Cord Blood Donor Qualification

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Ngaire J. Elwood

8.1 Introduction

Cord blood (CB) donor qualification is an active process to determine suitability and safety of a CB unit (CBU) for clinical use. In the context of hematopoietic cell transplantation (HCT), the CBU must be suitable and safe to provide long-term hematopoietic reconstitution posttransplantation. The hematopoietic $CD34^+$ cells contained within a CBU must be able to engraft post-infusion into the bone marrow niche in order to self-renew, proliferate, and differentiate into all lineages of the hematopoietic compartment to restore hematopoiesis. Therefore, the $CD34^+$ cells must engraft and result in successful patient outcome and the CB must not transmit infectious disease or genetic abnormalities.

The CB donor is the newborn baby. Consent on behalf of the donor is given by the mother (and sometimes father), who is considered a "surrogate". Sometimes, for clarity of documentation, the delineation of CB donor may be broken down to "infant donor" or "maternal donor." An infant donor is a newborn from whose placenta or umbilical cord the CBU is obtained. A maternal donor is the mother who carries the infant donor to delivery (FACT 2016). This may be the genetic or surrogate mother; knowledge of which is important for donor qualification.

In contrast to other types of hematopoietic progenitor cell (HPC) donors, where the cells are usually used within a short time of the donation, a CBU donation is stored long term. Therefore, there is the potential to perform follow-up medical history of mother and donor (infant) and repeat infectious disease testing on the

N.J. Elwood, Ph.D.
BMDI Cord Blood Bank, Murdoch Children's Research Institute, The Royal Children's Hospital, Parkville, VIC, Australia

Department of Paediatrics, University of Melbourne, Parkville, VIC, Australia
e-mail: ngaire.elwood@mcri.edu.au

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mother, if desired. This potential is to be maximized for CBU donor qualification. The majority of unrelated CB banks (CBBs) around the world collect, process, and store CB for the purposes of unrelated CB transplants (CBT). CBU donor qualification is therefore vital prior to long-term storage, as these products may be stored for many years before they are released to patients. The content of this chapter is directed toward CBU donor qualification for unrelated CBBs, but it is also relevant for those CBBs storing family or related CB units for CBT. The degree of qualification and the acceptable minimum criteria may not need to be as stringent within the family CBB setting due to autologous or directed use of these CBU.

The parameters that can and should be considered for CBU donor qualification include quality, infectious disease screening, and genetic risks. Steps include donor history questionnaire, genetic screening, and infectious disease testing and product quality assessment.

8.2 Cord Blood Donor Qualification Process

8.2.1 Recruitment of Potential Donors

The CB donor selection commences with an expectant mother deciding to donate her infant's CB to a CBB. Sometimes this decision might be the result of a mother proactively investigating CBU donation options but more often is a result of targeted recruitment by the CBB. This may be in the form of brochures or information provided during antenatal care, may be a conversation with an obstetrician or midwife, or may be via active recruitment at the time of delivery.

8.2.2 Informed Consent

Prior to the collection and processing of CB, informed consent must be obtained from the maternal donor (and in some CBBs also the other partner with parental responsibilities) for the CBU to be collected, processed, tested, stored, and administered for CBT and potentially for research. A CBU will only be acceptable for banking and distribution if appropriate informed consent has been obtained. In the case of family banking, this consent may be in the form of an agreement between the CBB and the family. For unrelated CBB, the information provided to potential donors and the consent process will have been approved by an appropriate Institutional Review Board (IRB) or Human Ethics Committee and must comply with applicable law relevant to that country and any published code of practice on consent. The "informed consent" procedures should be designed to protect the interests of the infant donor's family and educate the maternal donor about the various options for CBU use. Furthermore, it is important that the "informed consent" or an agreement between the mother and the CBB is obtained and documented while the mother is able to concentrate on the information and is not distracted by the labor

during the process. Thus, some CBBs will use "mini-consent" or "consent for collection only" if the mother is progressed in labor, with a full consent being obtained after delivery but before any processing of the collected CBU takes place. CBU donor qualification must ensure that an approved consent or agreement process is in place and that appropriate informed consent has been obtained for the CBU collection, processing, testing, storage, and use.

8.2.3 Donor History Questionnaire

CBU collection starts with the recruitment and screening of potential donors, usually by ensuring up-front such expectant mothers who would like to be CBU donors and meet requirements similar to those set by AABB's hematopoietic progenitor cell, CB donor history questionnaire. Prior to, or following, the successful collection of CBU, the maternal donor will be asked to complete the donor history questionnaire relating to parental and family health, travel, obstetric, and delivery history. Since the only way that the CBU could be exposed to infectious disease is via the placenta while in utero, maternal blood is used as the surrogate to screen for infectious disease markers.

When a potential maternal donor indicates an interest in donating CBU to an unrelated bank or sometimes soon after they have provided consent for CBU collection and had the CBU collected, an initial screening is undertaken to exclude donors whose CBU may provide a potential risk for transmission of diseases such as hepatitis B and C, HIV-1 and HIV-2 (AIDS), syphilis, and HTLV-I and HTLV-II. CBBs require that the maternal donor complete a CB donor history questionnaire (DHQ), where key questions are asked to identify risk factors for infectious diseases that can be transmitted by transfusion. The types of questions asked are sensitive and personal (Table 8.1), but questions should be answered accurately. Through asking such questions, it is often possible to exclude high-risk donors at this early stage of the donation process, thereby saving time, resources, and money from going through with the collection process or, if the CB has already been collected, from processing, testing, and storing the unit long term.

Every CBB will have written criteria against which the mother and infant are evaluated in terms of their eligibility as a CB donor. Accrediting bodies, such as the Foundation for the Accreditation of Cellular Therapy (FACT), do not define an acceptable donor but instead require that the CBB define its own specifications for CBU banking. Many CBB will use the criteria outlined by their local authorities (e.g., FDA) or will use the guidelines to develop guidelines specific to CB. Ideally these guidelines will provide the acceptable answers to questions that are asked in a comprehensive maternal and family history questionnaire, which includes questions regarding travel and infant donor birth details, and then provide guidance as to how to manage answers that are unacceptable for that CB to be stored for banking or used for CBT. The guidelines used to evaluate the answers to the questions are beyond the scope of this chapter but should reference each disease or issue and provide guidance as to whether to accept or reject the CB.

Table 8.1 Cord blood donor history questionnaire example (Source: AusCord Donor Declaration)

To the best of your knowledge have you	
1.	Ever thought you could be infected with HIV or have AIDS?
2.	Used drugs by injection or been injected, even once, with drugs not prescribed by a doctor or dentist in the past 5 years?
3.	Ever had treatment with clotting factors such as Factor VIII or Factor IX?
4.	Ever had a test that showed you had hepatitis B and C and HIV or HTLV?
5.	Received a blood transfusion or injection of blood or blood products (red cells, Platelets, granulocytes, or plasma) in
5a.	The United Kingdom (i.e., England, Scotland, Wales, Northern Ireland, the Channel Islands, Isle of Man, Gibraltar, and the Falkland Islands) or France **after 1 January 1980**?
5b.	Central/South America or Mexico **ever**?
In the last 12 months have you	
6.	Had an illness with swollen glands with a rash, with or without a fever?
7.	Engaged in sexual activity with someone you think would answer "yes" to any of questions 1–6?
8.	Engaged in sexual activity with a **new partner** (less than 12 months ago) who currently lives or has previously lived overseas?
9.	Engaged in sexual activity with a male who you think might be bisexual?
10.	Been a sex worker (e.g., received payment for sex in money, gifts, or drugs)?
11.	Engaged in sexual activity with a male or female sex worker?
12.	Been imprisoned in a prison or lock-up?
13.	Had (yellow) jaundice or hepatitis or been living with, or had sex with, someone who has?
During pregnancy have you	
14.	Been injured with a used needle (needlestick injury)?
15.	Had someone else's blood or body fluid splash to your eyes, mouth, nose, or to a broken skin?
16.	Had a tattoo (including cosmetic tattooing), skin piercing, electrolysis, or acupuncture?
17.	Had a blood transfusion or injection of blood or blood products (red cells, platelets, granulocytes, or plasma), including an intrauterine transfusion?

Maternal and infant donor evaluation and management are critical components of CB donor qualification.

8.2.3.1 Family Medical and Genetic History

A maternal history is taken to identify infectious or genetic disease in the mother that may affect the HPCs of the fetus, either by placental transfer or by genetic inheritance. Key questions are asked of the mother in order to cover the full scope of potential medical issues, which can then be delved into should a positive answer be given. A detailed family medical and genetic history with specific questioning is crucial. A range of medical and genetic diseases can be transmitted from either parent to the fetus and, if affecting the hematopoietic lineage, be passed on through the donor to a recipient of the CB. Thus, the history must document all diseases that

occur in the family and must include family on both the maternal and paternal side. It is important to have documented history of problems in parents, children, grandparents, aunts, uncles, and cousins. Some diseases may not be apparent in the newborn until after 6 months of age, and hence, where possible, a CBB should impress on mothers the importance of remaining in touch and informing the CBB of changes in the health of the infant. In assessing CB donor qualification, it is also important to ask questions about the family ethnic background**.** Some genetic diseases are more prevalent in specific racial groups, e.g., sickle cell disease in African, African-American, and Middle Eastern individuals; thalassemia in individuals from Mediterranean and Asian countries; and rare, recessively inherited metabolic diseases and immunodeficiency disorders in racial groups where consanguinity has been common.

8.2.3.2 Obstetric History

The CB donor qualification assessment should also include a full review of obstetric history (for both for pregnancy and delivery). The prime risk during pregnancy relates to exposure to infections and to medications, where the importance of most medications is the disease for which they were given. As part of the CB donor qualification assessment, it is important to identify that the infant donor is healthy and well at the time of birth and thereafter. Labor and delivery information, as well as physical assessment of the mother and baby, is documented as part of donor qualification. Physical or laboratory abnormalities identified at birth may, apart from leading to exclusion of the CB, reflect a disease in the newborn baby. An illness in the perinatal period may indicate that the CB is not suitable for use.

8.2.3.3 Travel History

A maternal travel/residency history is an important aspect of CB donor qualification. Certain countries have an increased frequency of infectious diseases (such as HIV, Chagas disease, Ebola virus, Zika virus, and malaria). If the mother is infected, this disease may be transmitted via the placenta to the fetus. It is important for the CBB to record details of country of travel/residency, as well as year(s) of residency and duration of stay, that can then be assessed to determine CB donor qualification. Each CBB will usually refer to a table or document (often based on the local blood authority guidelines in their country) that classifies countries and regions for the purpose of assessing possible maternal risk, highlighting which infectious diseases may be of concern or endemic in a particular country. Donors with a possible risk of acquiring these diseases are not necessarily excluded from being CB donors, but rather this knowledge allows appropriate infectious disease screening that is pertinent to the area of travel/residency (e.g., malaria antibody screening). Table 8.2 lists some of the infectious diseases that are of concern when assessing a travel/residency history (Source: AusCord Guide to selection of mothers and donors). The list of relevant countries or regions will be updated from time to time, dependent of outbreaks of transmittable disease in new regions or countries.

Table 8.2 Infectious diseases of concern when assessing a travel/residency history

HIV	Pertains to the risk of sexually acquired HIV infection in donors with *new sexual partners* who have resided in those areas. Examples of countries of risk: Botswana, Cambodia, Congo
Chagas	Mothers who were born in or transfused in these areas could have chronic Chagas infection without symptoms. Examples of countries of risk: Argentina, Belize, Honduras
Ebola/Marburg	Endemic in some countries in Africa. Examples of countries of risk: Angola, Congo, Kenya
Malaria	Mothers who have travelled or resided in these areas could have malaria without displaying symptoms for some time. Examples of countries of risk: Afghanistan, Indonesia, Papua New Guinea
Dengue and chikungunya	There are countries or regions where outbreaks of either of these two very similar arboviruses are known to occur but where no malaria restriction applies. Examples of countries of risk: Martinique, Dominica, Singapore
West Nile virus	Historically endemic to a number of countries in Africa, Asia, and the Middle East. A virulent strain emerged in 1999 in North America. Examples of countries of risk: the United States, Saint Pierre and Miquelon, Canada
Schistosomiasis (also known as bilharzia)	Endemic in some countries. Mothers who have travelled or resided in these areas may have a past history of bilharziasis. Examples of countries of risk: Iraq, Jamaica, Saudi Arabia
Rabies	Most countries, including many developed areas like North America, continue to report rabies transmission. Mothers who have suffered *an animal bite or scratch* in these areas may have infection without symptoms and/or have received rabies immunoglobulin from an overseas source. Examples of countries of risk: Bangladesh, France, the Philippines
Zika virus	This virus, first identified in 1947 but confined to Africa and Asia until 2007, is transmitted to humans principally by the *Aedes* mosquitoes, but sexual transmission has been documented from infected males to females. An outbreak was identified in Brazil in early 2015, and more than 34 countries and territories have now reported active transmission

8.3 Donor Testing

8.3.1 Infectious Disease Marker (IDM) Testing Profile

To determine the infectious disease status of CB donors, samples of the maternal blood are collected for the purpose of infectious disease screening. The maternal blood samples serve as a surrogate for the CB unit, and testing should reflect the health of the mother at the time the unit is collected, ideally having been collected within 7 days of CB collection. Testing of maternal blood samples also needs to take into account any factors that may cause plasma dilution that may alter serology test results, such as large-volume infusions of blood or crystalloids prior to collection. Depending upon the country of the CBB, these IDM tests may utilize FDA-approved,

EC-marked, in vitro diagnostic device (IVD)-registered testing kits or some other licensure or registration required by applicable law. Although regulatory authorities and accrediting bodies around the world differ in the infectious disease marker testing mandated by each body and country, there appears to be consensus that all CBUs must be tested for HIV-1/2, HCV, syphilis, and HTLV-I/II antibodies, HBs antigen, HIV-1 nucleic acid amplification technique (NAT), and HCV NAT. Most CBBs also require anti-HBc antibody testing and HBV NAT. Additional testing may be required depending on the donor's history and the characteristics of the cells donated (e.g., malaria, West Nile virus, CMV, Chagas disease, toxoplasma, EBV) and may include emergent disease testing depending on travel history and disease outbreaks (e.g., dengue fever and Zika virus). The results of the IDM tests performed will be evaluated by the CBB prior to the CBU being listed on the cord blood registries and are evaluated by both the CBB and requesting transplant program prior to release.

8.3.2 Microbiological Testing

CBU collection and processing are undertaken using validated aseptic techniques. While the nature of the environment in which CB is procured is such that genital and gastrointestinal microorganisms are prevalent, the cleaning of the cord and procedures for CBU collection should be validated and carried out by sufficiently trained and experienced collection personnel such that the microbial contamination is minimized. Once inside the collection bag, ideally, the CB will be processed within a closed system, with samples removed for testing and addition of cryoprotectant handled in accordance with current good manufacturing practices (cGMP) requirements. It is imperative for unrelated CBU qualification that sterility of the final product is confirmed. However, it is often acceptable for CB units stored for related/autologous use to test positive for microbial contamination, as long as the contaminating microorganism is known and antibiotic drug sensitivity confirmed prior to infusion of the unit. Screening includes aerobic and anaerobic bacteria and fungi, using validated testing methods. Microbial testing validation will have confirmed that the samples and the testing method used will detect the range of commonly observed and expected microorganisms. Often the organisms that are to be tested for are prescribed by applicable law, for example, in accordance with those prescribed in the British Pharmacopoeia. Consideration must also be given to the fact that many mothers are given prophylactic antibiotics at the time of delivery, thereby impacting upon the ability to accurately detect microbial contamination in the CBU. Any microbial-contaminated CBU in an unrelated CBB should be discarded in order to reduce the risk of cross-contamination during long-term cryostorage and avoid the risk of recipient contamination.

8.3.3 Hemoglobinopathy Screening

In the United States, universal newborn screening (NBS) for sickle cell disease (SCD) and other hemoglobinopathies has been performed since 2006 (CDC 2015).

Hemoglobinopathy testing on newborns is not routinely undertaken in most other countries, unless there is a family history of one of the hemoglobinopathies or a genetic risk based on ethnicity. At a minimum, all CBUs banked for unrelated use should be screened for sickle cell disease (SCD) or thalassemia through the maternal and family history questionnaire, and also if ethnicity suggests there may be a higher risk. If not performed on the infant donor at birth, all CBUs released for unrelated use should undergo hemoglobinopathy testing prior to release, using one of the appropriate diagnostic tests, such as isoelectric focusing, high-performance liquid chromatography (HPLC), or molecular methods, in an appropriately accredited testing laboratory. Information relating to hemoglobinopathy risk may also be required in the related CBU setting.

8.4 CBU Quality

As part of the CBU qualification, checks will be made as to the quality of the CBU, both pre- and post-processing. Each CBB will have established criteria for processing and banking of a CBU, with the aim of ensuring the product is acceptable for clinical use. This means the product must be safe and efficacious; there must be enough cells to engraft a recipient; the cells must be viable and show potency. A product must meet all the requirements of safety, quality, identity, potency, and purity, also referred to as SQuIPP (Hillyer 2007; Quinley 2013).

8.4.1 Pre-processing Quality

The volume of CBU collected provides an estimate of the total number of cells that will be present. CBBs have criteria for the minimum acceptable volume of collected CBU that will be taken for processing; this criterion is usually less stringent for family CBB than unrelated CBB, where the intent for unrelated CBB is to bank CBU with a high number of total nucleated cells (TNC), as these will be the more desirable units for CBT. The training and experience of the CBU collector will often impact upon the volumes obtained, but factors such as delayed cord clamping will also impact the volume obtained; the longer the time between delivery and clamping of the cord, the less volume obtained. The mode of CBU collection will also impact upon the volumes obtained; in general higher volumes are obtained with in utero collections compared to ex utero collections (Solves et al. 2003). Both the storage of the CBU at the collection site and the transport from the collection site to the processing facility should be monitored and confirmed to have remained within a validated temperature range to maintain viability and potency of the cells. Upon receipt by the processing laboratory, the CBU will be assessed and should be free of large clots, with the TNC count of sufficient number to meet the minimum criteria for processing. The time between collection and processing must be recorded and confirmed to have occurred within a validated

time frame. For unrelated CBUs this ideally should occur within 48 h to ensure the best maintenance of viability and potency (Hubel et al. 2003; Kurtzberg et al. 2005). Longer time periods (e.g., up to 72 h) are often acceptable for related CBUs, where a potentially compromised viability is balanced against the opportunity to bank a family CBU.

8.4.2 Post-processing Quality

Whatever the processing platform used, minimum acceptable criteria, should be achieved with respect to post-processing TNC recovery, cell viability, TNC number, and $CD34^+$ cell number and viability. The sixth edition of the NetCord-FACT Standards for CBB now defines the minimum acceptance criteria for pre- and post-processing parameters (FACT 2016). Each CBB will have established its own minimum criteria for processing and banking, taking into account local economic and operational factors; CB donor qualification is not always based on quality parameters alone.

8.5 Expert Point of View

The fact that CB is a biological product that is collected, processed, and banked for long-term use increases the complexity of donor qualification. Adding to this complexity is the fact that as new tests are developed and introduced over time, it may not be possible to perform these tests on units that are already banked; there may need to be a mechanism to "grandfather" in CBU in the inventory that was banked prior to the new test being available. Donor qualification commences with the recruitment and selection of a suitable maternal donor. Product qualification involves infectious disease monitoring, microbiological testing, and performance of tests to assess cell number, viability, and potency. There are factors that may affect CBU quantity, quality, and potency that are beyond the control of the CBB and collection staff, including the time period between cord clamping and collection, the method of delivery and how protracted the labor time is, damage to the cord and placenta during the delivery process, and size of the placenta, all of which may impact upon the collection volume obtained and contamination of the unit. However, a robust training program for collection personnel to ensure the best possible collection in terms of aseptic process, volume obtained, and integrity of the product from the collection site to the processing laboratory is within the control of the CBB and is the foundation upon which cryopreservation of a quality product is built. With the increasing complexity of CBU donor and product qualification comes the need to recognize that the criteria change as more information is gained, such as emerging infectious diseases, new assays, and CBU use. As the technologies improve and the field of CBT transplantation evolves and matures, an active process is in place across CBBs to constantly refine and improve qualification criteria.

8.6 Future Direction

The future directions of CBU donor and product qualification are directly related to an evolving field. CBBs need to have the ability to respond and adapt quickly. For example, new emerging infectious diseases, such as the Zika virus, require the urgent need to develop guidelines for travel and potential exposure to the virus that may impact upon placental and CBU transmission, along with the development of licensed tests and mandated testing requirements. The potential serious implications of exposure to Zika virus means that as each new piece of information is discovered, new rules and procedures are set in place by CBBs, who need to respond and adapt quickly to protect the quality of banked CB.

The idea of what comprises a high-quality CBU may change over time, but SQuIPP will always be central to any assessment. The evolution and adaptation of CBBs and the CBU donor and product qualification criteria to external influences, along with the requirements of transplant programs, will ensure CBBs remain relevant and are manufacturing products of the highest quality.

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