about serious reactions in recipients of double cord blood transplants. Some laboratories have reported problems with cord blood thawing practices. In general, many transplant centers are not adequately prepared for thawing cord blood according to the various cord blood bank instructions. Dr. Kurtzberg suggested the following approaches to improve consistency:

- ☐ Formalize guidelines for single and double cord blood infusion.
- ☐ Reduce the number of different thawing protocols recommended by cord blood banks
- ☐ Require transplant centers to validate their thawing procedures or use the procedure indicated by the bank.
- ☐ Ask accrediting agencies to create additional relevant standards.
- ☐ Improve centralized reporting and review of infusion-related adverse events.
- ☐ Create a training program for cord blood thawing.
- ☐ Require transplant centers to institute practice training in thawing techniques.
- ☐ Consider a randomized trial comparing thawing alone with thawing plus washing.
- ☐ Recommend that transplant centers identify a backup cord blood unit before beginning the transplant.

Finally, Dr. Kurtzberg offered some actions the Council could take:

- ☐ Work with NMDP, CIBMTR, and the Blood and Marrow Transplant Clinical Trials Network to implement preparedness training in thawing.
- ☐ Ask the American Association of Blood Banks (AABB) and the Foundation for the Accreditation of Cellular Therapy (FACT) to enhance inspection standards for cord blood thawing and administration for transplant centers seeking accreditation.
- ☐ Publish the white paper currently in development by NMDP on cord blood thawing and infusion.
- ☐ Create a Cord Blood Thawing Work Group.

Discussion
Dr. Champlin noted that because no standards for training exist, the new work group would have to reach consensus on a specific standard. Dr. Kurtzberg said it might be appropriate to identify a few different methods that are effective. She noted that thawing, diluting, and washing cord blood is conducted in the laboratory, but units may also be thawed at the bedside by a nurse. Ms. Holiman said information and recommendations should be communicated to nurses as well as laboratory staff. Dr. Schriber said transplant centers are probably looking for guidance on best practices. Ms. Regan suggested collaborating with NMDP to avoid duplicating efforts.

Kathy Loper of AABB said her organization and FACT require that instructions for thawing be included by the bank with each unit shipped. If the new work group developed recommendations, Ms. Loper suggested publishing them as additional HRSA requirements for cord blood bank accrediting organizations. Jeffrey McCullough, MD, pointed out that concerns go beyond thawing and washing to include a broad range of practices and potential problems that begin with the delivery of the unit to the transplant center. The Council agreed that the new work group may establish a broad scope of issues as part of its charge.

> **Action Item**
> The Council will establish a new work group to address consistent, safe practices for cord blood handling by transplant centers. Dr. Milford appointed Dr. McCullough as chair of the new group. Those interested in joining the new group should contact Dr. McCullough.

Financial Incentives for Adult Donors
Michael Boo, JD, Strategic Development Officer, NMDP

Mr. Boo noted that international standards and the National Organ Transplant Act prohibit compensating marrow donors. A suit was filed in October 2009 by the Institute of Justice and several other plaintiffs against the Federal government claiming that the prohibition against compensation limits individuals' access to health care and that Congress had no rational basis for treating marrow donors differently than blood donors (who may receive compensation). The case was dismissed in March but an appeal has been submitted and will be heard. Mr. Boo clarified that "compensation," in this case, refers to financial inducement to donate marrow or stem cells;

it is legal and routine to reimburse donors for out-of-pocket costs associated with donating marrow, including travel costs and lost wages.

In the suit, the plaintiffs propose to implement a study to determine whether offering donor compensation increases the likelihood of donation. The study would be undertaken by an organization that has potential grant funding to pay donors at the time of donation. The payment would be no more than $3,000.

Mr. Boo believes the plaintiffs will not prevail in the case for two reasons: 1) Congress had a rational basis and supporting information for distinguishing marrow donation from blood donation. 2) The lack of compensation does not directly interfere with an individual's access to transplantation, although it may affect the specific cell source. The appeal is tentatively scheduled to be heard in January 2011. The NMDP and a coalition of numerous stakeholders in the field who oppose donor compensation will file amicus briefs in the case.

Mr. Boo noted that if the plaintiffs were to win, the plaintiffs would have to establish their own registry of potential donors who have been promised compensation if they do donate. The NMDP is concerned about how a registry offering donor compensation would affect those in existing registries. A number of Council members and meeting participants emphasized that money does not enter into the decision to donate. Mr. Chell said that of the reasons that potential donors do not donate when they are contacted, only a small portion do so because they have changed their minds and are no longer interested. He said donor compensation is an expensive approach to sway a small percentage of people who *might* be motivated by financial inducements. Mark McGinnis said courts rarely overturn laws on the argument that Congress lacked a rational basis for the legislation; however, some members of Congress may be interested in the question of compensation when the law comes up for reauthorization. Dr. Milford proposed and the Council unanimously agreed that donor compensation should not be allowed.

The Council encourages NMDP and its coalition of stakeholder organizations to work together to establish recommendations opposing donor compensation.

Scientific Factors Necessary to Define a Cord Blood Unit as High Quality Work Group
Overview—Joanne Kurtzberg, MD, Work Group Chair

Dr. Kurtzberg described the characteristics used to determine the quality of cord blood and the information obtained from patient and family history about cord blood units. Units are tested at numerous points, from collection through thawing. Assessment indicates that viability of cells in cord blood differs substantially even among units that have been processed in the same way.

Dr. Kurtzberg outlined the methods used to assess viability and noted that the most predictive methods take too long to be clinically useful. Her organization is collaborating with CIBMTR to study cord blood segments at two reference laboratories to identify correlations between the potency of the cord blood and the success or failure of engraftment. The project began officially in April 2010, and results are expected within 2 years. The goal is to test the validity of a so-

called cord blood Apgar score. Dr. Kurtzberg described the study methodology and the rationale supporting the hypothesis that testing can identify units more likely to engraft.

The next steps in the process are to validate the scoring test prospectively and, ultimately, develop a selection method that enhances the likelihood of engraftment on the basis of the potency of the cord blood.

Discussion
It is possible that some cord blood would be rejected because of its low potency, Dr. Kurtzberg said, which would make it necessary to expand the inventory. The proposed test is based on characteristics that most cord blood banks measure, but better tests could optimize the approach, she noted.

Review of Reimbursement Criteria—Robert Baitty, Director, Blood Stem Cell Transplantation Programs, Division of Transplantation, HRSA

Mr. Baitty asked the Council to review the NCBI's reimbursement criteria, which have been in place for several years. He proposed expanding the charge of the Scientific Factors Work Group to review the criteria. HRSA is particularly interested in input from the Council on the following areas:

- ☐ Age of the mother at the time of cord blood donation
- ☐ Minimum acceptable level of HLA typing
- ☐ Cryopreservation and storage criteria, especially minimum cell counts
- ☐ Postprocessing characteristics
- ☐ Infectious disease markers

Discussion
Regarding a cell count threshold, Dr. Kurtzberg said it's difficult to establish a minimum level at which a unit is useful without identifying the individual recipient. However, she believes the Work Group could propose a formula that takes several relevant factors into account. A meeting participant asked that the Council reconsider the maternal age limit, because it reduces the pool of potential donors, especially among minorities.

> **Action Item**
> The Scientific Factors Necessary to Define a Cord Blood Unit as High Quality Work Group will evaluate the NCBI's reimbursement criteria.

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

Dr. Snyder outlined NMDP's plan to evaluate and address workforce and infrastructure challenges to the use of hematopoietic stem cell transplantation. NMDP has applied for grant funding from the Agency for Healthcare Research and Quality to support its effort to bring together key stakeholders, form working groups to identify barriers, facilitate symposia across

the country to discuss potential solutions, host meetings around the country to gather regional input and feedback, and develop recommendations.

Dr. Snyder explained the organizational structure that underlies the proposal and described the primary focus areas of each of the working groups:

- ☐ Physician Workforce: Recruitment and mentoring, shortage, attrition, education, compensation, and quality of life
- ☐ Nursing Workforce: Recruitment (especially among minorities), curriculum, potential specialty certification, training, mentoring, and education for nurses in other clinical areas caring for transplant patients
- ☐ Advanced Practice Professionals: Education (curriculum and training), recruitment (especially among minorities), expanding role, retention, and compensation (Dr. Snyder noted that many hospitals rely on nurse practitioners, advanced practice registered nurses, and physician assistants to staff transplant centers, with physicians called in as needed to address complications.)
- ☐ Facility/Bed Capacity: Current capacity and utilization, future demands, and outpatient transplant procedures
- ☐ Care Delivery Model: Barriers and best practices (especially for minority populations), subspecialties, and various models
- ☐ Financial: Covered indications (in cooperation with ACBSCT), Medicare reimbursement, Medicaid coverage, and search costs (especially for minority populations)

Dr. Snyder said white papers generated by the proceedings of the meetings will be published in various venues. It is hoped that the stakeholder organizations will transform the recommendations into priority initiatives. The steering committee for this effort and the working groups have all met at least once this year. The first symposium is scheduled for September in Chicago.

New Business
Edgar Milford, Jr., MD, Chair

Dr. Schriber asked the Council what could be done to reverse the decision of Arizona legislators not to cover transplants involving unrelated donors under Medicaid. He is concerned that other States may follow suit. Mary Horowitz, MD said that her organization provided Arizona legislators with data that transplants from unrelated donors are as effective as those involving related donors. Claudio Anasetti, MD, noted that no studies exist or are planned that compare unrelated with related donors, but Dr. Horowitz countered that large comparative effectiveness studies indicate the outcomes are similar. Dr. Schriber said that Arizona's decision is irrational because it purports that a transplant from an unrelated donor is no better than other alternatives to a related donor transplant, including no treatment at all.

Dr. Milford noted that Federal policy covers allogeneic stem cell transplantation as an effective method of treating disease. James Bowman of HRSA said the Council could recommend that the Secretary use her influence to ensure that Medicaid beneficiaries in Arizona have access to therapy that is covered by most Federal health care programs and most private payers. Dr.

Schriber proposed the Council recommend that the Centers for Medicare and Medicaid Services (CMS) evaluate the effect of Arizona's policy on access to care for Medicaid beneficiaries in Arizona. Dr. Anasetti pointed out that if CMS demands the most stringent evidence to support the coverage of unrelated donor transplants, the effort to reverse Arizona's decision could backfire and jeopardize coverage for the whole country—as was the case with stem cell transplantation for myeloma, which is still not covered by Medicare.

Action Item
The Council will gather input and consider whether to make a recommendation to the Secretary about Arizona's decision not to cover allogeneic stem cell transplantation involving unrelated donors under its Medicaid program.

Public Comment
There were no public comments.

Conclusion and Adjournment
Edgar Milford, Jr., MD, Chair

Ms. Stroup thanked the Council members for their hard work and invaluable input. She added that a delegation from Japan had attended the meeting as observers, and she wished them well. Dr. Milford adjourned the meeting at approximately 4:20 p.m.

ATTACHMENTS
- Summary of recommendations to the Secretary and Council action items
- List of attendees (by type)
- Full text of Council recommendations to the Secretary with accompanying rationale (Appendices 1–4)

ADVISORY COUNCIL ON BLOOD
STEM CELL TRANSPLANTATION

Summary of Recommendations and Action Items
May 5, 2010

RECOMMENDATIONS

Access to Transplantation: Convening an Expert Panel on Indications for Stem Cell Transplantation

The ACBSCT recommends that the Secretary convene an Expert Panel, including experts regarding hematopoietic transplantation, experts in the candidate diseases, and representatives of the medical insurance industry, public payers and patient advocates to develop a consensus, evidence-based list of diagnoses for which hematopoietic transplantation is an accepted standard of care. The panel should also consider whether there should be different indications for related and unrelated donor transplants, degrees of HLA match and mismatch, and different hematopoietic cell sources (bone marrow, peripheral blood progenitor cell, cord blood transplants). This panel will publish its conclusions and meet from time to time to update this listing. The panel will report to the ACBSCT Council, which will make recommendations to the Secretary. (See Appendix 1 for the full recommendation.)

Access to Transplantation: Covering Patient Participation in Clinical Trials Involving Hematopoietic Transplantation

The ACBSCT recommends that the Secretary mandate that Medicare and Medicaid cover the standard patient care costs for patients who are participating in clinical trials involving the use of hematopoietic transplantation and supported by or conducted under the auspices of NIH or NCI, NCI-designated cancer centers and cooperative groups, the Department of Veterans Affairs, or an FDA IND/IDE. The ACBSCT recommends that the Secretary encourage private insurance carriers to immediately provide coverage for standard patient care costs for patients participating in clinical trials involving hematopoietic transplantation. (See Appendix 2 for the full recommendation.)

Cord Blood Collections: Increasing and Improving Cord Blood Collections

- ☐ The ACBSCT recommends that the Secretary promote education about public donation as another front-line option in regions where cord blood banking is available.
- ☐ The ACBSCT recommends that the Secretary guides expectant parents to the HRSA Program's website for accurate, unbiased information and refers expectant parents to position statements from professional societies which are accessible there. In addition, as state-based educational websites are developed, similar information about public donation and private banking should be posted. Packets of information presenting this information, including the *Pregnancy Passport*, could be provided through HRSA and the C.W. Bill Young Cell Transplantation Program.
- ☐ The ACBSCT recommends that the Secretary encourages medical school and residency programs, particularly obstetrical training, introduce cord blood banking concepts, and provide updates on clinical and research applications of cord blood therapies.

- ☐ The ACBSCT recommends that, if offered, compensation must not incentivize medical professionals to alter safe delivery practices or to include ineligible donors. The ACBSCT further recommends that banks should take all feasible steps to ensure that mothers or their insurance companies are not charged for costs associated with cord blood collection.
- ☐ The ACBSCT recommends that the Secretary encourage the creation of harmonized legislation that asserts accurate and balanced language regarding public donation and private banking.
- ☐ The ACBSCT recommends that FDA consider innovative collection alternatives, particularly for public donation, as the industry pursues licensure of unrelated allogeneic cord blood as a biologic product.
- ☐ The ACBSCT recommends that the Secretary supports the establishment of best practice guidelines for industry, to exploit economies of scale, and encourage efficient, cost effective practices. *(See Appendix 3 for the full recommendation.)*

Cord Blood Collections: *Pregnancy Passport* and Public Health Websites

The ACBSCT recommends that the following language be included in the *Pregnancy Passport* and on public health websites:

> "Besides nourishing your baby during pregnancy, cord blood can save lives. After a baby is born, the umbilical cord and placenta are no longer needed and are usually discarded. However, the blood remaining in the umbilical cord and placenta is rich with blood-forming stem cells. (These are not embryonic stem cells.) By collecting and freezing this blood, the healthy blood-forming cells can be stored and may later be used by a patient who needs them.
>
> "For patients with leukemia, lymphoma, sickle cell disease, or certain inherited metabolic or immune system disorders, a cord blood or bone marrow transplant (also called a BMT) may be their best treatment option. Cord blood can be especially promising for patients of racially or ethnically diverse backgrounds and for patients needing a transplant quickly.
>
> "Learn how umbilical cord blood can help others through public donation, directed donation for an affected family member, or research studies. Talk with your health care provider or visit http://bloodcell.transplant.hrsa.gov or www.bethematch.org for more information. Your decision could help save someone's life."

Financial Incentives for Adult Donors

The Council encourages NMDP and its coalition of stakeholder organizations to work together to establish recommendations supporting its opposition to donor compensation.

ACTION ITEMS

Realizing the Potential of Cord Blood

The Council will establish a new work group to evaluate research, technology, and economics of cord blood. Dr. Milford appointed Liana Harvath, PhD, as chair of the new group. Those interested in joining the new group should contact Dr. Harvath. Before the September 2010

meeting of the Council, the new group will convene to draft its charge and to assess what relevant efforts are already underway, and it will present the draft charge and assessment to the Council. Dr. Harvath hoped that transplant physicians who deal with reimbursement issues would take part in the new group. Dr. Milford invited all the meeting participants to volunteer their expertise.

Thawing and Infusion of Cord Blood for Transplantation
The Council will establish a new work group to address consistent, safe practices for cord blood handling by transplant centers. Dr. Milford appointed Dr. McCullough as chair of the new group. Those interested in joining the new group should contact Dr. McCullough.

Scientific Factors Necessary to Define a Cord Blood Unit as High Quality Work Group
The Scientific Factors Necessary to Define a Cord Blood Unit as High Quality Work Group will evaluate the NCBI's reimbursement criteria.

New Business
The Council will gather input and consider whether to make a recommendation to the Secretary about Arizona's decision not to cover allogeneic stem cell transplantation involving unrelated donors under its Medicaid program.

APPENDIX 1
Advisory Council on Blood Stem Cell Transplantation (ACBSCT)
Recommendation: Convening an Expert Panel
on Indications for Stem Cell Transplantation

ACBSCT recommends to the Secretary that an expert panel be convened to review and determine indications for stem cell transplantation.

Background

Allogeneic hematopoietic transplantation is an effective, potentially curative treatment for a broad range of hematologic, malignant, immunologic and genetic diseases. It is important that patients have access to this treatment modality. Public and private medical insurance providers have independently determined which diagnoses should be covered. There is no authoritative body which determines the accepted indications for hematopoietic transplantation, and there is considerable variability in coverage policies and covered diagnoses. Some payers have different criteria for related and unrelated donor transplants, degrees of HLA matching and different hematopoietic cell sources.

The ACBSCT recommends that an expert panel be convened, including experts regarding hematopoietic transplantation, experts in the candidate diseases, and representatives of the medical insurance industry, public payers and patient advocates, to develop a consensus, evidence-based list of diagnoses for which hematopoietic transplantation is an accepted standard of care. The expert panel should also consider whether there should be different indications for related and unrelated donor transplants, degrees of HLA match and mismatch, and different hematopoietic cell sources (bone marrow, peripheral blood progenitor cell, cord blood transplants). This panel will publish its conclusions and meet from time to time to update this listing. The panel will report to the ACBSCT Council, which will make recommendations to the Secretary.

APPENDIX 2

ACBSCT recommends that the Secretary mandate that Medicare and Medicaid cover patient participation in clinical trials involving hematopoietic transplantation.

Background

Hematopoietic transplantation is a rapidly evolving area where incremental changes in treatment and supportive care have progressively improved safety and treatment outcomes. This has occurred through clinical trials. Improved approaches for hematopoietic transplantation are needed. New and promising treatments are being rapidly designed to improve safety and effectiveness.

It is important that patients have access to participate in clinical trials. Many insurance carriers do not cover standard patient care costs for patients participating in clinical trials. This deprives patient access to the most promising new treatments and limits the further vital improvements in the standards of care for hematopoietic transplantation.

Some years ago, a Presidential Executive Order mandated that Medicare cover patient care costs for clinical trials, but this has not been effectively implemented for studies of hematopoietic transplantation. Many States have laws requiring insurance carriers to cover standard patient care costs while participating in clinical trials, and this is included in the recent federal health care reform legislation, but only becomes active in 2014. This remains a major problem for patients.

The ACBSCT recommends that the Secretary mandate that Medicare and Medicaid cover the standard patient care costs for patients who are participating in clinical trials involving the use of hematopoietic transplantation and supported by or conducted under the auspices of the National Institutes of Health or National Cancer Institute (NCI), NCI-designated cancer centers and cooperative groups, the Department of Veterans Affairs, or a Food and Drug Administration Investigational New Drug (IND)/Investigational Device Exception (IDE). The ACBSCT recommends that the Secretary encourage private insurance carriers to immediately provide coverage for standard patient care costs for patients participating in clinical trials involving hematopoietic transplantation.

APPENDIX 3

ACBSCT recommends to the Secretary that cord blood collections be increased and improved.

Awareness of cord blood donation and the procurement of high quality products is critical to providing life saving cord blood grafts for patients in need of stem cell therapies. Collection practices yielding larger cord blood units, particularly from ethnically and racially diverse donors, will increase access to curative treatments for patients in need.

1. *Awareness*: The collection of high quality products depends on the commitment of the medical community and the motivation of families to positively impact the life of an unrelated individual. Private banking has had greater visibility compared to public cord blood donations in large part because millions of dollars are spent for marketing by private banks. The materials advertising private storage are typically a parent's first exposure to the concept of cord blood banking and influence their decisions for managing the disposition of their baby's cord blood. **The ACBSCT recommends that the Secretary promote education about public donation as another front-line option in regions where cord blood banking is available.**

2. *Parent Education*: Tools have been created to educate parents about the potential disposition of their baby's cord blood. **The ACBSCT recommends that the Secretary guide expectant parents to the HRSA Program's website for accurate, unbiased information and refer expectant parents to position statements from professional societies which are accessible. In addition, as state-based educational websites are developed, similar information about public donation and private banking should be posted. Packets presenting this information, including the Pregnancy Passport, could be provided through HRSA and the C.W. Bill Young Cell Transplantation Program.**

3. *Medical Professional Education*: To support an efficient collection process which maximizes effort and resources, physicians must be educated. Cord blood collection programs and federally funded websites are sources for information regarding donation options and current applications for cord blood products. **The ACBSCT recommends that the Secretary encourage medical school and residency programs, particularly obstetrical training, introduce cord blood banking concepts, and provide updates on clinical and research applications of cord blood therapies.**

4. *Compensation:* Many physicians support the concept of cord blood donation. When obstetricians collect cord blood, the donation opportunities are enhanced for most delivering mothers. Although compensating medical professionals for cord blood collection may increase the operational costs of public cord blood banks, it may confer a greater value for this resource and service. **The ACBSCT recommends that, if offered, compensation must not incentivize medical professionals to alter safe delivery practices or to include ineligible donors. The ACBSCT further recommends that banks take all feasible steps to ensure that mothers or their insurance companies are not charged for costs associated with cord blood collection.**

5. *Legislation*: Cord Blood Legislation has been enacted in at least 18 states to date and is initiated by private cord blood bank marketing rather than the incentive to inform expectant parents about cord blood banking options. **The ACBSCT recommends that the Secretary encourage the creation of harmonized legislation that asserts accurate and balanced language regarding public donation and private banking**.

6. *Licensing*: As the industry proceeds to obtain product licensure, cord blood banks may infer a requirement to strictly standardize practices and forego novel approaches to procure and manufacture safe, quality products. **The ACBSCT recommends that FDA consider innovative collection alternatives, particularly for public donation, as the industry pursues licensure of unrelated allogeneic cord blood as a biologic product**.

7. *Resources*: With an annual rate of four million births per year, it appears that collection opportunities would be sufficient to create an inventory that adequately addresses diversity and patient access. However, processing, testing and storage costs limit the number of products that can be banked. Over the next few years, facilities that obtain licensure from the FDA will be able to support manufacturing through commercial charging mechanisms, but this revenue will be limited by what the market will bear. **The ACBSCT recommends that the Secretary support the establishment of best practice guidelines for industry, to exploit economies of scale, and encourage efficient, cost effective practices.**

APPENDIX 4
Advisory Council on Blood Stem Cell Transplantation (ACBSCT)
Recommendation: Cord Blood Donation Language for
***Pregnancy Passport* and Public Health Websites**

The ACBSCT recommends that the following language be included in the *Pregnancy Passport* and on public health websites:

> "Besides nourishing your baby during pregnancy, cord blood can save lives. After a baby is born, the umbilical cord and placenta are no longer needed and are usually discarded. However, the blood remaining in the umbilical cord and placenta is rich with blood-forming stem cells. (These are not embryonic stem cells.) By collecting and freezing this blood, the healthy blood-forming cells can be stored and may later be used by a patient who needs them.
>
> "For patients with leukemia, lymphoma, sickle cell disease, or certain inherited metabolic or immune system disorders, a cord blood or bone marrow transplant (also called a BMT) may be their best treatment option. Cord blood can be especially promising for patients of racially or ethnically diverse backgrounds and for patients needing a transplant quickly.
>
> "Learn how umbilical cord blood can help others through public donation, directed donation for an affected family member, or research studies. Talk with your health care provider or visit http://bloodcell.transplant.hrsa.gov or www.bethematch.org for more information. Your decision could help save someone's life."