



Italian Bone Marrow Donor Registry

Italian National Standards for Unrelated Haematopoietic Stem Cell Donations

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0. Abbreviations

ADMO: National Bone Marrow Donor Association
AIBT: Italian Association of Immunogenetics and Transplant Biology
AIEOP: Italian Association of Paediatric Onco-Haematology
ASHI: American Society of Histocompatibility and Immunogenetics
ASR: Agreement between the Health Department and Regions
CBB: Cord Blood Bank
CBU: Cord Blood Unit
CC: Collection Center
CC-P: PBSC collection center
CC-M: Bone Marrow collection center
CFU: Colony Forming Unit
CIC: EBMT Center Identification Code
CNT: National Transplant Center
CNS: National Blood Center
DC: Donor Center
DLI: Donor Lymphocytes Infusion
EBMT: European Group for Blood and Marrow Transplantation
EFI: European Federation for Immunogenetics
FACT: Foundation for the Accreditation of Cellular Therapy
G-CSF: Granulocyte Colony Stimulating Factor
GITMO: Italian Group for Bone Marrow Transplant
HSC: Haematopoietic Stem Cell
HLA: Human Leucocyte Antigen
HR : High Resolution
HSCT: Haematopoietic Stem Cell Transplant
IATA: International Air Transport Association
IBMDR: Italian Bone Marrow Donor Registry
IDM: Infectious Disease Marker
IRB: Institutional Review Board
IR: International Registry
ITCBN: Italian Cord Blood Network
JACIE: Joint Accreditation Committee ISCT/EBMT
LR : Low Resolution
NCN: National Coordinating Center
PBSC: Peripheral Blood Stem Cell
QC: Quality Control
RC: satellite donor Recruitment Center
RR: Regional Registry
RTC: Regional solid transplant coordination centre
SIMTI: Italian Society of Transfusion Medicine and Immunohaematology
SIE: Italian Society of Haematology
SEAR: Serious Events and Adverse Reactions
SPEAR: Serious Product Events and Adverse Reactions
SSN: National Health Service
TC: Transplant Center
TNC: Total Nucleated Cells
UD: Unrelated Donor
WMDA: World Marrow Donor Association

1. PROGRAM HISTORY

The Italian Bone Marrow Donor Registry was established in Italy in 1989, by several medical and scientific societies working in this field: SIE, AIBT, AIEOP and SIMTI. In this “Bone Marrow Donation ” project, the IBMDR has the role of:

providing an unrelated volunteer with immunogenetic characteristics that may allow a treatment with high chances of success to haematological patients waiting for a transplant and who do not have the ideal donor (an identical sibling).

In order to realise this program, the above mentioned Societies identified several individual centres (RRs, DCs, CCs and TCs) to work together in the program, along with a National Co-ordinating Centre, which is responsible for co-ordinating all the structures involved.

The headquarters of the NCC was identified as the Tissue Typing Laboratory of the Galliera Hospital in Genoa, as it was here that software was developed to collect and to manage the bone marrow donor genetic data.

The activity was guaranteed by, and official recognition gained from, private donations through Foundations. The NCC was initially sponsored by a Swiss Foundation (LIMMAT) and subsequently, from 1993, by the IBMDR Foundation ONLUS, composed of ADMO, Nazionale Italiana Cantanti (Italian Singers Football Team) and the E.O. Galliera Hospital, thus permitting its present functioning status.

2. GENERALITY

In 2001, following the Law n. 52 - 6 March, the IBMDR received institutional recognition.

The IBMDR:

- coordinates the activities of the RRs and collaborates with analogous organisations in other countries,
- promotes UD searches and manages the National Donor Registry activities, in order to provide HSC from volunteer donors and/or from CBU for national and international patients.

The “*Agreement between the Health Department and Regions*” – 5 October 2006- n° 2.637 recognizes the IBMDR as the NCC and it has the following functions:

- to coordinate and manage HSC UD searches from adult donors and/or CBU;
- to manage the exchange of communications and information between the subjects involved in the search procedures.

In particular the IBMDR:

- manages unrelated CBU and adult donors searches both from national/international banks and registries as per Law n° 52, 6 March 2001;
- guarantees and certifies the correct action to be taken in HSC search procedures, from the histocompatibility tests to the collection and transport to the unit transplant;
- collects, registers and certifies all the costs related to the HSC search and provision, in Italy and abroad, taking charge of the related administrative aspects and paying the below mentioned fees.

The IBMDR, RRs and each facility involved in the program must follow and maintain the IBMDR Standards herewith.

The “*Agreement between the Health Department and Regions*” 29 April 2010, establishes that the IBMDR, the RRs, the DCs and the RCs, must comply with the IBMDR Standards in the management of unrelated HSC donors; these are annually updated following technical and scientific improvements by the National Registry.

The *National Commission for Allogeneic unrelated transplants* (instituted in observance to the Law n. 52 - 2001 paragraph 2) and the IBMDR Advisory Boards guarantee that the procedure guidelines are ethically correct and technically appropriate.

3. THE NATIONAL REGISTRIES

According to the Law n. 52 - 2001 art. 2, the IBMDR is similar to analogous institutions established in other countries; being a structure authorized to deal with HSC requests. Such institutions, called Registries, can coordinate, within their pertinent territory, the DCs, the CCs, the CBBs and TCs and activities related to the search, the selection and to the use of the unrelated donor. Such registries should be certified by the WMDA.

3.1 The Registry should document that its procedures meet the WMDA standards in a satisfactory manner. The inspiring principles of these standards are reported in reference publications (for example Goldman J., Special Report: bone marrow transplants using volunteer donors – recommendations and requirements for a standardized practice throughout the world - 1994 update. *Blood* (1994) 84: 2833-2839, Hurley, C. Raffoux: Special Report: 'World Marrow Donor Association: International Standards for unrelated hematopoietic stem cell registries' *Bone Marrow Transplantation* (2004) 34, 103-110; C.K. Hurley e coll. 'Standards, regulations and accreditation for registries involved in the worldwide exchange of hematopoietic stem cell donors and products' *BMT* (2010) 45: 819-824.

3.2 The Registry should comply with other WMDA recommendations as long as they do not contradict national laws and regulations.

4. THE ITALIAN NATIONAL REGISTRY

4.1 The IBMDR has the function to find HLA matched unrelated donors for a patient who lacks a compatible familiar donor, thereby allowing an HSC transplant with high chances of success.

4.1.1 The IBMDR should be certified by the WMDA.

4.1.2 The legal representative of the Galliera Hospital, in charge of the Registry, is responsible that the procedures are in compliance with the WMDA standards.

4.1.3 If the IBMDR relies on other entities to perform some of the duties described in these Standards, it is the responsibility of the Registry to ensure that these entities comply with IBMDR/WMDA Standards.

4.1.3.1 Those entities are subject to an audit process.

4.1.4 The IBMDR must ensure that the TC activates a search exclusively for those patients where a HSCT represents a medically acceptable procedure. The pathologies that are indicated for HSCT are defined, with annual revisions, by the EBMT.

4.1.5 The IBMDR must maintain written documents of the search process and of the protocols related to all procedures, including personnel training and quality management.

4.1.6 All information and communications related to patients and donors must be recorded, preserved and protected from unauthorised or accidental access, viewing, destruction or modification.

4.1.7 Other written or electronic information must be kept for the amount of time strictly necessary for the project and in compliance with current applicable law.

4.1.8 Every printed document must be dated. Every stage of the search process must be monitored in order to determine the time necessary for each stage of the procedure.

4.2 General organisation

4.2.1 The IBMDR achieves its institutional functions through a network of Regional or Inter-regional Registries (Law n. 52 - 2001 art. 3) and TCs.

4.2.2 Three Advisory Boards, established to have both a consultancy role and to implement proposals, must establish procedure guidelines that are ethically acceptable and technically appropriate. They are nominated by the AIBT, GITMO and SIMTI.

- AIBT Committee is designated by the pertinent scientific society and is composed of experienced immunogeneticists working in public health structures that act as RRs or DCs.
 - ✓ It establishes the HLA tissue typing to be performed on the patient and on the potential donor at the recruitment stage and at all further stages of the search process.
 - ✓ It determines the accuracy of the typing, indicating the antigens and alleles that must be investigated.
 - ✓ It establishes the tissue typing techniques to be used to investigate HLA characteristics.
 - ✓ It determines minimal compatibility criteria for the donor/recipient.
 - ✓ It carries out genetic studies of the patient and of the potential donor populations.
- GITMO Committee is designated by the pertinent scientific society and is composed of experienced haematologists working in public health structures where HSCT from unrelated donors are performed.
 - ✓ It certifies the previous activity of the TCs and of the CCs-M participating in the IBMDR program.
 - ✓ It establishes the eligibility criteria for patients in need of an HSCT from a volunteer unrelated donor.
 - ✓ It reviews and conveys the patient follow up data to the IBMDR.
- SIMTI Committee is designated by the pertinent scientific society and it is composed of experienced immunohaematologists working in public health structures that act as RRs, DCs or RCs.
 - ✓ It establishes the eligibility criteria for the recruitment of volunteer donors.
 - ✓ It issues guidelines to protect donor welfare and safety.
 - ✓ It reviews donor clinical outcome data.
 - ✓

4.2.3 The ITCBN (created on the basis of art.10, comma 3 Law 219/2005 and Decree 18 November 2009, published in the U.G. 31/12/2009) establishes procedure guidelines that are ethically acceptable and technically appropriate concerning the collection, validation, storage and release of CBUs donated for allogeneic purposes. The ITCBN Commission is composed of the Director (or delegate) of every CBB belonging to ITCBN.

4.2.4 The IBMDR collaborates with the CNT-ISS and with the CNS-ISS to achieve its institutional role.

4.2.5 The Commission's proposals and their procedures should be discussed by the RR Committee.

4.2.6 The coordination of the activities of the Regional or Interregional Registries, the tasks and responsibilities entrusted to the TCs are defined in the below stated manner.

4.2.7 The RR Committee meeting should be held at least once a year and the Committee is composed of:

- the Director of each RR;

- the President of ADMO Federation;
- the Coordinators of the IBMDR Committees,
- the Director of the CNT-ISS,
- the Director of the CNS-ISS,
- the IBMDR scientific and administrative manager.

4.2.8 Amendments to the IBMDR Standards must be proposed in writing to the RR Committee, which must approve them before their becoming effective.

4.3 Facility infrastructure

4.3.1 The IBMDR must have a fixed physical location with suitable spaces, equipment and instruments to carry out all the activities connected with HSC donor search and selection, in an environment designed to minimize errors and maintain confidentiality.

4.3.2 The IBMDR must have an adequate computerised system for donor data management (data recording, preservation, verification, revision, selection, tracking, comparison, use, interconnection, communication, diffusion, cancellation and destruction) to ensure record authenticity and integrity. Search algorithms must allow reliable searches which can be completed in a time frame consistent with WMDA recommendations.

4.3.3 Documentation of system development, maintenance and operations including policies and procedures must be complete and be written in an appropriate language. Modifications to the computer system must be authorised and documented.

4.3.4 The on-going backup and data restoration procedures must be appropriate, validated and documented.

4.3.5 Despite measures determined by the guarantor (*Authorization n. 258/2011 - U.G. of 11 July 2011 n. 159*) and with the consent of the interested party authorising the acquisition of information (personal, medical and genetic data), opportune measures must be set for sensitive data management (*Law 675/96 and Legislative Decree, 30 June 2003*).

4.3.6 An identification code number must be used both to store the donor's personal data and medical evaluation and to release donor information strictly pertinent to the search procedure.

4.3.7 Personal data, medical and HLA data must be recorded separately.

4.3.8 The IBMDR must have a tissue typing laboratory performing all the HLA typing tests needed for donor selection.

This laboratory must:

- be accredited by the ASHI or the EFI for the required techniques;
- guarantee full cooperation with analogous laboratories of the RRs.

4.3.9 The IBMDR must have sufficient communication links to facilitate searches. These links must include telephones, fax, email, internet and established software.

4.4 Personnel qualifications

4.4.1 The director and the key personnel must have demonstrated experience in the activities in which the IBMDR is engaged. The IBMDR must have a team of staff with sufficient training and that is large enough to assume the volume and variety of services required to manage its activities.

4.4.2 The IBMDR director is responsible for the management of the activities in compliance with all laws and regulations. The Registry director is also responsible for the supervision, the maintenance of personnel competency, training and continuing education.

5. THE REGIONAL AND INTER-REGIONAL REGISTRIES

5.1 Definition

According to Law n. 52 - 2001 art. 3, the Inter-regional or RRs are located the structures, identified by the competent Regional Health Authority. They represent the IBMDR on Italian territory and they must comply with applicable governmental laws and regulations (“*Agreement between the Health Department and Regions*” 29 April 2010). Besides contributing to enlarge the potential donors list, they pursue IBMDR objectives in managing entrusted powers and duties on their pertinent territory – **Form RR111**.

5.1.1 The RRs, which are part of the IBMDR network, should be certified by the WMDA, in the frame of the national accreditation program.

5.1.2 The RRs, like the IBMDR, must follow the “Rules for the enforcement of the Law n. 52 - 2001”.

5.1.3 The RRs should abide by other WMDA recommendations, as long as they do not contradict regional laws and/or regulations.

5.2 General organization

5.2.1 Organization

5.2.1.1 The HLA tissue typing laboratory of the RR must successfully participate in the annual QCs of the CNT and must be accredited by ASHI and/or EFI for HLA typing or for other tests required in HSCT.

5.2.1.2 This laboratory must ensure the accuracy of the HLA data required at donor registration or during potential donor selection procedure.

5.2.1.3 HSC collection must be performed by CCs.

5.2.1.4 The RR may use DCs and/or RCs to maintain and enlarge the number of listed volunteers (potential donors). Besides the tasks correlated to these listed volunteers, DCs may also perform the pertinent HLA tests.

5.2.1.5 In this case, the DC’s tissue typing lab must be ASHI or EFI accredited for the tests required in HSCT. The RR is responsible to establish procedures and to organize regional HLA quality controls.

5.2.1.6 The RR is responsible for regional donor HLA data and for updating and transferring them to the national database.

5.2.1.7 The RR elaborates strategies for the recruitment of new volunteers to maintain and/or enlarge the number of listed regional donors:

- it promotes awareness and provides consultancy for the problems connected with HSC donation and transplantation amongst health operators;
- it promotes activities to inform and educate the regional community on HSC donation, focusing its efforts on specific settings (schools, churches, community centres) in collaboration with local volunteer associations and with its pertinent DCs.

5.2.1.8 The RR must support the DC, if necessary, in:

- tissue typing testing to establish donor histocompatibility typing and/or donor suitability;
- the “*Final information session*” and “*Verification of the prescription for HSC collection* (# 10.6);
- the organization of the HSC collection.

5.2.2 Facility infrastructure

- 5.2.2.1 The RR must have a fixed physical location.
- 5.2.2.2 The Registry must have suitable spaces, equipments and instruments to carry out all the activities connected with its duties, in an environment designed to minimize errors and maintain confidentiality.
- 5.2.2.3 Donor data must be managed by an adequate computerised system provided by the IBMDR.
- 5.2.2.4 If any personal donor data are given to the DC, they must be treated using the national computerised system.
- 5.2.2.5 The RR must have sufficient communication links to facilitate searches. These links must include telephone, fax, and international telematic links (email, internet).
- 5.2.3 Personnel qualifications
 - 5.2.3.1 The director and the key personnel must have demonstrated experience in the activities in which the RR is engaged. They are responsible for maintaining procedures that are in compliance with the WMDA standards.
 - 5.2.3.2 The RR must have a team of staff with sufficient training and that is large enough to assume the volume and variety of services required to manage its activities.
 - 5.2.3.3 The RR director is also responsible for the supervision, for personnel continued competency, training and continuing education.

6. CRITERIA FOR PARTECIPATING TRANSPLANT CENTERS (TC)

- 6.1 The “*Italian National Guidelines for the search of unrelated donors*” (edited by CNT, Ministry of Health, 25 January 2011) defines the requirements for CNT and for geographically contiguous Clinical Programs that may activate a search for a UD or CBU.
 - 6.1.1 The Italian TCs that may run an HSC unrelated donor search, in collaboration with the IBMDR, are located within public hospitals authorised to perform allogeneic HSCTs from unrelated volunteers. They must be certified by GITMO – **Form CT333**. The TCs must be able to document to have performed, at least 10 HSCT on different recipients per year, in the previous two years, thus adhering to an EBMT requirement. The continuing maintenance of the requirements is determined by the data reported and registered in the GITMO lists.
 - 6.1.2 The geographically contiguous Italian Clinical Programs that may run a HSC unrelated donor search, in collaboration with the IBMDR, are located within public hospitals that are authorised to perform allogeneic HSCTs from unrelated volunteers and that must also be authorised by the CNT - **Form CT333 M**. They must be able to document:
 - to have a unique CIC (EBMT Centre Identification Code), the same as the clinical site of the Clinical Program Director, who is responsible for the unrelated donor search procedure;
 - a minimum of five (5) new allogeneic patients transplanted at each site per year;
 - formal approval from the Institution’s General Director, in the case of contiguous facilities;

- formal approval from the relevant Institution's General Director in the case of non contiguous facilities;
- Regional official approval of the Clinical Program;
- Regional transplant coordination center's official approval of the Clinical Program.

- 6.2 The TC must be compliant with the National guidelines and the IBMDR/WMDA Standards.
- 6.3 The TC must have access to and appropriate support from an HLA laboratory accredited by ASHI or by EFI. The laboratory, which performs the initial patient HLA typing, is also responsible for the HLA typing of the donor/recipient pair and for the "Final compatibility testing".
- 6.4 The TC must have sufficient communication links to facilitate searches. These links must include telephone, fax, email and internet and the protected access to IBMDR software.
- 6.5 No search can be run directly by an Italian TC with an IR or CBB. The search must be conducted through the IBMDR.
- 6.6 The TC must inform the patient about UD and CBU haematopoietic stem cell transplants, the search process and the related costs.
- 6.7 The TC must obtain the patient's spontaneous and informed consent before starting a potential UD and/or CBU search - **Form CT302**.
- 6.8 The TC must follow the search process and contribute to its rapid outcome using the transmission forms or information technology devices provided by IBMDR.
- 6.9 After an HSCT from an unrelated donor, the TC must register patient health status and follow-up in the GITMO/EBMT databases in an established timely manner, in order to comply with Article 10 of Law Decree 191/07 – "*Implementation of the EC Directive 2004/23*" – Reporting obligation of activity. The deficiency of data registration will determine the loss of TC accreditation for UD searches and transplantations.
- 6.10 The TC personnel must attend educational meetings organised by GITMO.
- 6.11 All communications between the TC and the RR are to be mediated by the IBMDR.
- 6.12 All TCs, if accredited by GITMO, must act also as CCs-M from UD, of their pertinent geographic area, except for paediatric centres not surgically equipped for operating on adults.

7. CRITERIA FOR PARTECIPATING COLLECTION CENTERS (CCs)

The CCs must be compliant with the National guidelines and IBMDR/WMDA Standards.

7.1 Marrow Collection Centres (CCs-M)

- 7.1.1 The Italian CCs-M which may perform marrow collection from an IBMDR volunteer UD are located within public hospitals authorised to perform autologous or allogeneic transplants.
- 7.1.2 The facility infrastructure, the personnel qualifications and the procedures for marrow collection are determined in the document "*Agreement between the Health Department, the Regions and the Autonomous Provinces of Trento and Bolzano upon HSC harvesting, manipulation and clinical use*", (Actions of the Cabinet – 10 July 2003, n.1770).

- 7.1.3 The CC-M must be GITMO accredited, in accordance with its pertinent RR. Applicant centres must have performed a minimum of one bone marrow collection procedure in the twelve months preceding their application, in accordance with JACIE requirements. The release of the **Form CP 222-m** by the IBMDR certifies that the CC-M is a National Italian Registry associated organization. The continual maintenance of these requirements is ensured by GITMO with periodic revisions of the **Form CP 201-m**.
- 7.1.4 The CC-M cooperates with the RR to ensure compatible donor protection and, if necessary, it collaborates in the medical evaluation of the prospective donor (**Form CD104-m, Form CD108-m**) contributing to the “*Verification of marrow prescription*” (**Form CD107-m, Form CD107-m**).
- 7.2 Aphaeresis Collection Centers (CC-P)
- 7.2.1 The Italian CCs-P which may perform PBSC and/or lymphocyte collection from an IBMDR volunteer UD are located within public hospitals, authorised to perform aphaeretic procedures from adult donors.
- 7.2.2 The facility infrastructure, the personnel qualifications and the procedures for haematopoietic cells collection, are determined in:
- the “*Agreement between the Health Department, the Regions and the Autonomous Provinces of Trento and Bolzano upon HSC harvesting, manipulation and clinical use*”, (Actions of the Cabinet – 10 July 2003, n.1770);
 - 3 March 2005 Decree “*Characteristics and modalities for blood and blood by-products donation.*” “*Protocols for ascertaining blood and blood by-products donor’s eligibility*”;
 - Law 219, 21 October 2005 art.2 and art.3 “*New guidelines for transfusion activities and blood by-products national production*”.
 - 25 January 2010 Decree “*Adoption of the Directive 2006/17/CE, 2006/86/CE, 2004/23/EC, pertinent to technical protocols for the donation, procurement, testing, as well as technical requirements for traceability and for notification of adverse events and reactions and technical prescriptions for coding, processing, preservation, storage and distribution of human tissues and cells.*”
- 7.2.3 The CC-P must fulfil the requirements of the above indicated documents and must fulfil the JACIE basic criteria. In particular it must:
- 7.2.3.1 have a designated site for donor evaluation and for the aphaeretic procedure;
- 7.2.3.2 have access to the following facilities: a reanimation service and a transfusion service to guarantee immediate donor safety in an emergency situation.
- 7.2.3.3 be directed by a physician who can demonstrate to have at least 1 year of experience in the specific field and to have performed or supervised at least 10 peripheral HSC procedures.
- 7.2.4 The release of the **Form CP 222-p** (in accordance with the pertinent RR) by the IBMDR certifies that the CC-P is an Italian National Registry associated organization. The continual maintenance of the requirements is ensured through periodic revisions of the **Form CP 201-p**.
- 7.2.5 The CC-P cooperates with the RR/CD to ensure compatible donor protection, and, if necessary, it collaborates in the medical evaluation of the prospective donor (**Form CD104-p/l, Form CD108-p/l**) contributing to the “*Verification of PBSC prescription*” (**Form CD107-p**) and to the “*Verification of Lymphocyte prescription*” (**Form CD107-l**).

8. CRITERIA FOR PARTECIPATING DONOR CENTERS (DCs)

8.1 It is highly recommended, respecting the organisational autonomy of the individual regions, that a number of DCs are created to be operative units which contribute to the formation of the RR.

8.2 The DC must be located within a public institution that offers a transfusion medicine service, and the requirements and duties are specified in the “*Agreement between the Health Department and Regions*” 29 April 2010. It must

- ✓ have documented experience in:
 - donor recruitment and management;
 - educational matters concerning donation;
 - donor eligibility evaluation;
 - donor privacy protection;
- ✓ have a designated site for donor management activities, a private space for donor counselling sessions, for health history data collection and for medical examinations;
- ✓ have a physician and a reference coordinator to manage and supervise the centre activities;
- ✓ have access to the following facilities:
 - a transfusion service accredited by the Regional Health Authority, which meets national guidelines for performing the services defined by law;
 - a laboratory for infectious disease marker testing, accredited by the Regional Health Authority, which meets national guidelines for performing these services.
- ✓ be compliant with the National guidelines and IBMDR/WMDA Standards
Compliance with the standards and the maintenance of the requirements determined by the Regional Health Authority, are carried out by the pertinent RR, **Form CD111**.

8.3 The DC is the solely responsible for the accuracy and updating of the personal data of enrolled donors. The DC is also responsible for checking and verifying that the unique donor code (created by IBMDR software) and the donor identity correspond. These data can be visualised by the pertinent RR, on the basis of having a shared regional policy and only after having received the appropriate informed consent from the donor.

8.4 The Donor Center is responsible for storing all the data to ensure the traceability of all steps related to the donation process from donor to recipient and viceversa.

8.5 If the RR delegates the DC to perform donor HLA typing, the RR, responsible for the HLA data management, must establish test validation procedures and QCs within its pertinent geographic region. The DC, in this case, must be EFI/ASHI accredited for I and II class HLA typing of UD.

8.6 Donor genetic data and personal data must be stored using the IBMDR computerised system as indicated in # 4.3.2, 4.3.3 , 4.3.5.

8.7 The DC must maintain and/or enlarge its regional donors list in accordance with the pertinent RR, see # 5.2.1.7.

8.8 All communications between the IBMDR and DC must be mediated by the RR.

9. CRITERIA FOR PARTECIPATING SATELLITE RECRUITMENT DONOR CENTRES

9.1 The RRs can identify public institutional structures within a Donor Center, to function as Satellite Recruitment Centres (RCs) **Form PR111**.

9.2 The RC's requirements and duties are specified in the "*Agreement between the Health Department and Regions*" 29 April 2010 and acts under the supervision of the tutor DC. The RC must fulfil IBMDR and WMDA Standards and in particular:

- ✓ they must have proved experience in recruiting and managing volunteers, in medical selection and in maintaining donors' privacy;
- ✓ they must have a designated site for donor management activities, a private space for donor counselling sessions, for health history data collection and for medical examinations.

9.3 The RR and the DC can delegate the RC to carry out one or all of the below stated activities:

- Volunteer recruitment;
- Medical evaluation;
- Donor identification;
- Peripheral blood sample collection.

10. CRITERIA FOR PARTICIPATING CORD BLOOD BANKS (CBBs)

10.1 The Italian CBBs that can provide HSC from unrelated CBU for the purpose of transplantation act according to:

- the "*Agreement between the Health Department, the Regions and the Autonomous Provinces of Trento and Bolzano upon HSC harvesting, manipulation and clinical use*", (Actions of the Cabinet – 10 July 2003, n.1770);
- the protocols indicated in Article 3, comma 4 of the Law 219/2005 and the actions of coordination and scientific technical control of CNS – as indicated in the article 12 comma 4 of the Law 219/2005, integrated with the necessary indications from the CNT;
- Decree Law 6 November 2007, n. 191 "*Implementation of European Directive 2004/23/CE on setting standards of quality and safety for the donation, procurement, testing, processing, preservation, storage and distribution of human tissues and cells*";
- the ASR – 29 October 2009 n. 184 "*Organizational, structural and technical minimal requirements for acting as a public cord blood bank*";
- Decree Law 25 January 2010 n. 10 "*Implementation of the Directive 2006/17/CE, 2006/86/CE, 2004/23/EC, pertinent to technical protocols for the donation, procurement, testing, as well as technical requirements for traceability and for notification of adverse events and reactions and technical prescriptions for coding, processing, preservation, storage and distribution of human tissues and cells.*"
- the ASR – 20 April 2011 n. 75 "*Guidelines for the accreditation process of public cord blood banks*";
- the national and european applicable laws and regulations.

10.2 The CBB must operate in compliance with the IBMDR, FACT/Netcord and WMDA Standards.

10.3 The CBB must have sufficient communication links to facilitate searches. These links must include telephone, fax, email, internet and protected access to IBMDR software.

10.4 The CBB must have a computerised system for collection, management and storage of the data related to its activity.

10.5 This system must guarantee the complete traceability of the CBU and the transmission of all pertinent information to the IBMDR, with the procedures and modalities established by the IBMDR.

10.6 The communication between CBB, TC and the IBMDR must be in writing, using the IBMDR forms and attachments and through the validated computerised system provided by the IBMDR.

10.7 The CBB must:

10.7.1 update the data of the stored CBUs destined for unrelated allogeneic transplantations;

10.7.2 send the CBU data to the IBMDR, by the predetermined deadline and according to the defined transmission data protocol;

10.7.3 perform the CBU HLA typing both at the database registration stage and during the subsequent search procedures, having the appropriate support from a HLA laboratory accredited by ASHI or EFI;

10.7.4 be able to organise the shipment of a DNA sample of the selected CBU (if available) upon specific request from the requesting TC;

10.7.5 be able to organise the shipment of a maternal serum sample of the selected CBU (if available) upon specific request from the requesting TC;

10.7.6 organise and coordinate, together with the courier in charge of the CBU transport, the preparation, packaging and shipment of the CBU to the requesting TC.

11. ADULT HAEMATOPOIETIC STEM CELL DONORS

11.1 Definition

The HSC potential donors are adults, who after having volunteered to donate HSC to any patient being treated in any part of the world and after responding to the donation eligibility criteria, are HLA typed and listed in the IBMDR. The potential donor status is maintained until to donation take place or until the person reaches the age limit.

11.2 Consent

The HSC potential donors must be properly informed about the correlated risks and give a fully informed written consent to be recruited in the Registry and to the use of their personal and genetic data. The consent must be obtained by personnel qualified in informing and educating volunteers, in applying confidentiality rules, in medical selection and clinical counselling.

11.2.1 Before signing the consent, the donor will be given a general explanation about the indications for and results of haematopoietic stem cell transplantation, the reasons for using unrelated donors, the donation process **Attachment A**, and the risks associated with it, **Attachment H**.

11.2.2 The donor should complete the anamnestic pre-registration questionnaire, stating that he/she has read the educational material about disease transmission by marrow or PBSC donation, and agrees, in a preliminary way, to undergo the HIV test - **Attachment C**, **Attachment B** and/or to identify a potential risk of disease transmissible through blood and HSC transplantation.

11.2.3 The donor should sign the “*Donor Initial Consent*”- **Form CD101** - acknowledging that he/she has been informed about:

11.2.3.1 his/her registration to a donor list, giving his/her availability to be called until his/her 55th birthday;

11.2.3.2 the importance of his/her commitment;

11.2.3.3 the importance of maintaining the donation anonymous, voluntary and without remuneration.

11.2.4 Once the identity of the donor has been verified by the health professional, the donor must provide a written informed consent before

joining the IBMDR and each time he/she is contacted during the donor selection process.

11.2.5 The donor must sign a further consent if blood or other biological material is stored and/or used for research projects or different purposes, even if it has been approved by ethical committees.

11.2.6 Records pertaining to donors must be preserved by the centre recruiting the donor for timing requested by law. Access to the database is limited only to authorised individuals.

11.3 Donor eligibility

A medical evaluation of the volunteer donor must be performed at every meeting, to verify donor eligibility. Due to the complex and serious nature of HSC donation, the medical examinations must be performed at each stage and must be thoroughly graded according to the step of the search process.

11.3.1 The minimum eligibility criteria for a prospective donor must fit the Italian, peripheral blood donor criteria.

11.3.2 The requirements defined by Italian law for transfusion (Law of 21 October 2005, n. 219 and relative current regulations) are indicated in **Attachment G**.

11.3.3 In general, the donor should be under 35 years of age when joining the IBMDR.

11.3.4 No blood sample can be taken from a pregnant donor who has been recruited, a pregnant prospective donor shall be invited to return for registration at least one year post delivery.

11.3.5 Donors must be free from physical and psychic chronic diseases. The potential bone marrow donor must fulfil the class I requirements of the “*Anaesthesiology Risks*” established by the American Society for Anaesthesiology – ASA.

11.3.6 The classes of risks are reported in the **Attachment F**.

11.3.7 The prospective donor in order to become a potential PBSC donor must not:

- be having treatment with acetyl-salicylic acid or platelets antiaggregants, anticoagulants, ACE-inhibitors or lithium;
- have splenomegaly;
- have personal and family history of coagulation disorders in particular arterious or venous thrombosis;
- have family history of iritis or episcleritis;
- be a sickle cell trait carrier;
- have difficult peripheral venous access, inappropriate for the aphaeresis procedure which is of considerable effort and duration.

11.4 Typing

11.4.1 If the prospective donor fits the recruitment criteria, he/she is typed for the HLA-ABC and DRB1 loci (by high/intermediate resolution molecular techniques – 2 fields); donor data are then registered in the national database.

11.4.2 Donor blood group typing must include at least ABO grouping and Rh typing.

11.5 Donor selection

- 11.5.1 The donor, informed of the search process status, must confirm his/her commitment to continue - **Form CD102** - before providing another blood sample for additional histocompatibility tests.
- 11.5.2 The health personnel of the DC must verify that the identity and data of the donor correspond with the IBMDR code before a recall for further tests for biological samples.
- 11.5.3 The DC, at every recall for further tests, is responsible for ensuring that the donor still meets the recruitment standards (for example an eventual pregnancy status).
- 11.5.4 The eventual unreachable or unavailable status of the donor should be reported to the Registry within 20 days after the selection date.
- 11.5.5 The tests on the donor cannot be performed in a subsequent moment if a donor is declared “temporarily unavailable”. If the request were however to remain open, the IBMDR will send a further communication.
- 11.5.6 When a TC wishes to proceed with DRB1 typing of a HLA I class matching donor, the DC should perform the test with low resolution molecular techniques – 1 field.
- 11.5.7 When an HLA –ABDR matched donor is selected for “*Molecular typing*”- EMDIS or **Form RC305** - the DC must provide, using a fresh blood sample:
- ✓ high resolution molecular typing – 2 fields - of HLA-DRB1;
 - ✓ other loci HLA typing if requested by the TC;
 - ✓ ABO, Rh and CMV status (IgG and IgM) if requested by the TC;
 - ✓ donor weight;
 - ✓ number of pregnancies (if female);
 - ✓ number of transfusions.
- 11.5.8 The HLA-DRB1 (LR or HR) typing results must be sent by the DC to the IBMDR within 30 days of the request date. The typing request is no longer valid if the IBMDR does not receive the results within 30 days and an invoice cannot be issued. The HR typing – 2 field - results requesting DRB1 together with other HLA loci must be sent to the Registry within 40 days of the request date. The typing request is no longer valid if the IBMDR does not receive the results within 40 days and an invoice cannot be issued.
- 11.5.9 If the TC cancels the HLA typing request, the HLA lab must provide the results within the timing specified above and no later than 30 days of the cancellation request date.
- 11.5.10 Having received the “*Blood sample request*” – EMDIS or **Form RC306** - in order to be able to perform the “*Final compatibility tests*”, the DC, must provide or organise:
- ✓ a new donor’s informed consent with more detailed information about donation procedure (**Attachment A-TC/B-TC**);
 - ✓ the donor’s IDMs, (Syphilis test, anti-HCV, HbsAg, anti-CMV IgG and IgM, anti-HIV 1/2) and ABO – Rh typing;
 - ✓ donor’s weight, number of transfusion and number of pregnancies (if female);
 - ✓ the blood sample shipment.
- If at the moment of shipment, the IDM results are not yet complete, the DC must send them as soon as possible to the IBMDR, that will be responsible for sending them on to the TC.

- 11.5.11 The request is no longer valid if the DC is not able to organise the shipment within 30 days from the request and an invoice cannot be issued.
- 11.5.12 If the TC cancels the shipment request, if not already shipped, an invoice cannot be issued.
- 11.5.13 The IDM results must be anonymous, identified by a donor code.
- 11.5.14 The HLA donor typing results, IDM results, parity, sensitizing events and/or donor unavailability must be reported to the IBMDR, via the protected access IBMDR software.
- 11.5.15 The final histocompatibility testing is performed by the TC HLA lab. The HLA typing results - **Form RC307 don** - must be sent to the TC by the lab within 40 days of receipt of the samples. The decision about the donor's suitability must be sent to the DC through the IBMDR, within 10 days of receipt of the HLA results.
- 11.5.16 The matched donor could be kept 'reserved' for a period of 90 days. After 90 days, without any written request of extension, the reservation will expire. Through a written communication, permitted only once, the RC can request another 90 days of reservation.
- 11.5.17 The DC is responsible for informing the donor about his/her selection status, basing the decision on:
- ✓ the compatibility tests performed as described at #10.5.5 and #10.5.7 and compared to the "minimal compatibility criteria" ;
 - ✓ the indication on **Form RC307 don**;
 - ✓ the unsuccessful receipt of **Form RC307 don** within the indicated time.
- 11.5.18 Following particular transplant protocols requiring specific compatibility criteria, the TC may request further tests (for example HLA-C locus molecular typing) on the already DRB1 typed donors or together with the DRB1 high resolution molecular typing request.
- 11.5.19 If a pre-donation donor's blood sample is requested, the shipment must be organised within 30 days of the collection date, if no other indications are provided by the TC.

11.6 First donation

A Haematopoietic Stem Cell donation can be carried out from both bone marrow and peripheral blood after administration of G-CSF.

The applicable laws and procedures are defined by:

- the Ministerial Guidelines, 3rd March 2005;
- the Health Department Committee resolution, session held on 5th July, 2001;
- the "Agreement between the Ministry of Health Department, the Regions and the Autonomous Provinces of Trento and Bolzano on HSC collection, manipulation and clinical use", (Actions of the Cabinet – 10th July 2003, n.1770).
- the SIMTI-GITMO recommendations for related and unrelated HSC donation for HSCT; Edition 2011.

11.6.1 Final donor information session (**Attachment WU-cl**)

11.6.1.1 A representative of the DC and/or RR, a representative of the CP and a haematologist, at least, must be present at the final donor information session.

- 11.6.1.2 In the final session, the prospective donor must be given detailed information about further tests to be carried out, the procedure of HSC donation, its risks and the period of time which he/she may have to commit.
- 11.6.1.3 It is strongly recommended that donor's personal physician or a close relative of the donor be present in this informative session.
- 11.6.1.4 The prospective donor must be informed about the right to withdraw at any time. However, the donor must also be informed about the extreme risk for recipient's life if the donation is not carried out once the patient's preparative regimen has commenced.
- 11.6.1.5 In particular, the prospective donor must be informed about:
- the possible complications related to the HSC donation **Attachment H**;
 - the possible depressive state following the donation;
 - the approximate time commitment;
 - that, in some circumstances, the donor may be asked an additional donation for the same patient. Following specific transplant protocols a mononuclear cell collection from peripheral blood (for DLI) may be required;
 - the right and the duty of anonymity both towards the recipient and towards third parties (*Legislative Decree, 30 June 2003*).
- 11.6.2 Should a PBSC donor result unsuitable or be no longer available for the bone marrow donation, the TC must be informed that, in the case of an unsuccessful mobilization, it will not be possible to proceed with a bone marrow donation.
- 11.6.3 Donor medical evaluation
The DC is responsible for protecting donor safety, evaluating his suitability and for determining any infectious diseases transmissible by the marrow or PBSC donation. - **Attachment B-WU**.
- 11.6.4 Collection procedure medical evaluation
The DC and the CC are responsible for protecting donor safety, evaluating his suitability for the specific collection type requested by the TC.
- 11.6.5 The physical examination must be performed by a team, identified by the DC, which is not the team that takes care of the patient.
- 11.6.6 The donor work-up process must be organised within 30 days before the collection date.
- 11.6.6.1 Marrow donation
Following the receipt of the “*Prescription for human bone marrow collection*” if the donor confirms his willingness to donate, the DC and the CC-M must complete the “*Verification of the marrow stem cell prescription*” - **Form CD107-m**.
Licensed physicians of the DC and the CC-M must complete a medical evaluation in writing having evaluated the results of the following:
- routine laboratory tests (complete blood count, electrolytes, either urea nitrogen or creatinine, bilirubin, serum total proteins, etc.), infectious disease markers (Anti HAV IgG and IgM, HBsAg, Anti-HBs, Anti HBcAg, Anti

HBeAg, Anti HCV, Anti HIV 1 and 2, Anti CMV IgG and IgM, toxotest IgG and IgM, syphilis test, HCV NAT, HIV NAT, HBV NAT and, in a population at risk of infection, HTLV I and II), and ABO blood group typing;

- instrumental examinations (electrocardiogram and chest X-ray);
- physical examination (with anaesthesiological evaluation);
- pregnancy test;
- personal and familiar anamnesis.

In the case of the donor's eligibility, the physicians must proceed with the "*Clearance of the donor for bone marrow collection*" - **Form CD104-m** that must be sent to the TC and to the IBMDR before the recipient preparative regimen can begin.

11.6.6.2 PBSC donation

Following the receipt of the "*Prescription for stimulated human peripheral blood stem cell collection*" if the potential donor confirms his willingness to donate, the DC, the CC-P and CC-M must fill in the "*Verification of PBSC prescription*" **Form CD107-p**.

Unless the donor can only donate PBSC, he/she must also be evaluated both for a bone marrow and peripheral blood donation. Therefore a licensed physicians of the DC, CC-P and CC-M, having evaluated the results of exams indicated in #11.6.6.1 together with the below-stated results must complete a medical evaluation in writing.:

- a thorough clinical examination, ascertaining donor cardiovascular condition;
- an ECG with effort tolerance;
- a splenic ultrasonography;
- an accurate coagulation screening for thrombophilia, genetic testing for ATIII, C protein, S protein and homocysteine; the investigation on factor V Leiden mutation and on prothrombin 20210A must be performed only if there is a positive personal and/or familiar anamnesis;
- an accurate blood cell count;
- a screening for HbS;

In the case of the donor's eligibility, the physicians must proceed with the "*Clearance of the PBSC donor*" - **Form CD104-p** - that must be sent to the TC and to the IBMDR before the recipient preparative regimen can begin.

- 11.6.7 The DC and the CC must notify the TC and the IBMDR of any temporary unsuitability to donate and, in the event of indefinite deferral, remove him/her from the prospective donor panel **Form CD108**.
- 11.6.8 Infectious disease testing of the donor must be repeated if the tests have been carried out more than 30 days prior to marrow donation. Donor pregnancy status must be assessed immediately before the recipient's preparative regimen.
- 11.6.9 If the transplant is postponed, the examinations/tests performed at time of work-up (with the exception of the examinations required by law) cannot be re-tested, if the new scheduled collection date is within 90 days of results.

- 11.6.10 Written documentation of counselling must be kept at the DC and CP.
- 11.6.11 Final consent
 - 11.6.11.1 The donor, if found eligible to donate, expresses his/her willingness to continue the process signing the “*Final consent to donate*” **Form CD103**.
 - 11.6.11.2 At the time of the “*Final consent to donate*” information, concerning the possibility of further donations for the same recipient, must be given to the donor.
 - 11.6.11.3 The DC must immediately notify the IBMDR in the event that the donor withdraws his /her consent to the donation using the **Form CD108**.
- 11.6.12 Pre-Collection Communication
 - 11.6.12.1 The HSC collection can only be performed if the patient’s clinical condition and disease status allow the treatment procedure at “*HSC prescription*” time.
 - 11.6.12.2 Before initiating the preparative regimen, the DC, the CC and the TC must agree with the volume and the number of HSC that have to be collected and sign the “*Verification of HSC prescription*” **Form CD107**.
 - 11.6.12.3 The HSC collection may not be initiated if the delegated courier has not communicated the itinerary – **Form C2** - and has not notified the CC of his arrival.
 - 11.6.12.4 Should a cancellation of HSC prescription take place when the donor has already undergone physical examinations and laboratory tests, the services will, however, be charged for.
 - 11.6.12.5 Should a HSC transplant be postponed (due to the patient’s disease relapse or for any other reason) but a new collection date has already been established, the donor will be reserved for 90 days.
- 11.6.13 Marrow collection
 - 11.6.13.1 Prior to blood marrow collection, the donor must have autologous blood units drawn. The number of pre-collected units depends on the marrow volume that the donor, according to the DC/CC-M physicians, can safely donate.
 - 11.6.13.2 Marrow collection should be performed in a different structure from the recipient TC.
 - 11.6.13.3 During marrow collection, the donor is transfused with pre-collected autologous blood.
 - 11.6.13.4 Bone marrow harvesting, performed in accordance with the **Attachment L**, must take place in an authorised CC-M, preferably near to the donor’s home.
 - 11.6.13.5 The characteristics of the collected bone marrow (unit identification code, nucleated cells parameters, volume) are certified by the CC-M with **Form CP201-m** that must accompany the bone marrow bags. The microbiological test results must be available to the TC and IBMDR as quickly as possible.
 - 11.6.13.6 After the HSCT, the TC must send the completed **Form CP200-m** and **Form CP201-m** to the IBMDR and the CC-M. The GITMO MUD Commission will evaluate the HSC collection, referring to the minimal quality requirements.

11.6.14 Peripheral blood stem cells collection after stimulation

11.6.14.1 Donor receives G-CSF, subcutaneously, at a maximum of 10µg/Kg donor body weight. The CC-P physician is responsible for the administration procedure.

11.6.14.2 The use of biosimilar G-CSF is not allowed.

11.6.14.3 The administration of G-CSF, the evaluation of possible side effects and the accuracy of the clinical follow-up are described in **Attachment R**.

11.6.14.4 In no case, is the use of a central venous catheter allowed.

11.6.14.5 In the event of serious G-CSF side effects, the treatment must be discontinued.

11.6.14.6 The HSC request can be satisfied by a marrow donation if the donor provides his/her consent and is fit for such donation.

11.6.14.7 The characteristics of the collected PBSC (unit identification code, nucleated cells parameters, volume) are certified by the CC-P with **Form CP201-p**, which must accompany the PBSC bags. The microbiological test results must be available to the TC and IBMDR as quickly as possible.

11.6.14.8 After the HSCT, the TC must send the completed **Form CP200-p** and **Form CP201-p** to the IBMDR and the CC-P. The SIMTI Commission will evaluate the HSC collection, referring to the minimum quality requirements.

11.6.15 Validation of the HSC collected product

11.6.15.1 The collected HSC product (BM/PBSC) must be validated by the DC/CC.

11.6.15.2 The following exams must be performed on a donor sample, taken on the day of collection:

- Anti-HCV;
- HBsAg;
- Anti-HIV1,2;
- Syphilis test;
- HIV/HBV/HCV NAT;
- ABO and Rh blood group.

11.6.15.3 The HSC product can be released by the CC, before the validation results (§11.6,15.2), that should be sent to the TC as soon as available - **Form CP200-p** and **Form CD104Q**.

11.7 Second or further donations for the same recipient

11.7.1 In the event of failure of the first HSC transplant, and at least 20 days having passed post transplant, the TC should send a new donation request, **Form RC309**, to the IBMDR, informing of:

- the patient diagnosis;
- the protocol applied at the first transplant;
- the patient's present clinical status;
- the reasons for the request;
- the blood component required.

The second donation may be for not stimulated peripheral nucleated cells in the case of relapse, or HSC in the case of non-engraftment or of poor graft function.

- 11.7.2 The volunteer, who has already donated peripheral HSC should, preferably, donate marrow HSC and, in any case, can only be submitted again for growth factor stimulation for HSC mobilization, if at least 12 months have passed since the first donation.
- 11.7.3 Any direct contact between the TC and the donor is strictly forbidden.
- 11.7.4 All the donation requests must be submitted to the GITMO MUD Committee.
- 11.7.5 Second/further lymphocyte donation requests must be submitted to the SIMTI Committee.
- 11.7.6 If the request is approved, the IBMDR will inform the DC and ask for the donor's availability.
- 11.7.7 The donor can be approached only if:
- he/she has been informed during the “*Final Information Session*”, about a possible additional donation - **Form CD103**;
 - he/she has provided his/her consent on the questionnaire on “*Health Status*” - **Form CD106**;
 - the donor follow-up data doesn't document abnormal values.
- 11.7.8 Before asking for the donor's consent, he/she must have been informed about:
- the indications for and the results of a second transplant;
 - the procedure for the required additional donation;
 - the risks and discomforts related to the new required donation.
- 11.7.9 No pressure of any kind may be exerted on the donor, who has the right to ask any questions concerning the donation and must have sufficient time to mature his/her decision, conscious that he/she has already come up greatly to the patient's expectations.
- 11.7.10 If the DC physician believes that the donor has not perfectly recovered from the first HSC collection or believes that there are reasons to discourage any further approach, he/she can refuse to contact the donor.
- 11.7.11 The denial to proceed, **Form CD108**, motivated and expressed in writing by the DC/CC directors, is mandatory for the IBMDR and represents the final decision in the matter.
- 11.7.12 Not stimulated peripheral nucleated cell collection
- The applicable laws and procedures are defined in §11.6.
- 11.7.12.1 Donor medical and collection procedure evaluation.
- The DC is responsible for protecting donor safety, evaluating his suitability and for determining any infectious diseases transmissible by lymphocyte donation – Attachment B-I. The DC and the CC are responsible for the specific collection procedure requested by the TC.
- 11.7.12.2 Following the receipt of the “*Prescription for not stimulated human peripheral blood stem cell collection*” if the potential donor confirms his willingness to donate, the DC and the CC-P should complete the “*Verification of PBSC prescription*” **CD107-I form**.
- Licensed physicians of the DC and the CC-P must complete a medical evaluation in writing having evaluated the results of the following:
- routine laboratory tests (complete blood count, electrolytes, either urea nitrogen or creatinine, bilirubin, serum total proteins, etc.), infectious disease markers (Anti HAV IgG and IgM, HBsAg, Anti-HBs, Anti HBcAg, Anti HBeAg, Anti

HCV, Anti HIV 1 and 2, Anti CMV IgG and IgM, toxotest IgG and IgM, syphilis test, HCV NAT, HIV NAT, HBV NAT and, in a population at risk of infection, HTLV I and II) and ABO blood group typing performed within 30 days prior to the collection date;

- pregnancy test (if female);
- personal and familiar anamnesis;
- lymphocytes typing (optional but recommended): CD3+, CD4+, CD8+, CD19+, CD56+.

In the case of the donor's eligibility, the physician must proceed with the "*Lymphocytes donor clearance*" **Form CD104-I** that must be sent to the TC and to the IBMDR as soon as possible to organise the cell transportation and of the patient infusion.

11.7.12.2 The donor, if found eligible to donate, must express his/her willingness to continue the process signing the "*Final consent to donate*" **Form CD103-I**.

11.7.12.3 The collected donation product:

- must be validated by the DC/CC according to §11.6.15.2.
- can be released by the CC- **Form CP200-I**, before the validation results which must be sent to the TC as soon as they are available – **Form CD104-Q**.

11.7.12.4 The characteristics of the collected lymphocytes (unit identification code, nucleated cells parameters, volume) are certified by the CC-P with **Form CP201-I** that must accompany the lymphocytes bags. The microbiological test results must be made available to the TC and IBMDR as quickly as possible.

11.7.12.5 After the infusion, the TC must send the completed **Form CP200-I** and **Form CP201-I** to the IBMDR. The SIMTI Commission will evaluate the lymphocyte collection, referring to the minimal quality requirements.

11.8 Donor follow-up and subsequent donor contacts

11.8.1 Following the donation, the well-being of the donor must be ascertained by the DC physician. Specific forms (**Attachment A-fu**, **Form CD105**, **Form CD106**) are given to the donor in order to be informed, in writing, about his/her feelings and any eventual claims or complaints and to thank the donor.

11.8.2 Following the HSC donation, donor follow-up, medical examinations and clinical screening must be performed by DC/CC in accordance with the protocol "Follow-up of the donor", as specified in – **Form CD109**.

11.8.3 If the donor were to have any abnormal ailments, he/she should be referred to the appropriate medical structure for assistance. If the found abnormality could have an impact on the patient outcome, the TC must be promptly informed.

11.8.4 Contact with the donor must continue at periodic intervals until the donor is free of ailments.

11.8.5 Should the donor no longer be available for a further donation, the TC must be promptly informed.

11.8.6 The DC/CC must notify the IBMDR of any Serious Events and Adverse Effects (SEAR) connected with HSC/lymphocyte donation that may appear sometime after the donation, in order to inform the competent authorities.

- 11.8.7 These data will be transmitted to the SEAR Registry managed by WMDA in an anonymous way.
- 11.8.8 The donor could be anonymously contacted by the patient, through the IBMDR. – **Form CT313**.
- 11.8.9 The patient could be anonymously contacted by the donor through the IBMDR – **Form CD110**.

11.9 Donor protection

- 11.9.1 The prospective donor must be informed about the right to withdraw at any time. However, the donor must also be informed about the extreme risk for recipient's life if the donation is not carried out once the patient's preparative regimen has commenced.
- 11.9.2 No kind of pressure must be exerted on the donor at any stage of the search process.
- 11.9.3 The donor may only donate for a single recipient.
- 11.9.4 The TC may ask for the HSC collection only if the transplant is immediately performed, not for cryopreservation. Should particular donor/recipient conditions occur that a collection storage is necessary, the approval must be obtained from the IBMDR.
- 11.9.5 Once the donor has donated, he/she no longer has any right to the collected product.
- 11.9.6 In the event that the collected product is not totally infused in the recipient, it is possible to cryopreserve the exceeding quantity so that, if needed, it can be used only for the same recipient – **Attachment L-CSE**.
- 11.9.7 Italian or international donor identity must be kept strictly confidential to guarantee the donor's anonymity. Donor protection procedures must prevent unauthorised access in order to avoid donor/recipient linkage.
- 11.9.8 Donor identity must be known only to DC, RR and CC authorised staff.
- 11.9.9 Donor personal and genetic data must be separately stored in a place protected from unauthorised access. Access must be strictly allowed only to DC and/or RR authorised and qualified staff; for relatives and friends of a patient for whom there is an active search, access is not authorised in these areas.
- 11.9.10 In every search procedure step and in any communication between DC, RR, TC and the IBMDR, the donor must be tracked using a unique identification code.
- 11.9.11 HLA typing data may be transmitted to the donor according to the *Legislative Decree 30 June 2003* and may not be used for purposes other than those for which the donor has provided his/her consent.
- 11.9.12 The donor has the right to receive the results of their health screening.
- 11.9.13 The donor, who moved to a country where a donor registry exists, can request to his/her DC to move his data to the other registry – **Form CD112**.
- 11.9.14 Donor's identity must always remain anonymous (*Legislative Decree of 30 June 2003*) to patient or any third parties.
- 11.9.15 The donor maintains the usual salary during all the procedures necessary for the time needed for his/her commitment (registration, typing, medical examinations, etc). The pertinent certificate is provided by the DC's or RR's relevant department.
- 11.9.16 A donor with salaried employment has the right to have paid leave from work to complete:
 - a) A collection of blood sample for HLA tissue typing;
 - b) further HLA testing for donor/recipient matching;

- c) medical evaluation for approval to donate;
- d) administration of grow factors to mobilize HSC;
- e) follow-up controls post donation.

- 11.9.17 The donor has the right to receive the usual salary for the necessary days taken off from work for the HSC collection and for the necessary days to reach a complete health status recovery, to be certified by the CC's medical personnel.
- 11.9.18 A donor follow-up, even if no particular events have occurred, must be performed at established times (up to ten years for bone marrow and PBSC donation and up to 6 months for lymphocyte donation).
- 11.9.19 The volunteer who donated HSC, should not donate blood for at least one year.
- 11.9.20 According to the *Law n. 52 of 6 March 2001 art. 5*, a donor must not be charged for anything related to the procedure.
- 11.9.21 The Galliera Hospital, registered office of IBMDR, is responsible for offering disability and death benefits through an insurance cover for complaints of the donor following blood with-drawal, evaluation, workup and collection.
- 11.9.22 The adequacy of the liability insurance coverage must meet the international standards and guarantees by financial grants according to the *Law n. 52 of 6 March 2001 art. 10*.

12. CORD BLOOD UNIT

12.1 Definition

CBU refers to whole blood including haematopoietic progenitor cells, collected from placental and umbilical cord blood vessels after the umbilical cord has been clamped. The present standards refer to CBU collected for unrelated donation: that is CBU intended for infusion into another individual who is not biologically related to the donor.

12.2 Consent

The biological mother (or both parents if applicable, or the legal representative if the mother is underage) must be properly informed – **Attachment A-sco** - on different aspects of cord blood donation, the collection procedure and related risks and benefits, and must release a written, legally valid, informed consent – **Form SCO101**- for:

- collection and storage of cord blood unit;
- collection and storage of blood samples and DNA from the mother and from the CBU for future testing;
- use of maternal and/or CBU samples for infectious and genetic diseases and other testing, as applicable;
- release of personal and family medical history necessary for the CBU evaluation;
- repeat infectious disease tests between six months and one year after collection;
- use of CBU for an allogeneic transplant of an unrelated national or international recipient.

12.3 Eligibility criteria

The medical evaluation of mother/parents must be done in accordance with the national applicable laws and regulations. (Ministerial decree 3 March 2005, EC 206/17 Attachment I, 2006/17/CE Directive attachment I, M.D. 25 January 2010 and others).

The CBU is suitable for storage when:

- mother, father and family medical history has been obtained, documented and recorded with the purpose to detect genetic, infectious diseases or other risk factors for transmission of infectious disease – **Attachment B-sco** – and medical records of the pregnancy;
- a maternal blood sample, collected at time of delivery, has been tested by a Regional Health Authority accredited laboratory, to detect IDM according to national law and regulation. These are:
 - HbsAg;
 - Anti HCV;
 - Anti HIV 1 e 2;
 - Anti HBc;
 - Syphilis test;
 - HBV NAT, HCV NAT, HIV NAT;
- the TNC count prior to the banking of the unit is over or equal to 120×10^7 .

12.4 Characterization

The CBUs, which comply with requirements related to the storage (Standard 12.3) for unrelated allogeneic transplant, must be characterized with following tests:

- CBU volume collected and stored;
- TNC count at time of collection and at time of storage;
- neutrophil, lymphocyte, monocyte and platelet count in the cryopreserved unit (optional but highly recommended);
- HLA A, B (low resolution – 1 field) and HLA-DRB1 (high resolution – 2 fields) molecular typing performed by an ASHI/EFI accredited lab;
- ABO grouping and Rh typing;
- erythroblast count;
- total number of CD34 positive cells;
- viability and/or CD34+ positive cell viable and /or CFU;
- microbial cultures (to detect aerobic, anaerobic bacteria and fungi).

Furthermore, before releasing a unit, the following test results must be available:

- HTLV1 and 2;
- CMV (IgG and IgM);
- Haemoglobinopathy screening.

12.5 The CBU data are recorded in the IBMDR national database only if the CBU is suitable for storage (standard 12.3), has been characterized for the minimum set of tests required for the storage (standard 12.4) and complies with the national applicable Law and regulations.

12.6 The sending of CBU data to the IBMDR national database makes the CBU available for all national and international patients searching for an unrelated source of HSC.

13. COSTS AND RATES

13.1 Description and liability

Administrative procedures must be established in order to provide the best possible match for any patient in the world as rapidly as is feasible and, within limits, without financial considerations or constraints.

The best possible match is intended as the unrelated donor with immunogenetic characteristics that may allow a treatment with the highest chance of success.

The IBMDR, guarantor of the search procedure, must establish non-profit administrative policies for the economical coverage of the services requested in the

process. The Registry fosters a free exchange of donors without imposition of artificial barriers, to ensure donors are chosen on the basis of criteria in the patient's best interest (e.g. tissue type) and no other factors (e.g. prices).

The IBMDR is only responsible for the accuracy of its administrative procedures and is not responsible for the services performed by the RR, TC, CC and BSC.

13.2 Financial responsibility for the search

Following the *Law n. 52 of 6 March 2001 art. 3*, the cost of the tests performed for donor registration is covered by the pertinent Regional administration. The costs for HLA typing, blood samples shipment, prospective donor medical evaluation, HSC or other blood components collection and transport are covered by the patient, in the following cases:

- a) Italian donor/CBU for Italian patient;
- b) international donor/CBU for Italian patient;
- c) Italian donor/CBU for international patient;

The costs related to services requested on behalf of patients a) and c) are detailed in the IBMDR current fee schedule (available on webpage www.ibmdr.galliera.it).

The costs related to services requested on behalf of patients b) are detailed by the international registries' pertinent schedules of fees.

Any cost not standardised or, for any reason, not accessible through such a schedule of fees should be estimated and communicated in advance to the TC.

13.2.1 Italian patients (a,b)

The services requested by the IBMDR are covered by the regional health system where the patient resides.

The procedures for invoicing Italian or international donor search procedure costs are regulated and defined by the Italian interregional compensation (applicable *Testo Unico*).

Generally speaking, IBMDR pays all the costs invoiced by the Italian structures and by international registries, according to the pertinent schedules of fees.

13.2.2 International patients (c)

The services performed for international patients, are invoiced to the TC according to the charges established in the IBMDR fee schedule.

IBMDR is responsible for refunding the pertinent Italian structures (DC, RR, CC, CBB) for services carried out.

13.2.3 Patients in the charge of an Italian TC , but not covered by the Italian National Health Service

Before activating search procedures, the TC must clearly establish who covers the costs of the search and transplant (# 15.5.5). If the patient is not covered by the NHS, he/she should pay for the medical services received, following the IBMDR indications.

14. IMPORTATION, EXPORTATION AND TRANSPORT OF BLOOD SAMPLES AND HSC

14.1 General

In order to determine donor/recipient matching grade, donor/CBU biological samples must be sent to Italian or international structures for further histocompatibility testing. In the eventuality of a donation request, the HSC collection must be transported to the TC, in Italy or from/to abroad. The shipment of samples and HSC transportation must comply with the national and international applicable laws, the IATA regulations and the IBMDR/WMDA standards.

References:

- Ministerial Decree of 7 September 2000 “*Regulations on the import / export of human blood and its component for therapeutic, prophylactic and diagnostic use*”.
- Ministerial Decree of 3 March 2005 “*Characteristics and procedure for donation of blood and blood components*”.
- Decree Law of 6 November 2007, n.191 “*Implementation of the EC Directive 2004/23*”.
- Decree Law of 25 January 2010 “*Implementation of the Directive 2006/17/CE, 2006/86/CE, 2004/23/EC*”.

14.2 Blood samples

14.2.1 General

Importation or exportation, as well as the national shipments, of blood samples, serum or human plasma for diagnostic purposes do not need a preventive authorisation from the Ministry of Health. However, due to the material importance, procedures must be established in order to:

- ensure a fast transport and delivery;
- protect the medical, administrative and auxiliary personnel involved in the procedure, the couriers and the general population from infectious risks (Ministry of Health, ordinance n.16, 25 July 1994; Ministry of Health, ordinance n. 3. 8 May 2003).

Careful attention is required in the labeling of the blood sample, using only the unique identification code to track the donor.

14.2.2 Transport, importation and/or exportation of blood samples and its components for diagnostic investigations, do not need a prior authorisation from the Ministry of Health.

14.2.3 The courier is chosen by Galliera Hospital.

14.2.4 Packaging

- The tubes containing blood samples/DNA must:
 - be hermetically sealed, preferably of unbreakable material;
 - report the donor identification code, anticoagulant used and volume, DC physician signature (readable), collection date and time.
- when hermetically sealed, there must be no external traces of the content;
- the tube must be placed in an outer bag which is sealed to prevent leakage; absorbent material must be placed between the two containers and these must be of sufficient quantity to absorb all the content in the event of leakage;
- the second container must be placed in a rigid container with insulating properties in order to avoid damages by external agents.

14.2.5 Documentation and labelling:

- the **Attachment M**, stating the contents and the results of infectious disease markers, must be affixed on the second container; the document should not be easily removable;
- a copy of this attachment must be sent to the courier;
- following the *Legislative Decree 626/94, art. 75*, a biohazard label, conforming to model shown in **Attachment N**, must be affixed on parcels containing infectious products;
- in order to send non-infectious diagnostic specimens, the international agreements request that a specific label stating: UN3373 BIOLOGICAL SUBSTANCE CATEGORY B” is affixed to the external packaging.

14.3 HSC/LYMPHOCYTES

Importation/exportation of HSC or other blood components intended for transplantation are regulated by the current applicable *Law of 21 October 2005, n. 219* art 16.

The authorisation of importing/exporting of HSC or other blood components is released by the Ministry of Health, case by case, in accordance with the *Ministerial Decree of 7 September 2000, n. 248*, if the criteria defined in Attachment 3 of the above-mentioned Ministerial Decree are compliant.

14.3.1 The HSC/lymphocytes must be transported by a courier appointed by the IBMDR.

14.3.2 The courier is completely responsible for the transportation, which means it is responsible for:

- the care taken during the transportation;
- security, conservation and preservation of the HSC/lymphocytes from the CC or the Banks to the TC;.
- the choice of the most suitable way to transport the HSC;
- the identification of the best itinerary for performing the delivery of the product provided by the CC or CB Bank within the time indicated (#14.3.6.8, #14.3.7.2)

The courier must organise the transport and send the planned itinerary **Form C2** to the IBMDR and the TC at least one week before the scheduled collection date.

14.3.3 Severe and adverse events related with the collection, process and transportation of the HSC/lymphocytes must be notified by the DC/CC/CBB/TC to IBMDR in order to inform the relevant Competent Authority. These data, in an anonymous status, will be transmitted to the SPEAR World Registry, managed by WMDA.

14.3.4 Importation

14.3.4.1 The IBMDR must inform the analogous IR about the infectious disease markers and the clinical and haematological screenings to be tested, to abide by the Italian applicable law.

14.3.4.2 The TC performing the HSC infusion must inform the Registry providing the HSC, of the laboratory tests that must be enclosed together the shipped product.

14.3.4.3 Should the IR be unable to perform the requested tests, the TC must request a blood sample, through the IBMDR, to be able to timely perform the necessary tests.

14.3.5 Exportation

14.3.5.1 The IBMDR must inform the RR, providing the HSC, about the infectious disease markers and the clinical and haematological screenings to be tested to abide by the applicable law of the country importing the product.

14.3.5.2 The RR must supply the laboratory test documents, which must accompany the HSC shipment.

14.3.5.3 Should the RR be unable to perform the requested tests, they must send a blood sample to perform the necessary tests in time, in collaboration with the IBMDR.

14.3.6 Labelling, packaging, documentation and transport of bone marrow and PBSC HSC and donor's lymphocytes – **Attachment P-cl** and **Form C1**

- 14.3.6.1 The HSC must be placed into hermetically sealed plastic bags (at least two in case of bone marrow donation), each with the possibility of aseptic access.
- 14.3.6.2 Each bag must be labelled with the following:
- ✓ the specification of the content:
 - “HPC, Marrow” ;
 - “HPC, Apheresis” ;
 - “TC, Apheresis”;
 - ✓ UNI code of the unit;
 - ✓ donor’s IBMDR identification code (the bag must never be labelled with the donor’s name or surname or other personal data);
 - ✓ donor’s ABO grouping and Rh typing;
 - ✓ the Collection Centre physician’s signature (readable);
 - ✓ the anticoagulant used and the total volume collected;
 - ✓ collection date and time, including time zone;
 - ✓ recipient’s identification code;
 - ✓ a biohazard label if the donor’s product could be a vehicle of infectious diseases.
- 14.3.6.3 Each bag should be placed in an outer container, which is also sealed to prevent leakage. Absorbent material must be placed between the primary receptacle and the secondary one. The absorbent material must be sufficient to absorb the entire content of the bags, in the event of leakage.
- 14.3.6.4 The second container should be enclosed in a rigid container with insulating properties in order to avoid damages by external agents.
- 14.3.6.5 The outer container must be correctly labelled with the “Delivery note” **Form CP200** and **Form CP201**.
- 14.3.6.6 HSC or blood components must be shipped at a temperature from 2° C to 4 °C , and in any case below 10 °C unless different specifications have been received from the TC. Dry ice must never be used.
- 14.3.6.7 Due to the importance of the material being transported, the transport must be planned in order to ensure HSC delivery at recipient’s TC as soon as possible: every effort must be made to complete the infusion within 24 hours from collection time, and in no circumstances must it be completed, if possible, more than 36 hours after collection.
- 14.3.6.8 If HSC or blood components are transported by air, they must never be X-rayed when going through the airport security area. The HSC or the blood component bag may be shown to and eventually handled with extreme care by the authorities. The isothermal container may be X-rayed, but only if emptied first.
- 14.3.6.9 The courier must keep the HSC or the blood component container with him at all times, it cannot be loaded in the baggage hold of an aircraft and the courier must comply with the “*Technical requirements for transport of HSC for transplantation purpose*” – **Attachment T**.
- 14.3.7 Labelling, packaging, documentation and transport of CBU from a CBB to TC

- 14.3.7.1 Procedures for transport of cryopreserved CBUs shall be designed to protect the integrity of the CBU and the health and safety of personnel.
- 14.3.7.2 The transit time between the CBB and facilities should be minimal. Plans for alternative transportation in an emergency should also be made.
- 14.3.7.3 Cryopreserved units stored at a temperature below -150° C must be transported in a liquid nitrogen-cooled "dry shipper" that contains adequate absorbed liquid nitrogen and has been validated to maintain the temperature for at least 48 hours beyond the expected time of arrival at the receiving facility.
- 14.3.7.4 The dry shipper must contain a device that continuously monitors temperature throughout the shipment period.
- 14.3.7.5 The CBU bag must be labelled with the minimum number of details (partial label):
- ✓ the proper product name "HPC-Cord Blood";
 - ✓ the unique numeric or alphanumeric identifier of the cord blood unit and the identity of the CBB.
- Any bag bearing a partial label shall be accompanied by the full information (attached securely to the CBU on a tie tag or enclosed in a sealed package to accompany the unit) that comprehends:
- ✓ date of CBU collection;
 - ✓ name and volume of any additives including anticoagulant and cryoprotectant.
 - ✓ volume or weight of the CBU;
 - ✓ product modifiers;
 - ✓ ABO group and Rh type;
 - ✓ HLA phenotype and techniques used for typing;
 - ✓ number of nucleated cells;
 - ✓ gender of CBU donor;
 - ✓ recommended storage temperature in degrees Celsius;
 - ✓ recipient's identifier.
- 14.3.7.6 The dry shipper must be accompanied by the "Delivery note" **Form CB200**, **Attachment M-CBU**, **Attachment U-CBU** and **Attachment P-CBU**.
- 14.3.7.7 The shipping methods shall conform to existing regulations regarding the mode of transport of such devices (e.g. dry-shipper kept in a vertical position), **Attachment T-CBU**.

15. MINIMAL COMPATIBILITY CRITERIA

15.1 Adult volunteer donor

- 15.1.1 According to the IBMDR Standards, if there is not a specific protocol, a donor is considered compatible for a given patient when they match at least for HLA-AB specificities (molecular typing low resolution – 1 field - if it discriminates the pertinent serological splits) and DRB1 alleles (molecular typing high resolution – 2 fields -).
- 15.1.2 For all patients, younger than 66, affected by diseases indicated in **Table III - Category A**, it is possible to select a donor with one specificity mismatch, following the below stated criteria:

- a) patients younger than 19 mismatching one antigen for either HLA Class I (preferable) or HLA Class II;
- b) patients over 19 mismatching one genetic characteristic for HLA Class I (different allelic group or serological specificity) or for HLA Class II (only at allelic level). In this latter case it is requested the allelic matching (2 fields) at HLA-A, B and C loci.

15.1.3 At the time of the “*Final compatibility tests*”, the donor’s HLA – ABC, DRB1, DQB1, DPB1 loci should be defined by high resolution molecular techniques – 2 fields-. In case of TC’s specific request or in accordance with specific transplant protocols, the donor’s HLA typing can be extended to HLA-DRB3/4/5, DQA, DPA, DPB loci. The results must be reported in the **Form RC307 don.**

15.1.4 According to specific transplant protocols, approved by the pertinent IRB (International Review Board), the International TC may select donors on the basis of different compatibility, but the HLA matching criteria should not be less stringent than IBMDR minimal compatibility criteria.

15.1.5 In case of the selected donor has more stringent compatibility criteria, the final compatibility tests must be compliant with those requirements.

15.1.6 The *Final Compatibility tests* must always comply at a minimum with #15.1.3.

15.1.7 At the time of the “*Final compatibility tests*” the recipient’s HLA – ABC, DRB1 loci should be defined by high resolution molecular techniques and the results reported in the **Form RC307 rec.**

15.1.8 In the case of a donor being acceptable, the IBMDR must be informed in order to start the work-up on the donor.

15.2 Cord Blood Unit

15.2.1 According to IBMDR standards, for an Italian TC a CBU is considered compatible for a given patient when the antigen (molecular typing low resolution – 1 field - if it discriminates the pertinent serological splits) mismatches are, at most, two at HLA first class (A, B loci) or one at HLA first class and one at HLA-DRB1 alleles (molecular typing low resolution – 2 fields). It is possible to select a CBU with a HLA-DRB1 antigen mismatching if the difference is in reject direction.

15.2.2 The recipient’s HLA typing must be repeated at time of the “*Final compatibility tests*” before selecting the CBU for transplant, to confirm at least the minimal compatibility criteria (HLA-A and B low resolution if it discriminates the pertinent serological splits and HLA-DRB1 high resolution).

15.2.3 According to specific transplant protocols, approved by the pertinent IRB, the International TC may select Italian CBU on the basis of different HLA matching criteria.

15.2.4 In the event of a CBU being acceptable for transplant, the IBMDR must be informed in order to start the selection procedure of the CBU.

16. SEARCH PROCEDURE

- 16.1 A search of an adult donor or/and CBU is permitted for all patients who can benefit from a HSC transplant. When the curative effect of the HSCT can be considered certain and its indication proved, the disease is classified in the *Category A* of **Table III**. The disease belongs to the *Category B* when the benefit from a HSCT is not so certain; in this case the indication is not considered absolute but reasonable. **Table III**

- indicates the diseases and their characteristics in compliance with the indication to the HSC transplant.
- 16.2 An HSC transplant from an adult donor may not be allowed when the patient's disease belongs to the *Category C*.
 - 16.3 An HSC transplant from an unrelated CBU is permitted for the diseases indicated in **Table III**.
 - 16.4 According to specific transplant protocols approved by the pertinent IRB, the International TC may select donors and /or CBU on the basis of different criteria.
 - 16.5 If a preliminary search - **Form RC 300** - provides sufficient chances of finding a donor, a search may be initiated – EMDIS or **Form RC 301** - when:
 - 16.5.1 the disease fulfils the criteria listed in Category A or B of **Table III**;
 - 16.5.2 the patient must be under 66 years (over if a specific transplant protocol is followed);
 - 16.5.3 the patient, eligible for HSCT and aware of the possible risks, has signed an informed consent form;
 - 16.5.4 the patient is included in the waiting list of the designated TC;
 - 16.5.5 the financial responsibility for the search and transplant is clearly established.
 - 16.6 If the patient's disease or its descriptive parameters, do not belong to A or B categories of **Table III**, the search procedure can be activated only after receiving GITMO Commission approval.
 - 16.7 Any communication among the involved structures during the search procedure must be in writing and is regulated by IBMDR forms and reports.
 - 16.8 Any communications between the involved structures at all the search stages are to be mediated by the IBMDR. Only at the time of the adult donor or CBU final selection for transplant (*Prescription of HSC* or *Formal request for a cord blood unit shipment*) can the TC and CC/CBB be in direct contact. The IBMDR must still be copied into any communication.
 - 16.9 The HLA patient's typing, to be carried out by an EFI/ASHI accredited laboratory, must be complete with the HLA I and II class characteristics, having also completed a full typing on the patient's family.
 - 16.10 At the time of the search activation, the patient's typing must be a minimum of HLA A, B LR and DRB1 HR and reported in the **Form RC 301**. It is strongly recommended that the patient's HLA-ABC typing is performed by molecular techniques at high resolution.
 - 16.11 The HLA patient's typing must be confirmed on a different blood sample from the one used for the activating search HLA typing (§15.1.7).
 - 16.12 Registration must be reactivated along with a new consensus from the patient, if the search has been suspended due to the recipient's HLA mistyping or in the case of a patient's transfer to another TC.
 - 16.13 Search for an adult donor
 - 16.13.1 The TC will receive a full list of potential donors as the first response to activating search.
 - 16.13.2 It is possible to request “*DR typing*” on HLA AB compatible donors through EMDIS or by fax; the DC will carry out the test in low resolution molecular techniques – 1 field -; class I typing is not usually repeated at this stage.

- 16.13.3 The IBMDR does not normally list donors who are HLA-DR or HLA-AB mismatched with the patients. On specific request, IBMDR can provide the mismatched donor list.
- 16.13.4 “*Genomic typing*” on HLA-ABDR matched donors can be requested using EMDIS or **Form RC 305**. In this case, the DC performs the tests reported in (#11.5.7). At the same time, it is possible to request the A, B, C, DRB3/4/5, DQA1, DQB1, DPA1, DPB1 locus alleles definition, the donor’s IDM and blood group.
- 16.13.5 Before finally selection of an HSC donor, the TC must perform “Final compatibility tests” to confirm both patient and donor HLA typing. The TC may ask -EMDIS or **Form RC 306** - for a blood sample from an HLA - ABDR matching donor. At this stage:
- the IDMs, performed by the pertinent DC, are sent to the IBMDR which, in turn, are forwarded to the TC;
 - the TC must confirm donor typing (standard 15.1.3);
 - the TC must perform any other tests that are considered necessary for the transplant.
- The IBMDR will reject requests that:
- need a blood sample of more than 40 mL. (including the 10 mL necessary for performing the IDMs);
 - indicate a preferred shipping date of more than 30 days after the request date;
 - follow a non-contested shipment (e.g. deterioration, use of anticoagulant different from the requested one, etc.), on behalf of the same patient.
- 16.13.6 It is highly recommended that at least the HLA-DRB1 high resolution typing is also performed by the DC. In the case of a specific request, the sample for “*final compatibility test*” and the “*molecular typing*” on HLA-ABDR match donors can be requested at the same time. The examinations performed by the DC at this stage are listed in Standards 11.5.7 and 11.5.10.
- 16.13.7 The TC is responsible for sending the “*Final compatibility tests*” results to the IBMDR, within 50 days from the delivery of blood sample, indicating a decision on donor acceptability - EMDIS or **Form RC 307**.
- 16.13.8 If, within 3 months from the donor acceptability, the IBMDR has not received any communication, the donor will be released and will return to the active donor search file. Through a written communication, permitted once only, the RC can request another 90 days of reservation. If the TC asks for an HSC donation, it must send the relevant “*Prescription for the collection of HSC*” - **Form RC 308** and **Form RC 308-m / RC 308-p**.
- 16.13.9 The TC may ask for the HSC, only if the transplant is to be performed immediately. HSC cannot be cryopreserved.
- 16.13.10 The TC may require a PBSC donation if the patient meets at least one of the eligibility requirements established by GITMO Committee:
- the patient is over 18 years old and enrolled in a low conditioning protocol;
 - the patient is in an advanced phase of the disease;
 - the recipient has a greater body weight than that of the donor.
- 16.13.11 Further to the “*Prescription for the collection of HSC*”, if the donor is considered a fit candidate for the donation and confirms his/her willingness to

donate, the DC sends the “*Verification of HSC prescription*”, - **Form CD107** - and the “*Clearance of the HSC donor*”, - **Form CD104** - to the TC. If the donor is not fit or does not confirm his/her willingness, the TC should receive the “*Cancellation of stem cell collection*” **Form CD108**.

16.13.12 It is mandatory that the TC send the IBMDR the answer using the form “*Verification of marrow prescription*” - **Form CD107**, the “*Clearance of the HSC donor*”, - **Form CD104** - or the “*Cancellation of stem cell collection*”- **Form CD108**. It must be signed by all the relevant medical personnel.

16.13.13 The recipient’s conditioning regimen cannot be initiated without having received and accepted the “*Clearance of the HSC donor*”, - **Form CD104**.

16.13.14 The TC has to consider, where feasible before beginning the immunosuppressive regimen, the possibility of collecting the recipient’s stem cells for an autologous recovery, in the event of failure of the allogeneic HSCT.

16.13.15 The collected product can be infused even if the product qualification test results are still pending.

16.13.16 Where an excessive quantity of the collected product has not been infused in the recipient – **Attachment L-CSE** -, the TC must notify the IBMDR using the **Form CP201**.

16.14 Request of a CBU

16.14.1 At the moment of selecting a cord blood unit for the first time, a report containing the CBU available characteristics will be sent to the TC (Unit report).

16.14.2 The CBB must send the CBU report, including the results of the investigation performed at storage (Standard 12.3. and 12.4), to the IBMDR within 3 working days from this first selection.

16.14.3 The TC can request (through EMDIS or by fax) the “*Molecular typing*” on HLA matching CBUs, specifying which HLA loci should be typed and at which resolution level.

16.14.4 The HLA A, B, low resolution and DRB1 high resolution typing results must be sent to IBMDR within 15 calendar days from the request date. The request is no longer valid if the IBMDR does not receive the results within 20 calendar days. **Form CB307**.

16.14.5 If HLA A, B high resolution or any other HLA loci typing, the CBB must send the pertinent results to the IBMDR within 25 calendar days. The request is no longer valid if the IBMDR does not receive results within 30 calendar days **Form CB307**.

16.14.6 In the event of cancellation of the request, if the test is still in progress, the HLA results must be sent within the time specified above.

16.14.7 The CBU becomes “*required*” when the TC requests services on it.

16.14.8 This “*required*” status is maintained for 60 days. After this period and with no any other request from the TC, the CBU returns to the active search file.

16.14.9 The “*required*” CBU are visible in the national and international search files.

16.14.10 In the event of an initial match or after the compatibility tests the CBU is considered suitable for transplant, the TC can request to reserve the CBU which acquires the status of “*reserved*”.

16.14.11 The CBU is “*reserved*” for a period of 60 days. After 60 days, without any written request of extension, the reservation expires. Through a written

communication, permitted once only, the TC can request another 60 days of reservation.

16.14.12 The “*reserved*” CBU cannot be selected for other patients and are not visible in the national and international search files.

16.14.13 The TC may request the shipment of a CBU reference sample (DNA or cryopreserved blood sample, depending on availability) and/or maternal serum if available, only if the CBU is selected for transplant, having using completed the relevant form “*Formal request of a CBU shipment*” - **Form RC308 cb**.

16.14.14 Once the CBU sample has been received, the TC is responsible for sending the “*HLA typing results*” **Form RC307 cb**.

16.14.15 The selection for transplant of the CBU is completed by sending to IBMDR the “*Formal request of a CBU shipment*” – **Form RC308 cb** only after the recipient HLA typing confirmation by the TC has been completed as specified in #16.11.

16.14.16 Following the “*Formal request for a CBU shipment*” - **Form RC308 cb**, the CBB should send the “*CBU procurement schedule*”, - **Form CB107**.

16.14.17 Before the CBU shipment, the tests listed in Standards 12.3 and 12.4 must be completed. The CBB must also provide:

- QC results performed on the CBU attached segment
 - CB cells viability;
 - CB HLA typing to check the donor’s identity as well as to confirm the previous reported results (A, B LR and DRB1* LR) **Form CB307**;
 - CFU;
 - TNC count;
 - Total number of CD34 cells (not obligatory but highly recommended);

the CBB must communicate the acceptable ranges of QC validation, the date of the tests and the utilized method to the TC.

In the event that CBU attached segments are no longer available for testing, the TC must be notified well in advance so that plans can be made to continue or decline further pursuit of this CBU.

- Confirmation of the CBU identity and of inherited maternal haplotype, through HLA typing or through any other validated procedure, described in the CBB policies;
- mother and baby’s follow up, if it has not yet been carried out.

16.14.18 The above listed QCs must be scheduled by the CBB in order to communicate the pertinent results to the TC (**Form CB104**) before the CBU shipment (generally 15 days after the request).

- With the exception of HLA and cells viability, if the other QCs results are available only after the scheduled shipment date, the CBB must inform the TC as soon as possible.
- If a CBU segment is no longer available or the QCs have already been performed in the previous 12 months, it is possible to release the unit, without repeating them. The TC must be informed in advance so plans can be made to continue or decline further pursuit of this CBU.

- If the TC considers the transplant procedure to be urgent and there is not time to wait for QC results (with the exception of the CBU HLA typing and the confirmation of the donor’s identity), the TC must specify, in written, the urgent nature, taking responsibility for this decision and having obtained a specific informed consent from the patient. The urgent procedure must be notified to the CBB – **Form CT 306-cbu**.
 - No further tests are permitted on the donor after the collection of CBU. Any additional tests requested by the TC must be performed on the available maternal or CBU samples.
- 16.14.19 The CBB must send the “*Quality Control results*” - **Form CB104** to the TC before release of the unit and as quickly as possible.
- 16.14.20 The CBB must send the “*Cancellation of CBU shipment*” **Form CB108** to the TC if it is no longer possible to ship the CBU.
- 16.14.21 Every form and written communication must be signed by the competent supervisor/director and the IBMDR should be copied into every communication.
- 16.14.22 The recipient’s conditioning regimen should not be initiated before the arrival of the CBU at the TC.
- 16.14.23 Prior to the conditioning regimen of the recipient, a verification typing (low resolution for HLA-A, B and DRB1) must be performed upon reception of the shipped unit on a segment attached to the unit, if available. Otherwise this step can be performed after transplantation after thawing the unit – **Form RC307-cbu**.
- 16.14.24 Once the transplant has been performed, the TC must send the “*CBU released follow up*” - **Form CBU 201**.
- 16.14.25 Once an unrelated CBU has left the CBB premises it cannot be returned to the general CBB inventory. It is mandatory to communicate to IBMDR if the transplant has been postponed and, if the procedure is definitively cancelled, the unit must be destroyed. If the CBU is not infused the CBB must be informed using the **Form CBU 201**.
- 16.15 At any stage, the search procedure can be stopped by the TC through EMDIS, **Form RC310** “*Cancellation of search*”. The IBMDR is responsible for communicating, as soon as possible, the cancellation notice to the relevant DC/CBB in order to stop, where possible, the pending requests.
- 16.16 IBMDR must receive a new **Form RC301** to re-activate a search procedure. In the event of reactivation following failure of previous allogeneic transplants, the new application must be first submitted to the GITMO Commission.

17. REGISTRATION OF INTERNATIONAL PATIENTS IN THE IBMDR

- 17.1 The IBMDR can accept a request on the behalf of foreign patients only if it comes from a National Registry (Hub) or directly from an EBMT accredited TC, in absence of a National Hub.
- 17.2 Any preliminary enquiry and formal search request must be sent to the IBMDR though EMDIS or by using the appropriate **Form RC300 / RC301**.
- 17.3 The IBMDR is the sole intermediary between the TC and DC/CBB; all the communications must be addressed to the IBMDR, except for those specified in standard 16.8.
- 17.4 The TC, after having performed a HSCT using an IBMDR donor, must update the IBMDR about the patient’s health - **Form RC311**.

Table III – Indications for MUD BMT according to Disease category

Disease	Category A APPROVED	Category B EXPERIMENTAL	Category C NOT APPROVED
APLASTIC ANAEMIA	FANCONI Anaemia SAA (after an IS cycle for patient over 18)	Severe Aplastic Anaemia transplanted with a CBU	
ACUTE LEUKAEMIAS LYMPHOBLASTIC and MYELOGENOUS	Complete Remission	Refractory AML	Relapsed or refractory acute myelogenous leukaemia with peripheral blood blasts
CHRONIC MYELOGENOUS LEUKAEMIA	1 st CP, AP, 2 nd CP		In blast crisis
MYELOFIBROSIS Agnogenic Myeloid Metaplasia	All phases except the blastic transformation		In blast crisis
NON HODGKIN LYMPHOMA /CLL	Relapsed/ resistant to autologous and /or polichemotherapy	frontline	Aggressive lymphomas in real progression
HODGKIN LYMPHOMA	Relapsed/ resistant		Aggressive lymphomas in real progression
MYELOYDYSPLASIA	Risk medium/high		Low risk
MULTIPLE MYELOMA	Chemorefractory/stable, chemosensible relapse, after induction answer		Chemorefractory in progression
NEUROBLASTOMA	In accordance with approved protocol		
SOFT TISSUE SARCOMA		In accordance with approved protocol	
INHERITED DISORDERS	At diagnosis or in accordance with protocol (see enclosed list)		

Requirements for Categories

	Age	Required Match level	IRB approved protocol
Category A APPROVED	Up to 66	In accordance with the minimum IBMDR criteria	Not required
Category B EXPERIMENTAL	For patients ≥ 66 and < 70 an IRB approved protocol is required	In accordance with the approved protocol criteria	YES

INHERITED DISORDERS BELONGING TO CATEGORY A

A) PRIMARY IMMUNE SYSTEM DISORDERS

- 1. Severe Combined Immunodeficiencies (SCID)**
 - Reticular Dysgenesis
 - Adenosine Deaminase Deficiency
 - Absence of T and B cells SCID
 - Absence of T cells, Normal B cell SCID
 - Common variable immunodeficiency (CVI)

- 2. Severe Immunodeficiencies**
 - Immunodeficiency with polyendocrinopathy, enteropathy X-linked
 - X-LP Syndrome (Duncan Syndrome)
 - Omenn's Syndrome
 - Hyper-IgM Syndrome
 - Nucleoside Phosphorylase Deficiency
 - Deficiency associated with HLA Class II antigens expression
 - Shimke Syndrome

- 3. Syndromic Immunodeficiencies**
 - Wiskott-Aldrich Syndrome
 - DiGeorge Syndrome
 - Chediak-Higashi Syndrome
 - Nijmegen Syndrome

- 4. Phagocyte Disorders**
 - Agranulocytosis
 - Protein Adhesion Deficiency
 - Haemophagocytic lympho-histiocytosis (HLH)
 - Langerhans cells histiocytosis (LCH)

B) INHERITED DISORDERS

- 1. Haematological disorders**
 - *Diamond-Blackfan Anaemia
 - *Sickle-cell Anaemia
 - *Thalassemia Major
 - Congenital Discheratosis
 - Glanzmann Thrombasthenia
 - Congenital Amegakaryocytosis
 - Thrombocytopenia-Absent-Radius (TAR) Syndrome
 - Granulocytic chronic disease
 - Osteopetrosis

C) LYSOSOMAL DISEASES

- 1. Mucopolysaccharidosis**
 - Hurler Syndrome (MPS I H)
 - Scheie Syndrome (MPS I S)
 - Hunter Syndrome (MPS II)
 - Maroteaux-Lamy Syndrome (MPS IV)
 - Metachromatic Leukodystrophy
 - Globoid Cell Leukodystrophy (Krabbe disease)

- 2. Sphingolipids**

GM1-Gangliosidosis

3. Others

Farber Disease

Mannosidosis

Mucopolipidosis type II

Fucosidosis (Tay-Sachs Disease)

D) NON-LYSOSOMAL DISEASES

Adrenoleukodystrophy

** transplant protocols requiring different compatibility criteria from the standard. The CBU transplant requires an IRB approved protocol.*