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

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Welcome and Introductions

Edgar Milford, Jr., MD, ACBSCT Chair, called the meeting to order at 8:30 a.m. and welcomed the Council members and participants. (A summary of the recommendations and action items from this meeting is included in attachment 1.)

New Business and Updates

Jeffrey R. Schriber, MD, said the State of Arizona restored funding for Medicare recipients to receive transplants. Bertram Lubin, MD, announced that California initiated a public cord blood bank at the University of California—Davis that will be supported by a birth certificate fee.

Cord Blood Bank Collections Work Group Update and 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. At the National Marrow Donor Program (NMDP) Expanded Access and Cord Blood Sustainability Summit in March, it became clear that many groups are working toward goals similar to those of the Council and the Collections Work Group and many members overlap, so there are opportunities for collaboration. One group at the summit presented an online questionnaire that potential cord blood donors could take to determine their eligibility, with links to local collection services for those who are eligible.

As part of the Stem Cell Therapeutic and Research Reauthorization Act of 2010, the ACBSCT is required to submit a report to the HHS Secretary on cord blood collections, specifically whether models for remote collection can go forward with limited but scientifically justified safety precautions and whether the Secretary should allow collections from routine deliveries without environmental monitoring in hospitals already accredited by The Joint Commission. In addition, questions have been raised recently about whether the U.S. Food and Drug Administration (FDA) Form 3356, Establishment Registration Form, requires all cord blood collection sites to register with the FDA as entities that perform recovery activities.

Requiring hospitals that collect cord blood in conjunction with a cord blood bank to register and be subject to the same FDA inspections as drug manufacturers and tissue banks would place an unnecessary burden on the hospitals. In a background statement (see attachment 2), the Collections Work Group explained in detail that hospital personnel have partnered with cord blood banks to collect umbilical cord blood for 20 years in a manner that has ensured the safety and integrity of the products.

Ms. Regan described the various arrangements in place to facilitate cord blood collection, noting that in every model, cord blood banks are the entities responsible for recovery. Advances in rapid testing have demonstrated that these arrangements are effective in preserving the sterility and identity of cord blood products. On the basis of a long and excellent track record of safety of cord blood collection in hospitals that already meet the stringent requirements of Joint Commission accreditation, and because requiring registration would hinder the expansion of collection sites that was mandated by Congress as part of reauthorization, the Collections Work Group proposed that hospitals not be required to register with the FDA as establishments responsible for recovery. The Work Group also proposes that the Secretary support cord blood collection in accredited hospitals without additional environmental monitoring. The Work Group's recommendations and the background statement together respond to the questions posed to ACBSCT in the Reauthorization Act as well as the concerns about FDA Form 3356.

Discussion

Ellen Lazarus, MD, clarified that entities involved in manufacturing human cell and tissue products are required to register with the FDA, and because recovery is a step in manufacturing, entities involved in recovery are required to register. However, there is an exception for an individual who is under contract or has an arrangement with a registered establishment. When that individual is engaged in recovery of human cell and tissue products, the individual is not required to register, although other rules governing the process must be followed. Dr. Lazarus further explained that if the agreement is between the hospital and the blood bank, it may fall under the registration requirement, while remote collection protocols may be exempt. She said FDA is having discussions with stakeholders and working to address the situation.

Mary C. Hennessey, JD, asked whether collection is seen by the FDA as facility-based or process-based in terms of distinguishing who falls under the regulation. Dr. Lazarus responded that the FDA makes a process-based determination, but recognizes that ultimately, a facility is responsible for recovery. Whether it is the tissue bank or the individual that performs the recovery step, Dr. Lazarus continued, it boils down to whether recovery is performed appropriately. The purpose of registration is for FDA to know what manufacturing steps are being performed by the facilities or sites, she said. Joanne Kurtzberg, MD, emphasized that banks take steps at the processing laboratory to ensure the quality of the product. Requiring hospitals to register with FDA will derail cord blood collection efforts, she added. Ms. Regan reiterated that banks have demonstrated their ability to control the quality of the process.

The Council members voted unanimously in favor of the following recommendations:

Recommendations to the Secretary

Consistent with Congressional mandates and strategic efforts to expand collection site participation, the Council recommends that the Secretary recognize public cord blood bank oversight of the collection process as sufficient means to ensure safe manufacturing practices, and oppose the requirement for hospitals to register with the FDA as the establishment responsible for recovery.

Based on data from nearly two decades of practice controlled by public cord blood banks to ensure safe collection processes and protect product integrity, the Council recommends

that the Secretary support the collection of cord blood from uncomplicated deliveries in accredited hospitals without environmental monitoring of delivery rooms.

Realizing the Potential of Cord Blood Work Group Update
Liana Harvath, PhD, Work Group Chair
Dr. Harvath reviewed the purpose of the Work Group, which was established one year ago, and identified its members. Among the recommendations proposed by the Work Group and passed by the Council in November 2010 was a call for detailed financial analysis of cord blood banking. The Work Group has been focusing on economic issues, primarily the effect of increasing the threshold for the total nucleated cell (TNC) count in a cord blood unit (CBU) from $>90 \times 10^7$ to $>125 \times 10^7$. That is, it has been proposed that the Health Resources and Services Administration (HRSA) would no longer pay for CBUs for the National Cord Blood Inventory (NCBI) with a TNC count of 125×10^7 or less.

There is increasing demand for cord blood with a TNC $>125 \times 10^7$ combined with the best human leukocyte antigen (HLA) match. While TNC count is often emphasized, Dr. Harvath stressed that the combination of TNC plus an HLA match is key. TNC count is not the only parameter that matters—it's the parameter for which we have the most data right now. Increasing the threshold would substantially lengthen the time to reach the stated goal of 150,000 CBUs in the NCBI. It would also substantially decrease the percentage of CBUs banked. At a threshold of $>90 \times 10^7$, approximately 24–55% of units collected from Caucasian donors are banked; using a threshold of 125×10^7, 9–13% of units collected would be banked. Among African American donors, the figures are lower: 20–24% of units are banked at the $>90 \times 10^7$ threshold, while 5% or less of units would be banked at the 125×10^7 threshold. Dr. Harvath noted that the Work Group focused on economic issues (not, for example, an individual bank's decision to bank units that best match the needs of the community it serves); from a bank's perspective, large units are better than small units in terms of long-term financial viability.

The Work Group outlined some potential strategies for differential banking that HRSA may wish to consider:

- HRSA reimburses NCBI banks more for units with higher TNC counts.
- Banks focus primarily on collecting units from minority populations with higher TNC counts and bank Caucasian units only when the TNC is $>125 \times 10^7$.
- HRSA reimburses a fixed amount for each CBU with TNC $>90 \times 10^7$ and offers a supplement for CBUs with TNC $>125 \times 10^7$.
- Smaller CBUs (TNC $>90 \times 10^7$ but $\leq 125 \times 10^7$) would accrue to the NCBI inventory, but HRSA would not reimburse for those CBUs.

The Work Group did not reach consensus on raising the TNC threshold because critical data are missing. Information is needed on which groups receive the lower-TNC CBUs ($>90 \times 10^7$ but $\leq 125 \times 10^7$), whether these units are used more frequently in African Americans because of rare HLA types, and whether the lower-TNC units achieve the best HLA match for recipients. In

addition, it is essential to conduct an analysis of transplant outcomes in terms of the TNC count and HLA match.

Dr. Harvath said the Work Group's mandate includes identifying new research opportunities with potential to advance the field. She provided information about two recent funding opportunity announcements from the National Heart, Lung, and Blood Institute of the National Institutes of Health (NIH).

NMDP Analysis on NCBI and Non-NCBI CBUs

Michael Boo, JD, Strategic Development Officer, NMDP

Mr. Boo presented data from an analysis of the NMDP registry to assess the demand for CBUs for transplantation. He noted that the analysis looks at the selection of units, not the quality of the decision-making at the transplant centers or whether units were selected because they were the best available option.

HRSA does not pay for units with TNC $<90 \times 10^7$, so the NCBI has no lower-TNC units, and units in the $90–124 \times 10^7$ range make up the largest proportion of both the NCBI and non-NCBI banks. While there is clearly a trend toward using higher-TNC units, analysis shows the number of shipments decreases as the availability of the higher-TNC units declines. Banks are responding to the market, however, and banking higher-TNC units. The pattern of availability of and demand for higher-TNC units is the same for both Caucasian and minority recipients, so at this level of analysis, said Mr. Boo, the choices and options for patients are the same. Analysis of cord shipments by TNC level from both NCBI and non-NCBI banks shows the same pattern of increasing demand for higher-TNC units, although lower-TNC units ($<90 \times 10^7$) are still used in some cases.

Looking at the entire inventory of CBUs, more non-NCBI units are used than NCBI units. However, from 2007 to 2010, minority populations demonstrated strong use of the NCBI as a source of CBUs, so it appears that minority populations benefit significantly from the availability of units supported by the NCBI. Mr. Boo added that there is no evidence that changing the lower threshold for TNC would hamper CBU use by minority patients.

Assessing the cost of banking per year according to the TNC count, Mr. Boo said that the higher the TNC count, the less costly to bank units, and the lower the TNC count, the more costly to bank. Thus the more cost-effective approach for banks is to collect high-TNC units; banking lower-TNC units requires subsidies to ensure availability of units to patients. African American patients use more lower-TNC units than other ethnicities. Mr. Boo concluded that a significant investment is being made in maintaining an inventory of lower-TNC units that is not used very much.

Mr. Boo presented both a short-term (2-year) and medium-term (5-year) model of costs and profits for banks following their current collection protocols compared with increasing the TNC threshold to 125×10^7 or 150×10^7. As the threshold increases, the percentage of collected units that is banked decreases, but the banks maintain profitability without subsidies. Moving banks toward self-sufficiency means that fewer units would be banked, resulting in a dramatic drop-off in inventory accrual, said Mr. Boo. Looking five years out, the losses are less for all models, and

profits are higher; distribution is increased, which increases sales income and leads to some growth. Mr. Boo explained that it's important to find a balance between bank self-sufficiency and maintaining an adequate inventory that meets the demand.

The analysis modeled the impact of some of the HRSA reimbursement options under consideration. A fixed reimbursement rate for all units above a specified threshold encourages banks to maximize their inventory and ensures consistent, predictable funding for the bank. While HRSA could cap the amount of funding for each minority group to encourage diversity in collection, the fixed model does not recognize the differences in costs of collection by ethnicity.

A reimbursement rate that varies by ethnicity recognizes the cost differences of collection and the different utilization patterns. It would create incentives for faster growth toward a diverse inventory. Funding would be somewhat consistent and predictable. This model also recognizes the need to subsidize banking to encourage diversity.

A reimbursement rate that varies by TNC count recognizes the economic value of higher-TNC units and encourages banking of those units. It allows for variation in targets at both the low and high end of TNC counts and can incorporate variations in demand according to ethnic groups. However, it's not clear that this model would encourage more banking. Because of the high demand for higher-TNC units, especially among Caucasian and Hispanic populations, banks already have a good incentive to bank higher-TNC units.

Mr. Boo summarized the impact of increasing the TNC threshold in light of the goals of increasing the CBU inventory, increasing diversity, and promoting self sufficiency. First, there is a need to significantly expand collection at new and existing sites, which costs money. Second, at higher thresholds, reaching diversity targets will take longer. (Mr. Boo noted that NMDP is currently analyzing whether using matching CBUs across ethnicities is as effective as matching CBUs between donors and recipients of the same ethnicity.) Finally, the proportion of units banked to units collected will decrease. At a threshold of $>150 \times 10^7$, only 10% of collected units are banked.

In conclusion, Mr. Boo said financial analysis must be married with clinical analysis of the impact of TNC count and HLA match on transplant outcomes.

Discussion

Richard Champlin, MD, pointed out that lower-TNC units may be adequate for children; looking at use by size might reveal more disparities. Focusing banking on higher-TNC units will better meet the needs of adults, he said, but it's not clear that we are close to meeting the needs of children at present. Mr. Boo responded that demand among pediatric patients is leveling off, while demand among adults is increasing. He also clarified that banking fewer units saves processing costs, and there's a trade-off between inventory growth and better utilization of CBUs.

Dr. Milford asked for a better evaluation of the disparities in use of lower-TNC units in relation to the lack of a good HLA match with higher-TNC units. Dr. Kurtzberg said the average-sized person needs a higher-TNC unit, but you can use lower-TNC units with a better HLA match to

achieve successful engraftment. However, Dr. Kurtzberg said, we may never get TNC counts high enough for adults that would make a big difference in engraftment. Pablo Rubinstein, MD, agreed that in adults with a perfect HLA match, lower-TNC units are quite useful. The size of the inventory is a major consideration, he said. Yet cell dose remains an important factor for adults, said Claudio Anasetti, MD.

Dr. Milford suggested looking at other characteristics of desirable units beyond TNC count and donor ethnicity. A retrospective analysis of different types of CBUs used, perhaps by genotype or phenotype, could reveal alternative ways of determining the inventory needs. Mr. Boo agreed to talk with NMDP staff about such an analysis.

Ms. Hennessey wondered whether modeling could look at which phenotypes are associated with better outcomes at which TNC levels. Dr. Kurtzberg said African Americans can do well with lower-TNC units but it's also harder to find good matches for that population. We should not compromise the definition of a high-quality unit because it's harder to get, she said. Dr. Rubinstein added that modeling is complicated by the fact that physicians choose very high-TNC units even when they are not needed, including for children.

Stephen Sprague reiterated that more discussion and clinical data about the role of HLA matching are needed. Robert Baitty noted that restricting banking to higher-TNC units would slow progress toward the Congressionally-established goal of a larger inventory. Dr. Schriber questioned whether the goal of 150,000 units makes sense; a lot of effort could go into collecting units that no one wants just to meet that goal, he said. Mr. Boo said the goal came from analysis of a 2004 Institute of Medicine study but there was not much clinical data. That figure is based on assumptions that have changed over the past five years on the basis of clinical results, he said. Dr. Milford concluded the discussion by noting that more information is needed to support decisions about recruitment and the amounts needed for the inventory.

Scientific Factors Necessary to Define a CBU as High Quality Work Group Update and Recommendations

Joanne Kurtzberg, MD, Work Group Chair

Dr. Kurtzberg outlined the purpose and membership of the Work Group, noting that HRSA charged the Work Group with revisiting the NCBI inclusion criteria. She said the group endorses the findings from the NMDP financial analysis but is still evaluating what technical characteristics can be assessed to determine the quality of CBUs.

Regarding the synchronization of accreditation requirements with HRSA NCBI criteria, the Work Group had advised that banks be accredited every two years but now sees that as burdensome. The Work Group proposed and the Council unanimously agreed to the following:

> **Recommendation to HRSA**
> The Council recommends that HRSA change the specifications for organizations recognized for accreditation of NCBI to a minimum of every three years.

Dr. Kurtzberg said the minimum age for donors is 18 years, but that limits potential donors. In most States, when a teenager becomes pregnant, she becomes an emancipated minor who has legal responsibility for herself and her baby. Thus, pregnant women under 18 should be eligible to consent to cord blood donation. Mark McGinnis, JD, noted that there is no Federal law governing maternal emancipation or consent. The Work Group proposed and the Council unanimously agreed to the following:

> **Recommendation to HRSA**
> The Council recommends that HRSA broaden the definition of minimal eligible maternal age to comply with local laws in each State. Thus, the age of maternal emancipation can be used if lower than 18.

Dr. Kurtzberg explained that overwrapping (placing the CBU collection bag inside a vacuum-sealed plastic bag before inserting it into the cassette that goes into the freezer for cryopreservation) creates another barrier to protect against leakage. The Work Group proposed and the Council unanimously agreed to the following:

> **Recommendation to HRSA**
> The Council recommends that HRSA continue to require overwrap on the CBU before cryopreservation and during long-term storage, as it may provide additional protection against transmission of infectious agents between CBUs during storage. Although not proven, the potential for increased benefit swayed the group to recommend continuing this practice for now.

Simplifying the consent process would help in the effort to increase collections. Currently, consent is obtained under the umbrella of investigative new drug (IND) research. With licensure, a more conventional approach to consent may be possible. For example, a mother could indicate when she is admitted to the hospital for delivery whether she is willing to allow collection of her baby's CBU; once the CBU is collected and screened, a more in-depth consent process for use of it could take place.

Discussion
Council members discussed the feasibility of a general consent process. Dr. Rubinstein said his organization has used the brief consent process successfully, but the organization has staff responsible for the process. Dr. Kurtzberg emphasized that the Work Group is seeking ways to dramatically increase collections without over-burdening the obstetric practitioners who collect the CBUs. Members discussed the current consent process involving hospital institutional review boards (IRBs) and the process for obtaining consent when remote collection kits are used.

Stability of CBUs
Dr. Kurtzberg said her organization has gathered more data on CBU stability and expiration dates that it will present to the FDA. She summarized the research (which looks at other parameters but not HLA match), concluding that there are no signs of deterioration in cryopreserved CBUs used within 10 years of collection. Currently, TNC counts are used to

measure the quality of CBUs because all banks measure them, but there are better measures of quality that are more predictive than TNC alone, said Dr. Kurtzberg. As more banks conduct routine assays to meet HRSA and FDA licensure requirements, better data on potency will become available. Such data could lead to increased use of lower-TNC or average-TNC units of adequate potency.

Discussion
Council members discussed storage factors that could affect the potency of samples after 10 years. Dr. Kurtzberg noted that engraftment rates have improved, which may be a function of CBU quality, selection procedures, or HLA matching. She added that few banks are more than 10 years old, and the relatively recent use of automated processing may improve recovery.

Collection Models
Dr. Kurtzberg's organization compared two collection models: bank-staffed sites versus hybrid sites where obstetricians and nurse-midwives perform most of the collections. Units collected by obstetricians and nurse-midwives had higher pre- and post-thaw TNC counts than those collected by staff. She concluded that both methods are viable.

Dr. Kurtzberg said her organization is also collecting cord blood from asphyxiated newborns by training practitioners in collection (including residents) and providing materials with every obstetric delivery cart. Dr. Kurtzberg wondered whether such techniques could be applied to encourage more CBU collection in general. She described how the process works for the remote collection kit, noting that the pregnant woman initiates the process by contacting the Carolinas Cord Blood Bank, and her obstetrician must act as her partner in the process. The bank provides the kit, which includes shipping materials, and the obstetrician must undergo training and perform the collection for free. In another model, the pregnant woman, the obstetrician's office, the nursing staff, and the obstetric practitioner take on different aspects of the remote collection process. Dr. Kurtzberg said using that model, the bank could, for example, send paperwork to the office, supplies to the practitioner, and shipping materials to the staff that returns the packaged units, thus saving some costs by not shipping the entire collection kit every time.

Discussion
Dr. Kurtzberg emphasized that pregnant women are great advocates for the things they want. Pregnant women who request kits talk with a nurse by phone and don't receive the kit until one month before delivery. The most difficult part of the process is ensuring that the obstetric practitioner who agrees to partner with the woman is the same one who performs the delivery and the collection. Word of mouth has been successful in reaching potential donors so far, but it's a small program with limited resources, Dr. Kurtzberg said. Of all the kits sent out, 20% meet all the donation criteria, including TNC $>90 \times 10^7$, to qualify for banking.

Dr. Lubin urged consideration of public-private partnerships to increase collections. Public banks face economic barriers, and private banks have resources, he said; private banks may be interested in helping. A member of the audience, Frances Verter, PhD, of the Parent's Guide to Cord Blood Foundation, said her organization's website provides education about both public and private cord blood donation equally. It receives most of its funding from private banks, she said, so the website could be considered an example of public-private collaboration.

Cord Blood Thawing and Washing Work Group Update and Recommendations
Jeffrey McCullough, MD, Work Group Chair
Dr. McCullough explained that the original charge of the Work Group has expanded to encompass broader concerns about communications between transplant center laboratories and other entities as well as policies and procedures around laboratory work. The group began by identifying many of the factors that affect laboratory procedures, from differences in bank processing instructions to variations in storage to use of the products in the transplant center. The Work Group is particularly concerned about variations related to infusion procedures, communication with banks, and adverse event reporting.

To address the original charge to evaluate approaches to cord blood thawing and washing, the Work Group is conducting a literature review. As the FDA's licensure requirements take effect, improving adverse event reporting will become a prominent concern. NMDP is addressing reporting, but questions remain about adverse events involving units not managed by NMDP.

The Work Group is conducting a literature review to better understand the clinical impact that laboratory activities have on transplant outcomes. The Center for International Blood and Marrow Transplant Research (CIBMTR) has completed some research and recently confirmed that it will begin a new study to gather more information on outcomes with CBUs.

Dr. McCullough concluded that there are many transplant center laboratories, and little is known about how they operate. The Work Group suggests fostering more interaction between these labs and the banks. NMDP can help facilitate the interaction, for example, by conducting a survey to better define the nature of the labs and hosting a conference with representatives of labs and banks to promote communication.

The Work Group developed a two-page list of recommended steps for advance communication; receipt, inspection, and storage of CBUs; preparation before transplant; quality control; and infusion and nursing care of the patient (see attachment 3). The group suggested that HRSA distribute the document for use in developing training, technical assistance, and operational policies.

Discussion
Dr. McCullough clarified that the NMDP, as the cord blood coordinating center, could use the list of recommended steps in working with transplant center labs and banks. In response to questions by Matthew Kuehnert, MD, of CDC, Dr. McCullough said initial efforts to improve adverse event reporting would focus on infusion-related toxicity within the first 24 hours, as opposed to long-term disease or complications. Dr. Milford emphasized that NMDP hopes to simplify the process and avoid duplicating reporting efforts. Dr. McCullough said a standard reporting approach is needed that is simple for the transplant centers and conveys information quickly to the banks.

Dr. Rubinstein said the interaction between a bank and a lab can have enormous value to both, because it fosters understanding of delicate issues around handling products and enhances communication. Informal discussion among bank and lab representatives can be very educational

to both, he said, but it happens less frequently now because transplant centers have different reporting relationships. Dr. Rubinstein also felt that recommendations from banks to labs could be simplified to minimize variances.

Mr. McGinnis noted that the Stem Cell Transplant Outcomes Database (SCTOD, coordinated by CIBMTR) collects information from all centers, not just those managed by NMDP, and should receive all adverse event reports. Dr. McCullough said outcomes reporting by banks to CIBMTR may not be timely enough to meet FDA licensure requirements or to address infusion-related toxicity. J. Douglas Rizzo, MD, MS, project director for the SCTOD, said the database is observational and collects information over time, not immediate adverse event reports. However, he said, CIBMTR is working closely with NMDP in an effort to gather and convey adverse events; it may be possible to link the SCTOD with the system being developed by NMDP.

Recommendation to HRSA

The Council recommends that the description of activities involving the transplant center laboratory (Transplant Center Laboratory-Related Activities, attachment 3) be used by the Cord Blood Coordinating Center of the National Marrow Donor Program as a blueprint to develop additional training, technical assistance, and operational policies.

Adverse Event Reporting

Willis Navarro, MD, NMDP

The process of developing an adverse event reporting system begins with focusing on the data of interest: serious expected and unexpected adverse reactions in patients and certain product deviations. NMDP is creating a list of expected adverse events and educating transplant centers about reporting through national meetings.

NMDP hopes to create a system that will minimize the burden on transplant centers while meeting reporting requirements. Reporting expected adverse events allows transplant centers to track data and monitor trends. The system for reporting unexpected adverse events will focus on relatedness (the likelihood that the event is related to the CBU infusion), seriousness, expectedness (with an expedited process for unexpected events), and timing. Infusion-related events usually occur within the first 24 hours, so timing can help clarify relatedness. Detecting transmission of an infectious agent through transfusion takes some time, but the system should encourage reporting as soon as an infection becomes apparent.

Dr. Navarro said NMDP is working on information technology (IT) that takes into account all the requirements. At present, NMDP envisions a web portal that allows the transplant center to log in and report an adverse event, regardless of the source of the unit. The portal will link the user with the appropriate reporting process. For units for which NMDP does not have reporting requirements, the system would convey information to the appropriate entity, such as the IND holder or the cord blood bank.

Once the IT solution is finalized, NMDP will develop and disseminate standard reporting procedures and a streamlined form for data gathering. Dr. Navarro said NMDP has reviewed and is likely to approve the IND/10-CBA protocol. The NMDP IT system is based on the same system that transplant centers currently use to report to the SCTOD. As part of its educational

efforts, NMDP will provide webinars; the website http://marrow.org provides updates on NMDP activities for transplant centers and banks.

Discussion
Dr. Kuehnert pointed out the advantages of standard definitions of adverse events. For example, CDC developed definitions to align with the International Society for Cellular Therapy's standards in categories of imputability (i.e., relatedness) and severity of reactions. He asked whether NMDP looked at other biological surveillance standards to establish criteria and how data from the NMDP system would be analyzed and used. Dr. Navarro said NMDP is still focusing on developing a mechanism to collect the data and having procedures in place by October 2011, when cord blood licensure requirements take effect. Dr. Kuehnert said CDC would like to work with NMDP on adverse event reporting. Dr. Navarro confirmed that NMDP has coordinated with other organizations that have already established definitions of adverse events.

Dr. Navarro emphasized that NMDP is looking to the FDA guidance to establish the definitions for reporting and so will avoid creating conflicting guidance. Dr. Kurtzberg hoped there would be an opportunity to harmonize reporting of adverse events for licensed products as well as those used under an IND. She asked whether the new FDA guidance applies to both licensed and IND products. Dr. Lazarus responded that many details have yet to be worked out but offered to connect Dr. Kurtzberg's organization with an FDA consultant.

Dr. Navarro said NMDP's system of using a single portal for all entities will facilitate participation by all the stakeholders. It would also gather information in real time and direct the information to the appropriate entity. He acknowledged that buy-in from all the entities is crucial. Under-reporting by transplant centers is an area of concern; Dr. Navarro hoped that the single-entry portal and the automation that directs the user to the appropriate reporting systems would encourage transplant centers to report more frequently.

Mr. Baitty wondered who would monitor the system to determine when a broader investigation of events is needed (for example, to evaluate a series of possibly related events). NMDP has an internal process for monitoring its own products and has the capacity to query the database, identify trends, and investigate them as needed, regardless of whether the products came from NMDP, Dr. Navarro said. Currently, NMDP plans to use the National Cancer Institute's Common Terminology Criteria for Adverse Events for short-term events and the International Classification of Disease (ICD)-9 classification for long-term events. Dr. Navarro also noted that NMDP will collect data on how units are managed in relation to instructions from banks to the transplant centers.

> **Action Item**
> The Council will invite a representative from CDC to take part in further discussion about adverse event reporting systems.

Current State of Knowledge: Cord Blood Transplantation

Mary Eapen, MD, Center for International Blood and Marrow Transplant Research
Dr. Eapen briefly reviewed some of the research on CBU transplantation from the past 20 years. Since 2006, CIBMTR has collaborated with national and international registries to foster collaboration and facilitate large studies that have great statistical power. It is an active participant in the Blood and Marrow Transplant Clinical Trials Network (BMT CTN) funded by the NIH. CIBMTR research generally compares the effectiveness of cord blood as an alternative

to adult donor graft sources (bone marrow and peripheral blood). It is also exploring selection criteria for CBUs that are not routinely considered.

Ms. Eapen summarized some earlier research demonstrating that use of cord blood resulted in fewer cases of graft-versus-host disease (GVHD) than bone marrow and that HLA-mismatched CBU transplantation is an acceptable alternative when HLA-matched adult donor units are not available.

A study published in 2007 found that mortality rates were particularly high following CBU transplantation. However, with matched CBUs, the risk was extremely low (6%)—lower than that for a matched marrow donor source. Furthermore, 90% of CBU transplantations involve a mismatch; with a single-antigen mismatch, the risk of mortality is no different than for a matched marrow donor source. However, with a lower TNC or double-antigen mismatch, the mortality risk with CBU is higher than that with matched marrow. The same study found the relapse rate particularly low among those who received a double-antigen mismatched CBU transplantation. Researchers concluded that patients died regardless of what type of transplantation they had, but the pattern differed depending on various factors. Dr. Eapen noted that the number of matched CBU transplantations makes up only about 10% of transplants, so it's difficult to confirm some of the findings in a larger data set.

A study comparing CBU transplantation with bone marrow or peripheral blood progenitor cell (PBPC) transplantation in adults found that single-antigen mismatched bone marrow or PBPC was no better than double-antigen mismatched CBU in terms of transplant-related mortality. The rates of leukemia-free survival were similar across donor sources, but the patterns of failure differed. Dr. Eapen noted that patients with active disease did poorly no matter what treatment they had. Thus, physicians can help by referring patients for transplantation earlier in the course of the disease.

Because about 40% of adults undergoing transplantation use a conditioning regimen, said Dr. Eapen, CIBMTR compared outcomes of PBPC transplantation with double CBU transplantation among leukemia patients who received reduced-intensity conditioning. The research found that the type of conditioning regimen had no significant effect on survival for PBPC transplant recipients, but CBU recipients had higher survival rates when total body irradiation (TBI) conditioning regimens were used. Among those who survived disease-free, those who received CBU plus low-dose TBI did as well as those who had matched and mismatched PBPC.

Researchers then compared transplant outcomes between single-CBUs with adequate TNC levels and double-CBUs. The study found that transplant-related mortality rates were similar for both groups. Thus, when a single CBU of adequate TNC is available, co-infusion of two units does not improve survival, but only 30% of recipients actually receive an adequate TNC dose, said Dr. Eapen. Research is underway comparing single- and double-CBU transplantation in children, all of whom would receive adequate cell doses with a single CBU.

The BMT CTN studied reduced-intensity conditioning for stem cell transplantation, comparing HLA-haploidentical bone marrow with unrelated cord blood. Overall and disease-free survival rates were similar at one year between the two groups, although the pattern of failure differed. In

the haploidentical group, transplant-related mortality is low (7%) but relapse rates are high (45%). For CBU recipients, the one-year mortality rate is 24% and the relapse rate is 30%. Further study will randomize patients to haploidentical or double cord blood transplantation.

To better understand how to lower transplant-related mortality, CIBMTR is looking at novel mechanisms, such as the effects of matching CBUs. Through partnership with NMDP, CIBMTR has access to samples and the ability to characterize them retrospectively.

The importance of matching at the HLA-C locus is not well defined, so CIBMTR collaborated with the European Group for Blood and Marrow Transplantation to evaluate the effects of mismatches and CBU transplantation. They concluded that with more than two mismatches, regardless of the loci, mortality increases, and matching at HLA-C does not matter. It may be possible to lower mortality by striving to match at HLA-C, said Dr. Eapen. Further analysis suggested that matching non-inherited maternal HLA antigens does confer a survival advantage. However, because only about 10% of transplants are matched, said Dr. Eapen, it's unclear how much survival rates can be improved with prospective selection.

Another novel mechanism proposed to improve mortality is expansion of one CBU in a mesenchymal-stem-cell (MSC)-based co-culture and comparing it with standard double-CBU transplant. Phase-II studies found no survival advantage in a small cohort after one year; a phase-III randomized, controlled trial is underway.

Dr. Eapen concluded that altering the current selection strategy may improve mortality in 25–30% of transplant patients. Physicians should consider matching at the HLA-C locus as well as HLA-A, HLA-B, and DRB-1. Optimizing donor-recipient HLA mismatches by matching non-inherited maternal HLA antigens may be helpful. Expansion of one unit of CBU in MSC-based co-culture, followed by co-infusion of the expanded unit and a second unit, leads to rapid hematopoietic recovery, said Dr. Eapen.

For future research using registry data, CIBMTR is accruing data to look at the role of allele-level HLA typing and parameters other than TNC. Other research may be best tested prospectively, such as ex vivo expansion of cells, infusion of ex vivo-expanded T-regulatory cells, and hematopoietic stem cell homing.

Discussion

In response to Ruben J. Rucoba, MD, Dr. Eapen said her colleagues at CIBMTR are setting up a web-based platform to collect quality-of-life data to look beyond transplant survival rates. Dr. Milford asked about the implications of HLA-C locus and natural killer alloantigen activity for GVHD or the graft-versus-leukemia effect; Dr. Eapen said there are plans to study the issue. In response to a question from the audience, Dr. Eapen provided some more detail about data on the effect of conditioning regimens. Richard P. McQuellon, PhD, and Dr. Milford both expressed the need for patients and their physicians to have more easily accessible, easy-to-understand resources describing how recent research could affect decision-making.

Access to Transplantation Work Group Update

Richard Champlin, MD, Work Group Chair

Dr. Champlin reiterated the Work Group's position that a list of indications for hematopoietic stem cell transplantation (HSCT) would help guide physicians, payers, and others in providing a rational and consistent approach to HSCT use and payment policies. Dr. Champlin presented data on the use of HSCT, including donor sources and indications in children and adults. He noted that clinical trials provide opportunities for patients to receive individualized treatment, often with superior outcomes, and the Council previously recommended that insurance carriers cover the costs of standard care for patients participating in clinical trials.

Other groups have developed lists of indications, including the States of California and Florida and the European Group for Blood and Marrow Transplantation. The Work Group is trying to build on those efforts and create a more comprehensive list that includes nonmalignant diseases. The document will also address general principles of cell sources and donor selection and provide some guidance on choosing allogeneic versus autologous sources. The final document will categorize indications as accepted, developmental, or not recommended.

Dr. Champlin presented some draft wording on general principles for consideration. Following long debate, the Work Group determined that evidence demonstrates that various cell sources are effective, so insurance coverage policies should not restrict the use of any of the available cell sources. Further, recent results from many centers are comparable for patients receiving transplants from matched related donor transplants, related haploidentical transplants, unrelated donor transplants, and cord blood transplants. Thus, coverage policies should not restrict use of any of these donor sources.

The Work Group seeks to simplify existing lists of indications by removing distinctions that are no longer relevant and to add indications for pediatric malignancies, many of which are rare. The group is working toward consensus on categorizing the indications for HSCT by the degree of risk, availability of alternatives, and benefit to the recipient. In terms of cost-effectiveness, the scales are now tipped in favor of transplantation over long-term drug therapy. Quality of life is another factor in decision-making, as is the timing of HSCT in the course of disease.

The Work Group now has data from the CIBMTR on the numbers of transplants by diagnosis. It is gathering more input through a survey of physician experts and plans a teleconference with an expert panel that includes payers, patient advocates, and HRSA representatives. Dr. Champlin said the Work Group aims to include input from all interested parties.

Discussion

Dr. Milford noted that a representative from the Centers for Medicare and Medicaid Services (CMS) said that CMS weighs the potential benefit of therapy against the severity of the condition in its coverage decisions. Dr. Champlin said CMS recently approved coverage for beneficiaries participating in some HSCT trials. Dr. Milford wondered whether the implementation of new cord blood licensing requirements would boost interest in HSCT. Dr. Champlin pointed out that procedures, such as transplantation, are not subject to licensure or approval, which contributes to the lack of clear guidelines. The challenge is to produce a meaningful list of indications along with general principles that are not so specific that they risk being outdated quickly, said Dr. Champlin.

Report on NMDP Cord Blood Financial Summit

Michael Boo, JD, Strategic Development Officer, NMDP

NMDP held a summit in March to identify and prioritize potential strategies to increase the number of CBU donors and improve the financial viability of cord blood banks. The meeting yielded a number of ideas for consideration, although the participants did not attempt to reach a formal consensus on recommendations. Mr. Boo summarized some of the ideas:

- Evaluate the TNC threshold.
    - Conduct a survey to better understand what banks are doing.
    - Update the NMDP model to better reflect the FDA impact and other developments.
    - Explore NCBI funding options that encourage banking of preferred units.
- Develop education programs for obstetrician-gynecologists.
    - Encourage participation.
    - Improve collection of high-quality units.
    - Work with obstetricians to improve the collection process.
    - Improve awareness during residency training.
- Expand partnerships with States.
    - Understand legislators' responses to public cord banking support. (California has a funding mechanism for cord blood collection and other States are considering it. How can the cord blood community engage with States more systematically, either through Federal programs or individually?)
- Work with FDA to eliminate collection requirements that burden the hospitals.
- Explore regional computerized donor registration, qualification, and referral systems to identify donors and take some burden off of hospital staff.
- Identify and pursue techniques to improve collection and shipping of larger units, e.g., a visual guide to volume collected or weighing or cell count at collection center.
- Explore the cost-benefit of group purchasing programs.
- Pursue relationships with hospital organizations, e.g., working with whole systems to get support. Establishing a relationship with one hospital takes six months to a year.

NMDP hopes to flesh out these ideas, some of which are also under discussion by the Council. Mr. Boo said the summit was not a duplication of effort but rather another forum in which to test ideas. As the recommendations are further developed, NMDP will seek out cost-benefit analyses to evaluate what would work. The NMDP Cord Blood Advisory Group will review and refine the recommendations. NMDP will create implementation plans and timelines as needed. Mr. Boo concluded that NMDP will work with the Council to gather more data and look at the suggestions from the summit in more detail.

Public Comment

Nancy Paltell, MD, of the Maryland Catholic Conference said Catholic hospitals are very interested in promoting cord blood collection but there are not enough banks in Maryland to support them. Dr. McCullough acknowledged that setting up collection systems is expensive and complicated, and current reimbursement levels make it impossible for most cord blood banks to expand their activities. Mr. Boo agreed that money is the issue; he suggested we may need to

work harder to collect better units, thereby increasing efficiency. Mr. Boo also thought that moving away from IND protocols and toward licensed products may eliminate some of the barriers to collection. Dr. Hartzman said collection is much more expensive than anyone anticipated, and he does not see any mechanism for making it cheaper. A lot of the existing regulations and requirements add to the cost and complexity but do not affect the quality of the product, he said, so cutting some regulations would reduce costs.

Ms. Regan appreciated the willingness of hospitals to reach out to promote cord blood banking. To be cost-effective for banks, the collection process requires a lot of commitment from hospitals and individual physicians. Dr. Kurtzberg described some of the barriers and costs to hospitals and their staff. Clive Callender, MD, said the lack of collection sites is the most common complaint he hears on this topic. To increase the diversity of the donated inventory, the blood community should acknowledge the barriers and look more closely at how to resolve them.

Suzanne Pontow, PhD, of the University of California—Davis encouraged everyone to work with their State legislatures to promote cord blood collection. California added a small fee for birth certificates to support a partnership with banks that takes advantage of California's genetic diversity, said Dr. Pontow. California needs more collection centers, not more banks. Dr. Pontow added that the cord blood collection authorization was the only spending appropriation to pass the California legislation this year, demonstrating the strong popular support for it.

Conclusion and Adjournment

Patricia A. Stroup, MBA, MPA, Executive Secretary, said the Council would meet again in approximately six months, date to be determined. She thanked the Council for its work on the recommendations to the Secretary regarding the reauthorization. She congratulated the Council on its effectiveness in terms of implementation of recommendations. Ms. Stroup said she hopes to get the nomination process for the next Council term underway quickly, as many members rotate off in January 2012. Dr. Milford adjourned the meeting at approximately 3:10 p.m.

ATTACHMENTS

1) Summary of recommendations and Council action items
2) Background Statement: Cord Blood Collections Work Group Recommendations to the Secretary
3) Transplant Center Laboratory-Related Activities

Attachment 1

ADVISORY COUNCIL ON BLOOD STEM CELL TRANSPLANTATION

Summary of Recommendations and Action Items
May 11, 2011

RECOMMENDATIONS

Cord Blood Bank Collections

Recommendations to the Secretary
Consistent with Congressional mandates and strategic efforts to expand collection site participation, the Council recommends that the Secretary recognize public cord blood bank oversight of the collection process as sufficient means to ensure safe manufacturing practices, and oppose the requirement for hospitals to register with the FDA as the establishment responsible for recovery.

Based on data from nearly two decades of practice controlled by public cord blood banks to ensure safe collection processes and protect product integrity, the Council recommends that the Secretary support the collection of cord blood from uncomplicated deliveries in accredited hospitals without environmental monitoring of delivery rooms.

Scientific Factors Necessary to Define a CBU as High Quality

Recommendation to HRSA
The Council recommends that HRSA change the specifications for organizations recognized for accreditation of NCBI to a minimum of every three years.

Recommendation to HRSA
The Council recommends that HRSA broaden the definition of minimal eligible maternal age to comply with local laws in each State. Thus, the age of maternal emancipation can be used if lower than 18.

Recommendation to HRSA
The Council recommends that HRSA continue to require overwrap on the CBU before cryopreservation and during long-term storage, as it may provide additional protection against transmission of infectious agents between CBUs during storage. Although not proven, the potential for increased benefit swayed the group to recommend continuing this practice for now.

Cord Blood Thawing and Washing

Recommendation to HRSA
The Council recommends that the description of activities involving the transplant center laboratory (Transplant Center Laboratory-Related Activities, attachment 3) be used by

the Cord Blood Coordinating Center of the National Marrow Donor Program as a blueprint to develop additional training, technical assistance, and operational policies.

ACTION ITEM
Cord Blood Thawing and Washing

The Council will invite a representative from CDC to take part in further discussion about adverse event reporting systems.

Attachment 2
Cord Blood Collections Work Group Recommendation 8, Council Recommendation 15
HHS Advisory Council on Blood Stem Cell Transplantation (ACBSCT)
Health Resources and Services Administration

April 2011

For over 20 years, umbilical cord blood has been collected after uncomplicated deliveries by obstetrical personnel or public cord blood bank staff for cryopreservation and long term storage for future transplantation. Public cord blood banks (CBB) enter agreements with appropriately accredited hospitals with obstetrical units to serve as collection sites. The banks provide education related to donor screening, informed consent and proper collection technique, along with supplies for collection, short term storage and shipping. Public banks screen, test and store qualified cord blood units which are listed on donor registries for distribution to patients in need of an unrelated donor for transplantation. Because they manufacture products intended for unrelated allogeneic applications, unlike private banks that contract directly with families to store for that family's potential future use, public cord blood banks are subject to rigorous requirements, including full Good Manufacturing Practice for Finished Pharmaceuticals (21 CFR Part 211) and register with the Food and Drug Administration (FDA) as required by Federal law (21 CFR Part 1271 – Human Cells, Tissues and Tissue-Based Products [HCT/Ps]). To date, collection hospitals have not registered with FDA as facilities for recovering cord blood nor have they performed environmental monitoring beyond the requirements of hospital accrediting agencies, according to FDA requirements for Current Good Tissue Practice (21 CFR Part 1271.195 – Environmental Control and Monitoring).

As manufacturers of HCT/Ps, public cord blood banks are responsible for approving or rejecting cord blood collections according to the donor eligibility and product qualification policies referenced above. At the request of the FDA in 1991, the cord blood banking community established rigorous accreditation standards and banks are encouraged to obtain accreditation based upon these standards (AABB, FACT-NetCord). Central to the evaluation of safety and potency is the capacity of cord blood banks to detect circumstances at collection sites that may compromise the integrity of the product. This is accomplished through training and oversight at the collection site and through qualification upon receipt and testing at the cord blood bank processing laboratory. There is strong evidence from over 20,000 transplants, that manufacturing of cord blood units in this manner results in a safe and potent product in the clinic. Each public cord blood bank is responsible for assuring the following:

- collection site suitability through confirmation of accreditation by appropriate certification agencies such as The Joint Commission, the Healthcare Facilities Accreditation Program (HFAP) or DNV (Det Norske Veritas) Hospital Accreditation;
- product integrity through evaluation of temperature conditions where supplies are stored prior to collection and fresh products await and undergo transportation;

- safety through adherence to donor eligibility requirements, as required by 21 CFR Part 1271, Subpart C—Donor Eligibility;
- product sterility through microbial surveillance testing; and
- product potency through nucleated cell, CD34 cell, colony forming cell, and viability analysis.

The cord blood bank confirms identity and potency (release testing) at the time a unit is being considered for transplantation but before distribution to the transplant center. Limited studies are also performed at the transplant center after thaw of the cord blood unit for infusion. Data resulting from nearly two decades of clinical practice has demonstrated safe transplantation outcomes, ie: infusion of products has avoided transmission of communicable disease, incidence of donor derived malignancies is very rare, and engraftment occurs at an acceptable rate.

The Stem Cell Therapeutic and Research Reauthorization Act of 2010 signed into law on October 8 2010 formally amended the Stem Cell Therapeutic and Research Act of 2005. The Act included a requirement for participating banks to "…provide a plan to increase cord blood unit collections at collection sites that exist at the time of application, assist with the establishment of new collection sites, or contract with new collection sites; for the purpose of increasing cord blood unit donation and collection from a genetically diverse population and expanding the number of cord blood unit collection sites...". While all cord blood banks are supportive of this mission, resources do not exist to achieve a significant increase in collections through increased staffing or opening of new collection sites without recruiting OB or hospital staff to participate in collections. Experience in existing community based models has shown that this opportunity to innovate collection models and engage hospitals, OBs and midwives to partner with banks in the collection process is absolutely possible without affecting purity, potency, sterility or stability of banked cord blood units.

At the same time, cord blood banks are in the process of preparing biologics license applications for submission to the Food and Drug Administration (FDA). According to regulations that will apply in a licensed environment, collection sites could be considered responsible for "recovery" activity (a component of the manufacturing processing), which might require them to register this activity on FDA Form 3356 and subject hospitals to FDA inspections. Requiring hospitals to follow the FDA regulations for tissue banks and for drug manufacturing (Current Good Manufacturing Practice for Finished Pharmaceuticals - 21 CFR 211) that are currently observed by public cord blood banks, will be a major impediment to public cord blood collections and obstruct innovative collection models which are essential for the overall success of the cord blood program going forward.

Over the past 20 years, cord blood banks - through regular education, evaluation of competence, control of supplies, management of storage and transportation processes, determination of donor eligibility and qualification of product - have demonstrated that manufacture of safe, high-quality products from cord blood collected in climate controlled delivery rooms of accredited hospitals is achievable. Furthermore, these

activities have occurred with minimal obstruction to hospital operations or imposition on their primary purpose of providing clinical care. Coordination of collection activities by the cord blood banks with limited interference to delivering hospitals is critical to their participation. Requiring collection sites to register and perform environmental monitoring beyond what their accrediting agencies mandate to keep their own patients safe and comfortable, will dissuade hospitals from participating in cord blood donation.

Recommendation: Consistent with Congressional mandates and strategic efforts to expand collection site participation, the Council recommends that the Secretary recognize public cord blood bank oversight of the collection process as sufficient means to ensure safe manufacturing practices, and oppose the requirement for hospitals to register with the FDA as the establishment responsible for recovery.

Recommendation: Based on data from nearly two decades of practice controlled by public cord blood banks to ensure safe collection processes and protect product integrity, the Council recommends that the Secretary support the collection of cord blood from uncomplicated deliveries in accredited hospitals without environmental monitoring of delivery rooms.

Attachment 3
TRANSPLANT CENTER LABORATORY-RELATED ACTIVITIES

ADVANCE COMMUNICATION BETWEEN CORD BLOOD BANK AND TRANSPLANT CENTER

It is recommended that a standard list of issues to be communicated from the bank to the transplant center because advance planning is important to ensure that the transplant center laboratory has staff available to receive the unit and has made proper plans to handle it correctly. Suggested standard communications are:

1. Bank or transplant coordinator should communicate to the transplant center laboratory.

2. The type and configuration of cord blood container should be communicated so the TC laboratory can assure proper storage arrangements for the cassette and placement within the storage container.

    - Clarify number of bags begin shipped or additional containers provided for research purposes.

3. Communication should identify any unique features of the cord blood unit/container.

4. Communicate any unusual features of the cord blood or its associated information.

5. Recommended thawing and processing procedures in case these are different from the TC laboratory's usual practice.

    - Determine whether to use existing unique number or assign new product number - advance
    - Review infectious disease testing results and determine that testing done on correct sample - advance
    - Review donor eligibility determination - advance

RECEIPT AND INSPECTION OF THE UNIT

Upon receipt of the unit in the transplant center laboratory, the following steps are recommended?

- Determine nature of container to plan for future thaw technique
- Inspect product and all accompanying records and data
- Verify identification and all label information and frozen condition
- If electronic monitoring device in place, verify temperature maintenance

- Inspect product for damage
- Complete all forms regarding receipt of unit
- Notify transplant coordinator unit has arrived and its condition for use
- Document any accompanying samples
- Determine if rapid HLA typing or other special testing is necessary for quality control

STORAGE OF THE UNIT

Proper storage of the unit is essential and may depend on the nature of the freezer in which they will be stored. Specific considerations include:

- Determine size and type of container
- Determine proper storage container and position within the container based on size of unit
- Place unit in storage container
- Document location of unit in storage container

PREPARATION IN TRANSPLANT CENTER LABORATORY BEFORE TRANSPLANT

It is important for the transplant center laboratory to anticipate activities that will occur on the day of transplant in order to have all necessary staff and procedures in place and to avoid last minute difficulties. A suggested list of these pre-transplant activities is:

- Verify planned infusion date with transplant coordinator
- One day prior to transplant date, contact patient care unit to schedule infusion
- Review all unit related records for any deviation documentation
- Review Physician Request form to verify that unit meets request
- Complete laboratory section of infusion form
- Confer with clinicians to establish total acceptable volume of final product

QUALITY CONTROL OF THE PROCESS AND CRITICAL VALUES

Each transplant center and its associated laboratory should have established guidelines for quality of the units to be transplanted. At the time of preparation of the units for transplant, quality control test results should be reviewed against the transplant center laboratory's critical values. All QC results should be entered on processing and infusion forms in order to verify that the unit is suitable for infusion.

INFUSION OF THE CORD BLOOD UNIT AND NURSING CARE OF THE PATIENT

The quality of the cells must be maintained during the infusion process and the patient must receive proper care during the transplant so the unique nature of the cell product and the procedure must be properly planned and carried out. This should include for instance:

- Methods of transport of unit to patient care location
- DO NOT IRRADIATE
- Verify physician order
- Verify patient identification
- Determine proper use of filters
- Select line for infusion
- Determine proper IV solutions
- Determine time/rate for infusion
- Determine sequence and timing of infusion of double units
- Review nursing care of patient
- Determine and clarify volume of product to be infused and suitability for the patient