Guidelines for Umbilical Cord Blood Banking

Collection, Processing, Testing, Storage, Banking and Release for Clinical Application

(2023)

Indian Council of Medical Research

Department of Health Research

Ministry of Health and Family Welfare

Government of India

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FOREWORD

The use of hematopoietic stem cells obtained from umbilical cord blood has gained tremendous popularity in the field of bone marrow transplantation/Hematopoietic Stem Cell Transplantation owing to its distinct advantages over bone marrow-derived or peripheral stem cells. This brings us the challenge of ensuring the safe and ethical collection, processing and storage of umbilical cord blood by umbilical cord blood banks. In view of the establishment of several Umbilical Cord Blood Banks in recent years, we felt that it is imperative to educate all stakeholders on various aspects of umbilical cord blood collection and storage for therapeutic purposes. This document corroborates the existing regulatory requirements of Umbilical Cord Blood Banking as given in the Drugs & Cosmetic Act 1940 & Rules 1945 (Amendments 2016) and further provides advice and guidance on the therapeutic use of umbilical cord-derived hematopoietic stem cells.

I congratulate all the Advisory and Working group for participating in preparation of these guidelines. I look forward to this document being widely referred to ensure quality standards and safety of umbilical cord blood for clinical applications.

Dr. Rajiv Bahl
Secretary, Department of Health Research
Ministry of Health & Family Welfare
&
Director General, ICMR

Acknowledgments

The **Guidelines for Umbilical Cord Blood Banking 2023** is the culmination of years of deliberation and relentless efforts of stakeholders including experts, government agencies, clinicians, scientists, cord blood banking industry, parents and NGOs who contributed to shaping the document in its present form through either their inputs, communication, or queries.

I profusely thank Prof Narinder Mehra the Chairman, Advisory and Working Group for his unflinching support in finalizing these guidelines.

I wish to record my heartfelt gratitude to the Advisory Committee for their expert guidance and erudite suggestions. I am profusely elated to thank the Working Group members under whose leadership this document could be prepared.

Indian Council of Medical Research (ICMR), Department of Health Research (DHR) gratefully acknowledge the contributions made by various stakeholders for their comments and suggestions on the draft guidelines.

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I appreciate the efforts of Dr. Gitika Kharkwal, Dr. Hemlata, Dr. Varsha Dalal, Dr. Munna Lal Yadav and Dr. Geetanjali Sageena who have extended their wholehearted cooperation and extensive support for the compilation of the guidelines.

I am thankful for the administrative support extended by the Division of Basic Medical Sciences staff including Sh. GS Sandhu, Sh. Shatrughan Kumar Sh. Kundan, Sh. Rahul and Ms Divya for logistics support.

It is hoped that this document accomplishes its aim of adequately addressing the concerns of all stakeholders involved in Umbilical Cord Blood Banking.

Dr. Geeta Jotwani

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ABBREVIATIONS

AABB	Association for the Advancement of Blood & Biotherapies
ACOG	American College of Obstetricians & Gynecologists
APHSCT	Appropriate Supply of Hematopoietic Stem Cells for Transplant
CB	Cord Blood
CBB	Cord Blood Banking
CBU	Cord Blood Unit
CD	Cluster of Differentiation
CDSCO	Central Drug Standards Control Organization
CFU	Colony Forming Unit
CJD	Creutzfeldt-Jakob disease
CMV	Cytomegalovirus
CPD	Citrate Phosphate Dextrose
D&C Act	Drugs and Cosmetics Act
DGHS	Directorate General of Health Services
DMLT	Diploma in Medical Laboratory Technology
EBV	Epstein-Barr Virus
EC	European Commission
EUTCD	European Union Tissues and Cells Directive
FACT	Foundation for the Accreditation of Cellular Therapy
GVHD	Graft versus Host Disease
HBV	Hepatitis B Virus
HCT	Hemopoietic Cell Transplantation
HCT/Ps	Human cells, tissues, and cellular and tissue-based products
HCV	Hepatitis C Virus
HIV	Human Immunodeficiency virus
HLA	Human Leukocyte Antigen

HPLC	High-performance liquid chromatography
HSCT	Hematopoietic stem cell transplantation
HTA	Human Tissue Authority
HTLV	Human T-cell Lymphotropic Virus
ICMR	Indian Council of Medical Research
IC-SCR	Institutional Committee for Stem Cell Research
IEC	Institutional Ethics Committee
INAP	India Newborn Action Plan
IND	Investigational New Drug
LN2	Liquid Nitrogen
MLT	Medical Laboratory Technology
MoHFW	Ministry of Health and Family Welfare
NABL	National Accreditation Board for Testing and Calibration Laboratories
NAT	Nucleic Acid Test
NGHCT	National Guidelines for Hematopoietic Cell Transplantation
NGSCR	National Guidelines for Stem Cell Research
NIH	National Institutes of Health
PCR	Polymerase Chain Reaction
QA	Quality Assurance
QC	Quality Control
RMP	Risk Management Program
SoHO	Substance of Human Origin
SOP	Standard Operating Procedures
TGA	Therapeutic Goods Administration
TNCs	Total nucleated cells
TPHA	*Treponema Pallidum* Haem-Agglutination
UCB	Umbilical Cord Blood
USFDA	US Food and Drug Administration (FDA)

1. Background

Ever since the first successful umbilical cord blood stem cell transplant done in Paris (France) in 1988, over 35,000 such transplants have been performed worldwide both in children as well as adults for a variety of indications. These include inborn errors of metabolism, hematopoietic malignancies, genetic disorders of the blood and immune system, and several other indications. All this was possible due to the recognition of the presence of a sizable number of hematopoietic stem cells in the umbilical cord as a valuable biological product. Accordingly, rather than being regarded as a wasteful tissue after birth, the umbilical cord came to be recognized as an alternate and useful source of stem cells.

Successful use of UCB from a sibling to treat a child with Fanconi's Anemia further opened new avenues for its use as an alternative source of HSCs, apart from the routinely used similar cells from the bone marrow, for patients with a variety of hematological disorders and cancers [1].Establishment of the first-ever public cord blood bank (CBB) at the New York Blood Centre in 1992 through funding provided by the National Institutes of Health (NIH), USA ushered in a new era of hope for patients in need of hematopoietic cell transplantation (HCT). Since then, there has been a period of rapid growth in UCB banking because it does not pose any important risk to the donor mother/baby. Further, ease of storage and transport of the frozen tissue, the possibility of performing HLA mismatched HSC transplants with reduced chances of graft versus host disease (GVHD) are added advantages of using HSCs from the cord blood [2]. Recognition of the clinical utility of UCB both in pediatric and adult patients along with refinement in techniques for its collection, storage and transplantation has led to establishments of UCB banks in several countries, including in India.

Though this is a promising area, there are no standard indications for the use of UCB derived HSCs at present other than for allogeneic HCT. There is also a lack of valid scientific data proving the therapeutic value for the use of autologous cord blood stored for preventive purposes. Consensus has emerged in recent years that stored autologous cord blood in private enterprise should notbe used for treating one's own genetic condition in future (including hemoglobinopathies, storage disorders, hemophagocytic lympho-histiocytosis, primary immunodeficiencies and others) because these stem cells could harbor the same genetic abnormality that caused the primary disease.

Apart from HCT, the cord derived stem cells have recently been suggested as a good biological source for possible gene therapy and regenerative medicine. Nevertheless,

much of this is still at investigational stage and usage of autologous cord stem cells for such purposes cannot be permitted outside the purview of an approved clinical trial [3]

There has also been a debate whether it is appropriate at all for expectant parents to store their new-born baby's cord blood in private banks for future therapeutic use. This is based on the registry data, whereby the utilization of cord blood as a source for HSCT is declining in the USA, Europe, and Australia. The Indian Society of Blood and Marrow Transplantation registry data shows that only 60 unrelated cord blood transplants have been done in India from 2012 to 2020 with a further trend for decreasing utilization in recent years. Presently, the cord blood stored in private cord blood banks remains under-utilized, is expensive and has not been fully compliant with the required regulatory guidelines.

It was brought to the notice of Government of India &ICMR through various grievances and complaints that private cord blood banks are circulating persuasive literature projecting UCB banking as a 'once in a lifetime opportunity' for treating a variety of diseases in future by offering mothers the option to store their own baby's cord HSCs on long-term basis. The advertisements claim that UCB banking is a biological insurance for stem cell therapy of the child or his/her siblings in case of future need, not only for conditions with SCT is indicated but also where the use unjustified or at best experimental. The information is widely circulated through leaflets distributed at antenatal clinics, assisted conception units, women's magazines and on internet.

These issues have been deliberated upon in a series of inter-agency and inter-ministerial meetings of the Government of India whereby it was felt that it is imperative to spread awareness about the correct utility of umbilical cord blood storage among all stakeholders and thus curtail misleading advertisements for profit making. Parents offered cord blood banking must have accurate information on the exact utility of cord blood storage for self-directed use, functioning of the private versus public cord blood banks, international status and the likelihood of private banking resulting in benefit vis-a-vis the possibility of contributing to a lifesaving therapy for someone else by offering the storedcord blood to a public cord blood bank.

This document has been prepared with the primary aim of providing information on the scientific basis behind umbilical cord blood storage, status on its therapeutic use and guidance for various associated issues. Further, it elaborates on both the quality and ethical considerations of umbilical cord blood banking. It has been prepared through stakeholder consultation, opinion of experts and through intensive debate on current

scientific evidence. The document is adapted from the Drugs & Cosmetic Act 1940 and Rules 1945 (Amendments 2016) and has been influenced by various international documents available in public domain like the NetCord FACT Standards and AABB Standards for Cellular Therapies [4,5,6]. It represents the current thinking of scientists and clinicians on the available evidence and will be updated as the evidence grows in future.

It may be stated that these guidelines are not meant to be construed to replace or overrule but to substantiate the existing regulatory requirements as described in Drugs & Cosmetic Act 1940 and Rules 1945 (Amendments 2016) that are already in place for Umbilical Cord Blood Banking.

2. Introduction

2.1. What is Umbilical Cord Blood?

2.1.1. It is the blood that remains in the placental blood vessels and in the attached umbilical cord, which connects the unborn baby to the mother's womb. It contains stem cells that can be used to treat hematopoietic and genetic disorders including cancer [7].

2.1.2. This UCB is collected from the placenta when the expectant mother is in the third stage of labor (after delivery of baby) or after the delivery of placenta. The procedure is essentially safe and does not pose any risk either to the baby or the mother if done appropriately [8,9,10].

2.1.3. UCB is very rich in HSCs, which possess the properties of self-renewal as well as the ability of differentiation into myeloid and lymphoid cell lineages.

2.1.4. UCB is also known to be rich in mesenchymal cells, which are self-renewing and minimally immunogenic and play a key role in immune suppression in response to Graft-versus-host disease (GVHD).

2.2. What is the therapeutic use of Umbilical Cord Blood?

2.2.1. As per the Mendelian segregation rule, only 25% of the children in a family have the possibility of finding an HLA-identical sibling. In actual practice however, this figure is around ~30% for all categories of disorders put together. This therefore greatly limits the possibility of performing HLA matched transplants for many needy patients who may require allogeneic HCT as a possible cure for their disease. Unlike bone marrow, cord blood transplantation is not dependent on very stringent criteria of HLA matching.

Accordingly, UCB serves as an alternative stem cell source in all such situations, particularly for children and young adults [11].

2.2.2. However, with the advent of HLA-haploidentical stem cell transplantation wherein practically everyone has the possibility of a donor available within the family, the usage of UCB as a source for allogeneic stem cell transplantation has been steadily declining in India as well as globally [12,13,14].

2.2.3. To date, UCB is permitted only for use in HCT for approved indications as mentioned in NGHCT 2021 [15].

2.2.4. Apart from these indications, the use of UCB is experimental at present and stem cells derived from it should be used only under the purview of well-designed clinical trials after obtaining necessary regulatory approvals.

2.3. Advantages and disadvantages of using UCB as a source of stem cells [9,16]

2.3.1. Advantages:

i. Ease of collection
ii. No risk for the mother or the child
iii. Less time needed for processing (more quickly available for use)
iv. More economical than bone marrow collection
v. Decreased risk for transmission of infection.
vi. Lesserrequirements for stringent HLA typing as compared to mature cells in bone marrow.
vii. Relatively lesser possibility of graft rejection

2.3.2. Disadvantages:

i. Slower degree of engraftment
ii. Limited cell dose in the inoculum making its use limited to children.
iii. Small volume of the Unit
iv. Additional cell doses unavailable
v. Storage issues at ultra-low temperatures and related costs

2.4. What is UCB Banking?

2.4.1. Banking of UCB is done for collection and storage of umbilical cord derived stem cells. Worldwide, both public as well as private cord blood banks have been established.

2.4.2. A private bank is essentially a for-profit company that stores umbilical cord blood for personal or self-directed use. In contrast, the public umbilical cord blood banks are state owned that offer gratuitous cord blood banking from

consenting parents to be used for any patient in need of a hematopoietic stem cell transplant (allogeneic umbilical cord blood transfusion). The cord units stored in public banks are notuniquely available to a specific person or family [17,18].

2.4.3. At present, India does not have any public UCB banks.

2.5. International Scenario vis-a-vis India:

2.5.1. UCB banking is a regulated activity across the world.

2.5.2. In the USA, all cord blood banks, whether public or private are obliged to be registered with the Food and Drugs Administration (FDA), while in Australia, the same are licensed by the Therapeutic Goods Administration (TGA) which mandates compliance with the FACT-NetCord Cord Blood Standards [6,19,20,21].

2.5.3. Similarly, the Human Tissue Authority (HTA) of UK set up under the Human Tissue Act 2004 regulates umbilical cord blood collection while in Europe, the European Commission has updated the regulations on the use of Substance of human Origin (SoHO), which also includes the UCB banking [22,23,24].

2.5.4. In Japan, the supply of UCB to public banks is authorized by the Ministry of Health, Labor, and Welfare (MHLW), and the procedures for collecting, harvesting, preparing, and storing of such blood are regulated by the “Act regarding the Promotion of the Appropriate Supply of Hematopoietic Stem Cells for Transplantation (APHSCT) [25].

2.5.5. Likewise, in India the UCB banks are licensed and monitored by the Central Drugs Standard Control Organization (CDSCO), a constituent of the Ministry of Health and Family Welfare (MoHFW).

2.5.6. In India, the UCB banks are required to comply with the provisions specified under Part X-B and Part XII-D of Schedule F of Drugs and Cosmetics Act 1940 and Rules 1945 (Amendments 2016). The Indian rules define umbilical cord blood as “the whole blood including Hematopoietic Progenitor Cells collected from placental and/or Umbilical cord blood vessels after the umbilical cord has been clamped”. These rules define cord blood bank as “a place or organization or unit for carrying out and responsible for operations of collection, processing, testing, banking, selection and release of cord blood units” [26,27,28].

2.5.7. The Indian rules specify all requirements for collection, processing, testing, storage, banking, and release of UCB derived stem cells.

2.5.8. At present, there are 22 licensed UCB banks in the country https://www.cdsco.gov.in/opencms/opencms/en/BloodCentre/.

2.6. Need for Guidelines

2.6.1. Although the D&C Act 1940 &Rules, 1945 (Amendments 2016) are adequate to regulate the UCB banks, these do not provide succinct information on the quality and ethical aspects of UCB collection, processing, banking, and release. Guidelines are needed because all UCB units may not meet the established criteria for storagedue to insufficient volume, delayed processing and/ or low stem cell count.[3]

2.6.2. More often than not, the private enterprise market cord blood bankingas a 'biological insurance' for the family for a long list of genetic and acquired disorders, but this is not supported by the available evidence [29,30].

2.6.3. In general, there is a lack of awareness among clinicians regarding the established and approved indications of using cord blood for autologous and/or allogeneic stem cell transplantation.

2.6.4. Available evidence indicates that the initial stem cell count of banked UCB is directly correlated with the outcome following transplantation. Often early clamping of cord after birth is therefore done to get a greater volume of UCB for banking. However, this is unethical because delayed cord clamping is recommended in national guidelines to prevent anemia. Therefore, it is important to collect UCB blood without altering the recommended practice of umbilical cord clamping [31].

3. Aims & Scope

3.1. The main objective of the National Guidelines for Umbilical Cord Banking is to provide all stakeholders with a guidance document on the quality and ethical aspects of UCB collection, processing, banking, and release; and specify additional requirements to address these aspects.

3.2. It strives to guide evidence informed practice that is ethical and beneficial to the patient.

3.3. The document will be periodically updated based on research updates and scientific developments in the field.

3.4. These guidelines are meant to substantiate the existing regulatory requirements, and not construed to replace or overrule the same.

3.5. The guidelines are applicable to all stakeholders including UCB banks and personnel involved in all its procedures, obstetricians, neonatologists, and transplant physicians along with parents and all individuals providing support services.

4. Donor Management [5,6]

4.1. Maternal and Infant Donor Evaluation

4.1.1. Donor eligibility and medical suitability evaluation procedures are required to protect the recipient against a possible communicable disease and to ensure confidentiality of the cord blood donor and mother. It is important to assess the risk of disease transmission from the infant donor to the recipient, besides assessing any risks to the infant donor or the mother from the collection procedure employed by the facility.

4.1.2. The facility shall establish procedures to assess the health status of the infant donor. This is important since it may potentially affect the safety of the recipient or the therapeutic value of the UCB unit.

4.1.3. The facility shall establish procedures to record the personal, family, medical and genetic history of the families of both parents before UCB collection.

4.1.4. In the case of a surrogate mother, her medical history shall also be recorded and documented in addition to that of the biological parents. A genetic history of the surrogate mother is not required.

4.2. Maternal screening and testing

4.2.1. The facility shall establish written criteria for maternal screening. It shall also establish a process for maternal and infant donor identification and linkage.

4.2.2. Donor screening should include detailed physical examination and review of the relevant medical history and records to identify potential risk, if any for acommunicable disease.

4.2.3. Personal information: The facility shall evaluate the donor's personal information that may adversely affect the potential therapeutic value of the UCB unit. Information on the donor's lifestyle (e.g., drug abuse, prostitution) should also be available.

4.2.4. Medical history: Maternal screening is an important requirement for UCB collection. This should include a review of the medical history and records and a review of the physical examination findings. This evaluation should be conducted by an RMP before the mother is distracted by aspects of labor. Detailed genetic history should also be obtained from the mother. This includes:

4.2.4.1. Risk of any acquired condition, such as malignancy or an inherited condition or family history of a genetic disease that could be transferred to the recipient through CBT.

4.2.4.2. Family history of haemoglobinopathies like thalassemia or sickle cell disease.

4.2.4.3. The facility shall also develop a detailed Performato document conditions and behaviors that could specifically increase the donor's risk for transmission of communicable diseases like HIV, Hepatitis B and Hepatitis C.

The Performa should include information on the following:

a) Persons who have injected drugs for a non-medical reason in the preceding 5 years, including intravenous, intramuscular, or subcutaneous injections.

b) Persons with hemophilia or other related clotting disorders who have received human-derived clotting factors concentrate in the preceding 5 years.

c) Persons who have engaged in sex in exchange for money or drugs in the preceding 5 years.

d) Persons who have been exposed in the preceding 12 months to known or suspected HIV, HBV, and/or HCV-infected blood through percutaneous inoculation (for example, needle stick) or through contact with an open wound, non-intact skin, or mucous membrane.

e) Persons who have lived with another person who has hepatitis B or clinically active (symptomatic) hepatitis C infection in the preceding 12 months.

f) Persons who have undergone tattooing, ear piercing or body piercing in the preceding 12 monthsfrom suspect locations wheresterile procedures may not have been used. These include use of contaminated instruments and/or ink or shared instruments that had not been sterilized between uses.

g) Persons who have had a history or diagnosis of clinical, symptomatic viral hepatitis after their 11th birthday. (Excludinghepatitis caused by hepatitis A virus, Epstein-Barr Virus (EBV), or cytomegalovirus (CMV), based on the documentary evidence).

h) Donors who have been treated for or had Chlamydia trachomatis or Neisseria gonorrhea infection in the preceding 12 months.

4.2.5. Travel history of the mother should be obtained as this could relate to:

4.2.5.1. Contagious diseases transmission (malaria, Zika virus) or,

4.2.5.2. Risk for Creutzfeldt-Jakob disease (CJD) is based on the travel history of the person having spent 5 years or more cumulatively in Europe until the present.

4.2.6. Testing of maternal blood for infectious agent

Maternal blood samples should be tested for blood borne pathogens which include HIV, HBV,HCV, HTLV, CMV, Malaria and *Treponema Pallidum* (https://biosafety.utk.edu/biosafety-program/the-biosafety-program/biosafety-manual/10-bloodborne-pathogens/).This may be done within 7 days before or after delivery [32]. Investigations shall be performed by a laboratory qualified by a Competent Authority, for example, NABL accredited laboratories.

4.2.7. Consent form and process

An informed consent shall be obtained from the mother prior to delivery and not when she is in labor. Mother's right to refuse consent without prejudice is to be respected. The information sheet should explain details of the cord blood collection procedure. All aspects of participation in cord blood donation shall be discussed with the mother in a language and with terms which she understands. If a translator is utilized, the identity of the translator must be documented. Family members are not permitted to serve as translators. In case of surrogacy the surrogate mother should be well informed regarding the procedure for UCB collection.

The informed consent shall include information on the following elements:

4.2.7.1. Overall purpose: Based on the current evidence, the purpose of a UCB bank is to storehematopoietic stem cells for treatment of a variety of hemopoietic and genetic diseases including cancer. Further use of UCB for purposes other than the aboveis currently a matter of scientific discovery.

4.2.7.2. The possible risks and benefits to the mother and/or infant donor include medical and ethical concerns.

4.2.7.3. Any possible alternatives to participation.

4.2.7.4. Intent of the donation: Explain clearly whether the donation is for unrelated (unit to be made available for other individuals and not just for the infant donor or the infant donor's family later) or related use (unit available for family of the infant donor only) [33,34].

4.2.7.5. For unrelated use, the parents should not be charged for donation and storage. In such situations, the infant/parents cannot make any claim on the donated cord blood unit later in life. They may, however, be given priority over others.

4.2.7.6. Personal and family medical history of the mother.

4.2.7.7. Reference samplesbe always collected from the mother and cord unit for testing for communicable diseases.

4.2.7.8. The reference sample to be used also for genetic and other testing as applicable.

4.2.7.9. Information on storage of reference samples for future testing as per scientific developments.

4.2.7.10. UCB bank retains the right to contact the mother at any time, while information related to the infant donor and family shall remain confidential.

4.2.7.11. Information on possible use of UCB unit for research, quality control or validation studies.

4.2.7.12. Information on the cord blood bank policies for disposal of the cord blood unit including - nonconforming units, related units if no longer required.

4.2.7.13. Information on the agreed upon duration of storage for related units and the cord blood bank policies for disposition of cord blood units in the event of cessation of operation.

5. Requirements for UCB Collection and Transportation to UCB Bank

5.1. Infrastructure:

The requirements for collection have been described in Part XII D of D&C Rules, 1945 (Amendments 2016) [3]. In addition, the following points need to be taken into consideration:

5.1.1. There should be adequate space for collection and temporary storage of UCB samples.

5.1.2. There should be a specified area for storage of supplies and required reagents for processing. All reagents should be used prior to their expiry date.

5.1.3. Universal precautions to prevent infection should be followed during collection and handling of samples.

5.1.4. Materials required to collect a particular sample should be available together in the form of a "kit" with clear instructions on the method of collection. The kit should be transported under the prescribed temperature, while the documents collected should record all details on the reagents used, including batch number and the expiry date.

5.2. Personnel

5.2.1. As per D&C Act 1940 & Rules 1945 (Amendments 2016), collection of UCB shall be done under the direction of a certified RMP responsible for the delivery. UCB collections should be carried out by the RMP / registered nurse / health careand medical professionals trained in the collection procedures.

5.2.2. The cord blood collection sites should all have sufficient staff to carry outall the activities needed for the purpose. In addition to the hospital staff, the Procurement Supervisor, who is employed by the UCB Bank shall be responsible for UCB collection. This staff will be provided by the UCB bank.

a. The Procurement supervisor should have a degree in Physiology or Cell Biology or, Pharmacy or Biosciences or Microbiology or Biochemistry or Zoology or Botany with atleast minimum of three years' experience in UCB collection.
b. A Diploma in DM.L.T. with05 years' training or experience in theUCB collection.
c. The personnel should be trained in all the involved steps beginning from sample collection up till the transportation of UCB unit.

5.2.3. Documentation should be in place for initial training and continuing of the required competency of staff.

5.3. UCB Collection Procedure

5.3.1. The facility shall ensure that the cord blood collection is performed by a trained andcertified health care and medical professional into an approved or validated container, having an anticoagulant. The following points must be taken into consideration during the collection procedure:

5.3.1.1. The UCB collection practice shall safeguard the mother and infant. It should be ensured that there is no impact on the obstetric practice or mother and infant care with an intent to increase UCB unit volume [35].

5.3.1.2. UCB shall be collected from hospitals/nursing homes/birth centers where a consenting mother delivers under supervision of the qualified Registered Medical Practitioner responsible for delivery.

5.3.1.3. UCB shall be collected aseptically in a disposable Polyvinyl chloride (PVC) bag, procured from licensed manufacturers, and containing an adequate quantity of sterile pyrogen free anticoagulant like CPD / CPD-A(Citrate-phosphate-dextrose/Citrate-phosphate-dextrose-adenine) and sealed effectively.

5.3.1.4. UCB collection may be *in utero* (after the infant has been delivered but before delivery of the placenta) or *ex utero* (after delivery of the placenta).

5.3.1.5. For *in utero* UCB collection, the facility shall ensure additional safeguards so as to ensure the safety of both the mother and the infant donor.

5.3.1.6. UCB collection should be done only in uncomplicated deliveries.

5.3.1.7. In case of multiple gestation, the babies should be delivered prior to UCB collection.

5.3.1.8. if the baby is delivered at less than 34 weeks of gestation, the safety of the infant must be ensured by the supervising RMP before UCB collection.

5.3.2. For written policies and SOPs on UCB collection, the reader may refer to NetCord FACT standards 7th edition [6].

5.4. Transportation of collected UCB to the processing facility.

5.4.1. The following criteria should be met for the transportation of UCB units from collection facility to processing facilityIntegrity of the UCB units should be protected and health and safety of the personnel involved in the transportation should be ensured. Temperature should be maintained to protect the cell viability of the UCB unit.

5.4.2. UCB shipping should be that it prevents or withstands leakage of contents, shocks, and pressure changes during transportation.

5.4.3. Containers for transport of UCB unit should be appropriately labeled.

5.4.4. Records shall permit easy traceability of the UCB unit from the collection facility to storage in the designated UCB bank. A shipping list identifying each UCB unit, reference samples and associated documents are to be enclosed in the package which shall include information on the following:

a. Collection facility.
b. Date and time of shipping
c. Identity of the courier service

d. Date and time of receipt of the package by the UCB bank.
e. Condition of the package upon receipt

6. Requirements for UCB Bank

The UCB Bank shall develop and implement quality and operational procedures in compliance with all applicable regulations. The infrastructure, personnel and operational requirements as defined in Part XII-D of Schedule F of Drugs and Cosmetics Act 1940 and Rules 1945 (Amendments 2016) are to be complied with. In addition, refer to requirements as stated in NetCord FACT Standards, 7th edition and AABB Standards for Cellular Therapies,10th edition [3,5,6].

7. Requirement for Sample Processing, Cryopreservation and Storage

7.1. Prior to processing, it should be ensured that the UCB unit has been received within an acceptable time frame with maintained cold chain. It should be appropriately labelled, documented, and verified for the identity of maternal and infant donor samples.

7.2. The processing of UCB units should be performed in a closed system with specified air quality and cleanliness and should be completed within 72 hours with proper labeling.

7.3. Post processing, prior to cryopreservation, the UCB units should be tested as mentioned in the NetCord FACT Standards 7th edition and AABB Standards for Cellular Therapies 10th edition [5,6]

7.4. For cryopreservation, the UCB units should be stored in proper freezing bags at a temperature of ≤-150^{0}C. Proper SOPs should be followed to maintain the viability, potency, and stability of the unit with minimal contamination. Proper alarm and monitoring systems should be in place to maintain and record the temperature of the stored unit every four hours.

7.5. Proper criteria should be in place for disposal of the UCB units that are non-conforming as per the standards defined by the SOPs of the UCB bank.

7.6. The UCB bank should ensure proper labeling and tracking of the UCB unit from receipt up to release or disposal.

7.7. The UCB bank should have a system to review, approve and record all the documents before use. Any changes made in the SOPs/procedures should be controlled and documented.

7.8. All forms of Errors, non-conformance, deviations, and adverse events should be recorded, and corrective and preventive actions should be in place for the same. SOPs should be in place for risk mitigation.

For more details, refer to NetCord FACT Standards 7th edition and AABB Standards for Cellular Therapies 10th edition [5,6]

8. Requirement for release and transport for banked UCB

8.1. Prior to the release, safety, potency, viability, and integrity of UCB units should be ascertained and documented and should comply with the predefined release standard as mentioned in NetCord FACT Standards 7th edition and AABB Standards for Cellular Therapies 10th edition [5,6].

8.2. During transportation of the UCB unit, the cold chain should be maintained. The unit should be accompanied by proper shipping records mentioning the details of the unit, time of dispatch, intended recipient and final destination. The safety of the healthcare personnel involved in this process should be ensured.

For more details, refer to NetCord FACT Standards 7th edition and AABB Standards for Cellular Therapies 10th edition [5,6].

9. Publicity and Advertisements in All Media

It may be noted that actions can be taken against the erring cord blood banks/entities for misleading advertisements and publicity as per the following existing rules and regulations.

9.1. The Drugs and Magical Remedies (The Objectionable Advertisements) Act- 1954 –prohibits misleading advertisements relating to drugs and magical remedies. DGHS and relevant state authorities are mandated to take necessary action for violation of this act [36].

9.2. The advertisement of treatment of several diseases as listed in Schedule J of Drugs and Cosmetics Act, 1940 and rules therein (Annexure VII) is not permissible. Hence publicity claiming available cure for these conditions using stem cells and its derivatives is prohibited. CDSCO, DGHS and relevant state authorities are mandated to take necessary action for violation of this act.

9.3. No advertisement which violates the code for self-regulation in advertising, as adopted by the Advertising Standards Council of India (ASCI), Mumbai for public exhibition, from time to time, shall be published [37].

9.4. Complaints regarding unethical practices can be made to the zonal offices of CDSCO with information to central CDSCO and the ICMR. One can also move to the consumer court for this purpose.

10. Education and Awareness

10.1. It is the democratic right of the expecting parents to be aware of the cord blood banking options available and the usefulness of the banked cells for future self-use of the baby or a family member. The parents should also be adequately made aware of the voluntary donations and importance of the same.

10.2. In addition to treating doctors and banking professionals, policy makers including regulators own the responsibility to create awareness and update about the rightful status of cord blood stem cells and their applications on the basis of peer reviewed scientific evidence.

10.3. Public awareness needs to be created through periodic interactions with the public/stakeholders held across the country. The focus of such interactive sessions will be to educate the masses to avoid their exploitation and to provide a forum for free and frank exchange of views. Different print and electronic media modules can be used to this effect.

10.4. Continuous education modules need to be introduced for updating the medical/scientific community as well as individuals involved in all processes of cord blood banking for correct use of cord blood stem cells.

10.5. The status of new scientific developments and innovative technologies relevant to cord blood banking, ethical issues related to them, and regulatory approval pathways need to be made a part of the curriculum for medical/science/lab technician/nursing education.

Glossary

Accreditation: A process in which an authorized or a government entity evaluates if every step performed (from collection to storage) during umbilical cord banking meets the recognized standards.

Allogeneic: Cells/tissue obtained from a random donor and intended for administration into a genetically distinct related or unrelated recipient.

Autologous Transplantation: In an autologous transplant, the patient's own stem cells harvested from the bone marrow and/or peripheral blood are reinfused into the same person with minimal manipulation. The patient receives high dose chemotherapy and/or radiation therapy so as to destroy the circulating cancerous cells. The extracted stem cells are also treated to destroy cancer cells, if any and then re-infused into the same patient.

Autologous: Derived from and intended for use in the same individual.

Bone Marrow Donation: A surgical procedure by which a healthy person donates a portion of his/her bone marrow containing hemopoietic stem cells to a patient who has a disease which requires a bone marrow transplant.

Bone Marrow Transplant (BMT): A procedure in which a patient receives healthy stem cells (blood-forming cells) to replace his/her own stem cells that have been destroyed by treatment with radiation or high doses of chemotherapy. The healthy stem cells may come from the bone marrow of the patient or from a related or unrelated donor. A bone marrow transplant may be autologous (using a patient's own stem cells that were collected and saved before treatment), allogeneic (using stem cells from a related or unrelated donor), or syngeneic (using stem cells donated by an identical twin).

Bone Marrow: The soft, spongy tissue found in the cavity of large bones that contain cellular components of blood forming cells, also known as hematopoietic stem cells (white cells, red cells, and platelets). It is also a potential source of mesenchymal and endothelial stem cells.

Calibration: Periodic scheduled activity to check and maintain the accuracy against a known standard

Clinical grade: Compatible and certified for administration to humans.

Clinical trial: A research study in which participants are prospectively assigned to one or more interventions to evaluate the effects of those interventions on health-related biomedical or behavioral outcomes.

Consent: A process by which a subject voluntarily confirms his or her (or their next of kin/legal heir) willingness to participate in a particular study/clinical trial, after having been informed of the aims, methods, required data collection procedures and schedule, anticipated benefits and potential hazards of the study and the discomfort it may entail. Informed consent is

documented by means of a written, signed and dated informed consent form. The consent, besides being voluntary and informed must be without any coercion or inducement. It can be withheld, or even withdrawn at any time, without giving any reason or prejudice to present or future treatment of the individual.

Cord blood unit (CBU): The nucleated cells including stem and hematopoietic progenitor cells harvested from placental and umbilical cord blood vessels from a single placenta after the umbilical cord has been clamped. Unless otherwise specified, the term cord blood unit in this document refers to any cord blood unit regardless of the method of collection, intended use, or donor source.

Cord Blood Bank: An organization that helps to collect and store umbilical cord blood for transplantation. Cord blood banks recruit expectant mothers who donate their baby's umbilical cord blood for stem cell transplants. The blood in the umbilical cord contains large numbers of stem cells. The cord blood banks collect, process, test and store the donated umbilical cord blood. The process involves collection of available blood from each cord, which is then frozen (cryopreservation) for later use. An individual cord blood unit is made available for a single transplant.

Cord blood stem cells: These refer to cells isolated from the umbilical cord blood collected at the time of birth of the newborn. Cord blood contains hematopoietic and mesenchymal (stromal) stem cells. Cord blood hematopoietic stem cells are currently used to treat patients who have undergone chemotherapy to destroy their bone marrow due to cancer or other blood related disorders.

Cord blood: the blood from the umbilical cord and placenta, rich with hematopoietic stem cells.

Cryopreservation: Preservation of cells and tissue at ultra-low temperatures (-196°C or -321°F)

Donor: A person who provides blood, an organ, tissue, or cells for transplantation and/or transfusion.

Infant donor: The infant from whose placenta or umbilical cord, the cord blood is obtained.

Maternal donor: The mother who carries the infant donor to delivery. This may be the genetic or surrogate mother.

Unrelated donor: The infant donor whose cord blood is collected and stored for use by a person with no known genetic relationship.

Related donor: The infant donor whose cord blood is collected and stored for autologous use by the donor or for allogeneic use by a genetically related recipient.

Engraftment: The process by which the newly transplanted stem cells migrate to and nest in the appropriate site of the recipient's body and start producing normal quantities of healthy mature cells.

Graft Versus Host Disease (GVHD): A potential complication of transplants associated with the use of blood or tissue from a different person (allogeneic). In GVHD, the transplanted cells

reject the recipient's tissue as foreign and attack the tissue. GVHD in stem cell transplants appears to be less severe with umbilical cord blood, which appears to be more tolerant of the new body's environment. To reduce the risk of GVHD or tissue rejection, HLA matching between the donor and the recipient is recommended.

Hematopoietic: pertaining to the blood system. Often used to refer to blood forming stem cells (Hematopoietic stem cells, HSC).

Hematopoietic Progenitor Cells (HPCs): Primitive pluripotent hematopoietic cells capable of self-renewal and/or differentiation as well as maturation into any of the hematopoietic lineages (granulocytes, monocytes, erythrocytes, and platelets), including committed and -lineage restricted progenitor cells, unless otherwise specified, regardless of source (for example, marrow, mobilized peripheral blood, or umbilical cord blood).

HLA Typing/Testing: This refers to the human leucocyte antigen (HLA) system and laboratory testing of alleles in various HLA loci, for example HLA-A, B, C (HLA class I) and HLA-DR, DQ proteins (HLA class II). Since the HLA system is highly polymorphic, the patients' HLA allelic phenotypes generally matched those of the stem cell donor or the cord blood units by DNA based testing methods and by comparing their HLA tissue types. Siblings are the first candidates tested for the purpose of finding a match, since a brother or sister may have inherited the same parental (paternal and maternal) HLA haplotypes. But even with siblings, there is only a 25% chance for a 'full house' match or HLA identity, leaving more than 75% of all patients seeking a life-saving match from an unrelated donor.

HLA: These refer to as the Human Leukocyte Antigens, present on the chromosome 6 of man. These encode proteins on white blood cells that make each person's tissue unique. The HLA-A, B, C and DR/DQ proteins are extremely important for matching patients and donors for a bone marrow or cord blood stem cell transplant. The process is commonly referred to as HLA matching. The more closely matched one is the recipient and donor's HLAs alleles, the more possibility that the transplanted tissue will be compatible and thus tolerated by the recipient.

Pluripotent stem cells: Stem cells with the ability to differentiate into a wide range of cells and tissues.

Private (family) cord blood bank: A private bank where the newborn's cord blood is collected and preserved for the exclusive use of the donor (baby) and/or a family member for a fee. Thus, securing a usable and available blood unit for a newborn and family member.

Public cord blood bank: A blood bank in which newborns' cord blood units are collected after birth, for use by the general public. The blood unit is not preserved specifically for the donor's family. Instead, it is made available to anyone in need of a hematopoietic stem cell transplant and is found to be a genetic match, or for research purposes – according to the public bank's defined conditions**.**

Regenerative medicine: Field of medicine devoted to treatments in which stem cells are induced to differentiate into the specific cell types in an organism required to repair damaged or destroyed cell populations and/or tissues.

Stem cells: These are undifferentiated cells with a capacity for self-renewal, proliferation, and differentiation into many different types of functional cells.

Transplantation: The process of transferring tissues or cells from a healthy person to an ill person to treat a particular disease. The tissue or cells transplanted may come from the same patient (autologous) or from another person (allogeneic).

Umbilical cord: The structure connecting the fetus to the placenta throughout the pregnancy – consisting of two arteries and one vein. The fetus receives oxygen and nutrients from the mother's blood through the umbilical vein. The fetus's waste products are removed through the umbilical artery to the mother's blood.

Undifferentiated Cell: This refers to a cell that has not begun the processes of differentiation or forming into other cells or tissues.

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Annexure I

Guidance to Stakeholders

- Umbilical Cord Blood (UCB) banks in India are permitted only under license and monitoring by the Central Drug Standards Controlling Organization (CDSCO). UCB banksmust comply with X B and XII D, schedule F of the Drugs and Cosmetics Rules, 1945 for which provides provisions on the collection, processing, testing, storage, banking, and release of stored UCB units. In addition, the UCB banks are guided by this document for ethical collection and for maintaining the quality of UCB units in harmonization with the international standards[36].
- Information on the UCB banks licensed by CDSCO can be obtained from its website https://www.cdsco.gov.in/opencms/opencms/en/BloodCentre/
- As per the D&C Act 1940 &Rules, 1945 (Amendments 2016), authorized UCB banks can only collect theumbilical cord blood for the purpose of UCB stem cells. Accordingly, the storage or banking of any other tissue, for example dental pulp, cord tissue, Wharton jelly etc. is not permitted [3].
- The scientific credibility of storing UCB for self-use of the baby has been discussed by national and international bodies such as the American Academy of Pediatrician, American College of Obstetrics and Gynecology (ACOG) [1], American Medical Association, and the Indian Academy of Pediatrics [31] etc. These scientific bodies do not recommend routine private banking for future self-use. The reasons being: The likelihood of the stored blood being used for Hematopoietic Stem Cells Transplant(HSCT) is very small, probably as low as 0.005 to 0.04% in the first 20 years of life. HSCT using an individual's own cord blood (autologous transplant) is not recommended for genetic disorders. Private banking is suggested in cases where there is a relative or sibling with a condition of a family history of malignant or genetic conditions that can be treated with HSCT. Moreover, banking for allogeneic transplantation is recommended when there are shared HLA alleles between the two parents [31].
- In view of the above, expectant parents should be wary of misleading and luring advertisements by private cord blood banks. Such advertisements often involve celebrities who are often hired as their brand ambassadors prompting storage as status symbols because such celebrities might be doing the same. The expectant

parents venture under the influence of such advertisements without full knowledge about the remote chances of possible self or family use of the banked cord units. They are emotionally as well as economically burdened to store the child's UCB as a form of biological insurance for future use. The advertisements are misleading the public into believing that the child's own UCB can protect it from a large number of medical conditions.

- Another claim often made on the websites of the private banks is about the utility of stem cells in several incurable diseases through blogs and testimonials of patients and doctors, resulting in expectant parents to think that they are depriving the child of a future panacea by not storing their UCB.Parents should be given accurate information regarding the utility of the stored tissue. There is no clarity if the tissues stored are viable, as there have been several instances when the UCB units, when asked for transplantation, were found to be without any viable cells. The customer has no idea what happens to the stored unit if the facilities close or in a situation involving natural calamities. There are several gray areas that need to be addressed.
- Complaints regarding the UCB bank practices and procedures can be made to the zonal offices of CDSCO with a copy each to the central CDSCO and the ICMR. One can also move to the consumer court.
- For misleading advertisements, one can register a complaint with the Advertising Standards Council of India.
- For more details, please refer to the FAQs placed on the ICMR website [38] (https://main.icmr.nic.in/sites/default/files/upload_documents/UCBB_eng.pdf).

Annexure II

Guidance to Health Care Professionals Involved in UCB Collection

- At the time of cord blood procurement, discretion of trained staff is required for clamping as the alteration in placental hemodynamics could cause hypervolemia in newborn.
- Health care professionals shall be well-informed about the purpose of cord blood collection and its storage and about factors that influence the volume, quality, and ability to collect a cord blood unit.
- Health care professionals caring for women and families who choose private umbilical cord blood banking must disclose any financial interests or potential conflicts of interest [30].
- Pregnant women shall be provided with unbiased information about umbilical cord blood banking options, including the benefits and limitations of public and private banks.
- Health care professionals shall obtain consent from mothers for the collection of umbilical cord blood prior to the onset of active labor, ideally during the third trimester, with ample time to address any questions.
- Health care professionals shall be trained in standardized procedures (*ex utero*and*in utero* techniques) for cord blood collection to ensure the sterility and quality of the collected unit.
- Umbilical cord blood collection must not adversely affect the health of either the mother or the newborn. Cord blood collection should not interfere with delayed cord clamping.
- Under the India Newborn Action Plan (INAP) MoHFW, delayed cord clamping is the recommended immediate newborn care.
- Delayed umbilical cord clamping, not earlier than 1 min after birth is recommended for improved maternal and infant health and nutrition outcomes [40].
- Cord blood collection is not advisable in complicated deliveries like twin gestation and prematurity.

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