



Italian Bone Marrow Donor Registry

Italian National Standards for Unrelated Haematopoietic Stem Cell Donations

Version XXII: March 18 2019



Document type:	Standards	Version:	XXII
Document Reference:	Standard ing mar 2019	Valid as of:	18 March 2019
Revised by:	RAQ IBMDR - SP	Approved by:	IBMDR, GITMO, SIMTI, AIBT , RR, ITCBN, CNT, CNS
Verified by:	IBMDR Director - NS		

0. Abbreviations
1. Program history
2. Generality
3. National Registries
4. The Italian National Registry
5. Regional and Interregional Registries
6. Criteria for participating Transplant Centers
7. Criteria for participating Collection Centers
8. Criteria for participating Recruitment Donor Centers
9. Criteria for participating Satellite Recruitment Centers
10. Criteria for participating Cord Blood Banks
11. Criteria for Histocompatibility Laboratories
12. Criteria for participating Tissue Establishments
13. Haematopoietic Stem Cell (HSC) Donors
 - 13.1 Definition
 - 13.2 Recruitment
 - 13.3 Donor selection
 - 13.4 First donation
 - 13.5 Second or further donation for the same patient
 - 13.6 Donor follow-up and contact after donation
 - 13.7 Donor protection
14. Cord Blood Unit
 - 14.1 Definition
 - 14.2 Consent
 - 14.3 Eligibility criteria
 - 14.4 Characterization
15. Costs and rates
16. Importation / exportation and transport of blood samples and HPCs
17. Minimal compatibility criteria
18. Search Procedures
19. Search activation on behalf of international patient

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
GRID: Global Registration Identifier for Donors
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
SEC: Single European Code
SPEAR: Serious Product Events and Adverse Reactions
SSN: National Health Service
TE: Tissue Establishment
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: GITMO, 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 (NCC), 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 register 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 the Law n. 52 - 6 March established the IBMDR recognizing the institutional value and assigning public funding to guarantee the continuity of the functions of national importance.

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:

- a) to coordinate and manage HSC UD searches from adult donors and/or CBU;
- b) 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.

Regarding personal data protection the following regulations are applied:

- Law Decree n.196 June 30 2003 “ Rules regarding personal data protection ”;
- EU 2016/679 Regulation “GDPR – General Data Protection Regulation”;
- Law Decree n.101 August 10 2018 “Disposition for adjustment of National Law to guidelines EU 2016/679 of European Parliament and of Council, of April 27 2016, related to natural person protection regarding personal data treatment, as well as free circulation of data which abrogate the guideline 95/46/CE”.

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 members of 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 GITMO.

4.1.5 The IBMDR must maintain, as electronic storage too, 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. Storing the data required for traceability purposes provides for a minimum period of thirty years after clinical use.

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 :

- collaboration with National competent authorities (CNT & CNS)
- network of Regional or Inter-regional Registries, Donor Centers, Recruitment Centers, Cord Blood Banks and Collection centers and Tissue Establishments;
- network of national and international Registries/Cord Blood Banks and/or TCs.

4.2.2 The National Commission for HSC transplant established by CNT Decree 15/05/2013 art. 14 DPR n.44 28/03/2013, three expert advisory Committees (established also to have a consultancy role and to implement proposals), boards of RRs and ITCBN must establish procedure guidelines that are ethically acceptable and technically appropriate.

4.2.3 Expert Advisory Committees are nominated by the AIBT, GITMO and SIMTI.

- AIBT Committee is designated by the pertinent scientific society and is composed of experienced in histocompatibility staff 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 promotes, evaluates and carries out genetic studies of the patient and of the potential donor populations (if it is involved more than a single regional donor population).
- GITMO Committee is designated by the pertinent scientific society and is composed of experienced haematologists working in public health structures and/or agreed upon SSN 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 defines the guidelines for marrow collection to prevent the donor health care.
 - ✓ 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 or holding documented and certified knowledge in the field.
 - ✓ Should be asked for an opinion on the eligibility criteria for the recruitment of volunteer donors and on exception in further phases.

- ✓ Should be asked for an opinion on the PBSC donation procedures and further donations.
- ✓ It reviews, manages and analyses donor clinical follow-up data.

4.2.3.1 The Committees have seven working days to provide their opinion in case of general requests and three days if the opinion is related to the pair donor-recipient. All the requests to be provided to Committees must be sent through IBMDR.

4.2.4 Boards.

The RR board is composed of:

- the Director of each RR;
- the Coordinators of the IBMDR Committees,
- the Director of the CNT-ISS,
- the Director of the CNS-ISS,
- the IBMDR scientific and administrative manager.

The ITCBN Committee is composed of:

- the Director of each BSC;
- the Director of the CNT-ISS,
- the Director of the CNS-ISS,
- the IBMDR scientific and administrative manager.

The Board meeting should be held at least once a year and each delegate could identify a substitute. The Board can request the participation of external expert consultants.

4.2.5 The external entity network responsibilities, activities, tasks, duties and functions are specified in this operation manual.

4.2.6 Detailed amendments to the IBMDR Standards can be proposed in writing by the Network of external entities. Before their becoming effective is necessary:

- the validation of the working group for standard review composed by a representative of IBMDR, CNT, CNS and three RRs, in office for two years (renewable for another two years) and elected during RRs Board;
- the approval of IBMDR, CNT, CNS, Advisory Committees, Regional Registries, ITCBN.

4.2.7 The associations collaborate with the Regional Registry and its functional joint, with IBMDR and with CNT to reach the purposes and modality stated in November 13 2018 Decree “*Criteria and strategy agreement between regions and independent province and associations of HSC adult donors*”.

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. Significant modifications to the computer system must be documented and to become effective must be approved by the competent Board.

- 4.3.4 The on-going backup and data restoration procedures must be appropriate, validated and documented.
 - 4.3.5 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.
 - 4.3.6 Personal data, medical and HLA data must be recorded separately.
 - 4.3.7 The IBMDR uses an histocompatibility referenced laboratory.
This laboratory must:
 - be accredited by the ASHI or the EFI for the required techniques;
 - guarantee full cooperation with analogous laboratories of the RRs.
 - 4.3.8 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, must be accredited by the WMDA, in the frame of the national accreditation program. In case of serious non-compliance with the operation manual it is possible that the certification is not extended to some of them.
- 5.1.2 The RRs, so as the IBMDR, must be compliant to what is stated in paragraphs 4.3.2, 4.3.3.
- 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 histocompatibility 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-I and II class HR 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 If the RR collaborates with more than one histocompatibility laboratory within the area of competence is its task to establish modalities and procedures for regional and interregional QC organization.

- 5.2.1.4 The RR may use DCs and/or RCs to maintain and enlarge the number of listed volunteers (potential donors).
- 5.2.1.5 The RR, it can also perform the DC function, elaborates strategies for the recruitment of new donors 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 functional collaborators;
 - it guarantees as well through its functional collaborators the participation of Associations in scheduling the recruitment activities and enrollment of HSC donors, in agreement with national plans and targets;
 - it defines the plans of technical-scientific information intended to HSC donation promotion;
 - it is responsible of organizing the recruitment *out door* events in regional areas scheduled together with the Associations;
 - it is responsible for training and maintenance of the expertise of health volunteer staff of Associations.
- 5.2.1.6 HSC collection must be performed by CCs.
- 5.2.1.7 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* (# 13.4);
 - 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 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 Definition

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 and/or healthcare provider covered by the SSN and authorised by the Regional Health Authority to perform allogeneic HSCTs from unrelated volunteers. They must be accredited 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 and/or healthcare provider covered by the SSN and authorised by the Regional Health Authority to perform allogeneic HSCTs from unrelated volunteers and that must also be recognized 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 in the program 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 histocompatibility 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, DC 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 informed patient’s consent in writing before starting a potential UD and/or CBU search - **Form RC302**.
- 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 update patient health status and follow-up in Promise 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 All communications between the TC and the RR are to be mediated by the IBMDR.
- 6.11 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 are responsible of procedure and collection of HSC/lymphocyte from unrelated donors.

They must be compliant with the National guidelines and IBMDR/WMDA Standards. Compliance with minimal criteria JACIE is strictly recommended. In details CCs must:

- have appropriate spaces dedicated to donor evaluation and collection procedure;
- have a location which guarantee immediate donor support in case of emergency;
- be managed by a physician who can prove at least one year of documented experience in the specific field and having done or supervised at least 10 allogenic collection procedures.

Furthermore in collaboration with RR/DC

- guarantee the donor safety;
- collaborate in medical procedures for evaluation and verification of donor suitability and eligibility (**DC104 Form, DC108 Form**) ;
- contribute to the “ *Verification of marrow prescription*” **DC107Form**.

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 allogenic 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. To maintain the accreditation the collection center must perform at least 1 allogenic collection per year over the past three years. The release of the **Form CP222-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 **TE201-m Form**.

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 the public blood banks, authorised to perform aphaeretic procedures from adult donors. The CC-P could also be differently located if operates under the Responsibility of the blood bank of reference and in presence of a written agreement and written procedures between the involved parties.
- 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);*
 - Law 219, 21 October 2005 art.2 and art.3 “*New guidelines for transfusion activities and blood hemocomponent 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.*”
 - The “*Agreement between the Health Department, the Regions and the Autonomous Provinces of Trento and Bolzano upon the minimal organizational, structural and technological requirements for the public blood banks, aphaeresis units and upon the model for the on-site inspection*” (Actions of the Cabinet – 16 December 2010, n.242).
 - Ministry Decree November 2 2015. “*Regulation on quality requirements and safety of blood and blood hemocomponents*”.
- 7.2.3 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.
- 7.2.4 Applicant centres must have performed a minimum of ten collections of HSCs from peripheral blood (allogenic) in the twelve months preceding their application, in accordance with JACIE requirements. To maintain the accreditation the collection center must perform at least 10 collections per year over the past four years.
- 7.2.5 The continual maintenance of the requirements is ensured through periodic revisions of the **TE 201-p Form**.

8. CRITERIA FOR PARTECIPATING DONOR CENTERS (DCs)

- 8.1 It is highly recommended, respecting the organisational autonomy of the individual regions, that a limited 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 duties;
 - ✓ have access to the following facilities:
 - a transfusion service accredited and authorized 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 IBMDR/GRID 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 Centre is responsible for storing all the data, even in electronic form, to ensure the traceability of all steps related to the donation process from donor to recipient and viceversa for a minimum period of thirty years after clinical use or for ten years since the donor loses the conditions to maintain enrolment in the Registry.

8.5 The DC :

- must have an EFI/ASHI accredited histocompatibility laboratory for I and II class HLA high resolution typing of UD, which ensures the accuracy of the genetic data required at donor registration or during potential donor selection procedure;
- is Responsible for the donor HLA data and for updating and transferring them to the national database;

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 # 5.2.1.6.

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 together with DCs can identify structures to function as Satellite Recruitment Centres (RCs) **Form PR111**. The number of the identified RCs is established by the RRs following local need and criteria in order to facilitate citizens' access to recruiting program.

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:

- ✓ must be located within a transfusion medicine service, a part from pre-existing entities;
- ✓ must have proved experience in recruiting and managing donors, in medical selection and in protecting donors' privacy;
- ✓ 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 RC must operate following the technical instruction of the DC/RR of reference and should be regularly audited by the DC/RR.

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

- 1) donors recruitment;
 - medical evaluation;
 - donor identification;
 - peripheral blood sample drawn.
- 2) blood sample shipment for verification typing (only if RC is located in a transfusion medicine service).

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 - **Form SCO111** act according to:

- Law Decree November 2 2015 “ *Disposition related to quality and safety requirement of blood and hemocomponent*”
- 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*”;
- Law Decree November 18 2009 stating “ *Establishment of a national network of banks for cord blood preservation*”
- the ASR – 29 October 2009 n. 184 “*Organizational, structural and technical minimal requirements for acting as a public cord blood bank*”;
- Law Decree 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 Histocompatibility 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. CRITERIA FOR HISTOCOMPATIBILITY LABORATORIES

The histocompatibility laboratory must operate in compliance with technical procedures, the operation manual of IBMDR, WMDA and following the operative instructions of the functional centers of IBMDR network and/or UD TCs.

It must be accredited by International Societies, such as EFI and /or ASHI, for Haematopoietic Stem Cell Transplantation (Donor Registry, Related/Unrelated donor Typing, Cord Blood) for HLA-I and II class HR typing and perform and pass the relevant national or international quality controls.

The histocompatibility laboratory provide services to the Regional Registries, Cord Blood Banks and TCs for the functions described below.

11.1 HLA typing - on behalf of IBMDR network:

- of potential adult donor for registration in IBMDR database;
- of Cord Blood Units and mother for the ITCBN network;
- of adult donor or Cord Blood Units for extended HLA typing;
- of the Cord Blood Units to confirm identity and previous typing before release it for transplantation;
- of adult donor after further HLA investigation for requalification;

11.2 HLA typing - on behalf of Transplant Centers:

- of hematological patient and its relatives;
- of hematological patient to start an UD search;
- of UD selected for VT and, if requested, of KIR genes;
- of cord blood units selected for transplantation.

It can also be a reference for:

- the analysis of familiar study and phenotype/genotype for hematological patients run to an UD search;
- evaluating the compatible match donor/patient;
- evaluating the DSA: donor-specific antibodies;
- evaluate post-transplant chimerism.

11.3 The histocompatibility laboratory must use the IBMDR computerised system to enter or update HLA typing data in the national database.

12. CRITERIA FOR PARTICIPATING TISSUES ESTABLISHMENTS

12.1 Definition

A “Tissue establishment” (TE), for the areas of application of these standards, is the laboratory/the processing unit covering the processing, preservation, storage and distribution of hematopoietic progenitor cell products and lymphocytes, (as defined in article 3 point Q) D.Lgs. November 6 2007, n.191 (GU n. 261 del 9-11-2007 - Suppl. Ordinario n.228), for clinical use and purpose of a hematopoietic transplantation **Form TE444**.

12.2 The processing unit operates:

- in the field of HSC and lymphocytes, Law Decree January 25,2010 , n.16 (G.U. Serie generale - n. 40) and smi, Agreement between the Health Department and Regions July 10,2003 n. 1770 and its subsequent amendments and FACT-JACIE Standards;
- in cooperation with the IBMDR network is responsible for ensuring the traceability of HPC products and lymphocytes in compliance with the regulations in force regarding cells and tissue codification.

12.3 The TE of the Collection Center operates with the following functions:

- performance of product quality and sterility controls;
- SEC assignment to collected product;
- labelling with SEC;
- distribution to Transplant Centers.

13. ADULT HAEMATOPOIETIC STEM CELL DONORS

13.1 Definition

13.1.1 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;
- can be enrolled at any functional center of IBMDR network, at the outdoor events or through a pre-recruitment web application specifically designed by IBMDR;
- could donate HSC for a maximum of three donations for a related and/or unrelated;
- could not be recruited if he/she donated for a related patient still alive or if already enrolled, he/she must be defined unavailable.

13.2 Recruitment

The recruitment must be done by health personnel of IBMDR Recruitment Centers qualified in informing and educating volunteers, in applying confidentiality rules, in medical selection and clinical counselling. The training of this personnel must be documented. The personnel must operate in compliance with the DC procedures, the national law and with IBMDR standard. The outdoor events – **Attachment out door** - of recruitment and collection of biological samples of HSC adult donors by buccal swab can be done by volunteer health personnel (doctors, nurses) of Associations involved in the fields, qualified and recognised by a training approved by the Region/province. It is possible to involve other health personnel, limited to biologists, adequately trained in pre recruitment counselling activities. The training is organized by the Regional Registry with the support of Donor Centers using expert personnel in donor selection preferably working in a Transfusion structure.

13.2.1 Informed Consent

The potential donors must be properly informed about the correlated risks and give a fully informed written consent to be recruited in the Registry in case of a future donation and to the use of their personal and genetic data.

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

13.2.1.2 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.

13.2.1.3 The health evaluation questionnaire can be distributed and undersigned also by health staff not physician (nurses, biologists) but adequately trained. The declaration of the donor's eligibility is responsibility of a physician, it may be following the initial consent.

13.2.1.4 The donor should sign the “*Donor Initial Consent*”- **Form DC101** - acknowledging that he/she has been informed about:

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

- the importance of his/her commitment;
- the importance of maintaining the donation anonymous, voluntary and without remuneration.

13.2.1.5 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.

13.2.2 Donor eligibility

A medical evaluation and the eligibility of the volunteer donor must be performed at every meeting, to verify donor eligibility.

13.2.2.1 The eligibility criteria for a prospective donor must fit the Italian transfusion and cells and tissue regulation with reference to definitively criteria of exclusion. Donor health issues not yet regulated by the above reference law, could be assessed according to the WMDA recommendations.

13.2.2.2 The requirements defined by Italian law for transfusion and for tissue and cells are indicated in **Attachment G**.

13.2.2.3 To evaluate the potential donor eligibility at recruitment must be fulfilled the requirements defined by **Attachment G – iscr** . With regard to the temporary exclusion criteria, provided for blood donors by the current legislation to protect the patient, these are not always applicable during the recruitment phase in relation to the fact that the period of suspension is generally exceeded by the time interval that is between the recruitment of the donor and his selection for the donation. Otherwise the same criteria for temporary exclusion should be taken into consideration in close proximity to the donation. No exception to donor eligibility criteria is allowed to protect the donor healthcare.

13.2.2.4 The donor must be under 36 years of age when joining the IBMDR, with the exception of subjects already typed for related.

13.2.2.5 No blood sample can be taken from a pregnant donor at time of recruitment by IBMDR.

13.2.2.6 Donors must be free from physical or psychic diseases considered as an obstacle to donation.

13.2.3 Characterization

The HLA typing must be carried out by the histocompatibility laboratory in compliance with the national regulations, as well as the IBMDR standards and international standards (WMDA e EFI/ASHI).

13.2.3.1 Biological materials (blood, saliva or buccal swab) could be collected for tissue typing only after the donor consent is given.

13.2.3.2 The peripheral blood must be drawn at RC or DC. However, it is allowed to draw blood in a different location (eg: events in the square) as long as in presence of documented facilities ready to intervene in case of adverse reaction, in formal agreement with the DC of reference.

13.2.3.3 The peripheral blood draw can be done by health care professionals (nurse or physician) or biologists in service at the facilities of the National Health Service with appropriate training and technical-practical skills acquired and certified. The saliva sample and/or buccal swab are generally carried out by the recruited donor, properly trained by the personnel; in this case the presence of specific facilities for the treatment of adverse reactions is not required.

13.2.3.4 The recruited donor is typed for the HLA-ABC, DRB1 and DQB1 loci – the latter is optional but strongly recommended - (by high/intermediate resolution molecular techniques – 2 fields - with possible use of WHO nomenclature with G/P and indication of rare ambiguities)- Donor data

(including weight, number of transfusions and pregnancies – if female) are then registered in the national database.

13.2.3.5 Donor blood group typing must include at least ABO grouping and Rh typing (recommended at time of recruitment).

13.2.3.6 It is strongly recommended the anti-CMV (IgG) antibodies test at donor enrollment.

13.2.4 Donor enrollment in National Registry database

13.2.4.1 The data entry in the IBMDR database completes the enrollment of the donor, who will be available to national and international patients in search.

13.2.4.2 The personal data are entered by the DCs, using the tool provided by the IBMDR, within 7 working days from the signing of the informed consent.

13.2.4.3 The HLA typing data are inserted are entered by the DCs, using the tool provided by the IBMDR, within 60 working days from the signing of the informed consent.

13.3 Donor selection

13.3.1 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.

13.3.2 The health personnel of the DC must verify that the identity and data of the donor correspond with the IBMDR/GRID code before a recall for further tests for biological samples.

13.3.3 The DC, at every recall for further tests, is responsible for ensuring that the donor meets the recruitment standards by Law and indicated in **Attachement G** (for example an eventual pregnancy status). If the donor eligibility criteria (protecting the patient) does not fulfil the requirements, the TC must be informed.

13.3.4 The eventual unreachable or unavailable status of the donor should be reported to the Registry within 20 days after the selection date.

13.3.5 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.

13.3.6 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.

13.3.7 When an HLA –ABDR matched donor is selected for “*Molecular typing*”- EMDIS or **RC305 Form** - the DC must provide, using a fresh blood sample:

- ✓ high resolution molecular typing – 2 fields - of HLA-DRB1 with possible use of WHO nomenclature with P alleles;

- ✓ other loci HLA typing if requested by the TC;

The donor center must provide also the following information:

- ✓ donor weight;

- ✓ number of pregnancies (if female);

- ✓ number of transfusion.

13.3.8 An HLA –ABDRB1 matched donor could be selected for:

a) “*Molecular typing*”- EMDIS or **RC305 Form**. The DC must provide, using a fresh blood sample:

- ✓ high resolution molecular typing – 2 fields - of HLA loci requested by the TC;

- ✓ ABO, Rh and CMV status (IgG and IgM– if not already reported IgG positive) if requested by the TC;

- b) “*Infectious disease markers*” – EMDIS. The DC must provide, using a fresh blood sample: syphilis test, anti-HCV, HbsAg, anti-CMV IgG and IgM (if not already reported IgG Positive), anti-HIV 1-2;
- c) ABO, Rh and CMV status and/or anti-CMV IgG and IgM (if not already reported IgG Positive),

The donor center must provide also the following information:

- ✓ donor weight;
- ✓ number of possible pregnancies (if female);
- ✓ number of possible transfusions.

- 13.3.9 The requested 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.
- 13.3.10 If the TC cancels the HLA typing request, the HLA lab must provide the results no later than 30 days of the request date.
- 13.3.11 After the typing, if the volunteer is still a potential matched donor, is selected for the patient for 15 calendar days.
- 13.3.12 Having received the “*Blood sample request*” – EMDIS or **RC306 Form** - in order to be able to perform the “*Final compatibility tests*”, the DC, must provide or organise:
- ✓ a new health questionnaire and 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 if not already reported IgG positive, anti-HIV 1/2) and ABO – Rh typing (if not already reported);
 - ✓ donor’s weight, number of possible transfusions and number of possible pregnancies (if female);
 - ✓ the blood sample shipment.
- It is strongly recommended an evaluation of the peripheral venous accesses (in case of inadequate access, the transplant center must be informed).
- 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.
- 13.3.13 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.
- 13.3.14 If the TC cancels the shipment request, if not already shipped, an invoice cannot be issued.
- 13.3.15 The IDM results must be anonymous, identified by a donor code/GRID.
- 13.3.16 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.
- 13.3.17 The final histocompatibility testing is performed by the TC HLA lab. The HLA typing results - **RC307 don Form** - 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.
- 13.3.18 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.

13.3.19 The DC is responsible for informing the donor about his/her selection status, basing the decision on:

- ✓ the compatibility tests performed as described at #13.3.6, 13.3.7 and #13.3.8 and compared to the “minimal compatibility criteria” ;
- ✓ the indication on **RC307 don Form**;
- ✓ the unsuccessful receipt of **RC307 don Form** within the indicated time.

13.3.20 If a pre-collection 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.

13.4 First donation (bone marrow/peripheral blood stem cells collection)

The applicable laws and procedures are defined by:

- 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.*”
- 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.*
- Ministry Decree November 2 2015. “Regulation on quality requirements and safety of blood and blood hemocomponents”.
- The operative procedure “*Management of allogeneic Peripheral HSC donor not mobilizing*” approved by GITMO, IBMDR, CNT, CNS, SIMTI e SIDEM.

13.4.1 The donor work-up schedule and donation procedure

13.4.1.1 Following the receipt of the “*Prescription for stem cell collection*” if the potential donor confirms his willingness to donate, the DC together with CC (preferably identified nearby the donor location) must fill in the “*Verification of stem cell collection prescription*” **DC107 Form** - for the HSC source agreed with donor and TC. The DC and the CC must notify the TC and the IBMDR of any withdrawal/ineligibility to donate **DC108 Form**.

13.4.1.2 The donor work up must be performed within 30 days from the collection date.

13.4.2 Medical evaluation and suitability to donation

The physical examination and the suitability to donation must be performed by a team with experience in transfusional medicine and PBSC/marrow donation, identified by the DC, which is not the team that takes care of the patient.

13.4.2.1 Donor medical evaluation

The DC is responsible for protecting donor safety, evaluating his suitability to donation and for determining any infectious diseases transmissible by HSC donation. - **Attachment B-WU**. Therefore it requires a careful personal and family medical history.

13.4.2.2 The volunteer must fulfill the minimal Law requirement for blood, cells and tissues donation and to be enrolled as a HSC peripheral donor must:

- not be on lithium treatment;
- not shown splenomegalia;
- not shown events of artery or venous thrombosis;

- not shown events of iritis or episcleritis;
- not shown drenopanocitic *trait*;
- have peripheral venous access suitable for apheresis drawn of long time and effort

The administration of antiplatelet drugs is not an absolute criteria of exclusion from the CSE donation but the decision must be taken case by case.

13.4.2.3 If the donor eligibility criteria does not fulfil the requirements defined by Italian law for patient protection, the DC and the CP can proceed with an exception only if the donor healthcare is protected - **Form DC107-d**. The TC and the patient must be informed and must agree to proceed. When the exception from the eligibility criteria concerns the protection of the donor, the DC should submit the case to the SIMTI committee.

13.4.2.4 Suitability to donation

The DC and the CC are responsible for protecting donor safety, evaluating, if necessary requesting and external expert advice, the donor suitability for both source of stem cell collection. The anesthesiologic risk related to marrow donation must be carefully evaluated from the anesthetist following the classes of risk established by *American Society for Anesthesiology* – ASA. Class of risks are indicated in **Attachment F**. It is always required an assessment of the donor venous accesses by the CC-P even in case of a bone marrow donation (if not suitable, the TC must be informed).

13.4.3 Clinical, instrumental and diagnostic examination pre-collection are described in **Attachment WU**

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

13.4.4.1 A representative of the DC and/or RR, a representative of the CPs involved and at least a haematologist and a transfusionist, expert in HSC donation, must be present at the final donor information session.

13.4.4.2 In the final session, the prospective donor must be given detailed information about further tests to be carried out, the type of HSC source requested from TC, the procedure of HSC donation, its risks and the period of time which he/she may have to commit.

13.4.4.3 It is strongly recommended that donor's personal physician or a close person of the donor, by choice of the donor, be present in this informative session.

13.4.4.4 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.

13.4.4.5 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 of commitment;
- the possibility that in case of poor mobilizing with G-CSF/HSC poor collection it is possible the use of Plerixafor as a way of saving the donation – **Attachment H-PL**;

- the possibility that, in case of complication with the scheduled HSC collection, it may request an immediate HSC donation from an alternative source;
- 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 donation is anonymous and donor identity must not be transmitted to recipient or to their family and viceversa.

13.4.4.6 Copies of documents and minutes of the informative session shall be stored at DC and CC.

13.4.5 Eligibility/suitability to donation statement

The DC and CP-M and CP-P physicians must report, in writing, the result of their evaluation. In the case of the donor's eligibility, the physicians must proceed with the "*Notification of the Donor Final Clearance*" - **DC104 Form** - that must be sent to the TC and to the IBMDR before the beginning of the recipient's preparative regimen.

Otherwise the DC, in accordance with the CC, must notify the TC and the IBMDR of any inability to clear the donor **DC108 Form** and, in the event of definitive deferral, remove him/her from the prospective donor panel.

The DC and CC should also provide to IBMDR a detailed relation to be evaluated by a Commission represented by: IBMDR, CNT, CNS, GITMO-MUD, SIMTI, SIDEM.

13.4.5.1 In case of donor unavailability or unsuitability to both source of donation, the TC must be informed in advance, since it will not be possible the back-up donation, if necessary.

13.4.5.2 Should a PBSC donor result no longer available for the bone marrow donation or available for the use of Plerixafor, the collected product could be cryopreserved by the TC.

13.4.5.3 Should a bone marrow donor result unsuitable or be no longer available for the PBSC donation, the collected product could be cryopreserved by the TC with the authorization of the Advisory Boards.

13.4.6 Final consent

The donor, if eligible to donate, expresses his/her willingness to continue the process signing the "*Final consent to donate*" **Form CD103**.

The "*Final consent to donate*" information concerning the possibility of further donations for the same recipient, must be given to the donor and must indicate:

- the availability of the donor for further donation for the same patient;

and, if requested by TC, it should be extended, in case of donor availability, to:

- donate further biological sample for purposes different from transplant;
- participate in an experimental transplant protocol;
- cryopreservation of collected product, previously authorized.

13.4.7 Communication between DC, CC and CT

13.4.7.1 The DCs/CCs and TC are in direct contact; copy of every communication must be sent to IBMDR knowledge.

13.4.7.2 Before initiating the preparative regimen, DC, CC and TC must agree upon:

- the volume and the quantity of HSC and sign the “*Verification of stem cell/lymphocyte collection prescription*” - **Form DC107**
 - the schedule of the collection procedure and sign the “*Notification of the Donor Final Clearance*” - **Form DC104.**
- 13.4.7.3 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.
- 13.4.7.4 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.
- 13.4.8 HPC collection procedure (Attachment P-cl)
The collection:
- can take place only if clinical condition and current patient disease status at “*Prescription for stem cell collection*” do not exclude transplant,
 - must be done at CC involved, who participated to the final information session;
 - it is recommended that takes place in a different structure from the recipient TC;
 - may not be initiated if the delegated courier has not communicated the itinerary – **Form C2** - and has not notified the CC of his arrival.
- 13.4.8.1 Marrow collection (Attachment L)
- 13.4.8.1.1 Prior to blood marrow collection, the donor must have autologous blood units drawn, with an interval of at least 7 days among the collected units; the last unit should be collected at least 7 days prior to HPC collection. The number of pre-collected units depends on the marrow volume that the donor, according to the DC/CC-M physicians, can safely donate.
- 13.4.8.1.2 During collection and, if necessary, after the donor is transfused with pre-collected autologous blood.
- 13.4.8.2 Peripheral blood stem cells collection after stimulation
The administration of G-CSF, the evaluation of possible side effects and the accuracy of the clinical follow-up are described in **Attachment R.**
- 13.4.8.2.1 The CC-P is Responsible of the G-CSF administration procedure and the HPC collection;
- 13.4.8.2.2 The administration of G-CSF shall be under the supervision of a licensed health care professional (identified by the CC-P) experienced in their administration and management of complications in persons receiving these agents;
- 13.4.8.2.3 In case of self-administration of the drug at least the first dose must be administered at suitable health facility and the donor must be informed of the procedure to be followed.
- 13.4.8.2.4 Donor receives G-CSF, subcutaneously, at a daily maximum of 10µg/Kg donor body weight. To date, there is not yet enough data to recommend routine use of the biosimilar G-CSF, however, its use is recognized as

appropriate in the absence of an alternative. In this case careful monitoring of the donor is recommended to identify any collateral effects due to biosimilar.

13.4.8.2.5 In no case, is the use of a central venous catheter allowed;

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

13.4.8.3 Management of PBSC donor not mobilizing

The use of Plerixafor administration, donor management and eventual side effects are described in **Attachment R-PL**.

13.4.8.3.1 The growth factor administration must be done by an expert doctor (identified by CP-P), responsible of the control and management of possible side effects and possible complication due to treatment, a donor consent is mandatory (**Form CD103-PL**) together with Transplant Center consent (**Form CT302-PL**).

13.4.8.3.2 Plerixafor is given, by subcutaneous way, a unique dose of 0,24 mg/Kg of donor weight on the evening of fifth day of G-CSF treatment, following CP-P indications. Auto-administration is not allowed.

13.4.8.3.3 PBSC collection is performed following the standard procedure as for mobilizing PBSC collection with G-CSF.

13.4.8.3.4 Once collected, all the data regarding mobilizing procedure and collection must be send to IBMDR - **Attachment S2-PL**.

13.4.9 Validation of the HPC collected product

The collected HPC product (BM/PBSC) must be validated by the DC/CC, performed on peripheral blood sample obtained at donation or within 7 days before the donation, according to the national law and regulation.

13.4.9.1 The following exams must be performed, at authorized laboratory for esecution of biological qualification examination in compliance with organization procedure:

- Anti-HCV;
- HBsAg;
- serological test for combined search of Anti HIV 1 and 2 antibody and HIV ;
- Syphilis test;
- HIV/HBV/HCV NAT;
- ABO and Rh blood group.

13.4.9.2 The biological product qualification text results must be sent to the Transplant Center before the infusion begins - **Form CC104Q** - if this is not possible, the Transplant Center must be promptly informed.

13.4.9.3 The product can be released from the CC to the TE and from the TE to the TC even if the biological qualification tests are still ongoing.

13.4.10 Quality controls of the collected product

The HSC unit is transferred from the CC to the responsible TE that will assign the SEC, will perform cultural examinations and will provide collection details (product cells count, volume, etc..) through **Form TE201**. The cultural exams results done must be communicated to the TC and IBMDR as soon as possible.

13.4.11 Distribution/traceability of the collected product

13.4.11.1 The TE will deliver the collected unit to courier assigned for transport together with the complete accompanying documentation – **Form TE200**, **Form TE201** and **Form CC104Q**, the last one if already available from DC/CC.

13.4.11.2 Once transplant will be performed the TC should provide **Form TE201** completed to IBMDR and DC.

13.4.11.3 The DC should provide the documentation to CC and TE.

13.4.12 Monitoring of the quality of the collection products

The compliance with the quality requirements of the collected products is evaluated by GITMO MUD and SIMTI Committees, each for its own competence, based on the reported data in **Form TE201** and/or IBMDR other forms.

13.5 Second or further donations for the same recipient

13.5.1 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, for DLI (Donor Lymphocyte infusion) or HSC (PBSC or bone marrow) in the case of non-engraftment or of poor graft function.

13.5.2 All the donation requests must be submitted to the GITMO MUD Committee.

13.5.3 Any direct contact between the TC and the donor is strictly forbidden.

13.5.4 The donor, who has already donated HPC-marrow can only be submitted again for marrow HPC collection, if at least 6 months have passed since the first donation or peripheral HSC if at least 45 days have passed (in the case of non-engraftment), 3 months (in case of poor graft function) or 6 months (in case of remission post relapse) since the first donation.

13.5.5 The volunteer, who has donated HPC-apheresis can only be submitted again for growth factor stimulation for HSC mobilization, if at least 12 months have passed since the first donation, however such donation is allowed after 6 months in case of remission post relapse only after SIMTI Committee assessment. HPC-marrow donation is allowed after 30 days since first donation.

13.5.6 The donor can donate lymphocytes only after 30 days from the HSC donation. The minimum interval among multiple lymphocyte donations must be 30 days (with the exception of an adverse event that causes the unavailability of lymphocytes collected at the previous donation; in this case the interval should be not less than 14 days). Subsequent lymphocytes donation requests must be submitted to the SIMTI Committee.

13.5.7 The requests submitted to SIMTI Committee have to be provided together with follow-up data of donor about previous donations.

13.5.8 If the request is approved, the IBMDR will inform the DC. If the DC and CC Responsibles believe that :

- the donor has not perfectly recovered from the first HSC collection;
- believe that there are reasons to discourage any further approach;

- if the donor has previously expressed a refusal to a further donation (**Form CD103 – Form CD106**), they communicate the procedure cancellation - **Form CD108**.

13.5.9 If the DC and CC responsables evaluate that a new collection can be proposed to the donor, they can move forward with donor counselling, medical evaluation.

The donor is informed about indications and second transplant results, the procedure and risks related to donation and must be free to ask for any clarification. The donor must not be subjected to any pressure and must have sufficient time to make a decision in the full knowledge that he/she has already fulfilled the patient's expectations.

13.5.10 Not stimulated peripheral nucleated cell collection – Attachment WU-cl and P-cl.

The applicable laws and procedures are defined in §13.4.

13.5.10.1 Following the receipt of the “*Prescription for not stimulated human peripheral blood stem cell collection*” **RC308-I Form** if the potential donor confirms his willingness to donate, the DC and the CC-P should complete the “*Verification of stem cell/lymphocyte collection prescription*” **DC107 Form**. Otherwise, the CD must promptly notify the TC and IBMDR of the donor consent withdrawal - **DC108 Form**.

13.5.10.2 The work-up must be done within 30 days prior to donation.

Donor medical and collection procedure evaluation.

13.5.10.3 The DC is responsible for protecting donor safety, evaluating his suitability and for determining any infectious diseases transmissible by lymphocyte donation – **Attachment B-I**.

13.5.10.4 If the donor does not comply with the eligibility criteria established by current regulation, the DC, in agreement with the CC, may adopt an exception to the eligibility criteria - see § 13.4.2.3.

13.5.10.5 The CC has the responsibility of venous access evaluation of the donor.

13.5.10.6 The pre-donation clinical, instrumental and diagnostic examination are reported in the **Attachment WU**.

Final donor information session – Attachment WU-cl

13.5.10.7 The final information session must be composed, as a minimum, by a representative of the DC and / or RR, by a representative of the CC involved competent in HSC donation.

13.5.10.8 It must be provided to the donor, during the session, detailed information about the further examinations to be performed, the procedures about lymphocytes collection, the risks associated with it and the presumed duration of the procedure and about the possibility that part of the donation product will be cryopreserved in aliquots.

13.5.10.9 The copies of the documentation and the minute of information session must be stored at DC and CC.

Donor suitability/eligibility to donation

13.5.10.10 The physicians of the CD and CC must report, in writing, the outcome of their evaluation. If the donor is eligible they proceed with the “*Notification of the donor final clearance*” - **DC104 Form** to be sent to the TC and IBMDR in time for the organization of the transport and the infusion procedure to the patient.

13.5.10.11 Otherwise, the CD, in agreement with the CC, must communicate any case of unsuitability to the TC and to the IBMDR - **DC108 Form**.

Final consent

13.5.10.12 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**. If the Transplant Center requires further biological samples for research, the consent must be extended, as well as in the case the collection product is cryopreserved in toto.

Biological qualification of the collected product

13.5.10.13 The collected donation product:

- must be validated by biological qualification as defined see #13.4.9;
- can be released by the CC to the TE and from the TE to the TC, before the validation results which must be sent to IBMDR and TC as soon as they are available – **CC104-Q Form**.

Quality controls of the collected product

13.5.10.14 The HPC unit is transferred to the competent TE that will assign SEC, will perform cultural exams and will declare the collection characteristics (product cell counts, volume etc.) using **TE201 Form**. The microbiological test results must be available to the TC and IBMDR as quickly as possible.

Distribution/traceability of the collected product

13.5.10.15 The collected unit will be allocated, traced and monitored following the standard for HSC units. (13.4.11 e 13.4.12).

13.6 Donor follow-up and subsequent donor contacts

- 13.6.1 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.
- 13.6.2 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**.
- 13.6.3 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.
- 13.6.4 Contact with the donor must continue at periodic intervals until the donor is free of ailments.
- 13.6.5 Should the donor no longer be available for a further donation, the TC must be promptly informed.
- 13.6.6 The DC/CC/TE 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. If the adverse event may get involved the patient, the Transplant Center must be immediately informed.
- 13.6.7 These data will be transmitted to the SPEAR Registry managed by WMDA in an anonymous way.
- 13.6.8 The donor could be anonymously contacted by the patient, through the IBMDR. – **Form CT313**.
- 13.6.9 The patient could be anonymously contacted by the donor through the IBMDR – **Form CD110**.
- 13.6.10 To preserve anonymity between patient and donor, the donor can't be notified about any kind of information related to health status of the patient.

13.7 Donor protection

- 13.7.1 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.
- 13.7.2 No kind of pressure must be exerted on the donor at any stage of the search process.
- 13.7.3 The donor may only donate for a single unrelated recipient.
- 13.7.4 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.
- 13.7.5 Once the donor has donated, he/she no longer has any right to the collected product.
- 13.7.6 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**.
- 13.7.7 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.
- 13.7.8 Donor identity must be known only to DC, RR and CC authorised staff.
- 13.7.9 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.
- 13.7.10 In every search procedure step and in any communication between DC, RR, TC, TE and the IBMDR, the donor must be tracked using a unique identification code.
- 13.7.11 HLA typing data may be transmitted to the donor according to the EU Regulation n. 2016/679 – artt.15 and followings and may not be used for purposes other than those for which the donor has provided his/her consent.
- 13.7.12 The donor has the right to receive the results of their health screening as well as a refund of the incurred and documented expenses.
- 13.7.13 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**.
- 13.7.14 The donor has the right to the protection of his/her data and protection of confidentiality, including anonymity towards the recipient and related family members according to art. 14 of Legislative Decree 191/2007.
- 13.7.15 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 - comma 1 art. 5 Law 52/2001.
- 13.7.16 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.
- 13.7.17 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.

- 13.7.18 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).
- 13.7.19 The volunteer who donated HSC, should not donate blood for at least one year.
- 13.7.20 According to the *Law n. 52 of 6 March 2001 art. 5*, a donor must not be charged for anything related to the procedure.
- 13.7.21 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.
- 13.7.22 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*.

14. CORD BLOOD UNIT

14.1 Definition

CBU contains stem cells and 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 transplant into another individual who is not biologically related to the donor.

14.2 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;
- possible 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.

14.3 Eligibility criteria

The medical evaluation of mother/parents must be done in accordance with the national applicable laws and regulations. (Ministerial decree November 2 2015, D. Lgs. 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 or neoplastic 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:
 - a) IDM according to national law. These are:
 - HbsAg;
 - Anti HCV;
 - serological test for combined search of Anti HIV 1 and 2 antibody and HIV antigen;
 - Syphilis test;
 - HBV NAT, HCV NAT, HIV NAT;
 - b) other IDMs, known to be potentially transmissible through transplantation, in population at risk of infection e.g.: HTLV I and II or seasonal e.g.: WNV according to national law and regulation for transfusion;
 - c) CMV (IgG and IgM);
- the TNC count prior to the banking of the unit is over or equal to 160×10^7 or between 120 and 160 only if the CD34+ count is at least 2×10^6 .

14.4 Characterization

The CBUs, which comply with requirements related to the storage (Standard 14.3) 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 intermediate/ high resolution molecular typing performed by an ASHI/EFI accredited lab of loci A, B, C, and DRB1* high resolution – 2 fields- with possible use of WHO nomenclature with G/P and indication of rare ambiguities;
- 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 there must be available the Haemoglobinopathy screening results.

14.5 The CBU data are recorded in the IBMDR national database only if the CBU is suitable for storage (standard 14.3), has been characterized for the minimum set of tests required for the storage (standard 14.4) and complies with the national applicable Law and regulations.

14.6 The transmission of CBU data to the national database (the compliance to EMDIS-CORD protocol is strongly recommended) makes the CBU available for all national and international patients searching for an unrelated source of HSC.

14.7 Follow-up of the donor and contacts after the release of the unit

14.7.1 If the biological mother (or both parents, where applicable, or who exercises parental authority in the case of a minor mother) inform the CBB of any changes in the health status of the child and if these conditions can have an impact on the patient's transplant who received the involved CBU, the bank has to inform the TC asap.

14.7.2 The parents (or the donor himself if not underage) can come into contact with the patient who received the donated CBU, through the IBMDR - for the protection and guarantee of anonymity -, only after signing of the "*Consent for communications to the donor*" - **Form SCO110**.

14.7.3 The patient can get in touch with the parents (or the donor himself if not underage), through the IBMDR - for the protection and guarantee of anonymity -, only after signing the “*Consent for communications to the patient*” - **Form CT313-sco**.

14.7.4 To guarantee the anonymity between patient and donor, parents cannot have access to any information regarding the health status of the patient to whom the donated CBU has been infused.

15. COSTS AND RATES

15.1 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.

15.2 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 at IBMDR 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.

15.2.1 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.

15.2.2 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.

15.2.3 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. If the patient is not covered by the NHS, he/she should pay for the medical services received, following the IBMDR indications.

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

16.1 General

In order to determine donor/recipient matching grade, donor/CBU biological samples (at room temperature if not specified by the requesting center) 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:

- 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.*
- Ministerial Decree of 10 October 2012 *“Regulations on the import / export of tissues, cells and reproductive cells for human therapeutic use”* (GU n. 15 of 18 January 2013) and others.
- Ministry Decree November 2 2015. *“Regulation on quality requirements and safety of blood and blood hemocomponents”.*
- Ministry Decree December 2 2016 *“ Import and export disposition for human blood and its products”* (GU n. 9 del 12/01/2017).

16.2 Blood samples

16.2.1 General

Importation or exportation, as well as the national shipments, of blood samples, serum or human plasma for diagnostic purposes (art. 13 Decree 2/12/2016), 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.

16.2.2 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.

16.2.3 The courier is chosen by Galliera Hospital.

16.2.4 Packaging

- The tubes containing blood samples/DNA must:
 - be hermetically sealed, preferably of unbreakable material;
 - report the donor identification code/GRID, 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.

16.2.5 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 81/2008*, a biohazard label, conforming to model shown in **Attachment N**, must be affixed on parcels containing infectious products;
- in order to send potentially infectious diagnostic specimens, the international agreements request that a specific label stating: UN3373 BIOLOGICAL SUBSTANCE CATEGORY B” is affixed to the external packaging.

16.3 HSC/LYMPHOCYTES

The authorisation of importing/exporting of HPC or other blood components is released by the Ministry of Health, case by case, in accordance with the art. 11 and 12 of the *Decree of 10 October 2012* **Form Min 401 - Min 402**. The imported/exported product which is not compliant with the criteria defined by the National regulation, could be imported/exported as an exception according to the art 13 of the above Decree **Form Min 403**.

16.3.1 The HPC/lymphocytes must be transported by a courier appointed by the IBMDR.

16.3.2 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 HPC/lymphocytes from the CC/TE or the Banks to the TC;.
- the choice of the most suitable way to transport the HPC;
- the identification of the best itinerary for performing the delivery of the product provided by the TE or CB Bank within the time indicated (#16.3.6.7, #16.3.7.2);
- the selection of the isothermal container, with hand carry dimension.

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.

16.3.3 Severe and adverse events related with the collection, process and transportation of the HSC/lymphocytes must be notified by the DC/CC/TE/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.

16.3.4 Importation

16.3.4.1 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.

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

16.3.4.3 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.

16.3.5 Exportation

16.3.5.1 The IBMDR must inform the RR, providing the HPC, 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.

16.3.5.2 The RR must supply the laboratory test documents, which must accompany the HPC shipment.

16.3.5.3 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.

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

16.3.6.1 The HPC must be placed into hermetically sealed plastic bags (at least two in case of bone marrow donation), each with the possibility of aseptic access.

16.3.6.2 Each bag must be labelled with the following:

- ✓ the specification of the content:
 - “HPC, Marrow” ;
 - “HPC, Apheresis” ;
 - “TC, Apheresis”;
- ✓ SEC and UNI identification code of the unit or product code (or eventually the compliant documentation);
- ✓ donor's IBMDR identification code, the use of GRID is strictly recommended, (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, if the product:
 - has not been evaluated for IDMs;
 - has been collected from a donor who has declared a risk factor for a transmissible disease;
 - has a reactive result at IDMs.

16.3.6.3 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.

16.3.6.4 The second container should be enclosed in a rigid container with insulating properties in order to avoid damages by external agents.

- 16.3.6.5 The outer container must be correctly labelled with the “Delivery note” **TE200 Form** and **TE201 Form**.
- 16.3.6.6 HSC or blood components must be shipped at a temperature from 2° C to 8 °C , and in any case below 10 °C unless different specifications have been received from the TC. Dry ice must never be used.
- 16.3.6.7 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 48 hours after collection.
- 16.3.6.8 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 - **Form CNC C2**. The isothermal container may be X-rayed, but only if emptied first.
- 16.3.6.9 The courier must keep the HSC or the blood component container with him at all times, it can be never loaded in the cargo of an aircraft and the courier must comply with the “*Technical requirements for transport of HSC for transplantation purpose*” – **Attachment T**.
- 16.3.7 Labelling, packaging, documentation and transport of CBU from a CBB to TC
- 16.3.7.1 Procedures for transport of cryopreserved CBUs shall be designed to protect the integrity of the CBU and the health and safety of personnel.
- 16.3.7.2 The transit time between the CBB and facilities should be minimal. Plans for alternative transportation in an emergency should also be made.
- 16.3.7.3 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.
- 16.3.7.4 The dry shipper must contain a device that continuously monitors temperature throughout the shipment period.
- 16.3.7.5 The CBU bag must be labelled with the minimum number of details (partial label):
- ✓ the proper product name “*HPC-Cord Blood*”;
 - ✓ the SEC and UNI identification code and the identity of the CBB (or eventually the compliant documentation);
- 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 identification code.

16.3.7.6 The dry shipper must be accompanied by the “*Delivery note*” **CB200 Form**, **Attachment M-CBU**, **Attachment U-CBU** and **Attachment P-CBU**.

16.3.7.7 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**.

17. MINIMAL COMPATIBILITY CRITERIA

17.1 Adult volunteer donor

17.1.1 According to the IBMDR Standards, if there is not a specific protocol, a donor is considered compatible (“full matched” or 8/8) for a given patient when they match at least for HLA-ABC and DRB1* alleles (molecular typing high resolution – 2 fields -) with the possibility to use WHO nomenclature with P alleles. The typing defined at HR must consider Null alleles exclusion.

17.1.2 For all patients eligible in **Table III** - *Category A*, it is possible to select a donor following the below stated criteria:

- 7/8 donor mismatching: one for either allele/antigen HLA Class I (considered HLA-A,B and C loci) or HLA Class II (DRB1* locus);
- 6/8 donor mismatching:
 - a) two for either allele/antigen HLA Class I (considered HLA-A,B and C loci);
 - b) one for either allele/antigen HLA Class I (considered HLA-A,B and C loci) and one allelic HLA Class II (DRB1* locus).

In these cases, it is strongly recommended allelic matching (2 fields) at DQB1 locus and to consider the HLA antibodies.

17.1.3 At the time of the “*Final compatibility tests*”, the donor’s HLA – ABC, DRB1, DQB1, loci should be defined by high resolution molecular techniques –2 fields- with the possibility to use WHO nomenclature with P alleles. The typing defined at HR must consider Null alleles exclusion. 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 **RC307 don Form**.

17.1.4 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.

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

17.1.6 The *Final Compatibility tests* must always comply at a minimum with #17.1.3.

17.1.7 At the time of the “*Final compatibility tests*” the recipient’s HLA – ABC, DRB1 loci should be defined by high resolution molecular techniques with the possibility to use WHO nomenclature with P alleles and the results reported in the **RC307 rec Form**.

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

17.2 Cord Blood Unit

- 17.2.1 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) with the possibility to use WHO nomenclature with P alleles.
- 17.2.2 The recipient's HLA typing must be repeated at time of the “*Final compatibility tests*” before selecting the CBU for transplant, as described at point 17.1.7 .
- 17.2.3 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.
- 17.2.4 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.

18. SEARCH PROCEDURE

- 18.1 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.
- 18.2 An HSC transplant from an adult donor may not be allowed when the patient's disease belongs to the *Category C*.
- 18.3 An HSC transplant from an unrelated CBU is permitted for the diseases indicated in **Table III**.
- 18.4 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.
- 18.5 If a preliminary search - **RC300 Form** - provides sufficient chances of finding a donor, a search may be initiated – EMDIS or **RC 301 Form** - when:
- 18.5.1 the disease fulfils the criteria listed in Category A or B of **Table III**;
 - 18.5.2 the patient must be under 66 years; for patients affected by AL, CML MDS, LNH the limit age is 71 years;
 - 18.5.3 the patient, eligible for HSCT and aware of the possible risks, has signed an informed consent form;
 - 18.5.4 the patient is included in the waiting list of the designated TC;
 - 18.5.5 the financial responsibility for the search and transplant is clearly established.
- 18.6 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 MUD Commission approval.
- 18.7 Any communication among the involved structures during the search procedure must be in writing and is regulated by IBMDR forms and reports.
- 18.8 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/TE/CBB be in direct contact. The IBMDR must still be copied into any communication.
- 18.9 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.

- 18.10 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 **RC 301 Form**. It is strongly recommended that the patient’s HLA–ABC typing is performed by molecular techniques at high resolution with the possibility to use WHO nomenclature with P alleles. The typing defined at HR must consider Null alleles exclusion.
- 18.11 The HLA patient’s typing must be confirmed on a different blood sample from the one used for the activating search HLA typing.
- 18.12 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.
- 18.13 Search for an adult donor
- 18.13.1 The TC will receive a full list of potential donors as the first response to activating search; 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.
- 18.13.2 The IBMDR allows the selection of donors who meet the minimum requirements for compatibility set out in Chapter 17.
- 18.13.3 The TC is allowed to select for donation a donor, whose typing has been already confirmed by another HLA typing laboratory (EFI/ASHI accredited). The TC could decide to retest the donor using pre-collection peripheral blood samples before the beginning of the patient’s conditioning regimen.
- 18.13.4 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.
- 18.13.5 “*Molecular typing*” on HLA-ABDR/DRB1 matched donors can be requested using EMDIS or **RC 305 Form**. At the same time, it is possible to request the A, B, C, DRB3/4/5, DQA1, DQB1, DPA1, DPB1 locus alleles definition and/or the donor’s IDM and blood group.
- 18.13.6 The TC can asks samples for “*Final verification typing*” of donors not typed at HR DRB1*. In this case is recommended that DC perform in the meantime the typing at HR for DRB1* - 2 fields- .
- 18.13.7 Before finally selection of an HSC donor, the TC must perform “Final compatibility tests” to confirm both patient and donor HLA typing extending HR typing for DRB3/4/5, DQA1, DPA1 and DPB1 loci if included in a transplant Protocol. The TC may ask - EMDIS or **RC 306 Form** - 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;
 - 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.
- 18.13.8 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 **RC 307 Form**.

- 18.13.9 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*” - **RC 308 Form** and **RC 308-m Form / RC 308-p Form**.
- 18.13.10 The TC may ask for the HSC, only if the transplant is to be performed immediately. HSC cannot be cryopreserved - **RC 308 Form**.
- 18.13.11 The PBSC donation can be requested, according to the eligibility requirements established by GITMO MUD Committee, only if the patient meets one of the following conditions:
- 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 patient has a greater body weight than that of the donor.
- 18.13.12 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*”, - **DC107 Form** - and the “*Clearance of the HSC donor*”, - **DC104 Form** - 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*” **DC108 Form**.
- 18.13.13 It is mandatory that the TC send the IBMDR the forms duly signed.
- 18.13.14 The recipient’s conditioning regimen cannot be initiated without having received and accepted the “*Clearance of the HSC donor*”, - **DC104 Form**.
- 18.13.15 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, to be used in the event of failure of the allogeneic HSCT or failure in obtaining the requested HSC product.
- 18.13.16 The collected product can be infused even if the product qualification test results are still pending.
- 18.13.17 Once received the product, in case of change of transplant program, TC is kindly required to notify IBMDR.
- 18.13.18 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 **CC201 Form**.
- 18.14 Request of a CBU
- 18.14.1 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).
- 18.14.2 The CBB must send the CBU report, including the results of the investigation performed at time of banking, to the IBMDR within 3 working days from this first selection.
- 18.14.3 The TC can request (through EMDIS or by fax **RC305-cb Form**). the “*Molecular typing*” on HLA matching CBUs, specifying which HLA loci should be typed and at which resolution level.
- 18.14.4 The HLA typing results must be sent to IBMDR within 13 calendar days. The request is no longer valid if the IBMDR does not receive the results within 20 calendar days- **CB307 Form**.
- 18.14.5 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.
- 18.14.6 The CBU becomes “*required*” when the TC requests services on it.

- 18.14.7 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.
- 18.14.8 The “*required*” CBU are visible in the national and international search files.
- 18.14.9 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*”.
- 18.14.10 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.
- 18.14.11 The “*reserved*” CBU cannot be selected for other patients and are not visible in the national and international search files.
- 18.14.12 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*” - **RC308 cb Form**.
- 18.14.13 Once the CBU sample has been received, the TC is responsible for sending the “*HLA typing results*” **RC307 cb Form**.
- 18.14.14 The selection for transplant of the CBU is completed by sending to IBMDR the “*Formal request of a CBU shipment*” –**RC308 cb Form** only after the recipient HLA typing confirmation by the TC has been completed as specified in #17.1.7.
- 18.14.15 Following the “*Formal request for a CBU shipment*” - **RC308 cb Form**, the CBB should send the “*CBU procurement schedule*”, - **CB107 Form**.
- 18.14.16 Before the CBU shipment, the tests listed in Standards 14.3 and 14.4 must be completed. The CBB must also provide:
- QC results performed on the CBU attached segment, if available, with :
 - 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) **CB307 Form**;
 - 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 (**CB307-m Form**);
 - mother and baby’s follow up, if it has not yet been carried out in compliance with the National Law and regulation.
- 18.14.17 The above listed QCs must be scheduled by the CBB in order to communicate the pertinent results to the TC (**CB104 Form**) 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.
 - 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.
- 18.14.18 The CBB must send the “*Quality Control results*” - **CBU104 Form** to the TC before release of the unit and as quickly as possible.
- 18.14.19 A CBU, which does not fulfill the requirements of the National regulation for transfusion, could be release as an exception only if the TC and the patient have been previously informed and agreed to proceed **CBU306 Form**.
- 18.14.20 In this case, the Transplant Center will be charged for the procured unit, even if the transplant will not take place for any reason.
- 18.14.21 The CBB must send the “*Cancellation of CBU shipment*” **CBU108 Form** to the TC if it is no longer possible to ship the CBU.
- 18.14.22 Every form and written communication must be signed by the competent supervisor/director and the IBMDR should be copied into every communication.
- 18.14.23 The recipient’s conditioning regimen should not be initiated before the arrival of the CBU at the TC.
- 18.14.24 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.
- 18.14.25 Once the transplant has been performed, the TC must send the “*CBU released follow up*” - **CBU201 Form**.
- 18.14.26 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 **CBU201 Form**.
- 18.15 At any stage, the search procedure can be stopped by the TC through EMDIS, **RC310 Form** “*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.
- 18.16 IBMDR must receive a new **RC301 Form** to re-activate a search procedure. In the event of reactivation following failure of previous transplants performed using HPC collected to an IBMDR donor, the new application must be first submitted to the GITMO MUD Committee. CBU searches are always allowed.

19 SEARCH ACTIVATION ON BEHALF OF INTERNATIONAL PATIENT

- 19.1 The IBMDR can accept a request on the behalf of foreign patients only if it comes from a National Registry (Hub) or directly from a TC EBMT/National Authorities accredited, in absence of a National Hub.

- 19.2 The IBMDR is the sole intermediary between the TC and DC/CBB; all the communications must be addressed to the IBMDR.
- 19.3 Any preliminary enquiry and formal search request must be sent to the IBMDR through EMDIS or by fax/e-mail using the appropriate **RC300 / RC301 Form**.
- 19.4 The TC will receive a full list of potential donors as the first response to activating search; 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.
- 19.5 In case the patient Registry has different patient's eligibility or donor matching criteria (only for CBU), IBMDR assumes that the TC requests have been checked and validated according to the national policies and procedures.
- 19.6 Search activation for patient affected by solid tumours or older than 76 years old will be denied.
- 19.7 Search activation selecting a donor mismatched (< 6/8) will be denied.
- 19.8 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 (search activation at diagnosis/transplant after IS cycle failure)	Severe Aplastic Anaemia transplanted with a CBU	
ACUTE LEUKAEMIAS LYMPHOBLASTIC and MYELOGENOUS	Complete Remission	Relapsed or refractory acute myelogenous leukaemia	
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 Sezary Syndrome	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 at search activation	Required Match level	IRB approved protocol
Category A APPROVED	Up to 66, extended to 71 for patients affected from AL, CML, MDS, LNH	In accordance with the minimum IBMDR criteria	Not required
Category B EXPERIMENTAL	For patients ≥ 71 and < 76 an IRB approved protocol is required (if HCT-I < 3)	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.*