Banking and Use of Umbilical Cord Blood

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Abstract

Umbilical Cord Blood (UCB) is an alternative source of hematopoietic stem cells for transplantation. A UCB bank is a multidisciplinary structure that is responsible for the recruitment, collection, processing, testing, cryopreservation, storage, listing, reservation, release, and distribution of units for administration. Also, UCB can be transferred for life-saving research. Before labor, adequate information and consent, including possibility of repurposing donation shall be performed. After delivery and using appropriate techniques placental blood can be collected and processed for therapeutic purposes. Cell processing normally consists of volume reduction to achieve a reasonable reduce of storage area. Automatic procedures have some advantages on reproducibility. A banking project starts with an establishment phase where banks should have a rapid growth to achieve their operational size. Then a maintenance phase follows, once the optimum inventory is achieved where UCB banks should focus in increasing quality and diversity. As consequence a decrease in numbers of newly added units are expected. The fact that less than 20% of collected units have more than 150x107 total nucleated cells, estimated to be the threshold for efficient inventories, challenge ethics of donation programs. Therefore, UCB banks need to research on alternative uses to add value to the surplus units and the available inventory. Finally, integration with other cell therapy services will reduce fix costs of operation and contribute sustainability.

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3.1 Introduction

Umbilical Cord Blood (UCB) transplantation is an alternative source of hematopoietic stem cells for transplantation. After the first procedure performed in Paris by Dr Gluckman team, more than 40,000 procedures have been performed up to 2020 [1]. According to the World Marrow Donor Association (WMDA), more than 750,000 units are registered in Bone Marrow Donor Worldwide searchable for any patient in need [2].

The use of UCB cells has several advantages including absent risk for the donor, to be an off-the-shelf medicinal product, and, clinical benefits like low incidence of graft-versus-host disease which result in an increase of the donor pool availability [3]. Presence of UCB banks have therefore allowed to decrease substantially the unmet needs and facilitate the universal access to the therapy for patients searching for an adequate stem cell donor. However, the number of stem cells is relatively low delaying engraftment, and there is no possibility to use a donor lymphocyte infusion after transplantation [4]. There are interesting approaches to improve outcomes including the use of very high cellular units, and protocols for progenitor cell ex vivo expansion that is being successful. Most used protocol in older patients uses reduced intensity conditioning and the double graft approach [5]. Recently, immune active properties like an enhanced graft-versus leukemia effect has been proposed and reconstitution of the immune system is the current research area for achieve an improvement of UCB transplant methods [6].

What is a UCB Bank?

A UCB bank is a multidisciplinary structure that is responsible for the recruitment and subsequent management of maternal donors as well as the collection, processing, testing, cryopreservation, storage, listing, reservation, release, and distribution of units for administration [7]. According their purpose and organization banks can be public, familiar or hybrid:

- Public UCB banks: They are dedicated to the collection and storage of UCB after donation for unrelated use to patients who require a stem cell transplant and do not find an HLA-matched donor within their own family. The mother signs the informed consent and is the source material for the mandatory Infectious Disease Marker (IDM) testing. Units in public UCB banks often have stringent quality criteria (high volume and cell counts, absence of contamination). Units that do not meet these criteria may be used for research purposes if a proper consent is in place. In this model, HLA typing is typically performed after cell processing. Then, UCB unit information gets confidentially uploaded to a registry that transfers to different search engines networks.
- Family UCB banks: “Private” banks are for-profit companies that facilitate the collection and storage of UCB for a possible future use of the donor or by a member of the child’s immediate family. Here, the family has the right to use the UCB unit for their own anticipated need or for future use where the UCB unit is

perceived as "biologic insurance". There is a cost associated with private banking. Often private banks do not have the same stringent quality criteria that are in place in public UCB banks and then mother donor may dispose of the unit based on the wishes of the family. The units are not normally HLA typed. Information about privately stored UCB units is not uploaded onto search registries or match programs.

– Hybrid UCB banks: The hybrid approach consists of collecting units both for private storage and for public banking that will be searchable and available for unrelated transplant. This model allows the advantages of private banking to those who wish to use the service but also funding collection of UCB for public sector.

Regulatory Framework

The regulatory framework of UCB collection and processing to make it available to patients in need has evolved considerably over the past two and a half decades. What began as an effort to broaden the available transplant options has evolved into an expensive industry with robust regulation. UCB has become the first FDA licensed tissue product in the United States. Before licensure, concerns about safety and efficacy led the industry to develop voluntary standards, mainly crafted by NetCord-FACT and AABB (international reference on standards) [7, 8]. These accreditation programs established international standards. This is particularly important as there is significant exchange of UCB across national boundaries that has increased over time. Regulations establish standards for safety, quality, identity, purity, and potency from a given point in time going forward. Questions can remain regarding units banked before implementation of the regulations. Some form of regulatory guidance is in place in virtually every country with a UCB bank [9]. Accreditation and regulation has instilled confidence in clinicians, allowing them to select a UCB unit from across a wide range of banks in many different countries.

In this chapter we will focus in public UCB banks and review UCB donation programs, processing and storage of therapeutic products, their clinical use for HPC transplantation, following what is required in the international standards, and finally will discuss challenges that UCB banks confront for their future maintenance.

3.2 Donation Programmes

After delivery and the preceptive cord clamping, a residual amount of newborn blood is left in the placenta. Using appropriate techniques this blood can be collected and processed with therapeutic purposes. As this medicinal product of human origin has been extensively regulated, recycling of this blood shall be done fulfilling the necessary steps of information and consent under an ethical environment. This has required the design of donation programs that will be described below.

3.2.1 Collection Sites

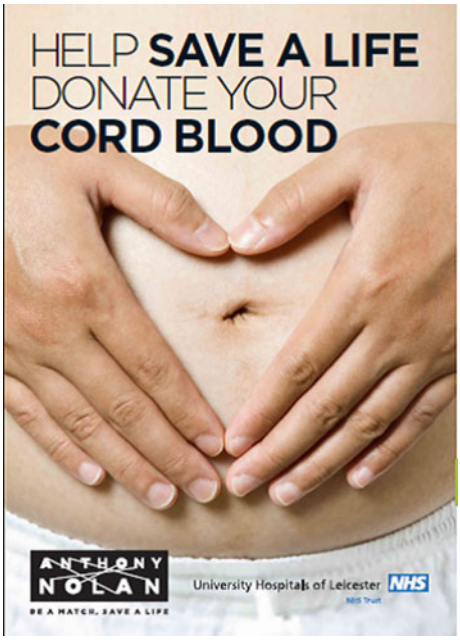
Collection sites are places were a UCB unit is collected. A collection site should have an agreement with the UCB bank to delimitate their responsibilities. Commonly, they are defined as fixed and non-fixed collection sites:

- Fixed UCB Collection Site: A fixed collection site requires an agreement between collection site and the bank for collecting UCB units. This agreement shall describe the interaction between the site and the bank for all aspects of the collection including, at a minimum, personnel training, record keeping, collection, storage, and transportation or shipping of UCB units. Staff for collecting units is usually part of the maternity. There are banks hiring their own staff and the agreement allows them to work on the hospital premises.
- Non-fixed UCB Collection Site: A non-fixed collection site is one with an agreement/contract between a licensed health care professional and UCB bank, to perform the collection and has been trained to cover every aspect of the collection process. This is normally done case by case when the collection is programmed.

3.2.2 Recruitment and Consent

Donor recruitment could be done using different models; although usually starts during the antenatal period, with information given by woman's health care provider, it may also occur as late as at admission into the labour. Programme often provide information leaflets or brochures to inform the mothers-to-be about banking. Pictures below show leaflets used in our banks. Topics described are about defining the therapeutic product, the importance of UCB banking for public use, the collection method, the risks and benefits, and the steps required to donate. For future uses, it is important to include possibility of re-purposing donations. It is during this period that the expectant mothers are encouraged to gather information and ask questions about procedure either directly or through a phone call or a website.

Motivated personnel at collection sites are important to approach potential donors. Training on this step is vital to make sure information provided to these mothers is real and all their questions can be answered. Another aspect to have in mind when designing a UCB program is the targeted population. It's important to understand the ethnicities, their diversity, and how to cover all patients that can benefit from this UCB program.



Educational leaflet used in Anthony Nolan UCB programme (UK)

Educational leaflet used in the Programa concordia banc sang i teixits (Spain)

After information is given, we need to obtain the informed consent of the mother donor. On this consent all aspects related with donation must be written and mothers must sign. Normally, there are questions about performing Infectious Disease Marker (IDM) tests, contacting maternal donor in case an IDM test is positive, using units for research, checking medical notes, etc. all these aspects might be covered and make sure that mothers have given their consent to them. Below, we described some ways of obtaining consent:

- Pre consent: It is preferable to obtain consent in the antenatal period of the mother's pregnancy. This allows her the opportunity to obtain information about UCB banking, to ask questions and make an informed decision regarding her decision to donate. Consent for the collection may be obtained during this period by the mother's health care provider/clinic staff or by bank staff.
- Full Consent: For mothers to give the full informed consent, they must be provided with information regarding all the procedures for collection, processing, testing, storage and use of the UCB donation. It is important that they be informed that their personal and medical information will be kept confidential. Mothers also should be counselled about how potential abnormal test results will be handled and disclosed to them and the importance for mothers to contact the UCB bank in the event that their child develops a serious illness.

Informed consent is not recommended being achieved during active labour since they can be distracted with physical and emotional stress. An alternative option has been proposed if mother arrives to the hospital in labour with no consent and it's not possible to get the consent at this time. A two-step procedure where the information given is basic, as a sort of verbal pre consent that could be signed by the health care personnel as witness, and after delivery, when mother is calm and she can understand and make questions about UCB, obtain the full consent for donation [10].

For private banks, informed consent is wider, as it's a contract between parents and bank. In this case all aspect about donation, UCB unit maintenance and future uses might be thoroughly explained there. Each bank will have their model and contract; however, aspects about informed consent might be similar than for a public bank, as most of the regulatory bodies enforce this step.

3.2.3 Donor Elegibility

After donor recruitment, a trained personnel, needs to determine donor eligibility. It's important to ensure that donation is safe for future patients. Maternal and infant donor eligibility shall be determined based upon results of screening and testing in accordance with each country regulations. To assess donor eligibility a donor medical history interview, that includes assessment for high-risk behaviors, shall be conducted identifying risk factors for transmissible and genetic diseases. The mother will be asked to provide personal and family medical details. There shall be

written criteria for maternal and infant donor evaluation and management. Results of this evaluation shall be documented and reviewed by trained personnel.

The medical history review shall be obtained while mother is able to concentrate on the questionnaire and is not distracted by aspects of labour. Language used must be understood by her. It's not recommended that neither family nor friends serve as interpreters or translators. Confidentiality shall be preserved. If responses generate medical concern the collection should be rejected or cancelled. The mother's travel history to endemic areas shall be obtained and documented and eligibility determined according to national regulations. Screening for human transmissible spongiform encephalopathy, including Creutzfeldt-Jakob disease, shall be documented. Also, for any infectious risks that could occur seasonally or in epidemics. If history for communicable disease risk was obtained in advance of the maternal donor's presentation for delivery, the history shall be updated to include information up to the time of delivery. In the case of a surrogate mother who gives birth to an infant donor not genetically hers, a communicable disease risk history of the surrogate mother shall be obtained. The questionnaire shall include questions to obtain at a minimum genetic history, malignant disease, and inherited disorders that may be transmissible to the recipient.

In addition, IDM tests, performed to maternal blood samples will be obtained within seven days before or after collection of the UCB unit. These samples will be tested for evidence of infection of HIV 1, HIV 2, Hepatitis B, Hepatitis C, HTLV I, HTLV II, Syphilis, and any additional markers according to local regulations [11]. Assays used for testing must be validated for use in volunteer blood or tissue donations. In some countries there is a requirement for a second testing for IDM after six months of donation. In Europe this is not mandatory if a determination using nucleic acid tests (NAT) at time of delivery is performed to the maternal sample.

3.2.4 Collection Techniques

A successful UCB collection should have a high collection volume, a high total nucleated cell count, be non-contaminated and have the proper documentation. These factors are necessary to produce a unit that can be used for transplantation. A UCB banking program's continued viability depends on its ability to maximize the proportion of the units that it collects that are suitable for banking and transplantation.

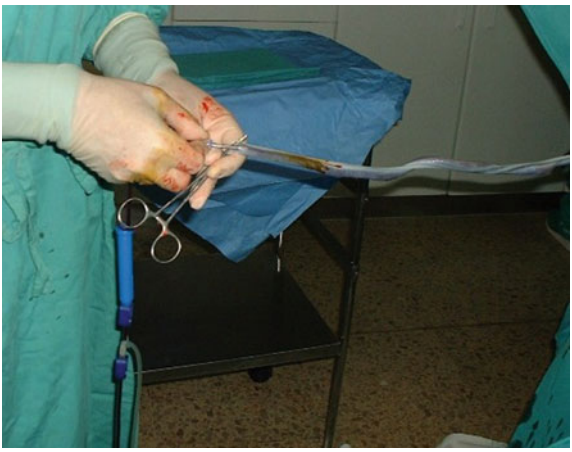
A UCB collection typically involves the following steps:

- The umbilical cord is clamped as distal from the placenta as possible. No interference with labor shall occur. Nowadays, many obstetrical medical associations recommend delay clamping [12]. Evidences suggest that an acceptable time of 1–2 min is compatible with public UCB banking [13].
- A section of the cord is cleaned with alcohol or another disinfectant.

– A needle that is attached to the collection bag is venipunctured into the umbilical cord vein.
– The collection bag is filled via gravity until the cord looks "white" and the placenta and umbilical cord are drained of the UCB bag.
– The collection bag should be labeled appropriately.

There are two main techniques to collect UCB from the cord vein: before the placenta is delivered (in-utero) or after the placenta is delivered (ex-utero). Both collection techniques have their own unique advantages and disadvantages, but both techniques require that the individuals performing the collections be adequately trained. With either technique, the collection is done in a collection bag that contains an anti-coagulant to avoid clotting:

In-Utero Collections: Collection is performed in the delivery room after the baby has been delivered and the placenta is still inside. After the baby has been assessed and the umbilical cord has been clamped and cut, the UCB is collected by venepuncture after the area of the needle insertion has been disinfected. The umbilical cord is cleaned by wiping a large area around the insertion site to clean up excess blood and then scrubbed a topical antiseptic. The UCB unit is collected by gravity, during which time the collection bag should be gently rocked to mix the blood with the anticoagulant in the bag. The collection is complete when blood stops entering the bag. The total time required for an in-utero collection by a health care provider (i.e., physician or nurse/midwife) is less than 5 min. A benefit of in-utero collection is lower collection cost, because the collection is performed by physicians and midwives rather than dedicated UCB bank personnel, and could result in higher volume collected [14].



In utero UCB collection (courtesy of programa concordia banc sang i teixits, Spain)

Ex-Utero Collections: Normally an ex-utero collection is performed by dedicated, trained staff in a separate clean collection room as soon as possible after the placenta has been delivered. This method has the benefit of not interfering with the birthing process. In the delivery room, immediately following the delivery, the physician, nurse or midwife clamps and cuts the cord before passing the placenta and cord in a recipient to the collection staff. The placenta is usually suspended on a stand or frame, allowing UCB to be collected by gravity. The cord is disinfected with an aseptic solution and the needle from the collection bag is inserted into the vein. The collection of the UCB unit can take 5–10 min and should not stop until the cord is "white" or the flow stops. Some of the benefits of ex-utero collections could include less clotting, less bacterial contamination and fewer labelling errors due to dedicated and trained collection staff, but also in less volume collected. However, the added collection staff in the hospitals adds increased expenses to a UCB bank.

Ex utero collection (courtesy of Anthony Nolan UCB bank, pictures taken by Alex Griffiths)

After collection, typically health care provider in charge will complete a report describing labour and completing variables that could be useful to release the unit like presence of fever, complications, type of delivery, etc. If there are any observation of severe adverse reactions need to be communicated according what regulatory requirement established. This should be done through the biovigilance competent authorities in Europe.

3.2.5 Donor Follow up

The UCB bank shall have a policy for follow-up of donors and for management of donation-associated adverse events. In the UCB donation, there are 2 donors, maternal and infant donor, so follow up should be done in both.

Health Questionnaire: All congenital diseases originating from bone marrow derived cells are transmissible on a hematopoietic transplant. Transmission of genetic diseases by UCB units has a higher risk than stem cells from peripheral or bone marrow donation since the disease might not be easily recognized at birth or even for some time later. It is possible that some genetic diseases will be missed as they might not be manifested until six months of life or later. So, ideally UCB bank should request information on the health status of the newborn to be provided by the family even sometime after the donation and prior to the listing of the unit. Mothers shall be provided with information to contact the UCBB if the infant donor later develops a serious disease. This second health questionnaire should be performed usually within at six months after donation but it is not generally mandatory.

Counselling: Mechanisms to inform back the family should be in place in the event of a positive test result for any IDM (other than CMV), an abnormal hemoglobinopathy screening or any other abnormal test found. Any attempt should be made to notify the mother and/or her physician. The UCB Bank shall have policies for handling specific cases.

3.2.6 Non-Frozen Transportation

After collection, UCB units shall be shipped or transported to the processing facility and sometimes, these facilities are far away from the collection sites. A validated procedure for transportation between these two facilities is needed to demonstrate a reliable method. Standard procedures shall be in place to describe current methods.

Time and temperature of storage. After collection, an appropriate conservation will be in place to preserve cell viability and potency as well as to protect the health and safety of the collection unit personnel. A validated method, which assesses maximum time for this transportation shall be in place, to assure that UCB units won't lose their viability and potency, and that they arrive at the bank in an acceptable condition. Standards require that an unrelated UCB unit is frozen before 48 h after collection.

Transportation from the Collection Site to the UCB Bank: UCB units will be transported at an appropriate temperature which will keep the integrity and safety of the cells. As happens with transportation time, a validation shall be done to have the most appropriate procedure regarding the transport conditions. For this validation, transport boxes/containers will be used and it will be performed in a standard and worst case scenarios to make sure all possible conditions are contemplated. UCB units will be transported with a validated and trained courier, following standard procedures written by the UCB Bank.

UCB collection bag will be identified with the following labels/paperwork:

- Unique UCB unit number and maternal blood
- Product name
- Collection site name
- Date/time of collection
- Name and volume/concentration of anticoagulants
- Recommended storage temperature
- Biohazard sign and/or other warning labels, following Regulatory Authorities of the country.

This collection bag shall be placed in a sealed secondary container which avoids any leakage. This secondary container shall be placed in an outer container validated to keep recommended temperatures during transportation to the processing laboratory. There shall be in place a procedure to document that the recommended temperature is kept or a continuous electronic monitor will be used. The outer container will be labeled with the product name and made using a material that avoids any leakage, pressure changes, shocks or other incident or deviation which could affect the UCB unit integrity.

All transportation records shall allow tracking back to the UCB unit from the collection site to the UCB Bank and any deviation reported. Transportation records shall identify the personnel at the collection site responsible for the transportation, date/time of transportation, identity of the trained courier and date/time of reception at the bank's processing lab. Upon receipt, the integrity of the UCB units and their containers will be checked and any deviation will be recorded within the processing records.

3.3 Umbilical Cord Blood Processing and Storage

A UCB bank must have appropriate facilities and personnel for the receipt, processing, testing and storage of UCB and maternal blood. All processes should be performed in compliance with the Regulatory Authorities of the country where the bank is located. Where aspects of processing, testing or storage are performed by an external party to the UCBB, there must be a written agreement in place between the bank and the external party providing the service. Below we describe processing aspects in place in our UCB banks.

3.3.1 Banking Structure and Resources

Processing Laboratory

The UCB Processing laboratory needs to be secure and have adequate space to perform all activities in a safe and sanitary manner. There must be a well-documented process for cleaning and sanitation. Relevant environmental conditions, such as temperature and humidity, need to be defined by the bank and monitored. Environmental monitoring including colony growth and particle counts should be carried out on a regular basis to ensure the facility maintains within the acceptable limits that have been set within the standards. The data on environmental monitoring should be recorded and trended over time to identify early any rising risk to the processing facility.

Cryogenic Storage Area

UCB units are stored in either liquid or vapor phase liquid nitrogen at −150 °C or colder. In order to maintain long term stability all refrigerators, freezers and cryostorage tanks used for storage of UCB units, associated reference samples, and maternal samples, have a system to continuously monitor or regularly record the temperature. In addition, there use alarm system in place 24 h a day in order for staff to be notified immediately, and with adequate time to respond, if a problem occurs with rising temperatures or liquid nitrogen levels. Finally, the processing laboratory needs additional storage devices of appropriate temperature in the event that a primary storage device fails.

Cryogenics area in Anthony Nolan cell therapy centre-UK (Picture taken by Stephen Pennells)

Long-term storage device in the clean room of the barcelona UCB bank (Banc Sang i Teixits, Spain)

Testing Laboratories

The UCB Processing laboratory has testing control procedures in place to support the processing and characterization of UCB units. This is vital to ensure the integrity and quality of the UCB unit in terms of how well the unit will engraft post-transplant, but also to ensure the safety of the recipient with respect to transmission of disease and microbial contamination. Where a specific test is not performed by the UCB processing laboratory per se, the UCB Bank needs to have agreements in place with the external parties who perform these tests on behalf of the Bank. Testing should be undertaken in accordance with that required by the Regulatory Authorities of the country where the bank is located. Testing control procedures need to ensure the use of established and validated appropriate assays, standards, and test procedures for the evaluation of the UCB unit, with appropriate identification, linkage and handling of all reference samples.

3.3.2 Reception and Process Acquisition

Reception

The decision as to whether a collected UCB unit will be acceptable for processing and banking will be made based on the acceptance criteria specified by the bank. The acceptance criteria will include parameters such as UCB volume, total nucleated cell (TNC) count, factors identified by maternal and family history, transport conditions and cell viability. UCB unit acceptance criteria adopted by each bank should be based on rationale and justified, usually based on quality and safety of the end product. However, many banks have further refined their acceptance criteria based on economics and the desire to build an international inventory of UCB units with very high TNC or percentage of ethnic minorities. UCB units of high TNC are

highly desirable for adult transplants, where there is a positive correlation between number of TNC infused/kg and successful transplant outcome. Many UCB banks are now committed to processing and storing only those UCB units with high TNC (ex. > 120 × 10^7 TNC), based on the greater likelihood of these units being used and balanced against the cost of processing and storage of UCB units with lower TNC that have a low likelihood of being requested for transplant [15].

Triage

The collected UCB unit should be received at the processing laboratory in a validated, secure, temperature-monitored transport container. On receipt of a shipment a series of checks need to be performed on the collected UCB, associated samples, and documentation to verify contents and determine if the specific acceptance criteria are met.

Initial triage of a collected UCB unit and determination of its acceptance to continue to processing will be based upon parameters such as volume, TNC content, correct documentation and labeling, signed maternal donor consent, appropriate transport temperature, absence of large/multiple clots and acceptable time in transit from collection center to processing laboratory. For NetCord-FACT accredited UCBBs, the unrelated UCB unit must arrive at the processing laboratory in time to allow initiation of cryopreservation within 48 h of collection (this time is extended to 72 h for related or directed UCB donations).

Acquisition to Process

Once a UCB unit meets the initial acceptance criteria, as described above, it will continue on to be processed. The processing of UCB units is an expensive and time-intensive exercise and the establishment of appropriate initial acceptance criteria by a bank will ensure that only those UCB units of the highest quality are processed.

3.3.3 Volume Reduction

Volume reduction of UCB is considered essential to the provision of a high-quality product and cost-effective UCB banking. The final product volume and cellular characteristics are dependent on the collected starting product as well as the processing/separation methodology.

Rationale

Reducing the volume of the final product increases the stem cell yield available for transplantation. It allows for storage efficiency in terms of space and cost, and, most importantly, reduces the risk of ABO incompatibility and DMSO toxicity to the potential recipient [16]. Despite some loss of cells, volume reduction has additional practical and clinical benefits; the process yields RBC and plasma components as waste products that can be used for immediate or future testing, thereby minimizing the loss of the actual stem cell product for testing purposes.

Methods

Early attempts at volume reduction resulted in unacceptably high loss of haematopoietic progenitor cells (HPC). Over the years a variety of techniques have been explored, including density gradients, RBC lysis and differential sedimentation; however, most were unsuitable for large-scale banking as they were manual, labor intensive and employed open systems.

Over the past decade there have been three major methods used in large-scale banking which produce reproducible results that could be standardized (reviewed by Armitage [17]). These include the manual hydroxyethyl starch (HES) method, the semi-automated bottom and top method—BAT process, and the newer fully automated and programmable closed systems—Sepax (Biosafe SA, Eysins, Switzerland) and AXP™ AutoXpress™ (ThermoGenesis Corporation, Rancho Cordova, CA, USA) and more recently the SynGenX—1000 system (SynGen, CA, USA) which were designed specifically for the UCB banking market, although the latter is now discontinued for UCB processing. More recently, other UCB processing platforms have entered the market, such a Prepacyte-UCB, which utilizes a proprietary reagent for UCB processing and is being utilized by some banks. Additional platforms being assessed by those in the field include novel filtration methods and double extraction techniques.

Expected Results

Several groups have performed or reviewed in-depth comparative analyses of the various UCB processing platforms being utilized by UCBB around the world. These studies have evaluated TNC and $CD34^+$ recovery as well RBC reduction and colony forming unit (CFU) assays to evaluate engraftment potential. Each system has its advantages and disadvantages, with no one system at this stage being clearly superior to the other [18].

Whichever platform is employed by the bank for UCB processing, it is essential that the equipment and reagents used do not adversely affect the viability of the UCB units and that the process does not allow the introduction of adventitious agents or the transmission of communicable disease.

Acceptable end points for processing of UCB should be defined by the bank, based on documented rationale and validation. Examples of desirable end-points are:

- A minimum threshold for post-processing TNC recovery. Based on the literature, ideally this would be 70% or greater.
- A target range for RBC depletion
- A target limit for final volume after processing
- A target limit for viability.

3.3.4 Cryopreservation

The selection of a suitable protocol for cryopreservation of UCB for use in transplantation is critical to optimize the recovery of functionally viable progenitor cells, most of which lie within the CD34+ compartment. Some important considerations that are potential sources of cell damage include the type and concentration of cryoprotectant, the cell concentration, and the cooling and warming rates.

SOPs related to cryopreservation should specify that the following information is recorded for each unit:

- TNC concentration within a defined range
- The cryoprotectant, its final concentration, and the duration of the cell exposure prior to freezing
- Method of freezing and end-point temperature of cooling
- Cooling rate within a defined range
- Freezing curve parameter within a defined range
- Storage temperature.

UCB units must be stored in freezing bags designed and approved for the cryopreservation of human cells and placed into metal canisters to afford protection during freezing, storage, transportation and shipping. It is important that after filling, each freezing bag is visually examined for possible leaking and breakage of seals.

Cryoprotectant

Dimethyl sulphoxide (DMSO), a membrane permeating molecule, has been used for over 30 years as the cryoprotectant for freezing HPC, almost exclusively in a final concentration of 10%, although there are some reports to indicate that a 5% concentration is also appropriate. In general, a concentration of 10% DMSO is considered optimal for UCB.

Dextran-40 is a neutral polysaccharide of high molecular weight that does not easily permeate white blood cells and maintains a favourable osmotic environment. When used in conjunction with DMSO, Dextran-40 enhances the cryoprotective effect by allowing stabilization of the cell membrane.

While alternatives have been proposed, it is generally considered that a concentration of 10% DMSO and 10% Dextran-40 results in the best recovery rates for TNC, CD34 + and colony-forming units (CFU) and is therefore the ideal cryoprotectant [19].

Prolonged exposure of cells to DMSO can result in damage to cells. It is therefore essential that the duration from addition of cryoprotectant to initiation of freezing is minimized and the time allowed is validated by the cell processing lab.

Controlled Rate Freezers

Ideally, UCB units should be cryopreserved using a controlled rate freezer with a validated freezing program. Most, but not all, banks use cooling rates of 1–5 °C/min in order to allow the cells to slowly dehydrate as the ice phase progresses and the extracellular solute concentration increases. Traditionally liquid nitrogen-based

controlled rate freezers have been used, but newer technologies now use electric based engines to freeze down the cells in a controlled manner. This would allow for UCB banks without a strong liquid nitrogen delivery system to freeze UCB without compromising quality.

Where controlled rate freezing is not performed, an equivalent procedure, such as "dump freezing", may be used. If an equivalent procedure is used, it must be validated to maintain equivalent recovery and viability of nucleated cells. Although this is a suitable method, controlled rate freezers can compensate for the latent heat released when the UCB freezes below a certain temperature, which reduces ice formation within the cell. Ice build-up during freezing can have detrimental effects at the point of thawing to stem cell viability. The controlled rate freezing method for UCB is usually considered standard.

Cryo-freezing bag (courtesy of Anthony Nolan UUCB bank; picture taken by Stephen Pennells)

3.3.5 Testing and Product Conformity

Quality Assessment

UCB banks aim to provide a high-quality product capable of reconstituting a patient's immune system by preserving the ability for the stored cells to home to the bone marrow and repopulate the haematopoietic system in a timely fashion. As there are numerous different methodologies to collect, process and store UCB, each being a potential source of variability, reproducible manufacturing methods need to be adopted to ensure process consistency, reliability and more importantly predictability. Critical quality attributes (CQAs) are employed to select and compare whether the product will achieve this. The complexity of identifying characteristics of a cell population that guarantee its function is argued by some to be unachievable with current technology due to the complexity and number of potential dimensions in the data sets, and limited knowledge of mechanism of action.

We may have quasi-CQAs such as TNC count, CD34 expression, and the colony forming potential to monitor the effectiveness of the processes employed and to determine the impact, allowing assessment techniques to quantify variability inherent to the repertoire of processes and donor variability.

UCB users rely on the rigorous assessment carried out in banks to avoid poor engraftment post thaw and that cellular enumeration is used as a surrogate of graft potency in the absence of a better marker such as CD34+ , CFU or cellular viabilities due to ease of standardisation across all banks. As is accepted in bone marrow transplant (BMT) hematopoietic potential is proportional to the TNC and thus correlates to transplantation endpoints. Evaluating transplant data and by observation of UCB usage it is apparent that TNC is the greatest attribute (after HLA disparity) transplant Centre's (TC) consider during unit selection. As a result registries will facilitate algorithms that put the greatest emphasis on TNC dose above any other cellular attribute. TNC is of critical importance in predicting graft success alongside HLA disparity and that increasing TNC dose can mitigate the disadvantages of a greater HLA disparity at 5/6 level match. Other factors such as the colony forming unit (CFU) assay and markers such as CD34+ have been shown to correlate to engraftment however these factors are not weighted highly in selection algorithms.

A UCB bank must be able to confirm testing and product conformity in order to be able to release a UCB unit for transplant. All tests performed must use established and validated relevant assays and, if required, comply with that mandated by local Regulatory Authorities.

Safety

In order to provide a safe UCB product for release, it is essential that UCB is screened for those infectious diseases which can be transmitted via blood. Maternal blood obtained within 7 days before or after the collection of the unit is used as a surrogate test for IDM, and is strongly reflective of the infectious status of the UCB units due to the shared circulation during gestation. Testing the UCB unit for IDM provides an additional degree of safety. At a minimum, prior to release for administration, the maternal donor of each UCB unit must be tested for evidence of infection by at least the following communicable disease agents using licensed donor screening tests when available according to national regulations (below a list of virus to test is presented as required by Netcord-FACT standards):

- Human immunodeficiency virus, type 1
- Human immunodeficiency virus, type 2
- Hepatitis B virus
- Hepatitis C virus
- Human T cell lymphotropic virus, type I
- Human T cell lymphotropic virus, type II
- Treponema pallidum (syphilis)
- Any additional agents required by national regulations.

UCB units for unrelated use must be shown to be free of microbial contamination. Microbial testing must be performed using a system validated for the growth of aerobic and anaerobic bacteria and fungi.

Prior to release for administration, each UCB unit must have undergone hemoglobinopathy screening. Abnormal red blood cell diseases are carried by populations previously considered unable to be affected by them, and therefore hemoglobinopathy testing must be performed regardless of the family's ethnic background or history.

Identity

An error in UCB unit identity could be catastrophic to a transplant recipient and it is therefore imperative that all identity checks are performed on a UCB unit prior to release for administration [20].

Human leukocyte antigen (HLA) typing must be performed on a reference sample from each UCB unit. HLA-A, B and DRB1 loci must be determined using DNA-based methods and result included when listing a UCB unit on the search registries. Many transplant centers also use HLA-C and DQB1 matching in their UCB unit selection algorithm, and therefore the UCB Bank may also wish to determine and report HLA-C and DQB1 typing. At a minimum, DNA high resolution molecular typing must be performed for Class II DRB1 typing prior to release for administration. It is recommended that HLA typing is performed in an accredited laboratory.

Prior to release of a UCB unit for administration it is imperative that HLA-identity of the UCB unit to be shipped is confirmed to match that of the UCB unit requested for transplant. This is known as confirmatory HLA typing. Ideally, confirmatory typing will be performed on a sample taken from a contiguous segment of the UCB unit. However, this is often not possible in older UCB units, prior to the requirement for contiguous segments, and therefore processes must be in place to ensure linkage between the reference sample used for HLA typing and the UCB unit. The use of a contiguous segment to verify UCB unit identity through HLA typing of a UCB unit is considered critical to patient safety.

HLA typing on maternal blood may also be performed prior to release of a UCB unit. Haplotype matching between maternal donor and infant donor confirm linkage between the two and serves as a secondary confirmation of identity. Furthermore, many transplant centers now consider non-inherited maternal allele (NIMA) matching as part of their analysis of transplant outcome, which is not possible if maternal HLA typing is not performed.

ABO blood group and Rh type must be reported prior to listing a UCB unit for search and confirmed, if possible. Nowadays using NGS approached all these genetic tests can be done once with very few sample requirement (i.e. attached segments of the freezing bag) [21].

Purity

The purity or cellular content of a UCB unit is often an important factor in selection of a UCB unit for transplant. It is now well-established that a minimum of 2.5–

3×10^7 TNC/kg is required to ensure the best chance of engraftment and favorable outcome post UCB transplant. Since the number of TNC infused per kg will be dependent upon the size of the recipient, it is highly desirable the UCB units contain a high number of TNC (ideally greater than 120×10^7).

The total nucleated red blood cell count (nRBC) must be reported. This is in order to allow determination of the contribution of nRBC to the nucleated cell population for the Transplant Center to facilitate an informed UCB unit selection.

CD34 is a surface glycoprotein present on stem and progenitor cells, and the number of CD34+ cells in a UCB unit provides an indication of the number of stem / progenitor cells available for transplant. The total number of CD34+ cells is key to be reported since there are one the most important predictor of engraftment [22].

In order to screen for any hematological abnormalities the infant donor may have, a cell blood count with differential should be performed, with parameters for neutrophils, lymphocytes, monocytes and platelets defined.

Potency

Potency testing to determine the growth potential and viability of progenitor cells in a UCB unit should be performed post-processing (prior to cryopreservation), in addition to being performed on a thawed sample prior to release for administration.

Viability and/or potency can be assessed measuring viable CD34+ cells in the UCB unit using flow cytometry and/or by colony forming unit—assay (CFU) to enumerate clonogenic hematapoietic progenitor cell (HPC) growth and differentiation in semi-solid media. Potency assays should be performed both post-processing (prior to cryopreservation) and post-thaw, as the cryopreservation and thawing process inevitably leads to some loss of viability of cells; studies have shown that the post-thaw viability or potency of HPC are a more accurate indicator of how a UCB unit will perform post-transplant than the post-processing cell viability/potency results [23].

3.3.6 Inventory Management

The storage of UCB units and associated reference samples must be in a secure storage device, stored in a secure location. The storage device and/or area must be locked when the area is not occupied by Lab staff.

There must be an inventory management system to ensure that each UCB unit and its associated reference samples, maternal samples, and records can be located in a timely manner. This inventory management system should be designed in such a way to prevent mix-ups, contamination of the UCB units during storage, and the improper release of quarantined UCB units.

The inventory management system must be designed in a way to address the duration of the storage for cryopreserved UCB units. The UCB Bank, or facility storing the UCB units, needs to validate the duration and conditions of storage, with particular attention paid to the effects of long-term storage on UCB unit viability, function, and/or stability.

Quarantine

There must be procedures defined and maintained to minimize the risk of microbial cross-contamination of UCB units.

Each UCB Bank needs to have an SOP to define when a UCB unit can be released from quarantine. Each UCB unit must remain in quarantine storage until the UCB Bank Director or delegate has approved the release of the UCB unit from quarantine status based upon satisfactory testing and screening results pertinent to that UCB unit, and as required by the relevant Regulatory Authorities. Quarantine may be temporal, physical, or a designation within the UCB unit record.

Supplies, Reagents, and Equipment

The inventory management system must include a system to document receipt, inspection, verification, acceptance and storage of all critical supplies and reagents used for UCB processing.

It is important that refrigerators and freezers used for the storage of UCB units and all associated reference samples, and reagents used in UCB unit collection, processing or cryopreservation should not be used for any other purpose, in order to minimize the risk of cross-contamination.

Transient Warming Events

UCB units must be stored at −150 °C or colder. There is the potential for significant warmings events to occur when the UCB unit temperature rises above −123 °C [24]. Each UCB Bank needs to assess the potential risk within their processes for transient warming events to occur, such as when a UCB unit is outside of its proper storage temperature for extended periods of time. Examples of these opportunities include transfer of UCB units from the controlled rate freezer to the cryostorage tank, removal of segments for confirmatory testing and storage of UCB units in vapor vessels that may exhibit unstable temperatures when open. Each of the relevant scenarios pertinent to a bank's operations should be validated to show that at the end of processing and all accumulated transfers, the viability of the UCB unit has not been compromised.

Any warming events that may occur after the process of storage must be minimized in order to prevent the occurrence of transient warming events.

3.4 Use of Umbilical Cord Blood for Transplantation

Once a UCB unit is produced and validated, it should release for listing to a stem cell registry that made them available for any patient in need. Physicians on behalf their patient requiring bone marrow transplant procedures might search in these inventories to find the UCB unit that better match patient requirements.

UCB unit are made ready for listing in reference stem cell registries after comprehensively reviewing characteristics for each UCB unit, including maternal donor selection and maternal and infant donor evaluation for the specific medical requirements and testing and product conformity for the minimal product requirements. It is the bank responsibility to be able to ensure that the information provided to the Transplant Center is correct and complete.

3.4.1 Selection Principles

UCB unit selection is performed by transplant physicians usually with the help of transplant coordinators and the advice of HLA experts. They must provide full information on the patient including:

- age, sex, weight
- Diagnosis, stage of the disease, urgency of the transplant
- ABO and Rh blood group
- Infectious diseases marker results
- High resolution HLA typing for −A, −B, −C, −DRB1.

Transplant centers can send their search request to different organizations according to national regulations and registry policies.

Selection criteria may vary between transplant centers but there is a consensus provided by different organizations. For instance, in Europe, the Eurocord group edited a recommendation of how a UCB unit needs to be evaluated to benefit different types of patients [25]. This was also recently published in USA by National Marrow Donor Program (NMDP) and Center for International Blood and Marrow Transplant Research (CIBMTR) [26].

3.4.2 Request for Shipping

The bank must receive a formal request from a transplant center before the work up will start. Return of unrelated UCB units is generally not permitted by international standards. Next to reviewing the list of characteristics of a UCB unit, the bank must perform some required tests before the UCB unit will leave the bank premises.

Verifying UCB unit identity: UCB unit identity can be verified by performing HLA typing using a segment which is still connected to the freezing bag containing cryopreserved UCB cells. The UCB bank should have a policy in place for the cases where there are no remaining attached segments.

Verifying UCB potency: It is required to assess the functional capacity of the UCB unit prior to release to the TC. CFUs are grown from functionally viable cells and increase confidence in UCB unit quality and ability to engraft. Therefore, it is recommended to perform CFU from a frozen segment (or a UCB unit sample based on UCBB alternative policy) prior to release for administration.

Confirming safety if required: IDM testing of the maternal samples is understood to be a surrogate test, and strongly reflective of the infectious status of the UCB unit since the circulation is shared during gestation. Prior to release for administration the results of maternal donor screening tests (HIV1/2, HBV, HCV, HTLV-I/II and Syphilis) should be available. Because of differing requirements by various National regulations, transplant centers may require additional IDM test results.

3.4.3 Frozen Transportation

Cryopreserved UCB unit shall be transported or shipped in a liquid nitrogen-cooled dry shipper to maintain a temperature of −150 °C or colder for at least 48 h beyond the expected time of arrival at the receiving facility. It is mandatory to measure and to document the temperature in the dry shipper throughout the period of transportation or shipment. UCB banks need to arrange how the transport container will be returned to the bank.

The courier should be educated on how to handle the dry shipper and how to take care of the UCB unit. A plan for an alternative transportation or shipping in an emergency should be available. The identity of courier must be known and documented. Tracking and tracing of the transportation of the UCB unit in the dry shipper from the UCB bank to its final destination as well as information about the date and time of packaging and leaving the bank should be documented.

Information about date and time of receipt of the dry shipper and the UCB unit. The use of a reception form to note this information is preferred, including the questions about integrity and internal temperature of the dry shipper and integrity of the unit arriving at the final destination. The problems during transportation include temperature of cryoshipper, condition of UCB unit freezing bag when received at transplant center and post-thaw viability issues. When a problem is detected, this may generate delays in transplantation. It is important to notice that UCB unit shall be received at transplant center before starting any conditioning procedure.

3.4.4 Thawing and Infusion

It is important to ensure the TC receives information on how to handle and use the UCB UNIT. Handling includes thawing and washing of the UCB UNIT. Providing information about indications, contraindications and cautions is the responsibility of the UCBB. A jointly prepared document called Circular of Information for the Use of Cellular Therapy Products is available (www.ISCT.org or www.factwebsite.org). Next to this Circular, banks should be able to provide instructions for a validated thawing process of their UCB unit and the results of the validation. In general, there are three ways to administer the UCB product: direct infusion; 1:1 volume dilution with a hyperosmolar buffer (generally dextran and albumin mixture); or in cases where the infusing volume is too high or the product contains an excess of RBC using an additional washing step after dilution [27].

3.4.5 Transplantation Outcomes

UCB banks need to get information on transplant outcomes in order to fulfill requirements for accreditation as a control of quality of the unit. This information can be provided either by the transplant centers or through outcomes registries such as Eurocord or NMDP-CIBMTR. WMDA also collects severe adverse effects.

UCB banks must provide information on UCB unit characteristics (UCB ID, TNC and CD34 cell counts, HLA typing, ABO, infectious disease markers, date of collection and details on cell processing, cryopreservation, and shipping) to the registry of the transplant center. The transplant center registry will contact the transplant centers and collect information on transplant characteristics and outcomes. A specific form is sent to the center each time a UCB unit is released. Data are typically collected at 3, 6, and 12 months after transplant then annually after that.

The information required may include:

- Patient and disease characteristics
- Conditioning regimen and graft versus host disease (GVHD) prevention
- Numaternal blooder of cells infused
- Early adverse events
- Date of neutrophil and platelet engraftment, chimerism
- Acute and chronic GVHD
- Infectious complications and toxicity
- Relapse
- Transplant related mortality at 3, 6, 12 months and then annually.
- Overall survival and disease free survival.

Outcome data can be sent to the cord banks on request. Overall results are published every year by Eurocord-EBMT, NMDP-CIBMTR, WMDA and other organizations.

Collection of outcome data provides important guidelines on donor selection, indications, role of HLA, prognostic factors and comparison with other stem cell sources [28].

3.5 Future Challenges for Umbilical Cord Blood Banking

A banking project can be divided into two distinct developmental phases. First, the establishment phase where banks should have a rapid growth to achieve their operational size. For that, large collection programs are required to select and process the best donations. This phase normally requires public or charitable funding to compensate the decrease on effective rate of use during inventory growth. Second, the maintenance phase once the optimum inventory is achieved where UCB banks should focus in increasing quality and diversity. As consequence

a decrease in numbers of newly added units are expected. The fact that less than 20% of collected units have more than 150×10^7 total nucleated cells (TNC), estimated to be the threshold for efficient inventories, challenge the ethics of donation programs. More efficient programs are required to ensure collected UCB units meet clinical requirements. The maintenance phase requires very different banking structures for sustainability. Integration with other cell therapy services will reduce fix costs of operation. Finally, UCB banks need to research alternative uses of UCB to add value to the available inventory. We recently reviewed these vision in order to propose this evolution for future developments of UCB banks.

UCB Bank 2.0

A new public UCB bank project should be re-formulated to solve these inefficiencies by improving HSC registry service, reducing numbers of discarded donations, and developing a multidisciplinary cell therapy platform, in structures with low operational costs. Thus, the integration in bigger institutions like blood banks or cell therapy laboratories makes sense. UCB banks should focus efforts in developing new applications of innovative UCB-derived products and services within the following areas [29]:

(1) Improving donor provision service:

In the general inventory, many UCB units have very limited information on their specifications. This generates a number of uncertainties about the final characteristics of these units and a time delay in the donor selection process. Availability of NGS technology allows the upfront characterization of the best UCB unit to minimize releasing times. Developing an off-the-shelf, ready-to-use, high quality inventory of pre-released UCB units will help clinicians to fasten their decisions.

(2) Researching new cellular sources for advanced therapy medicinal products (ATMPs)

Developing a well characterized UCB panel will facilitate the use of these units for other applications. There are proposals formulated in the scientific literature covering areas of cellular immunotherapy and regenerative medicine that need further development. Third-party donor banks of Tregs, NK cells, antigen-specific T cells and iPS have been proposed. Availability of a large pool of GMP-compliant products could be used as starting materials to develop new ATMPs.

(3) Developing blood hemocomponents

High proportions of routinely and aseptically collected units of biological material donated by carefully qualified donors screened for transmissible diseases, whose data are registered in fully traceable electronic data sets, offer the opportunity for novel products development. Some innovative products developed from UCB

blood components have been described like cell and tissue culture media derived from UCB plasma and platelets, platelet gel for wound healing, plasma and serum eye drops, and even red blood cells for transfusion to preterm infants.

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