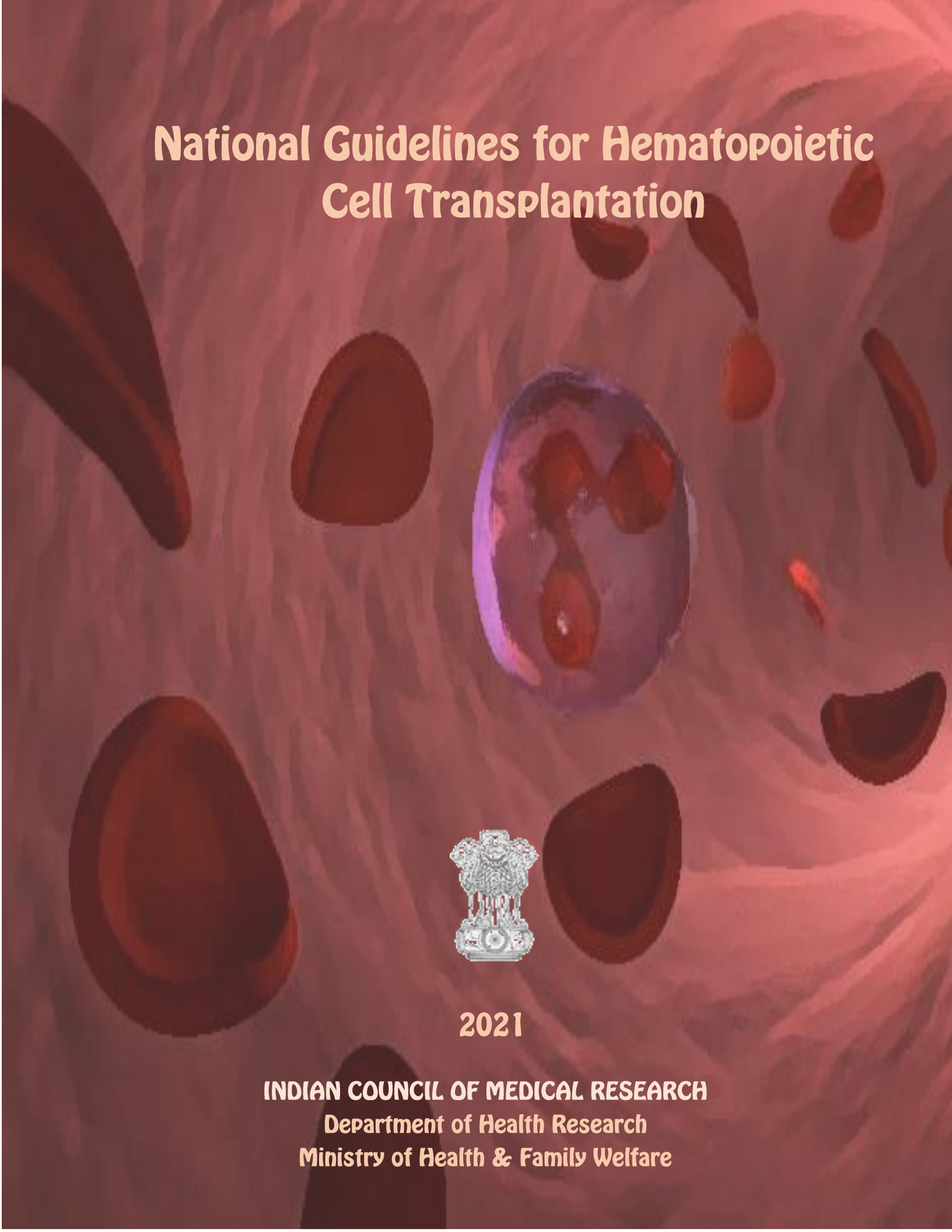
National Guidelines for Hematopoietic Cell Transplantation



2021

INDIAN COUNCIL OF MEDICAL RESEARCH
Department of Health Research
Ministry of Health & Family Welfare

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PREFACE

The journey of the bone marrow transplant (BMT) started with animal studies in the 1950s, wherein, the murine leukemia was treated with X-rays and homologous bone marrow. These studies formed the basis of clinical applications of BMT in humans in 1957, when the first successful transplant was performed in monozygotic twins in New York (syngeneic transplant) in a patient with acute leukemia. With this breakthrough, BMT gained popularity all over the world, including India where the first successful allogeneic BMT was done on 20th March 1983 at Tata Memorial Hospital., Mumbai. With the understanding that hematopoietic stem cells constitute the bone marrow, BMT was also known as Hematopoietic Stem Cell Transplantation (HSCT). Keeping pace with the contemporary nomenclature, the committee decided to adopt the presently accepted nomenclature of Hematopoietic Cell Transplantation (HCT).

HCT has revolutionized the treatment of many, hitherto, incurable diseases and is offered for serious life threatening conditions. It has now become the standard of care for numerous benign and malignant diseases and is integrated in many treatment protocols. It is one of the most complex and demanding of medical therapies posing several challenges to the transplant physician and unit.

India has come a long way in the field of HCT and undergone rapid expansion in its technology and use. As on date, our country has more than 95 transplant centers with over 19000 transplants reported, catering to foreign patients as well.

Despite HCT being a well-established clinical practice, a gap was felt in the distinction between its use for approved and unapproved indications. The National Guidelines for Stem Cell Research -2017 had listed the approved indications of HCT. However, the concerns related to rampant use of stem cells for unapproved indications needed to be addressed as they pose a threat to the well-being of vulnerable and diseased groups. Keeping the above in mind, Ministry of Health and Family Welfare (MoHFW) and NITI Aayog requested ICMR to formulate separate guidelines to bring about clarity for the stakeholders. Moreover, the expeditious development in this field with evolving transplant practices and the increasing numbers of long-term survivors necessitated the need for continuous awareness and education of all stakeholders which include physicians, nurses, healthcare providers who are involved in stem cell transplantation and patients.

ICMR Drafting committee consisting of eminent transplant physicians, clinicians, pathologists and scientists took upon the enormous task of framing this document. The committee recognized that despite the merits associated, HCT is associated with significant morbidity and mortality and will continue to remain a highly specialized and personalized medicine. It requires significant infrastructure and a specialized team under tertiary care

support. Hence, information on indications, use of specific technologies, and trends in the application of HCT is essential for optimizing transplant outcomes. The committee referred to EBMT and ASTCT guidelines along with the existing rules and regulations while drafting the document.

The aim of the National Guidelines for Hematopoietic Cell Transplantation (NGHCT)-2021 is to lay down a template and help transplant physicians and centers formulate their own protocols and policies to conduct HCT. These guidelines in over 12 chapters, highlights the significance of HLA typing in HCT, handling, processing and preservation of stem cells and follow up of patients after transplant. Most importantly, it also enlists the indications for HCT, both in adults and pediatric patients.

It should be noted that this guideline is a template, and it is ultimately left to the transplant physician's discretion and institutional policies to formulate protocols at the user end. Each transplant centre is expected to write their own SOPs, wherever applicable, using the guidelines as a template.

In addition to these guidelines, the drafting committee also decided to formulate another set of documents, on 'Evidence-Based Use of Stem Cell Therapy in Human Diseases' to address the experimental use of stem cells and assimilate available evidence in this nascent field. For this, ICMR invited Level I and Level II evidence, writing to professional societies and also through an open call on the ICMR website. Thereafter, fifteen thematic groups viz. Neurological and neuromuscular, Cardio-vascular etc. were identified. The clinical experts for each group were invited to review the literature and examine various claims on the use of stem cells. Based on the inputs received from the experts, evidence-based status of use of stem cells, for few such disease conditions have been framed.

We sincerely hope that this document explicitly brings forth the directions for permitted and experimental use of HCT in approved and unapproved indications respectively. Going forward, ensuring positive engagement with all stakeholders, this document will be reviewed and updated periodically in view of latest scientific evidence and research in the field.

Dr. Balram Bhargava
Secretary
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&
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ACKNOWLEDGEMENT

The Hematopoietic Cell Transplantation guidelines have come into existence due to the vigorous and untiring efforts of a group of medical experts from across the country. It was the vision of MoHFW and ICMR, DHR combined with the expertise of veterans in the field that resulted in the formation of this document. Transplant physicians all over India can now look up to these guidelines for knowing the best practices in the field of hematopoietic cell transplant.

We profusely thank members of the Core committee, Dr. Rajiv Sarin, Lt. Gen. (Dr) Velu Nair, Dr. Anurag Agrawal and Dr. Subrata Sinha for their vision in taking forward this task and continued directions.

We wish to extend our heartfelt gratitude to the Drafting Committee for HCT under the leadership of Lt. Gen. (Dr) Velu Nair for spearheading the mammoth task of shaping of this document and making it a reality. The committee comprising Dr. Lalit Kumar, Dr. Navin Khattry, Dr. Gaurav Kharya, Col. (Dr) Deepak Mishra, Col. (Dr) Jasmeet Kaur, Dr. Vikram Mathews, Dr. Sharat Damodar and Dr. Revathy Raj worked day in and out for considering and deliberating upon all comments and suggestions given by the stakeholders and addressed all their concerns in the final document. We also appreciate the valuable inputs given by Dr. Pankaj Malhotra and Col. (Dr) Suman Pramanik in the finalization of the document.

In this regard, ICMR also acknowledges the comments and suggestions given by the stakeholders when the draft document was placed in public domain. It is only with these combined efforts that we hope to make HCT a safe and easily available treatment modality for the diseased population.

The patience, furtherance and patronage of Prof. Balram Bhargava, Secretary, Department of Health Research and Director General, ICMR is truly avowed.

I appreciate the persistent support of Dr. Gitika Kharkwal and Dr. Varsha Dalal for coordinating and collating inputs. Lastly, the administrative and logistic support extended by the staff of Division of Basic Medical Sciences including Sh. G. S. Sandhu, Sh. Shatrughan Kumar and Sh. Laxman Singh Rawat is greatly appreciated.

(Dr. Geeta Jotwani)

Contents

Abbreviations

ASTCT/ASBMT: American society of transplantation and cellular therapy / American society of blood and marrow transplant
APBMT: Asia Pacific Blood and Marrow Transplant
BM: Bone marrow
BMT: Bone marrow transplant
CAP: College of American Pathologists
CBU: Cord blood unit
CDSCO: Central Drugs Standard Control Organization
CMV: Cytomegalovirus
CIBMTR: Center for International Blood and Marrow Transplant Registry
DMSO: Dimethyl sulphoxide
DLCO: Diffusion capacity of the lung for carbon monoxide
EBMT: European society of blood and marrow transplantation
EBV: Epstein Barr virus
FDA: Food and Drug Administration
GvHD: Graft versus host disease
HSCs: Hematopoietic stem cells
HCT: Hematopoietic cell transplant
HSCT: Hematopoietic stem cell transplant
HDC/ASCR: High dose chemotherapy/autologous stem cell rescue
HLA: Human leukocyte antigen
HCG: Human chorionic gonadotropin
HES: Hydroxy ethyl starch
HPCs: Hematopoietic progenitor cells
KFT: Kidney function tests
LFT: Liver function tests
LEVF: Left ventricular ejection fraction.
MMAD: Mismatched alternative donors
MSD: Matched sibling donor
MUD: Matched unrelated donor
MFI: Mean fluorescent intensity.
MUGA: Multigatedacquisition scan
MCI: Medical council of India
NABL: National Accreditation Board for Testing and Calibration Laboratories
NGGTPD&CT: National Guidelines for Gene Therapy Product Development and Clinical Trials -2019
NGSCR: National guidelines for Stem Cell research-2017
PBSC: Peripheral blood stem cells
PCR: Polymerase chain reaction
STR: Short tandem repeats
SOP: Standard operating protocols
SOS: Sinusoidal obstruction syndrome
VNTR: Variable nucleotide tandem repeats
TCR: T cell receptor
UCB: Umbilical cord blood
VOD: Veno occlusive disease
WHO: World Health Organization

1. Preamble

The first successful human bone marrow transplant (BMT) in 1959 marked a turning point in the history of medicine, laying the first-ever step towards haematopoetic stem cell transplantation (HSCT). The more recently accepted nomenclature of HSCT is, hematopoetic cell transplantation (HCT). HCT became established as a therapeutic option for a wide variety of life-threatening haematological including immunolymphoid, myeloid and genetic disorders where HCT has shown a proven benefit as listed in *Annexure I*. Another milestone was the successful treatment of a child with Fanconi Anemia with umbilical cord blood (UCB) from his sibling in 1987, which established UCB as an alternative source of hematopoietic stem cells (HSCs).

The present guidelines is restricted to the homologous use of non modified HSCs (as in a conventional allogeneic or autologous hematopoetic cell transplantation for specified indications).[1] Homologous use means the repair, reconstruction, replacement, or supplementation of a recipient's cells or tissues with human cells, tissues, and cellular or tissue-based product (HCT/P) that performs the same basic function or functions in the recipient as in the donor, https://www.fda.gov/regulatory-information/search-fda-guidance-documents/regulatory-considerations-human-cells-tissues-and-cellular-and-tissue-based-products-minimal

The distinction between homologous and non-homologous use also applies to autologous use of HCT products, where the donor and recipient are the same person. Recipient cells or tissues that are identical (e.g. skin for skin, HSCs for HSCs without manipulation) to the donor cells or tissues, and perform one or more of the same basic functions in the recipient as the cells or tissues performed in the donor is considered as homologous application. Also, in the scernario where recipient cells or tissues that may not be identical to the donor's cells or tissues, but that perform one or more of the same basic functions in the recipient as the cells or tissues performed in the donor are considered as homologous. Non-homologous use of hematopoietic progenitor cells (HPC) or hematopoietic derived cells (as in use of HSC/HPC to treat cardiomyopathy, neurological disorders etc) is still experimental and is not covered in these guidelines and one should refer to the National Guidelines for Stem Cell Research (NGSCR-2017)[2].
https://www.icmr.nic.in/sites/default/files/guidelines/Guidelines_for_stem_cell_research_2017.pdf

The new generation therapeutic products, including modified/manipulated hematopoietic derived cells such as NK cells, CAR-T cells and virus specific cytotoxic T cells are covered under National Guidelines for Gene Therapy Product Development and Clinical Trials[3] (NGGTPD&CT)-2019 and upcoming immunotherapy guidelines.
https://main.icmr.nic.in/sites/default/files/guidelines/guidelines_GTP.pdf

The last two decades, unfortunately, have witnessed a proliferation of indiscriminate use of stem cell-based therapies, without establishing their safety or therapeutic efficacy. These therapies could harm the patients health and incur a significant out of the pocket expenditure. Initially, the lack of clear guidelines and regulations compounded the problem of misuse of stem cells for unproven therapeutic interventions. To address this complex issue, Guidelines for Stem Cell Research and Therapy were first formulated in 2007 and revised in 2013 and 2017 as National Guidelines for Stem Cell Research (NGSCR).

BMT or hematopoietic cell transplantation (HCT), is recommended for hematological disorders outlined in *Annexure I*. Autologous transplant is primarily used for various hematological malignancies, some solid tumors, and autoimmune disorders. Other than HCT for approved indications (*Annexure I*) the use of stem cells in all other diseases is investigational and must be done within the purview of a clinical trial, as stated in NGSCR-2017. Despite this clarity, there is a misconception, that using autologous stem cells in non-hematological settings could be included as clinical practice. This misconception has led to the increased commercialization of stem cell therapy for unproven non-homologous indications. This practice has undermined genuine clinical trials using stem cells that would pave the way to establish the safety and efficacy of various unproven indications.

2. Aims and Scope

This document recommends a set of standards for HCT. The document's primary intent is to indicate those conditions for which HCT is the standard of care. However, this document does not include those conditions in which therapeutic use of stem cells/HCT is not yet proven, but is in the state of basic, translational, or clinical research, including clinical trials.

These guidelines apply to all stakeholders, including treating physicians and associated clinical establishments where HCT is being performed.

3. Hematopoietic Cell Transplantaion

In India, over 19000 transplants have been performed for various indications by more than 95 centers, majority (73%) of which have been done in the past eight years.[4] Seventy percent of all allogeneic HCTs in India are from, HLA matched sibling (MSD) donors, however, lately there is an increase in the matched unrelated donor (MUD) and haploidentical HCTs.[4] The rise in MUD transplants has been possible due to the establishment of various unrelated donor registries in the country over the last decade, increasing the pool of donors. Haploidentical HCT has also gained popularity in recent times, due to ease of donor availability, safe and better strategies in the absence of a fully matched donor.[5,6]

Though much progress has been achieved in India in this field, physicians still face many challenges. Lack of teams with multi-specialty personnel, inadequately equipped transfusion medicine departments, inaccessibility to many life saving drugs for various post-transplant complications, high cost and increasing incidence of multi drug-resistant gram-negative bacterial infections are some issues that need attention in our country to improve outcomes.

4. Approved Disease Conditions for Hematopoietic Cell Transplantation

Taking congnisance of the international status and the outcomes of the various clinical trials conducted in the field in past several decades and reviewing the recommendations of American Society for Transplantation and Cellular Therapy (ASTCT)[5] and EBMT[6], it was opined that the indications for which HCT is a recommended therapeutic option are as outlined in *Annexure I*.

5. HLA-typing in Hematopoietic Cell Transplantation

The human leukocyte antigen (HLA) system (the major histocompatibility complex [MHC] in humans) is an important part of the immune system and is controlled by genes located on chromosome 6. It encodes cell surface molecules specialized to present antigenic peptides to the T-cell receptor (TCR) on T cells. A close match between a donor's and a patient's HLA antigens is essential for a successful transplant outcome. Better HLA matching reduces the risk of graft-versus-host (GVHD) disease. Some patients may face a greater challenge in finding a matched donor because some HLA types are less common than others. Some HLA types are found more often in certain racial and ethnic groups. Following are the

requirements for Histocompatibility & Imunogenetics testing laboratories performing HLA typing for HCT:

5.1. HLA typing should be done at a NABL accredited facility.

5.2. If the HLA typing is outsourced, there should be a written agreement between the center and the concerned laboratory capturing the terms of agreement, accreditation details of the laboratory, and expected degree of resolution that is required.

5.3. Centers offering haploidentical HCT should either have in-house laboratory facility for testing anti-HLA antibodies or can be outsourced to a NABL accredited facility.

5.4. HLA typing definitions and results should use the official World Health Organization (WHO) HLA Nomenclature[7] http://www.hla.alleles.org for reporting HLA assignments. The typing assignments must conform to the WHO nomenclature of the HLA system. Slashes should be used to separate a string of alternative alleles while reporting (e.g., A*02:01/02:02/02:07/02:10 to mean A*02:01 or A*02:02 or A*02:07 or A*02:10).

5.5. The HLA typing report must include the loci tested, the level of resolution of the typing, the typing method used, and the version of the database used to interpret the results. A comment on the matching status of the donor/recipient pair should be stated in the report.

5.6. Standard Operating Procedures (SOPs) should be available in Histocompatibility and Immunogenetics testing laboratories for the following:

5.6.1. To confirm the identity of the patient and the donor sample.

5.6.2. To confirm the identity of the MUD HSC/HPC unit and Cord Blood Unit (CBU).

5.6.3. For sample testing procedures/ kits used for testing (CDSCO/CE/FDA certified)

5.6.4. To store samples, results, data and documents of patients and donors undergoing testing.

5.6.5. For anti-HLA antibody testing in the case of mismatched recipients and donors.

5.6.6. For reporting formats and release of reports

5.6.7. For validation, calibration and maintenance of equipment.

5.7. HLA matching criteria for donor selection[8]

5.7.1. Related Donor Hematopoietic Cell Transplants: The patient, siblings, and parents (where available) should be HLA-A, -B and -DRB1 typed at a minimum of low resolution. If there is homozygosity, high-resolution

typing should be done for the patient and prospective donor, at HLA –A, -B, -C, -DRB1 and DQB1 loci.

5.7.1.1. Where consanguinity exists within the family, other relatives may also be typed as prospective donors.

5.7.1.2. For a fully matched related donor, a repeat sample for confirmatory HLA typing may be done at the discretion of the BMT physician.

5.7.1.3. In case of non-availability of a fully matched family donor, a high-resolution typing is mandatory at HLA-A, -B, -C, -DRB1, and –DQB1 loci for the patient and alternate donors.

5.7.1.4. In haploidentical transplants, patients should be screened for the presence of allo-antibodies against potential donors. Donor specific allo-antibodies against HLA class I and class II of the prospective donors should be quantified by using the single antigen bead method on the Luminex platform and/or cell-based immunoassays.

5.7.1.5. In HCT for inherited disorders, the prospective related donors need to be screened for a similar genetic defect.

5.7.1.6. When MFI >= 2,000 the incidence of poor graft function/ graft failure is increased[7].

5.7.1.7. If the above prospective donor cannot be avoided, desensitization methods should be attempted.

5.7.2. Unrelated Donor Hematopoietic Cell Transplants

The availability of sizeable international voluntary donor registries and cord blood banks facilitate alternative source of stem cells for patients without a suitable related donor.

5.7.2.1. The recommendations are a 10/10 high-resolution match at HLAA, -B, -C,-DRB1, and DQB1 loci with the unrelated donor.

5.7.2.2. If a 10/10 match donor is not available, a single allele mismatch at HLA- DQB1 locus is most acceptable. Matching/mismatching at other loci should be considered on an individual basis following the transplant physician's evaluation of the patient's transplant-related risks**.**

5.7.3. Criteria for Choosing Umbilical Cord Blood Unit[9]

5.7.3.1. UCB units should be HLA typed to high-resolution for HLA-A, -B, -C, and -DRB1 loci.

5.7.3.2. The aim should be to select an unrelated UCB with ≤2 allele mismatches.

5.7.3.3. In a double UCB transplant where more than one unit is required, both the UCBs should be at least 4/6 matched to the patient using intermediate resolution (antigen level) for HLA loci A and B and high resolution (allelic) typing for HLA DRB1.

6. Source of Stem cells and the Process of mobilization and collection

Sources of HSCs include bone marrow, peripheral blood, and umbilical cord blood .

6.1 Bone Marrow Harvest

6.1.1. A marrow harvest has to be performed under general or loco-regional anesthesia or under sedation from the posterior superior iliac crest.

6.1.2. The harvest should be done in small aspirate volumes of 2 to 5 ml to avoid dilution with blood, changing aspiration sites each time.

6.1.3. The goal should be to collect at least 2-3 x10^8/kg nucleated cells of the patient's body weight. However, the maximum volume collected should not be more than 15-20 ml/kg of the donor's body weight. The optimal method to obtain the targeted nucleated cells from the bone marrow is to do a mid-way nucleated cell count to predict the total volume of marrow to be harvested.

6.1.4. All efforts should be attempted to avoid allogeneic blood transfusion to the donor post marrow harvest. If unavoidable, the allogeneic packed red cells should be leuco-depleted and irradiated before transfusion to the donor. An option of autologous blood transfusion from the donor can also be considered (3 weeks before harvest).

6.1.5. The use of granulocyte colony-stimulating factor (G-CSF) for 2 to 4 days at the discretion of the transplant physician, prior to marrow harvest, can be used to speed the engraftment. This strategy increases the yield of mononuclear cells. If the harvest is inadequate, an option of additional peripheral blood stem cells (PBSC) can be considered.

6.1.6. Bone marrow harvested in operation theatre and subsequent graft manipulation, if required, must be done under the direct supervision of a trained transplant physician /transfusion medicine specialist.

6.2 Peripheral Blood Stem Cell Collection (PBSC)

6.2.1 In the majority of patients, PBSC is the source of stem cells. The donor receives G-CSF 10 mcg/kg for 4 to 5 days and PBSC is collected on the 5th and if required, on the 6th day.

6.2.2 The goal should be to collect at least 2-3 x 10^6/kg CD 34+ cells of the patient's body weight for fully HLA matched related donor transplants and at least 5 x 10^6/kg for matched unrelated and haploidentical transplants.

6.2.3 Several studies have compared the outcome of allogeneic HCT using BM or PBSC. These studies uniformly show rapid engraftment with PBSC, but with an increased risk of chronic GVHD (cGvHD).

6.2.4 The donor's preferences must also be taken into account as there are risks of anesthesia in bone marrow harvest.

6.2.5 In most patients undergoing autologous transplantation, the stem cell source is usually PBSC.

6.2.6 Stem cell collection by apheresis and subsequent graft manipulation, whenever required, must be done directly under the immediate oversight and supervision of a trained transplant physician / transfusion medicine specialist.

6.3 Umbilical Cord Blood

6.3.1 Cord blood is predominantly used in children. It has less risk of GvHD but more time to engraftment and increased risk of graft failure.

6.3.2 The selection of UCB unit is based on various factors, such as patient's diagnosis, degree of HLA matching, cell dose, conditioning regimen to be used, age and recipient's weight.[9]

6.3.3 The collection, banking and release for administration of the UCB should be done as per the NetCord-FACT International Standards.[10]

6.4 Autologous back-up*:* While there is no level I evidence, autologous back up of HSCs may be considered on a case to case basis at the transplant physician's discretion especially in alternative donor transplants.

7 Strategies for Mobilization of Stem Cells in Autologous Transplantation

7.1 Cytokine-induced Steady State mobilization (without chemotherapy): G-CSF is administered subcutaneously at a dose of 10 mcg/kg for 5 consecutive days.A peripheral blood CD 34+ cell count is obtained on the 4th day and if the count is higher than 20/µL, then stem cell harvest is done on the 5th day after administering day 5 GCSF. If the count is less than 20/µL, then according to disease status and risk of mobilization failure, the use of plerixafor is recommended at a dose of 240 mcg/kg subcutaneously. The minimum total CD 34+ cell dose should be 2 x 10^6/kg

recipient body weight in 1-3 collections. If the collection goal is not reached after the third leukapheresis, a successful mobilization is unlikely. For tandem transplants, the requirement of cell dose is 2 x 10^6/kg recipient body weight for each transplant.

7.2 Chemotherapy-induced mobilization

7.2.1 The most commonly used agent for chemotherapy-induced mobilization is cyclophosphamide at a dose of 2-4 g/m^2. G-CSF is started at a dose of 5-10ug/kg/day on days 4 or 5, and the peripheral blood CD34+ cell count is measured at the start of leukocyte recovery from day 8 or 9. Stem cell collection is initiated when the peripheral blood CD 34+ cell count is greater than 20/µL.

7.2.2 Disease-specific salvage chemotherapy can also be exploited for stem cell mobilization as in lymphomas.

8 Pre-Transplant Work-up of Recipient and Donor

8.1 Recipient Work-up: The work-up of recipient undergoing autologous or allogeneic transplant is divided into two groups.

8.1.1 Disease-specific investigations that help assess the status of disease pre-transplant.

8.1.2 Investigations for assessing the function of various organs pre-transplant to predict the risk of post-transplant complications. These include:

8.1.2.1 Complete blood count, comprehensive biochemistry including liver function test (LFT), kidney function test (KFT), serum electrolytes, blood sugar level.

8.1.2.2 Coagulation profile, blood grouping, and antibody screening.

8.1.2.3 Urine- routine and microscopy examination

8.1.2.4 Chest X-ray or Non-contrast CT chest for the detection of active pulmonary infections.

8.1.2.5 Electrocardiogram (ECG).

8.1.2.6 Echocardiography or Multi-gatedAcquisition Scan (MUGA) for Left Ventricular Ejection Fraction (LVEF)

8.1.2.7 Pulmonary function test that includes spirometry and diffusion capacity of the lung for carbon monoxide(DLCO) for patients above the age of 8 years. Glomerular filtration rate (GFR) estimation

8.1.2.8 Serum beta-human chorionic gonadotrophin (β-HCG) levels to exclude pregnancy in female patients of reproductive age group. This test should be performed at least seven days before initiation of conditioning regimen.

8.1.2.9 Baseline blood sample for short tandem repeats (STR) or variable nucleotide tandem repeats (VNTR) based chimerism monitoring (for the allogeneic transplant) is recommended.

8.1.2.10 Fertility counseling regarding fertility preservation as and when applicable.

8.1.2.11 Screening tests for infection:

i. HBs Ag, anti-HBs Ag, anti- HBcIgG, anti-HBcIgM (optional), anti-HCV, anti-HIV1 and 2

ii. CMV IgG, CMV PCR (at the physician's discretion) for those patients undergoing allogeneic transplant

8.2 Donor Work-up

8.2.1 A thorough history and physical examination are required. The medical history should include questions to evaluate whether a transmissible disease is present.

8.2.1.1 Vaccination history,

8.2.1.2 Travel history,

8.2.1.3 Blood transfusion history,

8.2.1.4 To identify persons at high risk of transmission of infectious disease,

8.2.1.5 To identify persons at risk of transmitting inherited conditions,

8.2.1.6 To identify persons at risk of carrying a hematological or immunological disease and

8.2.1.7 To determine the history of malignant disease.

8.2.2 Potential allogeneic donors either fully matched or haplo-matched should undergo the following investigations:

8.2.2.1 Complete blood count, complete biochemistry including LFT, KFT, electrolytes, blood sugar, coagulation profile and blood grouping/antibody titres

8.2.2.2 Urine- routine and microscopy examination

8.2.2.3 ECG, Chest X- ray

8.2.2.4 Serum β-HCG to rule out pregnancy in female donors of reproductive age group.

8.2.2.5 Baseline blood sample for short tandem repeats (STR) based chimerism monitoring.

8.2.2.6 HBs Ag, anti-HBs Ag, anti-HBcIgG, anti-HBcIgM, anti-HCV, anti-HIV1 and 2

8.2.2.7 CMV IgG

8.2.2.8 Informed consent with details of the procedure of stem cell collection with all possible risks of stem cell donation (*Annexure II*).

8.2.2.9 Informed consent for data registration needs to be given by the patient for reporting to stem cell registries or use in research purposes (*Annexure-II*).

8.2.3 The work-up of unrelated donor depends on the registry coordinating the transplant but usually encompasses the above.

9 Processing of Hematopoietic Stem Cells (HSC)[10,11]

The processing of HSCs should maintain the purity and potency of the cells for transplantation. Flow-cytometric based cell counts, viability analysis, and sterility testing are done before cryopreservation and storage. HSC processing involves the following: (*Annexure-III*).

9.1 **Plasma depletion** is performed in recipients of minor ABO-mismatch allograft, children with a small blood volume or patients with coexisting renal or cardiac comorbidities. In the setting of minor ABO-mismatch allograft, plasma depletion is done when donor anti-recepient isoagglutinin titers are higher than or equal to 1:256 with a target of decreasing it to less than or equal to 1:128.

9.2 **Red cell depletion:** In major ABO-incompatible transplants with recipient anti-donor isoagglutinin titer >= 1:32, the red cell contamination in PBSC graft should be kept <20 ml and RBC depletion of BM grafts should be considered using sedimenting agents like hydroxyl ethylstarch (HES), centrifugation, or cell separator (automation) to prevent hemolytic transfusion reaction. Red cell depletion is also performed in patients with renal dysfunction, to help reduce lysed red cell fragments and free hemoglobin.

9.3 **Immuno-magnetic cell selection technology**: *In vitro* T-cell depletion:

9.3.1 A novel technique of T-cell depletion primarily used in haploidentical transplants is by use of *in-vitro* T cell depletion kits. This technique has

improved significantly over the years using the Miltenyi-Biotectechnique (CliniMacs or Prodigy system, Bergisch Gladbach, Germany).

9.3.2 It initially started with the use of positive selection of CD 34+ progenitor cells where the stem cells carrying CD 34+ cells were retained, and the rest of the cells harvested from either bone marrow or peripheral blood were discarded. This technique significantly decreased the risk of graft versus host disease but is complicated by an increased risk of rejection and opportunistic infections.

9.3.3 With advanced technology, a negative selection of CD 3+ and CD 19+ cells is now possible. TCR alpha/beta depletion and CR45RA depletion removes the T lymphocytes capable of causing GvHD.This technique is superior to the previous CD34+ selection as it is associated with a lesser risk of opportunistic infections and GvHD. The same process can also be used to process the graft or subsequent donor lymphocyte collection by apheresis to generate donor lymphocyte infusion (DLI), CD45RA depleted DLI products, NK cells, other cellular subsets for DLI or viral cytotoxic lymphocytes from a donor.

9.4 Chimeric Antigen Receptor (CAR) – Modified (CAR) T cells (CAR-T cells): T cells are a component of the adaptive immune system, as effectors of cell mediated-immunity. T cells exert their cytotoxic and potentially anti-tumoral effect upon engagement of the T – cell receptor is by a cognate peptide antigen, which is presented in the context of a specific major histocompatibility complex (MHC) molecule. The concept of tumor-targeted T cells has come to a reality as a result of genetic modification strategies capable of generating a tumor-targeting T cell receptor. Chimeric antigen receptors (CAR) are recombinant T cell receptors composed of an extracellular fragment derived from the immunoglobulin variable fragment, as single chain (scFv), which is, in turn, linked to intracellular signaling sequences that are derived from T cells. Insertion of a CAR in a T cell can induce activation of the T cell upon ligation of the scFv with its target antigen.

There are currently two US FDA approved CAR-T cells (i) tisagenlecleucel (Kymriah) (ii) axicabtageneciloleucel (Yescarta). There are many more in clinical trials. While this technology is not yet available in India, several groups are working to establish the technology and make it locally available. CAR-T cells will follow all the steps and regulatory requirements of HCT along with additional standards for the manufacturing and release of products for clinical use.

CAR-T cell therapy must be done only in centers with experience in HCT and under the supervision of physicians trained in HCT. A number of the process and complications are similar to those seen with HCT. Additionally, there are certain unique complications with CAR-T cells such as cytokine release syndrome and neurological toxicities that the physician will need additional training before administering CAR-T cell therapy. Until approved in India, all use of CAR-T cells will have to be done in the setting of a CDSCO approved clinical trial and in compliance with NGGTP&CT-2019.

9.5 **Cryopreservation** is performed using aseptic precautions in a microbiological safety cabinet within 72 hours of stem cell collection:

9.5.1 Dimethyl sulphoxide (DMSO) is a cryoprotectant that reduces the osmotic stress on the stem cell membrane and prevents dehydration of the cell. It prevents both extracellular and intracellular ice crystal formation during freezing.

9.5.2 All the consumables like gauze pieces, syringes, transfer bags, DMSO, and 5% human albumin bottles/autologous plasma bags are opened inside the cabinet.

9.5.3 The cryoprotectant solution is prepared in a sterile transfer bag with DMSO, 5% human serum albumin, and plasmalyte in the ratio of 1:1:3. In lieu of albumin and plasmalyte, autologous plasma could also be used.

9.5.4 The final DMSO concentration should be 5-10% with albumin and electrolyte solution for optimum preservation of HSCs.

9.5.5 Six percent HES could also be used along with 5% DMSO for cryopreservation of HSC. HES is a non-penetrating macromolecular cryoprotectant that forms a glassy membrane around the cell.

9.5.6 The final volume in each cryo-bag should not exceed 70-100 ml and air bubbles need to be expelled from the bag.

9.5.7 Care should be taken to add the DMSO slowly into the transfer bag because it dissipates heat, and the final cryoprotectant solution should be refrigerated for 30 minutes.

9.5.8 The cryo-bag labels bearing the product volume, patient and donor details are pasted on the left upper corner of the bag and placed inside cassettes.

9.5.9 Freezing: post cryopreservation freezing can be done in two ways:

9.5.9.1 Controlled rate freezing involves cooling of HSC product at a computer-controlled rate with close temperature monitoring of the product and freezer. It takes place in a device called

Planer that allows injections of liquid nitrogen gas into the freezing chamber in a programmed fashion to control the freezing rate. Initially, it is cooled at the rate of 1°C/minute until -14°C to -24°C (transition temperature). It is then supercooled to shorten the latent heat of fusion (i.e. the kinetic energy released at the freezing point). After solidification of a product-controlled rate, freezing is done by institutional protocol until the product temperature reaches -90°C. The cryo-bags in cassettes are then transferred to the liquid nitrogen tank for further storage, preferably in the vapor phase and stored maximum upto 5 years for clinical use.[12]

9.5.9.2 Non-controlled freezing or dump freezing involves the transfer of HSC product into a mechanical freezer at -80°C. Fresh HSC product can be stored at 2-8°C for upto 72 hours before processing for cryopreservation beyond which CD34+ number and viability may reduce. The stored product may be used for transplantation upto 24 months of storage[13]. Long term storage is recommended in the vapour phase of liquid nitrogen between -150°C to -196°C as it reduces the risk of microbial contamination of products.

9.6 Quality Control

Flow-cytometry based CD34+ cell enumeration is done before processing and a microbial detection system is employed to test for any contamination during processing and storage.

9.7 Transport

Fresh HSC product is transported at 2-8 °C in a sterile, cold box within 24-72 hours. Shipment of frozen HSC product is made in a secondary container to prevent leakage and contamination. The temperature is continuously monitored and maintained below minus 150°C.

9.8 Thawing, washing, and Infusion

Cryopreserved HSCs are wrapped in sterile zip-locked bags and rapidly thawed in a water-bath at 37°C with gentle rotatory motions until no traces of ice remain. A semi-automated, dry warming electrical device could also be used for thawing. To avoid DMSO toxicities, the dose limit of DMSO that can be infused shall not exceed 1g/ kg of recipient weight in a day. Washing of HSCs in plasmalyte with 5% albumin

would reduce lysed red cells, free hemoglobin, and DMSO but will lose some CD34+ cells. A post thaw CD34 viability assessment can be done at the discetion of the transplant physician or as per the institutional protocol.

9.9 Processing Facility

All processing of HSCs should be done in dedicated space within the institution or the blood bank under the supervision of transplant physician / transfusion medicine specialist. The blood bank should be licensed and/or accredited by appropriate authorities.

10 Conditioning Chemotherapy[7]

Conditioning chemotherapy is an integral part of any transplant, be it, autologous or allogeneic. The objectives of conditioning chemotherapy depend on the underlying disease for which HCT is being offered. For benign diseases the main objectives are to get rid or defective bone marrow or immune system, whereas, for malignant diseases the objectives are two fold, firstly to get rid of defective bone marrow and secondly to get rid of the malignant clone. To minimize the risk of graft failure or GvHD (in allogeneic HCT) conditioning chemotherapy is often integrated with some form of serotherapy. The intensity of chemotherapy depends on a number of factors, such as underlying disease, type of transplant (MSD, MUD or haploidentical HCT) and performance status of the patient. Based on the extent of myeloid or immune ablation, the conditioning chemotherapy is categorized as Myeloablative (MAB) or Reduced intensity (RIC). In the initial years of HCT, the conditioning used to be MAB but over the period of time the emphasis is more towards reduced intensity or myeloablative but reduced toxicity conditioning.

11 Immune Suppression[7]

11.1 In allogeneic HCT, there is an inherent risk of GvHD which increases with increasing HLA disparity. The risk is minimum with HLA identical sibling donor HCT and maximum with HLA haploidentical HCT. Apart from HLA disparity, the amount of alloreactive T cells infused with the graft also decides the extent of GvHD, thus the risk is less with bone marrow as source and its more with the use of peripheral blood as graft source. Over last few decades the transplant physicians have constantly tried to find ways to minimize the risk of GvHD despite HLA disparity. Historically standard immune suppression included calcineurin inhibitors (Cyclosporine) alone or in combination with methotrexate or steroids. Although cyclosporine continues to be the most frequently used immune suppressive agent, there are newer agents which are equally or more

immune suppressive with a better toxicity profile. Few such agents are second generation calcineurin inhibitors such as tacrolimus or mammalian target of rapamycin inhibitors such as sirolimus.

11.2 In Haploidentical HCT, post-transplant cyclophosphamide (PTCy) platform championed by the Baltimore group has been found to be effective GvHD control strategy. By the virtue of causing immune tolerance, it is known to reduce the risk of acute and chronic GvHD more effectively than the conventional GvHD strategies alone. Persistence of recipient antigen presenting cells in post HSCT period is known to increase the risk of GvHD by reacting to alloreactive donor T cells. Post-transplant cyclophosphamide given at 50 mg/kg for 2 days between day 3-5 addresses the alloreactive T cell and helps achieve better immune tolerance thus reducing the risk of GvHD.

11.3 Another strategy is using in-vitro T cell depletion which has been elaborated in section 9.3.

12 Post-HCT Follow-up in the Initial 12 weeks

Early post HCT follow-up is at the discretion of the transplant physician and guided by the institutional policies. However, a general outline is suggested is as follows,

12.1 Meticulous follow-up post HCT remains an integral part of the procedure to identify early side effects and prevent complications.

12.2 A minimum of 1 to 2 clinic visits weekly to check vitals and undergo a thorough clinical examination.

12.3 Close monitoring of therapeutic drug levels of cyclosporine/tacrolimus/sirolimus is recommended.

12.4 Monitor for side effects of calcineurin inhibitors, such as hypertension, renal impairment, and dyselectrolytemia.

12.5 Weekly complete blood count and blood biochemistry, including renal and liver function tests.

12.6 SOP for the care of central venous catheter.

12.7 Pre-emptive screening for viral infections is done depending on the underlying disease and type of transplant,.

12.7.1 Cytomegalovirus (CMV) by polymerase chain reaction (PCR) for allogeneic transplant recepients.

12.7.2 Blood Epstein Barr virus (EBV) and adenoviral monitoring is done for high-risk transplants such as MUD, haploidentical, and CB transplants.

12.8 Early imaging with non-contrast CT chest for investigation of cough

12.9 Donor chimerism post engraftment is usually done on days 28, 60, 90, 180, 270 and 365. at the discretion of the transplant physician.

12.10 It is recommended that the patient stays under the follow-up of the transplant center for a minimum period of time as decided by the institutional protocol.

12.11 All measures to ensure infection prevention need to be continued for a minimum of 100 days, including personal hygiene and a clean diet (cooked soft food and boiled water). Avoid raw vegetables, fruits, and crowded areas.

12.12 Disease-specific follow-up is advised as per standard guidelines.

12.13 The family must be issued clear instructions in the discharge summary with the points of contact in case of emergencies.

12.14 All cellular blood products transfused should be irradiated.

12.15 As general rule, live vaccines can be safely administered 24 months post transplant in the absence of active chronic GvHD / immunosuppression See 13.8 .

12.16 The common complications post HCT are as follows:

12.16.1 Neutropenic Sepsis: This complication occurs in almost all HCT recipients, and institutional policy should be in place for empirical antimicrobial therapy of bacterial and fungal infections, based on local sensitivity and resistance patterns. All personnel should adhere to hospital infection control policies to prevent and reduce infections in transplant patients.

12.16.2 Bleeding: Most patients develop bleeding with a platelet count of less than 10-20 x 10^9/L.A hospital transfusion policy should be in place to prevent management bleeding episodes.

12.16.3 Mucositis and Nutrition: High dose chemotherapy with or without total body irradiation leads to grade III or IV mucositis in over half of the patients undergoing transplantation. Supportive care in the form of enteral or parenteral nutrition and pain relief by the use of opioids should be considered.

12.16.4 Dyselectrolytemia: Hypokalemia, hypocalcemia, and hypomagnesemia are common causes of dyselectrolytemia in the transplant setting. These abnormalities need to be aggressively corrected.

12.16.5 Engraftment syndrome: Is defined as fever of a non-infectious origin, which develops when white cell count increases post-transplant. Classical features include fever >38.3^0 C, skin rash, non-cardiogenic pulmonary edema or hypoxia, or a sudden increase in CRP values >20mg/dL. Treatment includes stopping G-CSF and administration of a short course of steroids.[14,15,16]

12.16.6 Sinusoidal Obstruction Syndrome (SOS) or Veno-occlusive disease (VOD): SOS is characterized by jaundice, fluid retention, and tender hepatomegaly appearing in the first 35-40 days after HCT. Treatment includes liberal use of diuretics, restriction of fluids and defibrotide.[17,18,19,20]

12.16.7 Acute Graft vs Host Disease (aGvHD): This is the most dreaded complication of allogeneic transplantation. It is characterized by damage to skin, liver, or gut leading to skin rash, jaundice, or diarrhea. The initial classification by Glucksberg *et al*[21] was later modified by Przepiorka *et al*.[22] Early intervention with the use of corticosteroids leads to the resolution of signs and symptoms in approximately 50% of patients. Institutional policy to treat steroid-refractory GvHD should be in place.

12.16.8 Graft Failure: is an infrequent but often fatal complication of HCT seen in <5% of autologous, matched related and unrelated donor transplants. The incidence increases to 10% or more in haploidentical and CB transplantation, and its etiology is multi-factorial. The key is to take preventive measures following the early identification of risk factors.

12.16.9 Hemorrhagic cystitis (HC): Post-transplant can be categorized according to the time of occurrence as early or late-onset. Early-onset typically occurs within 48 hours of completion of chemotherapy and is due to the direct toxic effect of drug metabolites and radiotherapy on bladder mucosa. Late-onset HC usually starts after neutrophil engraftment and can occur several months post HCT. This is generally due to the reactivation of BK or adenovirus. Clinical diagnosis is based on the presence of signs and symptoms of cystitis. Supportive treatment includes maintaining adequate hydration, and bladder irrigation may be required in severe cases. Cidofovir may be useful in some patients with BK and adenoviral hemorrhagic cystitis, although the efficacy is uncertain.

12.16.10 CMV reactivation: With the growing number of alternative donor transplants and shift of emphsis from myeloablative to immuneablative stratagies, post transplant CMV reactivation has emerged as an important complication. The intent of the physician should always be to treat CMV reactivation and prevent progression to CMV disease. The drug of choice for management of CMV reactivation is ganciclovir/valganciclovir, however if the

reactivation is documented pre-engraftment then foscarnet is the preferred option. In ganciclovir non-responsive cases, foscarnet or cidofovir can be used as add on therapy as per institutional protocols.

13 Post-HCT Follow-up After 12 weeks

Post HCT follow-up is at the discretion of the transplant physician and guided by the institutional policies. However, a general outline is suggested is as follows,

13.1 Ensure smooth transition of care to primary referral physicians.

13.2 Early tapering of immune-suppression if there is no evidence of GvHD in hematological malignancies and delayed tapering in benign disorders.

13.3 If there are signs of GvHD, immune-suppression must be continued for a more extended period.

13.4 Adequate antifungal prophylaxis must be maintained for at least three months or longer if on steroids or dual immune-suppression. Antiviral and pneumocystis prophylaxis for atleast one year or beyond if on immune-suppressive drugs.

13.5 Monitor for herpes zoster in post HCT patients.

13.6 Signs of chronic GvHD include dry eyes and mouth, skin pigmentary changes, raised liver enzymes, lung involvement or any other organ involvement.[23]

13.7 Patients on steroids for GvHD need special monitoring to prevent infections, hyperglycemia, and osteoporosis.

13.8 Vaccinations with inactivated vaccines is recommended 6 months to 1-year post-transplant as outlined in *Annexure IV*[24-29]

14 Post HCT Follow-up for Late Effects

All HCT patients must be followed up long term. A visit to the physician monthly for the first one year followed by three monthly visits in the second year, six-monthly for the next three years, and yearly thereafter.

14.1 Height, weight, body mass index, blood pressure, urine analysis, complete blood count, renal and liver function test, lipid profile, and blood sugars to be done at each visit

14.2 Neurocognitive status and psychological assessment

14.3 Ocular examination for dry eyes or cataract

14.4 Mouth examination for xerostomia or ulcers

14.5 Thyroid function tests once a year

14.6 Echocardiography to assess ejection fraction once a year

14.7 Pulmonary function tests for age above 8 years once a year

14.8 Secondary sexual characteristics and puberty assessment where appropriate

14.9 Musculoskeletal examination for contractures or joint stiffness

14.10 In patients with chronic GvHD – bone mineral density for osteoporosis

14.11 Examination for second malignancies, especially breast and cervix in women; leukemia, bone tumor, thyroid and brain tumors for all patients.

14.12 Life style modifications to ensure physical activity, healthy diet and integration into all activities considered normal for that age group

15 Standards/Requirments for HCT Centers

The following criteria are necessary, at a minimum, for the safe and successful performance of HCT.

15.1 Patient Volume

15.1.1 A sufficient number of patients must be treated each year to allow the development of a designated transplant unit with an experienced, fulltime clinical and nursing team.

15.1.2 This would require, in general, that the center performs a minimum of ten transplants per year.

15.1.3 Sufficient transplants must be performed to preferably not have the unit empty.

15.1.4 If both allogeneic and autologous transplants are performed, at least a total of 10 should be performed annually to allow sufficient experience in the technical aspects of both procedures.

15.1.5 For alternative donor transplants, the center should have atleast performed 10 matched related donor transplants.

15.1.6 For new units, compliance with these volume goals should be attained within the first three years of functioning.

15.2 Infrastructure and Facilities

15.2.1 There must be a designated transplant unit with atleast two or more designated transplant beds. The unit could be part of a facility for treating immune-suppressed patients that also include patients with acute leukemia and other hematological disorders.

15.2.2 The necessary equipment and experience for *ex vivo* handling of marrow and/or PBSCs should be available. This includes at least the facilities with protocols for cryopreservation and management of ABO blood group incompatibility.

15.2.3 If allogeneic HCT is performed, the transplant unit must demonstrate access to a NABL-certified histocompatibility laboratory for the necessary tissue typing.

15.2.4 The transplant unit must have facilities in place to effectively manage these patients. This should include SOPs for air- handling (e.g. positive pressure, filtered air, or laminar airflow rooms) as well as monitoring of its quality. A minimum of 12 air exchanges per hour for a new unit and at least 6 air exchanges per hour for an old unit, functional for 6 or more months, is recommended. Support of trained house-keeping staff for maintaining the facility is also critical.[10, 30]

15.2.5 Twenty-four-hour, high-quality support from laboratories, blood bank, and radiology should be available. The facility for irradiation of cellular products, either in-house or outsourced, should be available.

15.2.6 Appropriate microbiology laboratory facilities, including bacteriology, virology, and mycology facilities, should always be available.

15.2.7 A radiotherapy unit with the ability to perform total body irradiation (TBI) should be available within the hospital or in its close proximity.

15.2.8 Intensive care unit (ICU), dialysis, bronchoscopy, and imaging facilities should be available for both adults and children within the institution.

15.3 Personnel

15.3.1 Transplant Physicians

15.3.1.1 Physicians who perform HCT should have documentable experience with the procedure.

15.3.1.2 If both autologous and allogeneic HCTs are being performed, the treating physicians should have documentable experience with both types of procedures.

15.3.1.3 Access to a broad range of subspecialty consultations in both medical and surgical specialties such as intensivist, infectious disease (ID) specialist, pulmonologist, nephrologist, cardiologist, and dermatologist must be available to treat complications associated with HCT.

15.3.2 The nursing team is a vital component of the transplant team. The ratio of nurse to a patient should not be more than 1:2.

15.3.3 Donor fitness should be certified by an independent physician and not by any member of the transplant team.

15.3.4 It is preferred to have a designated HCT coordinator and social worker for the transplant center.

15.3.5 Resident medical personnel should be available in the center for 24-hour medical cover.

15.3.6 A nutritionist should be available for dietetic advice for patients

15.4 Academic Qualification for BMT Physician

Physicians performing peripheral blood, cord blood, and bone marrow transplantations must be licensed to practice medicine. They should be certified and have the requisite training and experience in hematology, medical oncology, immunology, and/or pediatric hematology/oncology. Any of the following qualifications is mandatory for a BMT physician:

15.4.1 DM/DNB Clinical Hematology with training in HCT

15.4.2 DM/DNB Medical Oncology with training in HCT

15.4.3 DM/FNB Pediatric Hematology / Oncology with training in HCT

15.4.4 Candidates with MD/DNB (Internal Medicine /Pediatrics) should undergo at least 2-3 years of training in a recognized department of Hematology/ Medical Oncology with at least one year of training in HCT.

15.4.5 Equivalent qualifications from other countries recognized by the Medical Council of India (MCI) with at least one year of training in HCT.

15.5 Documentation and Data Management

15.5.1 All transplant performed must be meticulously documented and preserved as per the SOPs of the institution.

15.5.2 Physicians performing this procedure should be encouraged to report their data to available registries [e.g. Indian Society for Blood and Marrow Transplant (ISBMT), Center for International Blood and Marrow Transplant Registry (CIBMTR), Asia Pacific Blood and Marrow Transplant (APBMT), European Group for Blood and Marrow Transplant Registry (EBMT) and when appropriate, publish essential observations in the medical literature.

16 Unrelated Donor Registry

One of the main limiting factors in HCT is the availability of a suitable donor. Only 20 – 30% of patients needing HCT will find an HLA matched sibling donor. Another 5-10% may find a match among close relatives – in the setting of consanguinity or closely-knit communities. Hence, nearly 60-70% of patients requiring HCT will not have a fully matched related family donor.

16.1 The donor pool has expanded rapidly over the last few decades by the availability of matched unrelated donors and unrelated cord blood units from various donor registries, both national and international. Also, haploidentical transplants have further contributed to the expansion of the donor pool.

16.2 The first registry in the world was established in 1974 called the Anthony Nolan Bone Marrow Registry, established by the mother of Anthony Nolan, who suffered from Wiskott-Aldrich Syndrome.

16.3 Bone marrow donors worldwide (BMDW) was established in 1988 at Leiden, Netherlands, and has > 30 million donors and over 720,000 cord blood units registered. There are > 60 registries from over 45 countries registered with BMDW globally.

16.4 In India, presently there are more than 95 HCT centers, and the Indian registries include:

16.4.1 DATRI (blood stem cell donors registry), Chennai

16.4.2 JEEVAN BLOOD BANK, Chennai

16.4.3 MDRI (Marrow Donor Registry India), Mumbai

16.4.4 GENE BANDHU (Bharat Stem Cells), New Delhi

16.4.5 SCRI-BMST (Bangalore Medical Services Trust), Bangalore

16.4.6 BMCDT-BMR (Medical College Alumni), Bangalore

16.4.7 ARJAN VIR Foundation, Delhi

16.5 The Indian registries have a total of more than 500,000 voluntary donors

16.6 Matched unrelated donor grafts for Indian patients are also procured from international registries such as DKMS (Deutsche Knochen Mark Spenderdatei), National Marrow Donor Program (NMDP), and Anthony Nolan (AN).

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Annexures

Annexure I

Indications of HCT

The proposed indications for HCT in adult and pediatrics has been adopted from Durate et al[5] which has been included in 'The EBMT Handbook 2019'. However, since HCT is a dynamically evolving field, changes will be made periodically as indicated.

Table 1 – HCT indications for adults [5]

Disease	Disease status	MSD Allo	MUD Allo	MMAD Allo	Auto
Leukaemias					
AML	CR1 (favourable risk and MRD−)[a]	GNR/II	GNR/II	GNR/II	CO/I
	CR1 (favourable risk and MRD+)[a]	CO/II	CO/II	CO/II	GNR/II
	CR1 (intermediate risk)[a]	S/II	CO/II	CO/II	CO/I
	CR1 (adverse risk)[a]	S/II	S/II	S/II	GNR/I
	CR2	S/II	S/II	S/II	CO/II
	APL molecular CR2	S/II	CO/II	GNR/III	S/II
	Relapse or refractory	CO/II	CO/II	CO/II	GNR/III
ALL	Ph (−), CR1 (standard risk and MRD−)[a]	GNR/II	GNR/II	GNR/III	CO/III
	Ph (−), CR1 (standard risk and MRD+)[a]	CO/II	CO/II	CO/II	GNR/II
	Ph (−), CR1 (high risk)[a]	S/II	S/II	CO/II	GNR/III
	Ph (+), CR1 (MRD−)	S/II	S/II	CO/II	CO/III
	Ph (+), CR1 (MRD+)	S/II	S/II	S/II	GNR/II
	CR2	S/II	S/II	S/II	GNR/II
	Relapse or refractory	CO/II	CO/II	CO/II	GNR/III
CML	First CP, failing second- or thirdline TKI	S/II	S/II	CO/III	GNR/II
	Accelerated phase, blast crisis or >first CP	S/II	S/II	CO/II	GNR/III
Myelofibrosis	Primary or secondary with an intermediate or high DIPSS score	S/II	S/II	S/III	GNR/III

MDS	RA, RCMD, RAEB I and II	S/II	S/II	S/II	GNR/III
	sAML in CR1 or CR2	S/II	S/II	S/II	CO/II
	More advanced stages	S/II	S/II	S/II	GNR/III
CLL	Poor risk disease, not transformed	S/II	S/II	CO/III	GNR/III
	Richter's transformation	S/III	S/III	CO/III	CO/III
Lymphoid malignancies					
DLBCL	CR1 (Intermediate/high IPI at dx)	GNR/III	GNR/III	GNR/III	CO/I
	Chemosensitive relapse, ≥CR2	CO/II	CO/II	D/III	S/I
	Chemosensitive relapse after auto-HCT failure	S/II	S/II	CO/III	GNR/III
	Refractory disease	CO/II	CO/II	CO/III	CO/II
	Primary CNS lymphoma	GNR/III	GNR/III	GNR/III	S/I
FL	CR1, untransformed	GNR/III	GNR/III	GNR/III	GNR/II
	CR1, transformed to high-grade lymphoma	GNR/III	GNR/III	GNR/III	CO/III
	Chemosensitive relapse, ≥CR2	CO/III	CO/III	GNR/III	S/II
	≥CR2 after auto-HCT failure	S/II	S/II	D/III	GNR/III
	Refractory	CO/II	CO/II	CO/III	GNR/III
MCL	CR1	GNR/III	GNR/III	GNR/III	S/I
	CR/PR > 1, no prior auto-HCT	CO/III	CO/III	D/III	S/II
	CR/PR > 1, after prior auto-HCT	S/II	S/II	CO/III	GNR/II
	Refractory	CO/II	CO/II	D/III	GNR/II
WM	CR1	GNR/III	GNR/III	GNR/III	GNR/III
	Chemosensitive relapse, ≥CR2	GNR/III	GNR/III	GNR/III	CO/II
	Poor risk disease	CO/II	CO/II	D/III	GNR/III
PTCL	CR1	CO/II	CO/II	GNR/III	CO/II
	Chemosensitive relapse, ≥CR2	S/II	S/II	CO/III	CO/II
	Refractory	CO/II	CO/II	CO/III	GNR/II
Primary CTCL	EORTC/ISCL stages I–IIA (Early)	GNR/III	GNR/III	GNR/III	GNR/III
	EORTC/ISCL stages IIB–IV (Advanced)	CO/III	CO/III	D/III	GNR/III
HL	CR1	GNR/III	GNR/III	GNR/III	GNR/I
	Chemosensitive relapse, no prior auto-HCT	D/III	D/III	GNR/III	S/I
	Chemosensitive relapse, after prior auto-HCT	S/II	S/II	CO/III	CO/III

	Refractory	D/II	D/II	D/III	CO/III
MM	Upfront standard risk	CO/II	CO/II	GNR/III	S/I
	Upfront high risk	S/III	S/III	CO/II	S/I
	Chemosensitive relapse, prior auto-HCT	CO/II	CO/II	CO/II	S/II
AL		CO/III	CO/III	GNR/III	CO/II
Other diseases					
Acquired SAA and	Newly diagnosed	S/II	CO/II	GNR/III	NA
AA/PNH	Relapsed/refractory	S/II	S/II	CO/II	NA
Haemolytic PNH		GNR/II	GNR/II	GNR/II	NA
Constitutional SAA[b]		S/II	S/II	CO/II	NA
Breast Ca	Adjuvant high risk, HER2 negative	GNR/III	GNR/III	GNR/III	CO/II
	Metastatic, chemosensitive	D/II	D/II	GNR/III	D/CO/II
Germ Cell Tumours	Second line, high risk	GNR/III	GNR/III	GNR/III	CO/II
	Primary refractory, second and further relapse	GNR/III	GNR/III	GNR/III	S/II
Ovarian Ca	High risk/recurrent	D/II	GNR/III	GNR/III	GNR/I
Medulloblastoma	Post-surgery, high risk	GNR/III	GNR/III	GNR/III	CO/III
Small cell lung Ca	Limited	GNR/III	GNR/III	GNR/III	D/II
Soft tissue Sa	Metastatic	D/III	GNR/III	GNR/III	GNR/II
Ewing's Sa	Locally advanced/metastatic, chemosensitive	D/III	GNR/III	GNR/III	CO/III
Renal cell Ca	Metastatic, cytokine-refractory	D/II	D/II	GNR/III	GNR/III
Pancreatic Ca	Advanced	D/III	GNR/III	GNR/III	GNR/III
Colorectal Ca	Metastatic	D/III	GNR/III	GNR/III	GNR/III
Multiple Sclerosis	Highly active RR-MS failing DMT	D/III	GNR/III	GNR/III	S/I
	Progressive MS with AIC, and aggressive MS[c]	D/III	GNR/III	GNR/III	CO/II
Systemic sclerosis		D/III	GNR/III	GNR/III	S/I
SLE		D/III	GNR/III	GNR/III	CO/II
Crohn's disease		D/III	D/III	D/III	CO/II
Rheumatoid arthritis		D/III	GNR/III	GNR/III	CO/II
JIA		CO/II	CO/II	CO/III	CO/II
Monogenic AD		CO/II	CO/II	CO/III	GNR/II
Vasculitis		GNR/III	GNR/III	GNR/III	CO/II
PM-DM		GNR/III	GNR/III	GNR/III	CO/II
Autoimmune cytopenias		CO/II	CO/II	CO/III	CO/II
NeuromyelitisOptica		D/III	D/III	D/III	CO/II

CIDP, MG and SPS	GNR/III	GNR/III	GNR/III	CO/II
Type 1 diabetes	GNR/III	GNR/III	GNR/III	D/II
RCD type II	GNR/III	GNR/III	GNR/III	CO/II
Primary ID	CO/II	CO/II	CO/II	NA

AA aplastic anemia, AD autoimmune disorders, AIC active inflammatory component, AL amyloidosis, ALL acute lymphoblastic leukaemia, Alloallogeneic transplantation, AML acute myeloid leukaemia, APL acute promyelocyticleukaemia, Auto autologous transplantation, Ca cancer or carcinoma, CIDP chronic inflammatory demyelinating polyneuropathy, CLL chronic lymphocytic leukaemia, CML chronic myelogenousleukaemia, CNS central nervous system, CO clinical option (can be carried after careful assessment of risks and benefits), CP chronic phase, CR1, 2, 3 first, second, third complete remission, CTCL cutaneous T cell lymphoma, D developmental (further trials are needed), DIPSS Dynamic International Prognostic Score System, DLBCL diffuse large B cell lymphoma, DMT disease-modifying treatments, FL follicular lymphoma, GNR generally not recommended, HL Hodgkin lymphoma, HCT haematopoietic stem cell transplantation, ID immunodeficiency, IPI International Prognostic Index, JIA juvenile idiopathic arthritis, MCL mantle cell lymphoma, MDS myelodysplastic syndromes, MG myasthenia gravis, MM multiple myeloma, MMAD mismatched alternative donors (cord blood, haploidentical and mismatched unrelated donors), MRD minimal residual disease, MS multiple sclerosis, MSD matched sibling donor, MUD well-matched unrelated donor (8/8, 10/10 or 9/10 if mismatched is in DQB1), NA not applicable, PM-DM polymyositis-dermatomyositis, PNH paroxysmal nocturnal hemoglobinuria, PR partial remission, RA refractory anemia, RAEB refractory anamia with excess blasts, RCD refractory coeliac disease, RCMD refractory cytopenia with multilineage dysplasia, RR-MS relapsing–remitting multiple sclerosis, S standard of care (generally indicated in suitable patients), Sa sarcoma, SAA severe aplastic anemia, sAML secondary acute myeloid leukaemia, SLE systemic lupus erythematosus, SPS stiff person syndrome, TCL T cell lymphoma, TKI tyrosine kinase inhibitors, WM Waldenströmmacroglobulinemia. This classification does not cover patients for whom a syngeneic donor is available

- Levels of evidence
  - Grade I: Evidence from at least one well-executed randomised trial.
  - Grade II: Evidence from at least one well-designed clinical trial without randomisation; cohort or casecontrolled analytic studies (preferably from more than one centre); multiple time-series studies or dramatic results from uncontrolled experiments.
  - Grade III: Evidence from opinions of respected authorities based on clinical experience, descriptive studies or reports from expert committees.

[a]Categories are based on number of white blood cells, cytogenetics and molecular markers at diagnosis and time to achieve remission
[b]Constitutional SAA include Fanconianemia, dyskeratosiscongenita, Blackfan–Diamond anemia and other inborn bone marrow failure syndromes (see table for paediatric indications)
[c]Aggressive MS.

Standard of care (S): Indications categorised as S are reasonably well defined and results compare favourably (or are superior) to those of non-transplant treatment approaches. Obviously, defining an indication as the standard of care does not mean an HSCT is necessarily the optimal therapy for a given patient in all clinical circumstances. Standard of care transplants may be performed in a specialist centre with experience in HSCT and an appropriate infrastructure as defined by the JACIE guidelines.
Clinical option (CO): The CO category applies to indications for which the results of small patient cohorts show efficacy and acceptable toxicity of the HSCT procedure, but confirmatory randomised studies are missing, often as a result of low patient numbers. The broad range of available transplant techniques combined with the variation of patient factors such as age and comorbidity makes interpretation of these data difficult. Our current interpretation of existing data for indications placed in this category supports that HSCT is a valuable option for individual patients after careful discussions of risks and benefits with the patient but that for groups of patients the value of HSCT needs further evaluation. Transplants for indications under this heading should be performed in a specialist centre with major experience in HSCT with an appropriate infrastructure as defined by JACIE guidelines.

Developmental (D): Indications have been classified as D when the experience is limited, and additional research is needed to define the role of HSCT. These transplants should be done within the framework of a clinical protocol, normally undertaken by transplant units with acknowledged expertise in the management of that particular disease or that type of HSCT. Protocols for D transplants will have been approved by local research ethics committees and must comply with current international standards. Rare indications where formal clinical trials are not possible should be performed within the framework of a structured registry analysis, ideally an EBMT non-interventional/observational study. Centres performing transplants under this category should meet JACIE standards.

Generally not recommended (GNR): The GNR category comprises a variety of clinical scenarios in which the use of HSCT cannot be recommended to provide a clinical benefit to the patient, including early disease stages when results of conventional treatment do not normally justify the additional risk of a HSCT, very advanced forms of a disease in which the chance of success is so small that does not justify the risks for patient and donor and indications in which the transplant modality may not be adequate for the characteristics of the disease. A categorisation as GNR does not exclude that centres with particular expertise on a certain disease can investigate HSCT in these situations. Therefore, there is some overlap between GNR and D categories, and further research might be warranted within prospective clinical studies for some of these indications.

Table 2 – HCT indications for children and adolescents [5]

Disease	Disease status and subtypes	MSD Allo	MUD Allo	MMAD Allo	Auto
Haematological malignancies					
AML	CR1 (low risk)[a]	GNR/II	GNR/II	GNR/III	GNR/II
	CR1 (high and very high risk)[a]	S/II	S/II	CO/II	GNR/II
	CR2	S/II	S/II	S/II	GNR/II
	>CR2	S/II	CO/II	CO/II	GNR/II
ALL	CR1 (low risk)[a]	GNR/II	GNR/II	GNR/III	GNR/II
	CR1 (high risk)[a]	S/II	S/II	CO/II	GNR/II
	CR2	S/II	S/II	CO/II	GNR/II
	>CR2	S/II	S/II	CO/II	GNR/II
CML	First CP, failing second- or third-line TKI	S/II	S/II	CO/II	GNR/III
	Accelerated phase, blast crisis or >first CP	S/II	S/II	CO/II	GNR/III
MDS and JMML		S/II	S/II	CO/III	GNR/III
NHL	CR1 (low risk)	GNR/II	GNR/II	GNR/II	GNR/II
	CR1 (high risk)	CO/II	CO/II	CO/II	CO/II
	CR2	S/II	S/II	CO/II	CO/II
HL	CR1	GNR/II	GNR/II	GNR/II	GNR/II
	First relapse, CR2	CO/II	CO/III	CO/III	S/II
Non-malignant disorders and solid tumours					
Primary ID	Severe combined ID	S/II	S/II	S/II	NA
	Other primary ID	S/II	S/II	CO/II	NA
MPS	MPS-1H Hurler	S/II	S/II	CO/II	NA
	MPS-1H Hurler Scheie (severe)	GNR/III	GNR/III	GNR/III	NA
	MPS-VI Maroteaux-Lamy	CO/II	CO/II	CO/II	NA
Thalassemia and SCD		S/II	CO/II	CO/II	NA

Osteopetrosis		S/II	S/II	S/II	NA
Acquired SAA		S/II	S/II	CO/II	NA
IBMFS		S/II	S/II	CO/II	NA
Germ cell tumours		CO/II	CO/II	CO/II	CO/II
Sarcoma	Ewing's sarcoma (high risk or >CR1)	D/II	D/III	D/III	S/II
	Soft tissue sarcoma (high risk or >CR1)	D/II	D/II	D/III	CO/II
	Osteogenic sarcoma	GNR/III	GNR/III	GNR/III	D/II
Neuroblastoma	High risk or>CR1	CO/II	CO/II	D/III	S/II
Brain tumours		GNR/III	GNR/III	GNR/III	CO/II
Wilms' tumour	>CR1	GNR/III	GNR/III	GNR/III	CO/II
AD	Including monogenic AD	CO/II	CO/II	CO/II	CO/II

AD autoimmune disorders, ALL acute lymphoblastic leukaemia, Alloallogeneic transplantation, AML acute myeloid leukaemia, Auto autologous transplantation, CML chronic myelogenousleukaemia, CO clinical option (can be carried after careful assessment of risks and benefits), CR1, 2 first, second complete remission, D developmental (further trials are needed), GNR generally not recommended, HL Hodgkin lymphoma, HCThaematopoietic stem cell transplantation, IBMFS inborn marrow failure syndromes (Fanconi anemia, dyskeratosiscongenita, Blackfan–Diamond anemia and others), ID immunodeficiency, JMML juvenile myelomonocyticleukaemia, MDS myelodysplastic syndromes, MMAD mismatched alternative donors (cord blood, haploidentical and mismatched unrelated donors), MPS mucopolysaccharidosis, MSD matched sibling donor, MUD well-matched unrelated donor (8/8, 10/10 or 9/10 if mismatched is in DQB1), S standard of care (generally indicated in suitable patients), SAA severe aplastic anemia, SCD sickle cell disease (high risk). This classification does not cover patients for whom a syngeneic donor is available

a Categories are based on number of white blood cells, cytogenetics and molecular markers at diagnosis and time to achieve remission

- Levels of evidence
  - Grade I: Evidence from at least one well-executed randomised trial.
  - Grade II: Evidence from at least one well-designed clinical trial without randomisation; cohort or casecontrolled analytic studies (preferably from more than one centre); multiple time-series studies or dramatic results from uncontrolled experiments.
    - Grade III: Evidence from opinions of respected authorities based on clinical experience, descriptive studies or reports from expert committees.

Standard of care (S): Indications categorised as S are reasonably well defined and results compare favourably (or are superior) to those of non-transplant treatment approaches. Obviously, defining an indication as the standard of care does not mean an HSCT is necessarily the optimal therapy for a given patient in all clinical circumstances. Standard of care transplants may be performed in a specialist centre with experience in HSCT and an appropriate infrastructure as defined by the JACIE guidelines.
Clinical option (CO): The CO category applies to indications for which the results of small patient cohorts show efficacy and acceptable toxicity of the HSCT procedure, but confirmatory randomised studies are missing, often as a result of low patient numbers. The broad range of available transplant techniques combined with the variation of patient factors such as age and

comorbidity makes interpretation of these data difficult. Our current interpretation of existing data for indications placed in this category supports that HSCT is a valuable option for individual patients after careful discussions of risks and benefits with the patient but that for groups of patients the value of HSCT needs further evaluation. Transplants for indications under this heading should be performed in a specialist centre with major experience in HSCT with an appropriate infrastructure as defined by JACIE guidelines.

Developmental (D): Indications have been classified as D when the experience is limited, and additional research is needed to define the role of HSCT. These transplants should be done within the framework of a clinical protocol, normally undertaken by transplant units with acknowledged expertise in the management of thatparticular disease or that type of HSCT. Protocols for D transplants will have been approved by local research ethics committees and must comply with current international standards. Rare indications where formal clinical trials are not possible should be performed within the framework of a structured registry analysis, ideally an EBMT non-interventional/observational study. Centres performing transplants under this category should meet JACIE standards.

Generally not recommended (GNR): The GNR category comprises a variety of clinical scenarios in which the use of HSCT cannot be recommended to provide a clinical benefit to the patient, including early disease stages when results of conventional treatment do not normally justify the additional risk of a HSCT, very advanced forms of a disease in which the chance of success is so small that does not justify the risks for patient and donor and indications in which the transplant modality may not be adequate for the characteristics of the disease. A categorisation as GNR does not exclude that centres with particular expertise on a certain disease can investigate HSCT in these situations. Therefore, there is some overlap between GNR and D categories, and further research might be warranted within prospective clinical studies for some of these indications.

Annexure II

Informed Consent Documents

Components to be detailed in Informed Consent Document (Information sheet and informed consent form) is as given below. However, please note that the Informed Consents in this annexure are templates which can be modified by each transplant centerbut broadly should contain all elements listed below.

Patient Information Sheet

The following guidelines should be kept in mind while designing the information sheet:

1. The informed consent should not be technical but in lay man's language easily understood by the patient or her/his legally authorized representative (LAR).
2. It should be made available to the patient/representative in a language which can be read and understood by the patient or her/his LAR.
3. It should be provided to the patient/representative well in advance to help them making informed decision.
4. The components enlisted below must be included in the information sheet to help patient/representative in making informed decision:
    a. Disease diagnosis
    b. Existing standard of care and other possible alternatives with risk and benefits
    c. Post HCT complications (including but not limited to graft failure, infection, organ toxicity, relapse/rejectionetc.)
    d. Timeline for withdrawal
    e. Financial implication of all treatment options
    f. Time duration of the treatment either in hospital or OPD
    g. Follow up visit details
    h. Detailed information on national and international registry, to which the patient data is proposed to be submitted to. This should include but not limited to the background of the registry, its role, anonymization procedure, the details of data (identifiable and non-identifiable) to be submitted, proposed use of the data by the registries, and any benefits or unforeseen risks in sharing data.
    i. Details of the treating physician with contact and affiliation details.

Interpreter's Statement (If Applicable)

In case of a foreign patients or inter-state patients, where language can be a barrier a qualified interpreter will need to be used and the same documented in the informed consent form.
I have given a translation in _____ (State the patient's language here) of all the contents of the informed consent form, as well as all the verbal and written information given to the patient/ parent or guardian.

Signature: _____
ID of the interpreter: _____
Date/Time: _____
Name of the interpreter: _____

Informed Consent

I. Patient Informed Consent Form for Adults- Autologous HCT

1. Registration No.
2. I, the undersigned Mr./Ms._____, have been explained by my treating physician(s) in the language I understand, the procedure of autologous hematopoietic cell transplantation (HCT), which is now an accepted therapy for my disease. I understand that this treatment gives me a fair chance of improving my survival. I have also been explained the other treatment options. I have been explained the potential risks and possible complications.
3. Hematopoietic cell transplantation (HCT) can be associated with various complications. The most important of these are:
    - 3.1. Graft failure: This is extremely rare in autologous HCT as an adequate dose of stem cells is collected prior to transplant. However, delayed engraftment may occur in some heavily pre-treated patients.
    - 3.2. Relapse/recurrence: Despite transplant, some patients are known to have relapse/ recurrence. The same is monitored post-transplant. Treatment options for relapse/recurrence will be discussed by the treating physician with you.
    - 3.3. Infections: Following conditioning regimen, your neutrophil countdecrease to very low levels which makes you prone to infections(Bacterial, viral and fungal).
    - 3.4. Organ toxicity: High dose chemotherapy/radiation may potentially cause organ dysfunction which may be reversible or irreversible. The common organs affected are liver, kidney, lung and heart.
    - 3.5. Long-term complications: Long term complications such as sterility, other organ dysfunctions and second malignancy are known to occur post-transplant.
    - 3.6. The **financial aspects** of the aforesaid procedure have been explained to me and I understand that it may increase in case of untoward complications.
4. Before we can perform the HCT, all your question should have been answered. Please ask these, either to your primary oncologist, hematologist or one of the transplant consultants. You should only sign the consent form when you are satisfied that you have received sufficient information.
5. My signature (patient/authorized representative) below constitutes my acknowledgment that:
    - 5.1. I have read, understood and agreed to the foregoing and it has been explained to me in the language understood by me.
    - 5.2. All my questions have been satisfactorily answered and I have all the desired information to give an informed consent.

5.3. I hereby give my informed consent without any coercion or undue influence after understanding the benefits, risk and possible complications in my complete senses.

Signature of patient	Signature of witness
Name :-_____	Name:-_____
Date:	Relationship with patient_____
Address	Address
Contact Number	Date:
	Contact Number

Signature of Physician
Name:
Date:
Address
Contact Number

II Patient Informed Consent for Adults- Allogeneic HCT

1. Registration No.
2. I, the undersigned Mr./Ms._____, have been explained by my treating physician(s) in the language I understand, the procedure of allogeneic hematopoeitic cell transplantation (HCT), which is now an accepted therapy for my disease. I understand that this treatment gives me a fair chance of improving my survival. I have also been explained the other treatment options. I have been explained the potential risks and possible complications.
3. Allogeneic Hematopoietic Cell Transplantation (HCT) is associated with any of the following complications:
   - 3.1. Infections: Bacterial, fungal and viral infections frequently occur after HCT. Close observation for any signs of infection is an integral part of the patient's management after HCT. Various methods are used to try and avoid infections, including the use of prophylactic antibiotics, antifungal and antiviral agents.
   - 3.2. Organ toxicity: The patient's underlying condition together with the intensive treatments used before the transplant inevitably damages many tissues of the body. Most or all of the damage may be reversible. If it is irreversible, the patient may die as a result of organ failures. Your transplant physician will have given you an estimate of the chance of this happening to you
   - 3.3. Graft-versus-Host Disease (GvHD): This is the result of the donor cells reacting against the patient cells. It occurs in about 45% of all transplants, and is usually milder with matched family donors. It can be severe or fatal, even with a "good"match. The main sites affected are the skin, gut, and liver. We try and minimize its development by using drugs such as cyclosporin, methotrexate or steroids post-transplant.
   - 3.4. Relapse/Rejection: Relapse may occur following all transplants; it may be more common when no graft-versus-host disease occurs. Sometimes, the donor graft may not be accepted by the patient at all, or the graft may be lost after initially being accepted. These phenomena are known as primary and secondary graft rejection respectively. Patients may succumb to infections or bleeding until and unless the second transplant with the same or another donor is performed.
   - 3.5. Long-term complications: There may be some long term complications of the procedure and it is very likely that you will become sterile after the transplant. There is also a small risk of developing second cancer due to the treatment received.
4. There can be other potential complications not mentioned above as well.
5. No guarantee of success can be given with any transplant. The fact that you are being offered a transplant is a reflection of the likelihood of the disease persisting or returning without further intensive therapy. Once the conditioning therapy is started, the patient is committed to undergoing HCT.

6. **The financial aspects** of the procedure have been explained to me and I understand that it may increase in case of complications.
7. Before we can perform the HCT, all your questions should have been answered. Please ask these, either to your primary oncologist, hematologist, or one of the transplant consultants. You should only sign the consent form when you are satisfied that you have received sufficient information.
8. My signature (patient/authorised representative) below constitutes my acknowledgment that: I have read, understood and agreed to the foregoing and it has been explained to me in the language understood by me.
9. All my questions have been satisfactorily answered and I have all the desired information to give an informed consent.
10. I hereby give my informed consent without any coercion or undue influence after understanding the benefits, risk and possible complications in my complete senses.

Signature of patient

Name :-_____
Date:
Address
Contact Number

Signature of witness

Name:-_____
Relations to patient:_____
Date:
Address
Contact Number

Signature of physician

Name:_____
Date:
Address
Contact Number

III Patient Informed Consent Form for Children (≤18 Years Age)- Autologous HCT

1. Registration No.
2. I, the undersigned,_____, Father/ Mother/ Guardian of _____have been explained by my treating physician(s) in the language I understand, the procedure of autologous hematopoietic cell transplantation (HCT), which is now an accepted therapy for child's disease. I understand that this treatment gives my child a fair chance of improving his/hersurvival. I have also been explained about the other treatment options. I have been explained about the potential risks and possible complications.
3. Hematopoietic cell transplantation (HCT) can be associated with various complications. The most important of these are:
   - 3.1 Graft failure: This is extremely rare in autologous HCT as an adequate dose of stem cells is collected prior to transplant. However, delayed engraftment may occur in some heavily pre-treated patients.
   - 3.2 Relapse/recurrence: Despite transplant, some patients are known to have relapse/ recurrence. The same is monitored post-transplant. Treatment options for relapse/recurrence will be discussed by the treating physician with you.
   - 3.3 Infections: Following the conditioning regimen, your neutrophil count decrease to very low level which makes you prone to infections (Bacterial, viral and fungal).
   - 3.4 Organ toxicity: High dose chemotherapy/radiation may potentially cause organ dysfunction, which may be reversible or irreversible. The common organs affected are liver, kidney, lung, and heart.
   - 3.5 Long-term complications: Long term complications such as sterility, other organ dysfunctions, and second malignancy are known to occur post-transplant. Also there is an increased risk of growth retardation due to high doses of chemotherapy with or without radiation used for transplant.
   - 3.6 The financial aspects of the aforesaid procedure have been explained to me and I understand that it may increase in case of untoward complications.
4. Before we can perform the HCT, all your questions should have been answered. Please ask these, either to your primary oncologist, hematologist, or one of the transplant consultants. You should only sign the consent form when you are satisfied that you have received sufficient information.
5. My signature (patient/authorized representative) below constitutes my acknowledgment that:
   - 5.1 I have read, understood and agreed to the foregoing and it has been explained in the language understood by me.

5.2 All my questions have been satisfactorily answered, and I have all the desired information to give informed consent.

5.3 I hereby give my informed consent without any coercion or undue influence after understanding the benefits, risks and possible complications in my complete senses.

Signature of Father/Mother/Guardian

Name :-_____
Date:
Address
Contact Number

Signature of witness

Name:-_____
Relations to patient:_____
Date:
Address
Contact Number

Signature of physician

Name:_____
Date:
Address
Contact Number

IV Patient Informed Consent for Children (≤18 Years Age)- Allogeneic Hct

1. Registration No.
2. I, the undersigned,_____, Father /Mother/ Guardian of _____have been explained by my treating physician(s) in the language I understand, the procedure of allogeneic hematopoietic cell transplantation(HCT), which is now an accepted therapy for my child's disease. I understand that this treatment gives my child a fair chance of improving his/her survival. I have also been explained about other treatment options. I have been explained the potential risks and possible complications.
3. Allogeneic Hematopoietic Cell Transplantation (HCT) is associated with any of the following complications:
   - 3.1 Infections: Bacterial, fungal and viral infections frequently occur after HCT. Close observation for any signs of infection is an important part of the patient's management after HCT. Various methods are used to try and avoid infections, including the use of prophylactic antibiotics, antifungals, and antiviral agents.
   - 3.2 Organ toxicity: The patient's underlying condition together with the intensive treatments used before the transplant inevitably damages many tissues of the body. Most or all of the damage may be reversible. If it is irreversible, the patient may die as a result of organ failures. Your transplant physician will have given you an estimate of the chance of this happening to you
   - 3.3 Graft-versus-Host Disease (GvHD): This is the result of the donor cells reacting against the patient cells. It occurs in about 45% of all transplants and is usually milder with matched family donors. It can be severe or fatal, even with a "good"match. The main sites affected are the skin, gut, and liver. We try and minimize its development by using drugs such as cyclosporin, methotrexate, or steroids post-transplant.
   - 3.4 Relapse/Rejection: Relapse may occur following all transplants; it may be more common when no graft-versus-host disease occurs. Sometimes, the donor graft may not be accepted by the patient at all, or the graft may be lost after initially being accepted. These phenomena are known as primary and secondary graft rejection respectively .Patients may succumb to infections or bleeding until and unless asecond transplant with the same or another donor is perfomed.
   - 3.5 Long-term complications: Long term complications such as sterility, other organ dysfunctions and second malignancy are known to occur post-transplant.Also, there is an increased risk of growth retardation due to high doses of chemotherapy with or without radiation used for transplant.
   - 3.6 There can be other potential complications not mentioned above as well.

3.7 No guarantee of success can be given with any transplant. The fact that your child is being offered a transplant is a reflection of the likelihood of the disease persisting or returning without further intensive therapy. Once the conditioning therapy is started, the patient is committed to undergoing HCT.

3.8 The financial aspects of the procedure have been explained to me and I understand that it may increase in case of complications.

4. Before we can perform the HCT, all your questions should have been answered. Please ask these, either to your primary oncologist, hematologist, or one of the transplant consultants. You should only sign the consent form when you are satisfied that you have received sufficient information.
5. My signature (patient/authorized representative) below constitutes my acknowledgment that:
   5.1 I have read, understood and agreed to the foregoing and it has been explained to me in the language understood by me.
   5.2 All my questions have been satisfactorily answered and I have all the desired information to give an informed consent.
   5.3 I hereby give my informed consent without any coercion or undue influence after understanding the benefits, risk and possible complications in my complete senses

Signature of Father/Mother/Guardian
Name :-_____
Date:
Address
Contact Number

Signature of witness
Name:-_____
Relations to patient:_____
Date:
Address
Contact Number

Signature of physician

Name:_____
Date:
Address
Contact Number

V . Donor / Patient Informed Consent for Peripheral Blood Stem Cell / Bone Marrow Harvest

I, the undersigned Mr./Mrs._____
_____,Patient / Donor / Parent/ Guardian of Mr./Mrs./Master/Miss _____ have been explained by the treating physician, in the language I understand, about the procedure of peripheral blood stem cell / bone marrow harvest. Bone Marrow harvest is done under anesthesia, either General or Spinal. I have been explained that the morbidity of either procedure is minimal and is usually limited to procedure-related discomfort, vasovagal attacks, reversible calcium deficiency and pain at the vene-puncture or bone marrow puncture sites. I have also been informed that for peripheral blood stem cell collection, I will have to be given medications in the form of growth factors which can lead to minor discomfort / flu like syndrome. Very rarely serious complications such as splenomegaly, splenic infarction or rupture may occur due to growth factor administration. I have been explained that if marrow harvest is done, I / my child might be transfused with irradiated platelets and in rare situations I / my child may have to be given Irradiated Red Cell Concentrate from some other donor of the same blood group. Having understood all the facts completely, I willingly give my consent for myself /my child to undergo the procedure of peripheral blood stem cell donation / bone marrow harvest.

Signature of
Father / Mother /Patient/ Donor / Guardian
Name : - _____

Date:
Address
Contact Number

Signature of witness

Name: _____

Date:
Address:
Contact Number

Signature of the treating physician

Name : _____
Date :
Address:
Contact Number

VI. Informed Consent for Data Registration

PatientName:_____UHID No.:

_____

Age/Sex:_____Consultant Name: Dr._____

_____

In order to carry out research and develop new transplant procedures, data is collected and submitted to national and international registries. All of the data stored remains completely confidential with no patient names being used. This data will not be anonymous but your name will not be accessible to anyone.

I _____have been informed to my satisfaction regarding data collection and reporting to the EBMT (European Society for Blood and Marrow Transplantation)/ CIBMTR(Center for International Blood and Marrow Transplant Research)/APBMT(Asia Pacific Blood and Marrow Transplantation)and/or ISBMT (Indian Society for Blood and Marrow Transplantation).

- CONSENT / DO NOT CONSENT * to non-identifiable data being sent to any of the above registries and to their use in studies conducted, provided my privacy is protected.

Patient Signature_____Name_____Date/Time

_____WitnessSignature_____Name

_____Date/Time_____ Address

_____

_____

_____Relationship_____

_____DoctorSignature_____Name_____

_____Date/Time_____**If patient is not competent**

to give consent, relative to give thesame

RelativeSignature_____Name_____Date/Time

_____WitnessSignature_____Name

_____Date/Time_____ Address

_____

Interpreter's Statement (If Applicable)

I have given a translation in _____ (State the patient's language here) of all the contents of the consent form as well as all the verbal and written information given to the patient/ parent or guardian.

Signature: _____ID of the interpreter_____

Date/Time: _____Name of the interpreter_____

Annexure III

SOPs for Processing of Hematopoetic Cells for HCT

1. Infrastructure

1.1. The design and layout of the laboratory should allow an easy flow of work and prevent any cross-contamination.

1.2. The processing of products shall take place in a designated laboratoryarea /or in the Blood Bank with adequate light and ventilation.

1.3. The facility shouldpreferably have oxygen sensors in the rooms having a liquid nitrogen tank. Access to the processing laboratory to be controlled and only authorized persons allowed entry.

1.4. Critical facility parameters related to temperature, air quality, humidity should be periodically monitored and documented.

1.5. The laboratory operations should prioritize the health and safety of its workers and visitors.

1.6. Education and protocol for a safe waste disposal mechanism shall be in operation.

2. Personnel

2.1. There shall be a suitable, qualified, experienced and trained doctor, scientists, laboratory technologists, and quality manager.

2.2. There should be an organogram, that is displayed at the facility and easily understood by all staff.

2.3. There should be a clearly written job description for every laboratory personnel employed.

2.4. There should be continued education and training of laboratory staff in a relevant area of research. Personal protective equipment (including thermal gloves) shall be used by the personnel handling the liquid nitrogen tank.

3. Management of Data and Records

3.1. All the activities in the processing laboratory should be described in the SOP manual.

3.2. There should be detailed protocols on the operation of all equipment and corrective action in case of failure.

3.3. SOPs should be in sufficient detail and freely accessible to the staff.

3.4. The laboratory should establish testing, cryopreservation, storage, and dispatch procedures per validated methods.

3.5. The SOP on cryopreservation should mention the volume of cryoprotectant solution, maximum cell concentration to be frozen, cooling rate, endpoint temperature of cooling and storage temperature.

3.6. Nucleated cell dose of 2-3 x 10^8/Kg recipient body weight (Kg) is optimal for bone marrow harvest and CD 34+ cell dose of 2-3 x 10^6/Kg recipient body weight (Kg) and atleast 5 x 10^6/kg for matched unrelated and haploidentical transplants is optimal for PBSC collection.

3.7. Bone marrow harvest from the donor shall not exceed 15-20 ml / kg of donor weight.

3.8. Aseptic techniques should be followed to avoid microbial contamination while processing the product. There should be constant monitoring and record of the microbial cultures of the product.

3.9. The monitoring and maintenance of equipments should be documented.

3.10. There should be stock management records of supplies and reagents, mentioning the lot number, expiry date, and manufacturer's name.

3.11. The laboratory should have a policy on the disposal of biomedical waste.

4. Labelling

4.1. All cellular products should be labeled in conformance with ISBT128 standard terminology.

4.2. Labels should be clear and complete with permanent ink that sustains the processing and storage of the product at low temperatures.

4.3. The labels should be affixed to the product and bear a unique alpha numeric or numeric identifier, product type, volume, name and hospital number of recipient and donor, the name of the facility and biohazard warning.

5. Process Controls

5.1. Procedures should be validated to indicate acceptable cell viability and counts.

5.2. An adequate test should be performed to test the viability, safety, and integrity of the cellular products. Total nucleated cell count, CD34+ enumeration, and viability assays should be performed on HSC products. Any microbial contamination in the laboratory should be investigated, documented, and corrective action is taken.

6. Storage

6.1. The storage area is to be monitored and equipped with an alert system for any microbial contamination and temperature fluctuations.

6.2. Non-cryopreserved or post-thaw cellular products should be assigned an expiry date and time.

6.3. Cryopreserved products should be stored in vapour phase in a liquid nitrogen tank with appropriate coverings to prevent cross-contamination. Dump freezing in mechanicalfreezerat-80°C could also be used for cryopreservation.

6.4. Products having a positive microbial culture or positive for infectious disease are to be quarantined and discarded appropriately.

6.5. There should be an inventory control system to identify the exact location of the product in the storage tank.

7. Transport

7.1. Cellular products should be issued after receiving a written request from the physician mentioning the product type, recipient, and donor details.

7.2. The product needs to be transported in a temperature-controlled environment. Cellular products should not be exposed to X-ray irradiation.

Annexure IV

Post HCT Vaccination Schedule[24-29]

(Allogeneic transplant)

To be initiated once the patient is off immunosuppression (1 month) with no signs of GVHD

Name		Hospital No				Age	Sex	UPN	
Date of BMT		Immunosuppression stopped on (Date)					Chronic GVHD (Yes/No)		
S No	**Vaccine**	**Volume**	**Route**	**Start at**	**Comments**		**1st dose**	**2nd dose**	**3rd dose**
1	**Pneumococcal conjugate vaccine (PCV-13) 3 doses followed by**	0.5ml	IM	1 year	3 doses: 2 months apart. **0,2,4, months**				
2	**Pneumococcal polysaccharide capsular vaccine. (to be given in children after 24 months of age)**	0.5 ml	IM	At least 1 year 10 months post alllo BMT	**10 months after 1st dose of prevnar**				
2	**Inactivated Influenza (April to September)**	0.25ml (6mths – 3 yrs) 0.5ml (>3 yrs)	IM	6 months onwards and yearly	<9 years – 2 doses (0,1 month) >9 years – 1 dose				
3	**Inactivated polio**	0.5ml	IM	1 year	3 doses; 2 months apart.				

					0,2,4 months				
4	**H influenza B**	0.5ml	IM	1 year	3 doses; 2 months apart. **0,2,4 months**				
5	**DTaP/DPT**	0.5ml	IM	1 year	3 doses; 2 months apart. **0,2,4 months**				
3,4,5	**Combination vaccine: (IPV, HiB, DTaP) given 2 months apart)**	0.5ml	IM	1 year	3 doses; Alternative to vaccines 3,4 & 5 2 months apart **0,2,4 months**				
6	**Hepatitis B**	0.5ml	IM	1 year	3 doses; **0,2,6 months**				
7	**HPV: 9-26 years. Vaccine be administered in sitting/lying down position. And the patient be observed for 15 min post vaccination.**	0.5ml	I/M	1 year	3 doses **(0,2,6 months)**				
8	**Hepatitis A**	1.0ml (adults) 0.5ml (<18 yrs)	IM only (deltoid or anterolateral thigh)	1 year	**2 doses: 0,6 months**		Booster at 6mths – 5 yrs)	**Never to be given in gluteal region**	
9	**Typhoid (Conjugate)**	0.5ml	IM	1 year	**2 doses 0,2**				
LIVE VACCINES: To be started after 2 years and off immunosuppression for 12 months.									
10	**MMR (Live) (2-1-8 rule) (2yrs after BMT, 1 year after IST, 8 months after IVIg)**	0.5ml	**Deep S/C only**	2 years	**Chilrden 2 doses; 1 months apart. 0, 1 months Adults: 1 dose**			**2-1-8 rule**	

11	**Varicella (Varilrix) – Live (2-1-8 rule) (>12 months)**	**0.5ml**	S/C only	**2 years**	**2 doses; 1 month apart. 0, 1**			**2-1-8 rule**

POST TRANSPLANT OPTIONAL VACCINES

Meningococcal vaccine (Conjugate)	0.5ml	IM	1 Year				2 doses 2 months apart.

VACCINES CONTRAINDICATED POST BMT

BCG	**Not to be given**
Oral polio vaccine (live)	Not to be given – NOT TO GIVE ORAL POLIO VACCINE TO ANY ONE AT HOME They also have to be vaccinated with Inactivated polio vaccine.
Intranasal influenza	Not to be given
Cholera	No data were found regarding safety and immunogenictiy among HCT recepients

Vaccines for Contacts (Children and close family members) and Health Care Workers Sibling: Of the transplant patient should continue vaccination as per the age. Oral polio to be replaced by injectable polio (IPV)

Vaccine	**Volume**	**Route**	**Start at**	**1st dose**	**2nd dose**	**3rd dose**	**Comments**
Varicella (Varilrix)	0.5ml	**S/C only**	1 year of age				2 doses for >13 yrs.
Inactivated Influenza (Vaxigrip)	0.5ml (>3 yrs) 0.25ml (6 mon – 3 yrs)	IM	6 months post-transplant				And then yearly

Post HCT Vaccination Schedule[24-29]

(Autologous transplant)

Name	Hospital No	Age	Sex	UPN
Date of BMT				

S No	Vaccine	Volume	Route	Start at	Comments	1st dose	2nd dose	3rd dose	
1	**Pneumococcal conjugate vaccine (PCV-13) 3 doses followed by**	0.5ml	IM	6 months	3 doses: 2 months apart. **0,2,4, months**				
2	**Pneumococcal polysaccharide capsular vaccine. (to be given in children after 24 months of age)**	0.5 ml	IM	16 months post Auto BMT	**10 months after 1st dose of prevnar**				
2	**Inactivated Influenza (April to September)**	0.25ml (6mths – 3 yrs) 0.5ml (>3 yrs)	IM	6 months onwards and yearly	<9 years – 2 doses (0,1 month) >9 years – 1 dose				
3	**Inactivated polio**	0.5ml	IM	6 months	3 doses; 2 months apart. **0,2,4 months**				
4	**H influenza B**	0.5ml	IM	6 months	3 doses; 2 months apart.				

					0,2,4 months			
5	**DTaP/DPT**	0.5ml	IM	6 months	3 doses; 2 months apart. **0,2,4 months**			
3,4, 5	**Combination vaccine: (IPV, HiB, DTaP) given 2 months apart)**	0.5ml	IM	6 months	3 doses; Alternative to vaccines 3,4 & 5 2 months apart **0,2,4 months**			
6	**Hepatitis B**	0.5ml	IM	6 months	3 doses; **0,2,6 months**			
7	**HPV: 9-26 years. Vaccine be administered in sitting/lying down position. And the patient be observed for 15 min post vaccination.**	0.5ml	I/M	6 months	3 doses **(0,2,6 months)**			
8	**Hepatitis A**	1.0ml (adults) 0.5ml (<18 yrs)	IM only (deltoid or anterolateral thigh)	6 months	**2 doses: 0,6 months**		Booster at 6mths – 5 yrs)	**Never to be given in gluteal region**
9	**Typhoid (Conjugate)**	0.5ml	IM	6 months	**2 doses 0,2**			
LIVE VACCINES: To be started after 2 years and off immunosuppression for 12 months.								
10	**MMR (Live) (2-1-8 rule) (2yrs after BMT, 1 year after IST, 8 months after IVIg)**	0.5ml	**Deep S/C only**	2 years	**Chilrden 2 doses; 1 months apart. 0, 1 months Adults: 1 dose**			**2-1-8 rule**
11	**Varicella (Varilrix) – Live (2-1-8 rule)**	**0.5ml**	S/C only	**2 years**	**2 doses; 1 month apart.**			**2-1-8 rule**

	(>12 months)				**0, 1**			

POST TRANSPLANT OPTIONAL VACCINES

Meningococcal vaccine (Conjugate)	0.5ml	IM	1 Year			2 doses 2 months apart.

VACCINES CONTRAINDICATED POST BMT

BCG	**Not to be given**
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Vaccines for Contacts (Children and close family members) and Health Care Workers Sibling: (Of the transplant patients should continue vaccination as per the age. Oral polio to be replaced by injectable polio (IPV))

Vaccine	**Volume**	**Route**	**Start at**	**1st dose**	**2nd dose**	**3rd dose**	**Comments**
Varicella (Varilrix)	0.5ml	**S/C only**	1 year Post BMT				2 doses for >13 yrs.
Inactivated Influenza (Vaxigrip)	0.5ml (>3 yrs) 0.25ml (6 mon – 3 yrs)	IM	6 months post-transplant				And then yearly

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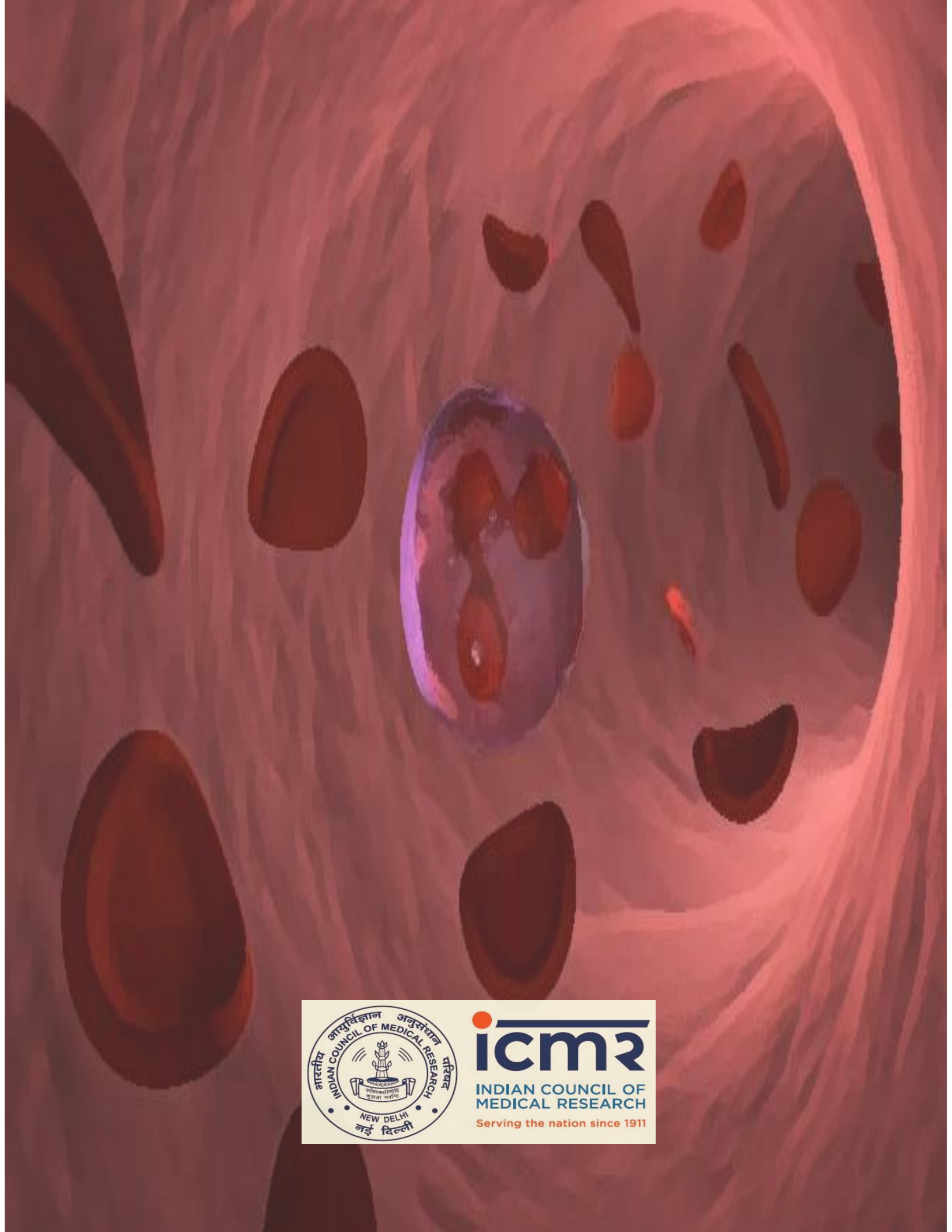
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