Italian **B**one **M**arrow **D**onor **R**egistry

Italian National Standards

for Unrelated Haematopoietic Stem Cell Donations

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0 ABBREVIATIONS

ADMO: National Bone Marrow Donor Association
AIBT: Italian Association of Immunogenetics and Transplant Biology
AIEOP: Italian Association of Paediatric Onco-Haematology
ASHI: American Society of Histocompatibility and Immunogenetics
ASR: Agreement between the Health Department and Regions
CBB: Cord Blood Bank
CBU: Cord Blood Unit
CC: Collection Center
CC-P: PBSC collection center
CC-M: Bone Marrow collection center
CFU: Colony Forming Unit
CIC: EBMT Center Identification Code
CNT: National Transplant Center
CNS: National Blood Center
DC: Donor Center
DLI: Donor Lymphocytes Infusion
EBMT: European Group for Blood and Marrow Transplantation
EBV: Epstein-Barr virus
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
HPC: Hematopoietic Progenitor Cell
HLA: Human Leucocyte Antigen
HR : High Resolution
HPCT: Hematopoietic 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
IT: Information Technology
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
SIDEM: Italian Society of Hemapheresis and cell manipulation
SIMTI: Italian Society of Transfusion Medicine and Immunohaematology
SIE: Italian Society of Haematology
SEAR: Serious Events and Adverse Reactions
SEC: Single European Code
SM: Search and Match
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. 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 goal 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 achieve this goal, the above mentioned Societies identified several centres (RRs, DCs, CCs and TCs) to co-operate in the program, under the National Co-ordinating Centre (NCC), which is responsible for co-ordinating all the affiliated centers involved.

The headquarters of the NCC was located in the Tissue Typing Laboratory of the Galliera Hospital in Genoa, since here a national software was developed to register and to manage the bone marrow donors' genetic data.

At the beginning IBMDR's activity was guaranteed by private donations till the official recognition. 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. GENERAL

In 2001, the Law n. 52 - 6 March officially recognized the IBMDR for the institutional national value. The Law assigned public funding to guarantee the continuity of IBMDR functions.
The IBMDR:

- coordinates the activities of the Regional Registries and collaborates with similar international organisations,
- promotes UD searches and maintains the National Donor Registry,

in order to provide HPC from volunteer donors and/or from CBU for national and international patients.
The "*Agreement between the Health Department and Regions"* – 5 October 2006- n° 2.637 recognizes the IBMDR as the NCC and it has the following functions:

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

In particular the IBMDR:

- manages unrelated CBU and adult donors searches both from national/international banks and registries as per Law n° 52, 6 March 2001;
- guarantees and certifies the correct action to be taken in HPC 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 HPC 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 comply with 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 HPC donors; these are periodically updated by the National Registry to be adapted to technical and scientific improvements.
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 HPC requests. Such institutions, called Registries, can coordinate, within their pertinent country, DCs, CCs, CBBs and TCs and activities related to the search, to the selection and to the use of unrelated donors. These registries must be members of WMDA.

3.1 The Registry should document that its procedures comply with the WMDA standards. 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.

4. THE ITALIAN NATIONAL REGISTRY

The IBMDR has the goal to provide an HLA matched unrelated healthy volunteer donor for a patient who lacks a compatible familiar donor, with the purpose to perform a HPC transplant with high chances of success.

4.1 The IBMDR is WMDA accredited.

4.2 The Galliera Hospital manages the IBMDR and its legal representative is responsible that IBMDR procedures are in compliance with the WMDA standards. The requirement to meet applicable laws and regulations can be accepted as a valid cause of deviation from WMDA Standards.

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

4.3.1 The compliance of these entities to the Standards are verified trough an audit process.

4.4 The IBMDR must ensure that TCs activate a search for those patients where a HPCT represents a medically acceptable procedure. The diseases eligible for a HPCT are identified, through annual reviews, by the GITMO.

4.5 The IBMDR establishes and documents the policy for data and document storage, including electronically storage, related to the search process, to protocols and procedures in place, including those on staff training and quality management, specifying the specific storage timing.

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

4.7 Other on paper or electronic data must be kept for the time strictly necessary for the achieving of declared purposes and in compliance with the current applicable law. The data required for traceability of process from donation to transplant must be stored for a minimum of thirty years after clinical use.

4.8 Every printed document must be dated. Every stage of the search process must be dated in order to check the time needed in each step of the procedure.

General organisation

The IBMDR achieves its institutional goals through:

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

4.9 The National Committee for HPC transplant (established by CNT Decree 15/05/2013 art. 14 DPR n.44 28/03/2013), the three IBMDR expert advisory Committees (with a consultant and proposal role), the board of RRs and the Italian CBB network establish procedures and guidelines ethically acceptable and technically appropriate.

Advisory Committees

4.10 IBMDR Expert Advisory Committees are established by the AIBT, GITMO, SIMTI and SIDEM.

- AIBT Committee is designated by the pertinent scientific society and is composed of HLA experts working in RRs or DCs.
  a) It establishes the minimum requirements for the HLA typing of the recipient and of the potential donors at the recruitment stage and at all further steps of the search process.
  b) It establishes the accuracy and quality of the HLA typing, indicating the antigens and alleles that must be investigated.
  c) It establishes the tissue typing techniques to be used to type HLA characteristics.
  d) It establishes minimal HLA matching criteria for the donor/recipient couple.
  e) It promotes, evaluates and carries out genetic studies of the patient and of the national potential donor populations.

- GITMO allogeneic transplant Committee is designated by the pertinent scientific society and is composed of experienced haematologists working in public hospitals where unrelated HPCT are performed.
  a) It certifies the activity of the TCs and of the CCs-M participating in the IBMDR network.
  b) It establishes the criteria for considering a patient eligible to be transplanted from a volunteer unrelated donor or eligible to subsequent donations.
  c) It establishes the guidelines for collecting bone marrow while protecting the donor's health and safety.
  d) It expresses an opinion on any issue not already regulated by these standards;
  e) It reviews and conveys the patient follow up data to the IBMDR.
- SIMTI/SIDEM Committee is designated by the pertinent scientific societies and it is composed of experienced immune haematologists working in RRs, DCs or RCs or with a documented and certified expertise in the donor management.
  a) It provides second opinion on the eligibility criteria for the recruitment of volunteer donors and in case of exception in further phases.
  b) It provides second opinion on the HPC donation procedures and in case of subsequent donations, monitoring the time-frame between the first and the second donation, while protecting the donor.
  c) It reviews, manages and analyses donor clinical after donation follow-up data.

4.11 These Committees must provide the requested opinion by seven working days in case of general requests and three days if the opinion is related to a donor-recipient couple. All the requests must be sent to the Committees through IBMDR.

The IBMDR Regional Registry board

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 CEO.

The RR board usually meets at least once a year upon convocation of the IBMDR and each member can be replaced by a proxy member. The RR board can convene a representative of the ITCBN technical group and/or, if necessary, external expert consultants.

Technical ITCBN Committee

The technical ITCBN Committee is composed of:
- the Director of each BSC;
- the Director of the CNT-ISS,
- the Director of the CNS-ISS,
- the IBMDR Director.

The RR board usually meets at least once a year upon convocation of the IBMDR and each member can be replaced by a proxy member. The RR board can convene a representative of the ITCBN technical group and/or, if necessary, external expert consultants.

IBMDR Standard

4.12 The IBMDR network responsibilities, activities, tasks, duties and functions are specified in these Standards.

4.13 Detailed request for changes to the IBMDR Standards can be proposed in writing by the IBMDR network members. Before their approval is necessary:
- the approval of the IBMDR Standard Committee composed by a representative of IBMDR, CNT, CNS and three RRs, in a biennial cycle (renewable for another two year period) and elected during RRs Board;
- the approval of IBMDR, CNT, CNS, Advisory Committees, Regional Registries, ITCBN.

Associations

4.14 The volunteer associations collaborate with the Regional Registry and its Donor Center, or Recruitment Center network, with IBMDR and with CNT to achieve the goals stated in November 13, 2018 Decree "*Criteria and agreement between regions and independent provinces and associations of HPC adult donors".*

Facility infrastructure

4.15 The IBMDR must have a fixed physical location with suitable spaces, equipment and instruments to carry out all the activities connected with HPC donor search and selection. Precautions must be adopted to minimize errors and to maintain confidentiality.

4.16 The IBMDR must have an adequate information technology (IT) 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 search results which can be completed in a time frame consistent with WMDA recommendations.

4.17 Documentation of the system development, maintenance and operations including policies and procedures, must be complete and be written in an appropriate language. Significant modifications to the IT system must be documented and must be approved by the competent Board before becoming effective.

4.18 The backup and data restoration procedures must be appropriate, validated and documented.

4.19 An identification code 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.

4.20 Personal data must be stored separately by medical and HLA data.

4.21 The IBMDR has HLA laboratory of reference.
This laboratory must:
- be accredited by the ASHI or the EFI for the required HLA typing techniques;
- guarantee full cooperation with analogous laboratories of the RRs.

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

Personnel qualifications

4.23 The director and the key personnel must have demonstrated expertise in the fields related to the IBMDR activities. The IBMDR must have a staff with appropriate training and large enough to assume the volume and variety of services required to manage its activities.

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

5. THE REGIONAL REGISTRIES

According to Law n. 52 - 2001 art. 3, the Regional Registries are identified by the competent Regional Health Authority. They represent the IBMDR in Italian regions and they must comply with applicable governmental laws and regulations ("*Agreement between the Health Department and Regions"* 29 April 2010). Besides contributing to increase the potential donor number, they pursue IBMDR goals in managing its activity in their pertinent geographic areas – **Form RR111**.

5.1 The IBMDR RRs must comply with 4.15, 4.16

Organization

5.2 The HLA laboratory of the RR must successfully participate in the annual CNT national QCs and must be accredited by ASHI and/or EFI for HLA-I and II class HR typing and for other tests required in HPCT.

5.3 This laboratory must ensure the accuracy of the HLA data at donor registration step and during potential donor selection procedure.

5.4 If the RR collaborates with more than one HLA laboratory within the area of competence it is its task to establish modalities and procedures for setting up regional and interregional QC.

5.5 The RR may use DCs and/or RCs to maintain and enlarge the number of recruited potential donors.

5.6 The RR can also cover the DC function and must develop strategies and policies for the recruitment of new donors to maintain and/or to increase the number of listed regional donors. To achieve this goal:

- the RR promotes awareness and provides consultancy and training on the HPC donation and transplantation to the health personnel;
- the RR promotes activities to inform and educate the regional community on HPC donation, focusing its efforts on specific settings (schools, communities etc.) in collaboration with local volunteer associations and with its collaborators;
- the RR guarantees the participation of Donor Associations in scheduling the recruitment activities and enrolment of HPC donors, in agreement with national plans and targets;
- the RR establishes the plans for technical-scientific training and information dedicated to promote HPC donation;

- the RR is responsible of organizing the *outdoor* recruitment events in their region and of any outdoor events organized by CD/PR, eventually planned with Donor Associations;
- the RR is responsible for training and maintenance of the expertise of healthcare volunteer members of Associations.

5.7 HPC collection must be performed by accredited CCs.

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

- donor testing to establish donor suitability;
- the "*Final information session*" and "*Verification of the prescription for HPC collection* (13.4);
- the organization of the HPC collection.

5.9 The RR should be able to organize urgent donation procedures (within 10 days of request) in case patient transplant urgency (e.g.: patient conditioned and no product available).

Facility infrastructure

5.10 The RR must have a fixed physical location.

5.11 The Registry must have suitable spaces, equipment and instruments to carry out all the activities connected with its duties, in an environment designed to minimize errors and maintain confidentiality.

5.12 Donor data must be managed by an adequate IT system provided by the IBMDR.

5.13 The RR must have sufficient communication links to facilitate searches. These links must include telephone, fax, and internet.

Personnel qualifications

5.14 The director and the key personnel must have demonstrated experience in the RR activities. They are also responsible for maintaining procedures that are in compliance with the WMDA standards.

5.15 The RR must have a dedicated staff with sufficient expertise and that is large enough to assume the volume and variety of services required to manage RR activities.

5.16 The RR director is also responsible for personnel supervision, training and continuing education.

6. TRANSPLANT PROGRAM FACILITIES

HPC transplant and donation must be performed within an organization composed by:

- Transplant unit;
- Apheresis unit;
- Bone marrow collection unit;
- Tissue establishment.
-

6.1 Transplant Unit (TC): requirements and regulations

The "Italian National Guidelines for the search of unrelated donors" (edited by CNT, Ministry of Health, 25 January 2011) defines the requirements for the Italian Transplant Centers CNT and Clinical Programs that may activate a search for a UD or CBU.

THE ASR 49/CSR 5 May 2021, defines the organizational, structural and technological minimal requirements and the guidelines for accrediting the transplant program facilities.

6.1.1 The Italian TCs may run an HPC unrelated donor search solely through IBMDR; they are located in public hospitals authorized by the Regional Health Authority to perform allogeneic HPCTs. They must be accredited by GITMO – **Form CT333**. The TCs must be able to prove to have transplanted 10 patients as a minimum, per year, in the previous two years. The continuing maintenance of these requirements is demonstrated by the data reported and registered in the GITMO database.

6.1.2 The Italian Clinical Program networks may run an HPC unrelated donor search solely through IBMDR; they are located in public hospitals authorized by the Regional Health Authority to perform allogeneic HPCTs from unrelated volunteers and they must also be recognized by the CNT - **Form CT333 M**.
They must be able to document:

- the usage of EBMT CIC assigned to the Transplant Unit where the Director who is also responsible of the UD search procedures works;
- a minimum of five (5) new allogeneic patients transplanted per year by each transplant unit of the network;
- formal approval from the Hospital General Director, in case of networking Transplant Units located in the same hospital;
- formal approval from the involved hospital General Directors in the case of in case of networking Transplant Units located in more hospitals;
- Regional official approval.

6.1.3 The TC must comply with the Italian national guidelines and the IBMDR/WMDA Standards. It should also comply with FACT-JACIE standard.

6.1.4 The TC must have access to HLA laboratory, accredited by ASHI or by EFI. The HLA lab, performs the initial patient HLA typing and it is also responsible for the HLA typing of the donor/recipient pair in the “Final compatibility testing”.

6.1.5 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.

6.1.6 No search can be run directly by an Italian TC with an IR, DC or CBB. All searches must be run through the IBMDR.

6.1.7 The TC must inform the patient about UD and CBU hematopoietic stem cell transplants, the search process and the related costs.

6.1.8 The TC must obtain the informed patient’s consent in writing before starting an UD and/or CBU search - **Form RC302**.

6.1.9 The TC must handle the search process and procedures, in a timely convenient manner, using the IBMDR forms and information technology devices provided by IBMDR.

6.1.10 For this task the TC must have at least one search coordinator, in compliance to the national regulation and appropriately trained according to the IBMDR defined search coordinator training plan.

6.1.11 On a quarterly basis, the IBMDR monitors key performance index related to the search and identification process for unrelated donors. The outcome of these KPI is shared with the TC and CNT.

6.1.12 After a HPCT from an unrelated donor, the TC must update patient health status and follow-up in Promise database in an established timely manner, in order to comply with Law Decree 191/07 – "*Implementation of the EC Directive 2004/23*" – Activity Reporting obligation.

6.1.13 All communications between the TC and DC/IR/CBB must go through IBMDR.

6.1.14 The TCs establish and document the policy adopted for the storage of data and documents, of which they are the owners; in their policy the retention times must be specified.

6.1.15 All TCs, if accredited by GITMO, can also act as CCs-M from UD for their geographic area with exception of pediatric centres not accredited for acting on adults.

6.2 Collection Centres: requirements and regulations

The CCs are responsible of collecting HPC/lymphocytes from unrelated donors.

6.2.1 They must comply with the national guidelines and IBMDR/WMDA Standards. They should comply also with FACT- JACIE criteria. CCs must:

- have appropriate spaces dedicated to donor evaluation and collection procedure;
- have a location which guarantee immediate donor support in case of emergency;
- have a medical director with one year of documented experience who has performed or supervised 10 allogenic collection procedures, as a minimum.

In collaboration with RR/DC, the CC must:

- guarantee donor safety;
- collaborate in medical procedures for evaluation and verification of donor suitability and eligibility (**CD104 Form**, **CD108 Form**);
- and collaborate in the "Verification of marrow prescription" **CD107 Form**.

6.2.2 The TCs establish and document the policy adopted for the storage of data and documents, of which they are the owners; in their policy the retention times must be specified.

<u>Marrow Collection Centres (CCs-M)</u>

6.2.3 The Italian IBMDR CCs-M which may collect bone marrow from an IBMDR UD are located in public hospitals authorized by the Regional Health Authority to perform allogeneic HPCTs.

6.2.4 The organizational, structural and technological minimal requirements are described in the ASR 49/CSR 5 May 2021.

6.2.5 The CC-M must be GITMO/CNT accredited, in accordance with the RR.

6.2.6 Applicant CC-M must have performed one bone marrow collection procedure in the twelve months as a minimum, in compliance with the national regulation.

6.2.7 The CC-M is registered in the IBMDR network through **CP222-m Form**.

6.2.8 To maintain the accreditation status, the collection center must perform at least 1 allogenic collection per year over the past two years. The compliance with this requirement is annually checked by GITMO through a specific procedure.

6.2.9 Compliance is checked by GITMO through the **TE201-m Form**.

Aphaeresis Collection Centers (CC-P)

6.2.10 The Italian CCs-P which may perform PBSC and/or lymphocyte collection from an IBMDR UD are usually located in public blood banks, authorised to perform aphaeretic procedures. The CC-P could also be in other departments if it performs its duty under the Direction of a blood bank and there is a written agreement and procedures between the involved parties.

6.2.11 The facility, the staff qualifications and the procedures for marrow collection are described in the following regulations:

- "*Agreement between the Health Department, the Regions and the Autonomous Provinces of Trento and Bolzano upon the minimal organizational, structural and technological requirements and guidelines for accrediting the transplant program facilities"*, (5 May 2021, n. 49).
- 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*).
- The *"Agreement between the Government, the Regions and the autonomous Provinces of Trento and Bolzano concerning Update and revision of the State-Regions Agreement of 16 December 2010 (rep. Acts no. 242/CSR) on the minimum organisational, structural and technological requirements of health activities of the transfusion services and collection units and on the model for verification visits". Rep. Acts n. 29/CSR of 25 March 2021.*
- Ministry Decree November 2 2015. *"Regulation on quality requirements and safety of blood and blood components".*

6.2.12 The CC-P is registered in the IBMDR network through **Form CP222-p**.

6.2.13 Applicant CC-P must have performed ten collections of HPCs from peripheral blood (for allogenic infusion) as a minimum in the last year, in compliance with JACIE requirements. To maintain the accreditation status the CC-p must perform at least 10 collections per year during the past two years.

6.2.14 Compliance with the number of collections required to maintain accreditation status is checked, on annual basis, by IBMDR through a procedure specifically designated for this purpose.

6.2.15 The continual maintenance of the requirements is ensured through periodic revisions of the **TE201-p Form** by SIMTI/SIDEM.

6.3 Tissue establishment: requirements and regulations

A TE is the processing unit for the processing, preservation, storage and distribution of hematopoietic progenitor cell products and lymphocytes, for clinical use and purpose of a hematopoietic transplantation **TE444 Form** (as defined in article 3, point Q) Law Decree, November 6 2007, n.191 (GU n. 261 del 9-11-2007 - Suppl. Ordinario n.228).

6.3.1 The TE operates:

- in compliance with "*Agreement between the Health Department, the Regions and the Autonomous Provinces of Trento and Bolzano upon the minimal organizational, structural and technological requirements and guidelines for accrediting the transplant program facilities"*, (5 May 2021, n. 49);
- in accordance with the current legislation for HPC and lymphocytes processing and manipulation, with IBMDR and WMDA standards. It is strongly recommended that it complies with FACT-JACIE Standards too;
- in cooperation with the IBMDR network. TE is responsible for ensuring the traceability of HPC products and lymphocytes in compliance with the regulations on cells and tissue coding and traceability.

6.3.2 The TE of the CC must:

- check the product quality and perform sterility controls;
- assign SEC code to collected product;
- label the product with SEC;
- distribute the product to the TC.

7. RECRUITMENT DONOR CENTER: REQUIREMENTS AND REGULATION

7.1 It is strongly recommended, while respecting the autonomy of the Italian regions, to establish a limited number of DC within the RR network.

7.2 The DC must be located in a public hospital transfusion medicine department; DC requirements and duties are specified in the "*Agreement between the Health Department and Regions"* 29 April 2010. The DC must

a) have documented staff expertise in:
   - donor recruitment and management;
   - educational matters concerning donation;
   - donor eligibility evaluation;
   - donor privacy protection;

b) have a designated site for donor management activities as a private space for donor counselling sessions, for health history data collection and for medical evaluation;

c) have a physician and a coordinator dedicated to manage and to supervise the donor activities;

d) have access to the following facilities:
   - a blood bank accredited and authorized by the Regional Health Authority;

- a dedicated laboratory for infectious disease marker testing, accredited by the Regional Health Authority, which complies with the national regulations and guidelines.
- a HLA lab ASHI/EFI accredited for first and second HLA typing at high resolution level of the UD. This lab guarantees the validity of donor's HLA at the recruitment and in the next steps of the search procedures.
- be compliant with the National guidelines and IBMDR and WMDA Standards. It is recommended, when applicable, the compliance with FACT-JACIE standards too.

7.3 The pertinent RR verifies the compliance with these standards and the maintenance of the requirements determined by the Regional Health Authority - **CD111 Form**.

7.4 The DC is the solely responsible for the accuracy and updating of personal data of its donors. The DC is also responsible for the matching between the IBMDR/GRID donor code (created by IBMDR software) and the donor's identity. These data can be accessed by the pertinent RR, only if a regional policy states it and only after having the donor's informed consent.

7.5 The DC must identify adequate systems for the storage -even in electronic form- of data provided by potential donors, of informed consent, of clinical and anamnestic data related to the donor suitability and to laboratory tests needed for registration and in all the following phases of the donation process, necessary to ensure traceability from donor to recipient and vice versa.

7.6 The DC establishes and documents the policy adopted for the storage of data and documents, of which it is the Owner, specifying the relevant retention times.

7.7 This documentation can be available for those who has the right of access or for accreditation or qualification processes.

7.8 The DC is responsible for the donor data updating and transferring to the national database.

7.9 Donor's genetic data and personal data must be stored using the IBMDR IT system (4.17, 4.18, 4.20).

7.10 The DC must maintain and increase its regional donor list in agreement with the pertinent RR, 5.8.

7.11 All communications between the IBMDR and DC must be through the RR.

8 SATELLITE RECRUITMENT DONOR CENTRES: REQUIREMENTS AND REGULATION

8.1 The RRs and DCs can identify Satellite Recruitment Centres (RCs) **PR111 Form**. The number of the RCs is established by the RRs according to local need and criteria in order to facilitate citizens' access to recruiting in IBMDR.

8.2 The RC's requirements are specified in the "*Agreement between the Health Department and Regions"* 29 April 2010. The tutor DC supervises the RC activity. The RC must fulfil IBMDR and WMDA Standards, and it:

- must be located in a transfusion medicine service;
- 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 as a private space for donor counselling sessions, for health history data collection and for medical examinations.

8.3 The RC must operate following the IBMDR procedures and the indications of the DC/RR of reference. It should be regularly audited by the DC/RR.

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

a) donor recruitment;
   - medical evaluation;
   - donor identification;
   - peripheral blood sample collection.

b) blood sample shipment for verification typing (only if RC is located in a transfusion medicine department).

9 CORD BLOOD BANKS: REQUIREMENTS AND REGULATION

9.1 The Italian CBBs that can provide HPC from unrelated CBU for the purpose of transplantation - **SCO111 Form -** must comply with:

- Law Decree November 2 2015 *"Disposition related to quality and safety requirement of blood"*
- 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.

9.2 The CBB must operate in compliance with the IBMDR and WMDA Standards. It is strongly recommended the compliance with FACT/Netcord standards, too.

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

9.4 The CBB must have an IT system for collection, management and storage of the data.

9.5 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.

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

9.7 The CBB must:
- update the data of the CBUs stored for unrelated allogeneic transplantations;
- send to the IBMDR and update the CBU data according to the defined data transmission protocol;
- perform the CBU HLA typing at the collection stage and during the search procedures. The HLA typing must be performed by HLA laboratory accredited by ASHI or EFI;
- have access to an accredited and/or certified laboratory for IDM tests, in compliance with pertinent legislation;
- be able to organise the shipment of a DNA sample of the selected CBU (if available) upon specific request from the TC;
- be able to organise the shipment of a maternal serum sample of the selected CBU (if available) upon specific request from the TC;
- 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.

9.8 The CBB establishes and documents the policy adopted for the storage of data and documents, of which it is the Owner, specifying the relevant retention times.

10 HLA LABORATORIES: REQUIREMENTS

10.1 The HLA laboratory:
- must operate in compliance with technical procedures, IBMDR and WMDA Standards and according to the indications of the centres of IBMDR network and/or UD TCs.
- must be accredited by 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 successfully participate to the national/ international quality controls.

10.2 The HLA laboratory provide typing services to the Regional Registries, Cord Blood Banks and TCs for:

a) on behalf of IBMDR network, HLA typing -:
- of potential adult donor for registration in IBMDR database;
- of Cord Blood Units and mother for the registration in the national database and ITCBN network;
- of adult donor or Cord Blood Units for extended HLA typing;
- of the Cord Blood Units to confirm identity and typing before the shipment to the TC;
- of adult donor in case of HLA extended typing;

b) on behalf of Transplant Centres, HLA typing:
- of haematological patient and its relatives;
- of haematological patient to activate an UD search;
- of UD selected for VT and, if requested, 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 haematological patients activating an UD search;
- evaluating the matching donor/patient couple;
- evaluating donor-specific antibodies (DSA);
- evaluating post-transplant chimerism.

10.3 The HLA laboratory must use the IBMDR IT system to upload or update HLA typing data in the national database.

11 RECRUITMENT, CONSENTING, TESTING AND REGISTRATION OF ADULT HPC DONORS

11.1 Donor characteristics:

- The adult HPC potential donor is a volunteer who express the willingness to donate HPC to any patient in any part of the world and who complies with the donor recruitment eligibility criteria. After the HLA typing, he/she is listed in the IBMDR as potential donor until the age of 55, unless he/ she donates HPC.
- The donor must be younger than 36 years when recruited or pre-registered in the IBMDR; it is acceptable a person younger than 55 years if previously typed on behalf of relatives.
- The donor can donate HPC for a maximum of three total donations on behalf of a related and/or unrelated recipient.
- The donor cannot be recruited or cannot be a potential IBMDR donor if he/she has already donated for a relative still alive.
- The donor must be free from physical or mental conditions that are not suitable for enrolment and must meet the eligibility criteria for HSC or lymphocyte donation according to the current legislation (**Attachment G-iscr**). In case of specific clinical conditions, not defined by the legislation, the specific recommendations formulated by the WMDA may be of assistance in assessing suitability.

<u>Recruitment</u>

11.2 Promotion activity must lead to the recruitment of candidates who, aware of the possible risks, confirm the intention of donating HSC and give, for this purpose and in writing, a specific consent to be recruited in the Italian registry with the goal of a possible future donation; in the same consent is included the permission for treatment of their personal data (personal and genetic).

11.3 Recruitment is carried out by healthcare personnel, whether structured in the DC/RC of the IBMDR network or by volunteers from the associations. These personnel must:

- operate in accordance with procedures shared and approved by the Donor Center, as well as in compliance with current legislation and IBMDR/WMDA standards;

- be adequately and specifically trained for information activities, donation education, about data protection and confidentiality regulation and on the criteria for excluding HSC donors. The training of such personnel must be formally recorded.

11.4 The training of the healthcare staff of the Associations must comply with the Decree of 13 November 2018. The RR must maintain and update the list of specifically trained and qualified healthcare staff of the associations.

a) <u>Enrolment</u>

11.5 A potential donor can be enrolled:
- at any Donor/Recruitment Centre of the IBMDR network;
- during outdoor events outside DC/RC (**Attachment out-door**);
- from home through *Match at home* procedure, where applicable;
- through the available web applications complying with IBMDR protocols.

b) Counselling

11.6 Regardless of the recruitment method, the potential donor must:
- be informed about the indications and the results of HSC transplantation, the reasons for selecting unrelated donors, the HSC donation procedure (**Attachment A)** and the risks involved in the donation (**Attachment H);**
- read the information statement on diseases communicable with donation, (**Attachment C**), give a preliminary consent to be tested, in case of following phases of selection, for HIV and other infectious disease markers to investigate a potential risk of a transmissible disease.

c) Assessment of conditions contraindicating the registration

11.7 The potential donor must:
- complete the pre-registration self-assessment questionnaire (**Attachment B1**) aimed at highlighting any conditions that permanently exclude registration, which therefore determine the impossibility of proceeding;
- have the opportunity to discuss with qualified healthcare personnel in case of need of further information.

11.8 The same healthcare personnel, by checking the pre-registration questionnaire filled in by the donor, certifies the absence of conditions excluding registration.

d) Informed consent

11.9 Once assessed the absence of conditions excluding registration, the donor signs the "Initial Donor Consent" - **DC101 Form**, confirming that he/she has received all the necessary information regarding:
– the purpose of registration in IBMDR registry;
– the meaning and the value of his/her commitment;
– the importance to keep donation anonymous, voluntary and unpaid;
– the duration of the registration into IBMDR database until 55th birthday.

e) Donor's sample collection

11.10 Once verified the identity of the donor through a valid ID, a donor's biological sample can be collected (blood, saliva or buccal swab) destinated to HLA typing, if:
- the donor has signed the informed consent;
- the donor is eligible to the recruitment.

The kind of sample collected is established by the pertinent RR.

11.11 A blood sample:
- can be collected only in a RC or DC facility. It is permitted to draw blood in a different location (e.g.: outdoor recruitment events) only if ambulance is in place to rescue the donor in case of any adverse reaction. In this case a written agreement with the pertinent DC must be in place.
- can be collected by health care staff (nurse or physician) or biologists on duty to NHS institutions, adequately trained and authorized with certified technical skills.

11.12 The saliva sample and/or buccal swab are generally collected by the donor himself, properly trained by the personnel; in this case the presence of specific facilities for the treatment of adverse reactions is not required. This sample collection can be done in a DC/RC, in an outdoor event or at donor's home.

Testing

11.13 The donor HLA typing must be performed by HLA labs, identified by the DC, compliant with the national regulations, as well as with the IBMDR and international standards (WMDA and EFI/ASHI).

11.14 The recruited donor must be typed for the HLA-ABC, DRB1, DQB1, DPB1 loci at high/intermediate resolution– 2 fields – by molecular techniques; WHO nomenclature with G/P groups can be used.

11.15 The already HLA typed donor (by an EFI/ASHI accredited laboratory) can be registered:
- if donor is younger than 36 years the typing level must be compliant with the standard;
- if donor is older than 35 can be used the available typing results.

11.16 The blood group testing of volunteer donors is recommended at time of recruitment. The ABO blood group and Rh factor testing must be performed by authorized laboratories, which participate with success in QC scheme.

11.17 It is recommended to test the donor for anti-CMV (IgG) antibodies at time of recruitment.

Donor data in the IBMDR National Registry database

11.18 The donor data (genetic data, personal data, weight, number of blood transfusions, number of pregnancies for women) uploaded to the IBMDR database, finalize the registration of the donor, who becomes available to national and international patients in search.

11.19 The donor personal data are uploaded by the DCs, using the web service provided by the IBMDR; these data must be registered within 7 working days from the signing of the informed consent.

11.20 The donor HLA typing results are uploaded by the DCs, using the web service and tools provided by the IBMDR; these data must be registered within 60 working days from the signing of the informed consent.

12 DONOR SELECTION FOR TESTING AFTER RECRUTIMENT

12.1 Donor can be selected verifying HLA matching or suitability for a specific national or international patient in active search.

12.2 The donor, when selected, must be informed of the purpose of the selection and before providing the blood sample for the tests as requested by the TC, must
- confirm his/her committment to continue - **DC102 Form***;*
- provide his/her anamnestic data **– Attachment B2***;*
- be compliant with the health conditions as required by the national regulation.

Any derogations to the temporary conditions of not suitability for the protection of the patient do not stop the provision of the requested service, but must be communicated to the TC.

12.3 The halthcare staff of the DC must verify the donor's identity and the correspondance of the donor data with the IBMDR/GRID code before proceeding with further tests and esaminations.

12.4 The TC/IR can specifically request to the DC to perform on a fresh blood sample:

a) "*Molecular typing*"
   - low resolution HLA – DRB1 typing: the donor must be typed by DC at low resolution level with molecular typing technique;
   - high resolution HLA – DRB1 typing: the donor must be typed by DC at high resolution level with molecular typing technique, four digits with possibility to use Group P alleles in accordance with the WHO nomenclature;
   - high resolution molecular typing of HLA loci: the donor must be typed by DC at high resolution level with molecular typing technique, four digits with possibility to use Group P alleles in accordance with the WHO nomenclature;

b) "*Infectious disease markers*":
   - syphilis test, anti-HCV, HbsAg, anti-HIV 1/2, anti-CMV IgG and IgM (if the donor is not already reported IgG Positive);
   - CMV status (IgG and IgM– if the donor is not already reported IgG positive);
   - anti-EBV

c) "*Additional tests*":
   - ABO, Rh factor. The testing is performed by a Immuno-haematology and transfusion service;
   - Other tests (e.g. HTLV I e II, CCR5 etc..) for which feasibility will be checked with the DC.

d) *"Blood sample for VT":* to be sent to the HLA lab of the TC to perform verification and confirmatory typing. The DC must:
   - obtain a donor anamnestic questionnaire and informative consent, giving further explanation of the process to the donor – **Attachment A-TC/B2;**
   - check the HPC source the donor is available to donate;
   - test the donor for the following IDMs: syphilis test, anti-HCV, HbsAg, anti-CMV IgG and IgM (if the donor is not already reported IgG Positive), anti-HIV 1-2 and ABO, Rh factor (if not already available);
   - perform a blood cell count, ferritin and homocysteine level;
   - check the donor apheresis venous access: if not adequate, the TC must be informed - **Attachment B2***.*

   If, at the time of shipment, the IDM test results are not yet available, the DC must report them to IBMDR as soon as possible.

e) "*Donor verification typing*": exceptionally the TC can ask the DC to test the donor for verification typing at HLA-ABC DRB1/3/4/5 DQA1 and DQB1 (or other loci according to the TC request). The typing will be performed at high resolution level according to WHO nomenclature including P alleles. The results must be provided within 15 days from the day of request. If the typing request is contextual to the work-up request, the results must be provided before the conditioning regimen of patient begins or before the donor administration of G-CSF, whichever occurs first.

The DC must always provide the following information:

- Donor's weight;
- number of pregnancies/ abortions (if female);
- number of blood transfusion (if any).

12.5 The requested typing results must be sent to the IBMDR by the DC within 30 days from the day of request. In case of Donor verification typing, the pertinent results must be provided by the DC in 15 days (if the request is for a *Fast-track* procedure the results must be available before the start of conditioning regimen or before the start of donor mobilization if HPC will be cryopreserved. The typing request will be no longer valid if the IBMDR does not receive the results within the time indicated above and, consequently the service will be not invoiced.

12.6 The DC must report any condition of not traceability /unavailability of the donor to IBMDR within 20 days from the date of selection.

12.7 If the donor becomes available again, the DC will not perform the requested services, unless there is a new request from IBMDR.

12.8 In case the TC cancels the HLA typing request, if the test is ongoing and it is no longer possible to interrupt the process, the DC must provide the results within 30 days from the date of the request.

12.9 If the DC organizes a sample shipment after the notification of a cancellation request by the TC, the shipment will be not invoiced.

12.10 After the verification typing the donor can be:

- released;
- reserved for 90 days;
- selected for "*Health and Availability Check* (HAC)" level 1 - after 3 months of reservation;
- selected for "*Health and Availability Check* (HAC)" level 2 – as back-up donor;
- selected for HPC donation.

12.11 HAC – Level 1 request. The DC contacts the donor (also by phone, messaging app etc..) and checks:

- donor willingness to donate;
- donor eligibility - **Attachment B2**;
- stem cell source the donor is willing/eligible to donate;
- any already scheduled commitment of the donor in the next 90 days e.g.: business/study duties, vacations, etc…

12.12 HAC – Level 2 request. The DC convenes the donor, checks the items listed in 12.11 and:

- informs the donor that he/she has been selected as a back-up donor;
- performs an accurate health evaluation - **Attachment B2** - to identify conditions that may exclude the donor from donation;
- evaluates the donor's vein access.

12.13 The Dc must send the HAC evaluation results the IBMDR within 15 days from the day of request.

12.14 The donor selected for a specific patient is maintained in the "reserved status":

- during the provision of the requested service;
- 15 days from the HLA typing result date (if the donor is still compatible);
- 40 days from the sample shipment date;
- 90 days from the HAC result date.

12.15 The donor data as blood group, availability for a specific HPC source donation, HLA typings, IDM results, number of pregnancies/transfusions, weight or donor temporary unavailability must be updated in the donor's file, via the IBMDR software.

12.16 The DC must inform the donor about his reserved or released status depending on:
- the results of the extended HLA typing according to the minimum matching criteria;
- the TC indication reported in the **Form RC307-don**;
- time expiration for receiving the results of the final compatibility test from the TC;
- the TC indication following the HAC.

13 DONOR SELECTION FOR FIRST HPC DONATION

HLA compatible donors can be selected for HPC first donation from bone marrow or peripheral blood, after growth factor stimulation.

The applicable laws, national guidelines of reference are:
- 25 January 2010 Decree "*Adopted 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*."
- "*Agreement between the Ministry of Health, the Regions and the Autonomous Provinces of Trento and Bolzano on HPC collection, manipulation and clinical use*", (10 July 2003, n.1770).
- *the SIMTI-GITMO recommendations for related and unrelated HPC donation for HPCT, 2011 Edition.*
- Ministry Decree November 2, 2015. "*National Regulation on quality requirements and safety of blood and blood components*".
- Standard operative procedure "*Management of allogeneic Peripheral HPC donor in case of mobilization failure"* approved by GITMO, IBMDR, CNT,CNS,SIMTI e SIDEM;
- *Agreement, pursuant to Annex I, point 3, of legislative decree no. 16 of 2010, between Government, the Regions and the autonomous Provinces of Trento and Bolzano on the document "Criteria for the selection of hematopoietic stem cell donors*".

<u>Donor work-up planning and donation procedure</u>

13.1 Upon receipt of the "*Prescription for stem cell collection",* the DC must update the TC within 7 days from the request. If the potential donor confirms his/her willingness to donate, the DC and the CC must fill in the "*Verification of stem cell collection prescription"* **DC107 Form,** including the HPC source agreed with donor and TC. In case of donor withdrawal or ineligibility, the DC must immediately inform the TC and the IBMDR - **DC108 Form**.

13.1.1 The TC is allowed to select for work up only one donor for each patient; if the TC wants verify the availability of one or more back-up donors, please refer to the HAC2 request.

13.2 The work up must be performed as a maximum 30 days prior to the collection date, as well as the shipment of the pre-collection samples, unless otherwise indicated by the TC.

Medical health assessment and suitability to donation

13.3 The donor physical examination and health assessment must be performed by a physician team with experience in blood transfusion and PBSC/marrow donation, identified by the DC. This team must not be the same in charge of the care of the recipient.

a) Donor medical evaluation

13.3.1 The DC is responsible for protecting the donor, for evaluating his/her suitability to the donation and for assessing the presence of any infectious disease transmissible by HPC donation **Attachment B-WU**. For this purpose, the DC must perform a careful medical evaluation by collecting personal and family medical history.

13.3.2 The donor must meet the law minimal requirement for blood, cells and tissues donation. In case of HPC peripheral donation the donor must not:

- be under lithium treatment;
- have splenomegaly;
- have an history of artery or venous thrombosis;
- have an history of iritis or episcleritis;
- have sickle cell trait;
- have poor venous access, unsuitable for long time lasting apheresis.

By default, the use of anticoagulant drugs does not constitute a reason for exclusion from donation. The assessment of donor suitability must be made on a case-by-case basis.

13.3.3 In case the donor eligibility criteria finalized the recipient protection do not comply with the national requirements, if the TC and the recipient are informed and agree in written to proceed **DC107-d Form,** the DC and the CC can go ahead with the donation. When the exception to the suitability criterion concerns the protection of the donor, the CD will have to submit the case to the opinion of the SIMTI/SIDEM committee.

b) Donor clearance

13.3.4 The DC and CC physicians are responsible to protect donor safety, evaluating the donor suitability for both stem cell collection types. If necessary, it is possible to request an expert/ committee advice.

13.3.5 The anaesthetic risk of bone marrow collection procedure must be carefully evaluated from the anaesthetist according to the risk classes established by American Society for Anaesthesiology – ASA (**Attachment F**).

13.3.6 An assessment of the donor vein accesses must be always performed by the CC-P, even in case of bone marrow donation. If the donor is not suitable for PBSC collection the TC must be informed.

Clinical and instrumental pre-collection examination

13.4 Donor clinical and instrumental pre-collection tests and examinations are described in **Attachment WU**.

Pre-donation donor information session

13.5 During the donor final information session before donation, a member of the DC and/or RR and a haematologist or transfusion medicine physician of the CPs with expertise in HPC donation, must be present - **Attachment WU-cl**.

13.6 In the final session meeting, the donor must be given detailed information on all tests and medical examinations to be carried out, the type of HPC source requested by the TC, the procedures of HPC donation, its risks and the duration of the procedure.

13.7 It is strongly recommended that donor's personal physician or a donor's relative/friend attend this informative session.

13.8 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 performed once the patient's preparative regimen has begun.

13.9 In particular, the prospective donor must be informed about:

- the possible complications related to the HPC donation - **Attachment H**;
- the possible depressive state after the donation;
- the duration of the procedure and donor commitment;
- the possibility that in case of poor/failed mobilization with G-CSF a rescue procedure with Plerixafor can be adopted to guarantee the donation– **Attachment H-PL**;
- the possibility that, in case of complication with the planned type of HPC donation, it may be requested an immediate donation from an alternative source;
- that, in some cases, the donor may be asked a subsequent donation for the same recipient. In specific transplant protocols the request of subsequent mononuclear cell collection from peripheral blood (for DLI) may be required;
- the donation is anonymous and the donor identity must not be transmitted to recipient or to patient's relatives and vice versa.

13.10 Documents and minutes of the informative session must be stored at DC and CC.

Donor clearance

13.11 The DC, CP-M and CP-P physicians must report, in writing, the result of their assessment. In case of donor clearance and suitability to the donation, 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 start of recipient conditioning.

13.12 In case of donor not suitability the DC and the CC must notify the TC and the IBMDR of impossibility to clear the donor - **DC108 Form**. In case of definitive deferral, the donor must be indicated as definitively unavailable in the IBMDR database.

13.13 In case of donor unavailability or not eligibility to the second choice HPC collection method, the TC must be informed in advance that it will not be possible to have any type of collection in case of failure of the first one.

13.14 In case of a planned PBSC donation, if the donor is not available for a back-up bone marrow collection neither for the usage of Plerixafor, the TC can plan the cryopreservation of the product.

13.15 In case of a planned BM donation, if the donor is not available for a back-up PBSC collection, the TC can plan the cryopreservation of the product.

Final donation consent

13.16 The donor cleared for donation confirms their willingness to donate by signing the "*Final consent to donate*" - **DC103 Form**.

13.17 The consent must indicate also the possibility of further subsequent donations for the same recipient. If case of a specific request from TC, the donor can agree in the same consent to:
- donate further biological sample for purposes different from transplant;
- participate in an experimental transplant protocol;
- the cryopreservation of the collected product, as previously authorized.

Communication between DC/CC and CT

13.18 During the work up the DCs/CCs and the TC are in direct contact; copy of every communication must be sent also to IBMDR.

13.19 Before the start of patient conditioning DC, CC and TC must agree on:
- the volume and quantity of HPC, by signing the "*Verification of stem cell/lymphocyte collection prescription*" **- Form DC107;**
- the planning of the collection procedure by signing the *"Notification of the Donor Final Clearance"* **- Form DC104.**

13.20 In case of a cancellation of HPC donation request when the donor has been already contacted, the services will be charged.

13.21 In case of a postponement of HPC collection (due to patient's disease relapse or for any other reason), if the new collection date has been already established, the donor will be reserved for 90 days.

HPC collection procedure (**Attachment P-cl**)

13.22 The HPC collection:
- can take place only if the current patient disease and clinical status indicated in the "*Prescription for stem cell collection"* does not exclude transplant,
- must be perfomed at the CC whose physician attended the final information session;
- must performed in a different facility/department other than the one in which is treated the recipient;

- cannot be initiated if the courier has not communicated the travel plan –**C2 Form** - and has not informed the CC of his arrival.

Marrow HPC collection (**Attachment L**)

13.23 Prior to bone marrow collection, the donor must have one or more autologous blood units drawn, with an interval of at least 7 days so the last unit is collected - as a minimum - 7 days prior to HPC donation. The number of pre-collected blood units depends on the marrow volume that the donor, according to the DC/CC-M physicians, can safely donate.

13.24 During collection or after in case of need, the donor is transfused with the pre-collected autologous blood.

13.25 The collected HPC must be stored in bags (at least two). These bags must be made from hermetically sealed plastic material and must be equipped with aseptic access.

Mobilization and collection of peripheral HPC after stimulation

13.26 The administration of G-CSF, its possible side effects and the appropriate clinical follow-up are described in **Attachment R**.

13.26.1 The CC-P is Responsible of the G-CSF administration procedure and of the HPC collection.

13.26.2 The administration of G-CSF must be under the supervision of a licensed health care professional (identified by the CC-P) experienced in its administration and in managing the possible consequences.

13.26.3 In case of self-admistration of the drug, at least the first dose must be administered at suitable health facility and the donor must be properly informed of the procedure to be followed.

13.26.4 Donor receives G-CSF, by subcutaneous injection, at a daily maximum dosage of 10µg/Kg donor body weight. Nowadays, the routine usage of the biosimilar G-CSF is recognized as appropriate in the absence of an alternative. In this case, careful monitoring of the donor is recommended to identify any side effects due to the use of biosimilars.

13.26.5 In case of serious events in reaction to G-CSF administration, the treatment must be suspended and the request of HPC can still be complied with a bone marrow colletion, if the donor confirms their consent and is suitable for this method of collaction.

13.27 The use of Plerixafor administration is allowed in case of poor mobilizing donor. The procedure, the donor management and possible side effects are described in **Attachment R-PL**.

13.27.1 The Plerixafor growth factor administration must be done by an expert physician (identified by CP-P), responsible of the management of the possible side effects and adverse events due to this treatment. The donor consent is mandatory (**DC103-PL Form**) together with Transplant Center consent (**Form RC302-PL**).

13.27.2 Plerixafor is administered, by subcutaneous injection, in 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 never allowed.

13.37.3 The data regarding Plerixafor mobilizing procedure and collection must be send to IBMDR - **Attachment S2-PL.**

13.28 The usage of a central venous catheter is never allowed for performing a PBSC collection.

Biological quality control of the collected product

13.29 The collected product (BM/PBSC) must be validated by the DC/CC. The biological quality control can be performed on a donor's peripheral blood sample that is obtained before the start of the collection or in the previous 7 days, according to the Italian national law and regulation.

13.30 The following tests must be performed by a licensed laboratory:
- Anti-HCV;
- HBsAg;
- serological tests to detect Anti-HIV 1 and 2 antibodies and HIV Ag;
- Syphilis test;
- HIV/HBV/HCV NAT;
- ABO/Kell blood group, and Rh phenotype.

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

13.32 The biological product qualification test results must be made available before the product is released to the courier or, as exception, must be made available to the Transplant Center before the recipient infusion - **CC104Q Form**.

Quality controls of the collected product

13.33 The HPC unit is moved from the CC to the pertinent TE that will assign the SEC code, will perform culture tests and will provide collected product details (cell count, volume, etc..) through **Form TE201**. The bacteria culture test results must be communicated to the TC and to the IBMDR as soon as possible.

Distribution/traceability of the collected product

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

13.35 Once product is infused, the TC provides filled **TE201 Form** to the IBMDR and to the DC. The DC provides this documentation to the CC and the TE.

Quality of the collected products

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

14 DONOR SELECTION FOR SECOND AND SUBSEQUENT DONATIONS FOR THE SAME PATIENT

14.1 The legal framework and national guidelines of HPC and lymphocyte donation are listed in Chapter 13.

14.2 A donor can be selected for a second or subsequent donation only in favor of the same recipient. The donor can be requested for a subsequent donation of lymphocyte intended for DLI (Donor Lymphocyte infusion) in case of recipient relapse or for HPC (PBSC or bone marrow) in case of non-engraftment or poor graft function.

14.3 In case of failure of the HPC transplant, as a minimum after 20 days from the first donation, the TC can request a second donation from the same donor to the IBMDR - **RC309 Form**. The request must be accompanied by:

- Patient's diagnosis;
- protocol applied at the first transplant;
- patient's current clinical status;
- reasons of the request;
- blood component /HPC type required.

14.4 All the donation requests must be submitted to the IBMDR GITMO MUD Committee, with the exception of a first standard request of lymphocyte – Table IV: Indications for Donor Lymphocyte Infusion (DLI).

14.5 A third donation request for lymphocyte donation must be approved by the IBMDR SIMTI/SIDEM Committee. The donor's follow-up data must be made available to the committee to express an opinion about.

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

Time interval between donations

14.7 The BM donor can be requested for a second marrow HPC collection, after a minimum of 6 months since the first donation. The BM donor can donate peripheral HPC after 45 days as a minimum (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.

14.8 The HPC-apheresis donor can be requested for a second peripheral HPC donation after a minimum of 6 months since the first donation; this donation is exceptionally permitted only upon IBMDR SIMTI/SIDEM Committee approval. An HPC-marrow second donation is allowed after 30 days since the first HPC donation.

14.9 The donor can donate lymphocytes only after 30 days from the HPC donation. The minimum time among multiple lymphocyte donations must be 30 days (exceptionally in case of an adverse event seriously impacting the quality of the donated product, the time interval can be a minimum of 14 days).

14.10 If the subsequent donation request is approved, the IBMDR will inform the DC.
In case:

- the donor is not fully recovered from the first HPC collection;
- there are reasons to discourage any further requests to the donor;
- the donor has previously expressed a refusal to be contacted for a subsequent donation (**DC103 Form** –**Form DC106**),

the DC and the CC communicate the procedure cancellation - **Form DC108**.

14.11 In case the donor is eligible and agree to a second donation, the DC and the CC organize the donor counselling and medical evaluation.

14.12 The donor must be informed about second transplant indications and results, about the procedure and risks related to subsequent 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.

Lymphocyte donation work up

14.13 Following the receipt of the "*Prescription for not stimulated human peripheral blood stem cell collection*" - **RC308-l Form** after the donor confirms his willingness to donate, the DC and the CC-P must fill the "*Verification of stem cell/lymphocyte collection prescription*" **DC107 Form**. In case of donor withdrawal, the CD must promptly inform the TC **DC108 Form.**

14.14 The work-up must be done within 30 days prior to donation, as well as the sending of pre-collection samples, unless otherwise indicated by the TC.

Donor medical and lymphocyte collection procedure evaluation

14.15 The DC is responsible for protecting donor safety, for evaluating his suitability and for determining any infectious diseases transmissible by lymphocyte donation – **Attachment B2**.

14.16 If the donor does not comply with the eligibility criteria established by Italian current regulation, the DC and the CC may adopt an exception to the eligibility criteria - see standard 13.3.3.

14.17 The CC has the responsibility to evaluate the donor's venous access.

Clinical, instrumental and diagnostic examinations in case of donation of lymphocyte

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

Final donor information session – **Attachment WU-cl**

14.19 In the final information session meeting a member of the DC and/or of the RR and a member of the CC involved in the collection procedure must be present.

14.20 During this meeting the donor must be fully informed about the further medical examinations, the lymphocytes collection procedure, the risks associated with the donation, the duration of the procedure and about the possibility that a part of the donation product will be cryopreserved.

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

Donor suitability/eligibility to lymphocyte donation

14.22 The physicians of the CD and CC must report, in writing, the outcome of their evaluation. If the donor is eligible, they send to the TC and IBMDR the "*Notification of the donor final*

clearance " - **DC104 Form.** This form must be sent in time for the organization of the transport and of the infusion procedure.

14.23 In case of not eligibility of the donor, the CD and the CC must communicate the cancellation of the donation to the TC and to the IBMDR - **DC108 Form**.

Final consent

14.24 The donor must express their willingness to donate, by signing the "*Final consent to donate*" **DC103-I Form.** If the Transplant Center requests further biological samples for research purposes, the consent must be extended, as well as in the case the collected product is totally cryopreserved.

Biological qualification of the collected product

14.25 The collected donation product:

- must be qualified as defined in standards 13.29,13.30;
- can be realeased from the CC to the TE, before the qualification test results. The biological product qualification test results must be made available before the product is released to the courier or, as exception, must be made available to the Transplant Center before the recipient infusion - **CC104Q Form.**

Quality controls of the collected product

14.26 The HPC unit is moved to the competent TE that will assign SEC, will perform cultural exams and will declare the product characteristics (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

14.27 The collected unit will be allocated, traced and monitored according to the standard for HPC units. (Chapter 13).

15 DONOR SELECTION FOR DONATION OF STARTING MATERIAL DESTINATED TO CELL THERAPY

The legal framework and operational guidelines of the procedure are:

- Regulation (EC) No. 1394/2007 of the European Parliament and of the Council of 13 November 2007 on advanced therapy medicinal products amending Directive 2001/83/EC and Regulation (EC) No. 726/2004.
- Commission Directive 2009/120/EC of 14 September 2009 amending Directive 2001/83/EC of the European Parliament and of the Council on the Community code relating to medicinal products for human use as regards advanced therapy medicinal products.
- Legislative decree 6 November 2007, n. 191 for the definition of minimum organizational requirements, structural and technological and accreditation guidelines for the structures relating to the hematopoietic stem cell (HSC) transplant program.
- Legislative Decree 25 January 2010, 16 "Implementation of Directives 2006/17/EC and 2006/86/EC, which implement Directive 2004/23/EC regarding the technical requirements for the donation, procurement and control of human tissues and cells,

as well as with regard to traceability requirements, notification of serious adverse reactions and events and certain technical requirements for the coding, processing, preservation, storage and distribution of human tissues and cells.".

- Decree of 2 November 2015 with the provisions relating to the quality and safety requirements of blood and blood components.
- ASR 49 of 5 May 2021 containing "Revision of the Agreement of 10 July 2003 for the definition of the minimum organisational, structural and technological requirements and the accreditation guidelines of the structures relating to the HSC transplant programme".
- Circular of the Ministry of Health Prot. 0050959 of 21/12/2022 containing "Indications for the export and import of cells of human origin intended to be used as raw material for the manufacturing of advanced therapy medicinal products authorized or administered in the scope of clinical trials or compassionate use programmes;
- SOP IBMDR/CNT/GITMO "Management of products of human origin from unrelated allogeneic donors in the context of HSC transplantation intended to be used as raw material for the manufacturing of advanced therapy medicinal products (ATMPs) authorized or administered in the context of clinical trials or compassionate use programmes.

Transplant Program Requirements

15.1 TC that request a collection of biological substances from an unrelated donor destinated to be used as starting material for cellular therapy must be:
- GITMO/CNT accredited for allogeneic transplantation (in case of Italian TC);
- certified by CNT/CNS according to ASR n. 49/2021 or JACIE accredited for allogeneic transplant activity (in case of Italian TC);
- have a documented activity in unrelated donor transplant.

15.2 TC units must operate in compliance with WMDA and IBMDR standards and technical procedures and, strongly recommended, FACT-JACIE standards.

Request for donation/use of unrelated donor's biological substances

15.3 Before using unrelated donor biological substances for cell therapy, it is the responsibility of the PT Director, or his delegate, to provide all the necessary information to IBMDR - **Form CT333-T2**, including:
-protocol synopsis;
- Eudract code (if applicable);
- copy of the AIFA authorizations and Ethics Committee opinion;
- type and method of collection of requested material;
- copy of informed consent and informative documents destinated to patient;
- copy of informed consent and informative documents destinated to donor (if available);
- guarantee of payment of the provision and transport of the requested biological substances.

15.4 Communications between the interested parties during all phases of the procedure must be in writing and are regulated by the IBMDR forms and management software.

15.5 Through IBMDR the clinical unit can request, solely for the same recipient, the donation of:

- whole blood (100 ml as a maximum) or stem cell apheresis quote if at the same time of donor selection for HPC donation aimed at transplantation;

- whole blood (100 ml as a maximum) or lymphocytes if in a step following the transplant.

15.6 If not at the same time of HPC donation, the request can be received after 30 days from donation as a minimum.

15.7 Any request for the use of donor material already cryopreserved at the PT must be sent to IBMDR, which will inform the DC for having a specific informed donor consent. Donor's stored material can be only used after receiving clearance from IBMDR.

15.8 The clinical unit is responsible for:

- providing the patient with explanations on the indications for advanced cell therapy and on the specific protocol in which he will be enrolled;
- sending the formal request for the material to IBMDR using the CT308-T form;
- sending indications for payment guarantee of expenses of the provision and transport of the requested material - **Attachment E1-t**;
- if the request is subsequent to the transplant, reactivate the search after having acquired and sent a new written informed consent - **RC302-t Form** - to IBMDR.
- recording the infusion of advanced therapy in both the IBMDR and EBMT databases.

Donor selection

15.9 The DC and CC inform the donor and start medical assessment and suitability procedures according to the requested substance (blood/lymphocytes).

15.10 The donor, informed about the indications of the request, the method of the subsequent donation and the risks associated, must be free to ask questions about; no pressure must be done on the donor who must have sufficient time to take his decision (with the help of information provided).

Work-up planning

15.11 If the donor confirms his/her willingness to donate, the DC and the CC-P (in case of lymphocyte donation) fill in the **DC107-t Form**; otherwise, the DC must promptly notify the TC and IBMDR of unavailability of the donor.

15.12 The pre-donation work-up must be carried out in the 30 days prior to the donation.

15.13 The DC has the responsibility for protecting the donor and assessing his suitability. It is also mandatory to identify any factor that could expose the patient to the risk to be infected by a blood/ blood component transmissible disease, according to the regulations in force for blood donation or HPC - **Attachment B2**. An accurate personal and family history of the donor is therefore necessary.

15.14 If the donor reports/presents conditions or behaviours for which the eligibility criteria established by current legislation to protect the recipient are not satisfied, the DC, in agreement with the CC-P (in case of lymphocyte donation) can clear the donor in derogation of the eligibility criterion - see paragraph 13.3.3.

15.15 The pre-donation clinical and diagnostic tests and specific expiration times are described in **Attachment WU**.

15.16 The DC and CC-P physicians must report the results of their assessment in writing. If the donor is eligible, they fill in the "Donor Clearance Notification" - **DC104-t Form** – and send it to the TC and to the IBMDR in time to organize transport. Otherwise, the DC, in agreement with the CC-P, must communicate any reason of unsuitability to the TC and to the IBMDR.

15.17 The donor must express his/her consent to the donation in writing - **DC103-t Form** -.

15.18 For the biological qualification, the quality controls, distribution/traceability of the collected substance, the same procedures required for HSCs and lymphocytes must be applied– **Form TE200-t TE201-t CP104Q**-t.

16 DONOR FOLLOW-UP AND SUBSEQUENT DONOR CONTACTS

16.1 Following the donation, the well-being of the donor must be ascertained by the DC physician. Specific forms (**Attachment A-fu**, **DC105 Form, DC106 Form**) are given to the donor in order to report, in writing, their feelings and any possible complaint.

16.2 Following the HPC donation the donor follow-up, the medical examinations and the clinical screening must be performed by the DC and CC in accordance with the protocol "*Follow- up of the donor*", as specified in – **DC109 Form**.

16.3 In case of any medical concerns or donation consequences, the donor must be referred to the appropriate physician for assistance. Donor health issues post-donation potentially affecting the health of a patient having received the donated product must be reported to the requesting TC.

16.4 The donor must be followed till when he/she is free from any post donation health issue.

16.5 The TC must be promptly informed if a donor is longer available for a subsequent donation

16.6 The DC/CC/TE must notify the IBMDR of any Serious Events and Adverse Effects (SEAR) occurring after HPC/lymphocyte donation in order to inform the competent authorities. If the adverse event may potentially affect the recipient, the TC must be promptly informed.

16.7 The SEAR data will be also transmitted to the SPEAR Registry managed by WMDA in an anonymous way.

16.8 The donor could be anonymously contacted by the recipient, through the IBMDR. – **RC313 Form**.

16.9 The recipient could be anonymously contacted by the donor through the IBMDR – **dc110 Form**.

16.10 To protect the anonymity between the recipient and the donor, the donor may not be informed on the health status of the recipient.

17 DONOR RIGTHS AND PROTECTION

17.1 The potential donor must be informed about the right to withdraw at any time. However, the donor must also be informed about the consequences for recipient if the donation is not carried out once the patient's preparative regimen has commenced.

17.2 No any pressure must be done on the donor at any stage of the process.

17.3 The donor may only donate for a single unrelated recipient.

17.4 The TC may ask for the HPC collection only if the transplant is immediately performed, not for cryopreservation. In case of specific donor/recipient conditions where the collected HPC should be cryopreserved, a specific approval must be obtained from the IBMDR.

17.5 Once the donor has donated, he/she doesn't have any right on the collected product.

17.6 In the event that the collected product is not totally infused, it is possible to cryopreserve the exceeding quantity so that, if needed, it can be used as boost only for the same recipient – **Attachment L-CSE**.

17.7 IBMDR and international registry donor identity must be kept strictly confidential in order to protect the donor's anonymity. Donor privacy protection procedures must be in place to avoid donor/recipient personal data disclosure

17.8 Donor 's identity must be known only to DC, RR and CC authorized staff.

17.9 Donor's personal and genetic data must be separately stored and must be protected from unauthorized access. Access to donor's data must be strictly allowed only to DC and/or RR authorized personnel. Patient's relatives and/or friends are not allowed to enter in IBMDR operative facilities.

17.10 In any communication between DC, RR, TC, TE and the IBMDR, for all the search procedures the donor must be identified by a unique identifier.

17.11 Donor 's HLA typing results can be provided to the donor according to the EU Regulation n. 2016/679 – artt.15 and may be used exclusively for the purposes for which the donor gave their consent.

17.12 The donor has the right to receive the results of their health screening. The registry is also responsible to refund the donor's documented expenses.

17.13 The donor, who moved to a country where a donor registry exists, can request to his/her DC to move his data to the international registry – **DC112 Form.**

17.14 The donor has the right of protecting confidentiality of their data, including anonymity with the recipient and his relatives, according to art. 14 of Legislative Decree 191/2007.

17.15 The donor is allowed to be absent from work during all the procedures necessary for his/her commitment (registration, typing, medical examinations, etc). The pertinent documentation for the employer is provided by the DC or CC - comma 1 art. 5 Law 52/2001.

17.16 An employed donor has the right to receive the usual earning even if absent from work, due to the procedures related to:

- collection of blood sample for HLA tissue typing at the registration;
- extension of HLA typing on behalf of a recipient;
- medical evaluation during work up;
- administration of grow factors before HPC donation;
- follow-up controls post donation.

17.17 The donor has the right to receive the usual salary for the necessary days taken off from work for the HPC collection and for the necessary days to reach a complete health status recovery, to be certified by the CC's medical personnel.

17.18 The donor follow-up must be performed at established times even if no complaints are reported, (up to ten years for bone marrow and PBSC donation and up to 6 months for lymphocyte donation).

17.19 The donor after HPC collection, should avoid to donate blood for at least one year.

17.20 According to the *Law n. 52 of 6 March 2001 art. 5*, a donor must not be charged for anything related to the procedure.

17.21 The Galliera Hospital, head quarter of the IBMDR, is responsible for establishing disability and death benefits through an insurance coverage for any complaints of the donor due to blood withdrawal, workup and donation.

17.22 The adequacy of the liability insurance coverage must meet the international standards Its fee is covered by national economic grant deriving from *the Law n. 52 of 6 March 2001 art. 10.*

18 THE CORD BLOOD UNIT

Umbilical cord blood contains stem cells and haematopoietic progenitor cells, collected from placental and umbilical cord vessels after the cord has been clamped. The present standards refer to CBU collected for unrelated donation, intended for transplant into another individual who is not biologically related to the donor.

CBU collection

18.1 The CBB must have in place procedure defining how to collect cord blood and to transfer the unit from the collection unit to the CBB.

18.2 The health personnel collecting the cord blood unit must trained according to the SOP in place between the collection unit and the CBB. The SOP must define the requirements to guarantee the quality of the product and a sterile collection. The collection must not interfere in the delivery process and the health of mother and newborn must be protected.

Consent

18.3 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 all issues of cord blood donation, about the collection procedure and related risks and benefits. The maternal donor must release a written, legally valid, informed consent – **Form CBU101**- for:

- the collection and the storage of cord blood unit;

- the collection and the storage of blood samples and DNA from the mother and from the CBU for future testing;
- the use of maternal and/or CBU samples for infectious and genetic diseases testing and other tests as applicable;
- the provision of personal and family medical history necessary for the CBU evaluation;
- the availability to repeat infectious disease tests in six months and one year after collection;
- the usage of the donated CBU for an allogeneic transplant of an unrelated national or international recipient treated in any part of the world.

The mother informed consent must be obtained and documented while the maternal donor is able to concentrate on the information and is not distracted by aspects of labour.

Eligibility criteria

18.4 The medical evaluation of the mother/parents must be done by qualified health personnel, in accordance with the national applicable laws and regulations. (*Ministerial decree November 2 2015, D. Lgs. 25 January 2010* and others).

18.5 The CBU is eligible for storage and unrelated donation 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** medical records of the pregnancy and information about the health of the fetus must be collected too.
- a maternal blood sample, collected at time of delivery, has been tested by a Regional Health Authority accredited laboratory to detect IDM according to national law. These are:
  a) HbsAg;
  b) Anti HCV;
  c) serological test for combined search of Anti-HIV 1 and 2 antibody and HIV antigen;
  d) Syphilis test;
  e) HBV NAT, HCV NAT, HIV NAT;
  f) other IDMs known to be potentially transmissible through CBU transplantation, in population at risk of infection (e.g.: HTLV I and II) or for seasonality transmission (e.g. WNV) according to national law and regulation for transfusion.

  The maternal donor has the right to receive the results of any health screening, in particular the maternal donor must be counselled in the case of positive disease results that pose health risks to the maternal donor or infant donor.
- the CBU TNC count prior to the banking is over or equal to 160 x 10e7. It is acceptable a TNC count between 120 and 160 if the CD34+ count is at least 2 x 10e6.

Characterization

18.6 The CBUs stored for unrelated transplantation purposes must be tested and characterized for the following:

- CMV (IgG/IgM) test on a maternal sample collected at the delivery time;
- CBU volume at time of collection and at time of storage;
- 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 typing performed by an ASHI/EFI accredited lab of loci A, B, C, and DRB1* high resolution – 2 fields- using WHO nomenclature with G/P and indication of HLA 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 the shipment of the unit, the hemoglobinopathy screening results must be available.

Data entry in the national database

18.7 The CBU data are uploaded in the IBMDR national database when the CBU suitable for storage has been characterized for the minimum set of tests required in compliance with national Law and regulations.

18.8 The import of CBU data into the national database according to the EMDIS-CORD protocol (strongly recommended) makes the CBU available for all national and international patients searching for an unrelated donor of HPC.

Maternal donor follow-up and contacts after the CBU shipment

18.9 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.

18.10 The parents (or the donor if not underage) can send anonymous communications to the recipient, through the IBMDR which guarantees the protection of privacy and anonymity, only after signing the "*Consent for communications to the recipient*" - **CBU110 Form**.

18.11 The recipient can send anonymous communications to the parents (or to the donor if not underage), through the IBMDR which guarantees the protection of privacy and anonymity only after signing the "*Consent for communications to the donor* "- **RC313-cb Form.**

18.12 To guarantee the anonymity between patient and donor, parents may not have access to any information regarding the health status of the recipient to whom the donated CBU was infused.

19 THE SEARCH PROCEDURE

The following chapter describes the requirements and guidelines for the identification and selection procedures of compatible adult donors and CBUs to be used for HPC unrelated transplant.

19.1 A search of an unrelated HPC donor or/and CBU is permitted for all patients who can benefit from a HPC transplant. The diseases and disease stages are classified in the **Table III** according to a demonstrated effectiveness in the treatment with HPC transplant. 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.

19.2 A search and a transplant from an unrelated CBU is allowed according to the disease indications listed in **Table III**, with no restriction due to the disease status.

19.3 Unrelated double CBU transplant is allowed only according to an Institutional Review Board approved protocol.

19.4 If a preliminary search - Search & match tool or **RC300 Form** - provides sufficient chances of identifying a compatible donor, the donor search may be activated when the disease fulfils the following criteria (listed in the **Table III)**:

- the patients affected by SAA and EPN must be younger than 66 years, for other diseases the age limit is 75 years;
- the patient, eligible for HPCT and aware of the possible risks, has signed an informed consent form;
- the patient is included in the waiting list of an accredited TC.

The pediatric and adult clinical unit can run unrelated searches for patients respectively up to and after 18 years old, exceptions must be approved by the Hospital where the TC is located.

19.5 The financial responsibility for the search and transplant expenses must be clearly established.

19.6 If the patient's disease or its characteristics and stage are not listed in the **Table III**, the search procedure can be activated only after receiving GITMO MUD Commission approval.

19.7 Any communication among the involved structures during the search procedure must be in writing and it is regulated by IBMDR forms and reports.

19.8 Any communications between the involved entities at all the search stages must be mediated by the IBMDR. Only after work up activation (*Prescription of HPC or Formal request for a cord blood unit shipment*) the TC and CC/TE/CBB are in direct contact. Nevertheless, the IBMDR must receive copy of any communication.

19.9 The HLA patient's typing must be performed by an EFI/ASHI accredited laboratory. The patient's HLA phenotype must be completed with HLA I and II class allele results. If applicable, the HLA typing should be confirmed by the patient's familiar study.

19.10 To formally activate the search, the patient must be typed for HLA A, B LR and DRB1 HR (**RC301 Form**) as a minimum. It is strongly recommended that the patient's HLA–ABC typing is performed at high resolution level using WHO nomenclature (P alleles are permitted). The HR typing must exclude Null alleles.

19.11 At the confirmatory typing stage before activating a work up, the patient's HLA typing must be confirmed on a new blood sample.

19.12 At the time of the search activation, it is strictly recommended that the TC informs IBMDR about the AB0/Rh and CMV status of the patient.

19.13 Patient's registration must be reactivated with a new patient' consent, in case the search is suspended due to the patient's HLA mistyping or if the patient's search is moved to another TC.

International recipients

19.14 International patient searches for adult donors/ CBU listed in the Italian national database, must be carried out through the IBMDR.

19.15 The requirements and search procedures for international patients must comply with these standards and any exceptions must be approved by the relevant IBMDR committees.

19.15.1 if the requesting registry is WMDA certified or in the presence of specific written agreements with IR, exceptions to the eligibility requirements (for patient's age, diagnosis, disease status) and compatibility (both for adult donors and CB units) can be admitted with no specific approval by the IBMDR Committees.

19.16 When the donor is selected for work-up, it is recommended that the results of the patient's confirmatory test are available. In any case CT results must be sent to the IBMDR and to the DC as soon as possible before the start of the patient's conditioning regimen or of the donor mobilization/marrow donation, depending on the first event.

19.17 IBMDR coordinates the search and will invoice the costs deriving from the services performed by its functional centers to the requesting center, according to the *international patient schedule of fees*.

Unrelated adult donor search and selection procedure

19.18 The IBMDR allows the selection of donors who meet the minimum HLA matching criteria described in Chapter 20 of these standards.

19.18.1. The first feedback to a new search request is the provision of a match list of IBMDR potential donors to the TC. The IBMDR does not usually provide a list of potential donors who are HLA-DR or HLA-AB mismatched with the patients. Upon specific request, IBMDR can provide the mismatched donor list.

19.18.2. The TC can select for work up a donor with a verification typing already performed by an HLA typing lab EFI/ASHI accredited. In this case the TC can confirm the donor using pre-collection peripheral blood samples.

19.18.3. It is possible to request the "*DR typing*" of HLA AB compatible donors through EMDIS or by email. The DC will perform the typing at low resolution, 1 field; the HLA I class typing is not usually repeated at this stage.

19.18.4. "*Molecular typing*" of HLA-ABDR/DRB1 matched donors can be requested. At the same stage it is possible to request the A, B, C, DRB3/4/5, DQA1, DQB1, DPA1, DPB1 allele definition and/or the donor's IDM and blood group.

19.18.5. The TC may request "*verification typing*" of donors HLA ABDR/ DRB1 matched as a minimum. This test is performed by the tissue typing lab of the TC. The results -**RC307 Form-** must be sent to the IBMDR within 40 days of the date of sample receipt.

19.18.6. The IBMDR will deny:

a) requests of more than 40 mL. of blood sample (including the 10 mL. for IDMs);
b) request for a shipping date more than 30 days after the request date;
c) requests following a previous non-contested shipment on behalf of the same patient aimed to the completion of a no-exhaustive previous test.

19.18.7. The TC must provide to the IBMDR and to the DC the indication on donor selection within 10 days from the receiving of the results.

19.18.8. The compatible donor, if not requested for donation, could be reserved by the TC for a specific patient for 3 months.

19.18.9. After 3 months, if not requested for donation, the TC can:

- extend the reservation period of 90 days;
- request the HAC 1;

if the IBMDR has not received any written communication, the donor will be released and will return to the active donor file.

19.18.10. The HAC 1 can be also requested on a compatible donor already verification typed, even if on behalf of other patients.

19.18.11. The TC can select donors already Verification Typed and compatible for a specific patient for:

- HPC donation by sending the "*Prescription for the collection of HPC*" - **RC308 Form** and **RC308-m Form** / **RC308-p Form**.
- HAC 1
- HAC 2, as Back up donor.

19.18.12. Before the donor final selection for HPC collection, it is strongly recommended that the "*Final compatibility tests*" of the patient are performed by the TC according to the requirements set out in standard 20.5. If not earlier available, the results must be sent to IBMDR and to DC as soon as possible and in any case before the start of the patient's conditioning regimen, donor mobilization or HPC collection, depending on the event that firstly occurs.

19.18.13. The TC can ask for donor recruitment together with final "Fast-track" compatibility verification test, in the following cases:

- unavailability of the donor selected for work-up;
- graft failure after related or unrelated transplant after at least 28 days (and within two months from the infusion as a maximum) when the first donor is no more available;
- other transplant urgency, which must be carefully documented.

Requests can be accepted only if the donor has A, B, C and DRB1 HLA typing at HR/IR molecular biology techniques (intermediate/high resolution). The results of the VT must be sent to the IBMDR and to the DC as soon as possible and in

any case before the start of the patient's conditioning regimen, donor mobilization or HPC collection, depending on the event that firstly occurs.

19.18.14. The TC must inform the IBMDR in case the patient has a back-up donor - RC308 Form.

19.18.15. The collected product is intended for immediate use. The cryopreservation must be approved in advance, if requested by the TC - **RC308 Form.**

19.18.16. In answer to the "*Prescription for the collection of HPC*", if the donor is suitable for the donation and confirms their willingness to donate, the DC sends the "*Verification of HPC prescription*", - **DC107 Form** - and the "*Clearance of the HPC donor*", - **DC104 Form** - to the TC. In the event the donor is not suitable or withdraws consent, the TC receives the "*Cancellation of stem cell collection*" **DC108 Form**.

19.18.17. The TC must send back to the IBMDR the work up forms duly signed.

19.18.18. The recipient's preparative regimen cannot start before the donor's clearance is received and accepted the "*Clearance of the HPC donor*", - **DC104 Form**.

19.18.19. The TC should evaluate, before recipient's preparative regimen, the possibility of collecting the recipient's stem cells for an autologous back up, in the event of failure of the allogeneic HPCT or failure in obtaining the requested HPC product.

19.18.20. In case of urgency the collected product can be infused, as exception, even if the HPC qualification test results are still pending.

19.18.21. Once received the product, in case of change of the transplant program, the TC is required to inform the IBMDR, providing the pertinent documentation which will be submitted to the pertinent Committee.

19.18.22. In the event of a great quantity of collected cells, that are not totally infused Attachment **L-CSE**, the TC must notify the IBMDR (**CC201 Form)**.

19.18.23. The TC must communicate to the IBMDR, **RC314 Form**, every further use of the cryopreserved aliquots.

19.19 Unrelated cord blood unit search and selection procedure

The IBMDR allows the selection of CBU which meet the minimum HLA matching criteria described in Chapter 20 of these standards.

19.19.1. When a cord blood unit is selected, a report containing the CBU characteristics is sent to the TC (*Unit report*).

19.19.2. The unit report includes the results of the CBU tests performed at time of banking and must be provided by the CBB within 3 working days from the CBU first selection.

19.19.3. The TC can request (through EMDIS or by fax **RC305-cb Form**) the "*Molecular HLA typing*" of a potential matching CBU, indicating HLA loci and typing resolution level.

19.19.4. 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**.

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

19.19.6. The CBU is listed as "*required*" when the TC requests additional information or tests.

19.19.7. The CBU "*required*" status remains for 60 days. After this time and with no any additional request from the TC, the CBU returns to the active search file.

19.19.8. The "*required*" CBU is still listed in the national and international search files, with this status.

19.19.9. In the event the CBU is considered suitable for infusion, the TC can request to reserve the unit that acquires the status of "*reserved*".

19.19.10. The CBU is "*reserved*" for a period of 60 days. After 60 days, without any further action or written request of extension, the reservation expires. Through a written communication, permitted once only, the TC can request to extend the reservation for following 60 days.

19.19.11. The "*reserved*" CBU cannot be selected for any other patient and is no more listed in the national and international search files.

19.19.12. The TC may request the shipment of a CBU attached sample (DNA or cryopreserved blood sample, depending on availability) and/or maternal serum if available, only when the CBU is selected for transplant, filling in the "*Formal request of a CBU shipment*" - **RC308-cb Form**.

19.19.13. Once the CBU sample has been received, the TC must fill and send back the "*HLA typing results*" **RC307-cb Form**.

19.19.14. The CBU selection for infusion is formalized by sending to IBMDR the "*Formal request of a CBU shipment*" –**RC308-cb Form.** The recipient's HLA typing, confirmed by the TC HLA typing lab, should be sent together with the CBU request; if not it must be sent before the CBU shipment.

19.19.15. Following the "*Formal request for a CBU shipment*" - **RC308-cb Form**, the CBB sends the "*CBU procurement schedule*" - **CB107 Form**.

19.19.16. Before the CBU shipment, the tests listed in Standards 18.5 and 18.6 must be completed. The CBB provides:

- QC results performed on a CBU attached segment (if available):
  a) CB cells viability;
  b) CB HLA typing to check the donor's identity as well as to confirm the previous reported results (A, B, DRB1 Low Resolution) - **CB307 Form**;
  c) CFU;
  d) TNC count;
  e) Total number of CD34 cells (highly recommended);

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

In the event that CBU attached segments are no longer available, the TC must be notified in advance so that plans can be made to keep or decline further selection of this CBU;

f) confirmation of the CBU identity and of the couple mother/baby through the HLA inherited maternal haplotype or through any other validated procedure, described in the CBB policies (**CB307-m Form**);
g) the cord blood bank must review all source documentation prior to shipment of the cord blood unit for transplantation;

– mother and baby's follow up, whether not yet performed been carried out in compliance with the National Law and regulation.

19.19.17. 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 by 15 days from the request).

19.19.18. 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.

19.19.19. In case the CBU segment is no more available or the QCs have been already performed in the previous 12 months, it is possible to ship the unit, without repeating them. The TC must be informed in advance so plans can be made to keep or to decline further selection of this CBU.

19.19.20. In case of an urgent transplant procedure and there is no sufficient time to have the QC results (with the exception of the CBU HLA typing and the confirmation of the donor's identity), the TC can decide to request any way the shipment of the CBU, taking the responsibility of this decision. In this case the TC must specify, in writing, the urgent transplant procedure and that has been obtained a specific patient's informed consent.

19.19.21. No further tests are permitted on the infant donor after the collection of CBU. Any additional tests requested by the TC must be performed on the available maternal or CBU samples.

19.19.22. The CBB must send the "*Quality Control results*" - **CBU104 Form** to the TC as soon as possible and, anyway, before the shipment of the unit.

19.19.23. A CBU, which does not fulfill the requirements of the Italian regulation for infusion, could be release as an exception only if the TC and the recipient are informed and agreed to proceed **CBU306 Form**.

19.19.24. In this case the TC will be charged for the shipped CBU, even if the transplant will not take place for any reason.

19.19.25. The CBB must send the "*Cancellation of CBU shipment*" **CBU108 Form** to the TC in case the CBU cannot be shipped.

19.19.26. Every form and written communication must be signed by the competent CBB supervisor/director and the IBMDR must receive copy of every communication.

19.19.27. The recipient preparative regimen must not be initiated before the arrival of the CBU at the TC.

19.19.28. Prior to the commencement of the recipient preparative regimen, the TC HLA typing reference lab must repeat the verification typing (HLA-A, B and DRB1 low resolution) on a segment attached to the shipped unit, if available. Otherwise, this test can be performed after thawing the unit for infusion – **RC307-cbu Form**.

19.19.29. When the CBU has been infused, the TC must send to the IBMDR the "*CBU released follow up* "- **CBU201 Form**.

19.19.30. A CBU that has left the CBB premises may not be sent back to the CBB inventory. It is mandatory to communicate to IBMDR if the transplant is postponed and, in the event the procedure is definitively cancelled, the unit must be destroyed. The CBB must be informed using the **CBU201 Form**.

19.20. At any stage, the search procedure can be stopped by the TC through EMDIS or **RC310 Form** *"Cancellation of search"*. The IBMDR is responsible for communicating, as soon as possible, the cancellation notices to the relevant DC/CBB in order to stop, where possible, the pending requests.

19.21. IBMDR must receive a new **RC301 Form** to re-activate a search procedure. In the event of reactivation following failure of the previous transplant of HPC collected from an IBMDR donor, the new application must be first submitted to the GITMO Committee. Exceptions are allowed in case of:

- reactivation of a CBU search;
- relapse of onco-hematological diseases or diagnosis of new onco-hematological disease, after 6 months as a minimum since the first transplant. Complete remission in case of acute diseases or disease control in case of chronic lymphoproliferative/myeloproliferative diseases must be documented at the work-up

20 MINIMAL COMPATIBILITY CRITERIA

Adult unrelated donor

20.1 According to the IBMDR Standards, without a specific protocol, a donor is considered compatible ("fully matched" or 8/8) for a given patient when they match at least for HLA-ABC and DRB1 alleles (at high resolution level, 2 fields) including WHO nomenclature with P alleles. The typing must be able to define Null alleles exclusion.

20.2 It is possible to select an HLA mismatched donor according to the following criteria (in order of priority):

- 7/8 matched donor: one HLA Class A, B or C loci allele or antigen or one HLA DRB1 allele or antigen;
- 6/8 matched donor:
  a) two HLA Class A, B or C loci alleles or antigens;
  b) one HLA Class A, B or C loci allele/antigen and or one HLA DRB1 allele.

In the mismatched couples it is strongly recommended to have an allelic match at DQB1 locus and to investigate the presence of DSA in the recipient.

20.3 National TC can select donors with other matching criteria according to transplant protocols approved by the relevant Ethics Committee/IRB (Institutional Review Board) and according to the opinion of the IBMDR Committees.

20.4 The donor HLA typing must be repeated at the "Final compatibility test" - **RC307 don Form**, on a new blood sample, different from the one used for registration; the donor must be typed at least for the HLA-AB loci in low resolution - 1 field - if this discriminates the equivalent serological split and DRB1* high resolution and, if not yet typed, be extended to the HLA-ABC, DRB1 and DQB1 loci in high resolution - 2 fields - using the WHO nomenclature and alleles of the groups P (with exclusion of Null alleles). Upon request of the CT the typing can be also extended to the HLA-DRB3/4/5, DQA1, DPA1 and DPB1 loci.

20.5 The HLA typing of the recipient must be repeated at the "Final compatibility test" - **RC307-rec Form**, on a new blood sample different from the one used for the activation of the search; the recipient must be typed at least for the HLA-AB loci in low resolution - 1 field - if this discriminates the equivalent serological split and DRB1* high resolution and, if not yet typed, be extended to the HLA-ABC, DRB1 and DQB1 loci in high resolution – 2 fields - using the WHO nomenclature and alleles of the groups P (with exclusion of Null alleles). Upon request of the CT the typing can also be extended to the HLA-DRB3/4/5, DQA1, DPA1 and DPB1 loci.

Cord Blood Unit

20.6 According to the IBMDR standards a CBU is considered compatible for a given patient when the mismatches are, as maximum, two alleles/antigens at HLA A, B loci or one at HLA A, B loci and one at HLA-DRB1 allele (HR – 2 fields).

20.7 The recipient HLA typing must be repeated at the "Final compatibility test" preferably before the selection for shipment of the CB unit, as described in paragraph 20.5 or at the latest before the release and distribution of the CB unit.

20.8 National TC can select CB units on the basis of different criteria on the basis of transplant protocols approved by the relevant Ethics Committee/IRB (Institutional Review Board) or according to the opinion of the IBMDR Committees.

20.9 In the event of a CBU selected for infusion, the IBMDR must be informed in order to start the selection procedure of the CBU.

21 IMPORTATION, EXPORTATION AND TRANSPORT OF BLOOD SAMPLES AND HPC

Donor/CBU biological samples (at room temperature if not differently specified by the requesting center) can be sent to Italian or international requesting centres for further histocompatibility testing.

Following to a donation request the HPC collected product must be delivered to the TC, including import/export shipments. The shipment of samples and HPC transport must comply with the national and international applicable laws, the IATA regulations and the IBMDR and WMDA standards.

The applicable laws, national guidelines and procedures of reference are:

- Decree Law, 6 November 2007, n. 191 *"Implementation of the EC Directive 2004/23.*
- Decree Law, 25 January 2010 "*Implementation of the Directive 2006/17/CE, 2006/86/CE, 2004/23/EC.*
- Ministerial Decree, 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, 2 November 2015. "*Regulation on quality requirements and safety of blood and blood hemocomponents*".
- Ministry Decree, 2 December 2016 "*Import and export disposition for human blood and its products"* (GU n. 9 del 12/01/2017).

Blood samples

21.1 Import/export, as well as the national shipments, of blood samples, serum or human plasma for diagnostic purposes do not need a preventive authorisation from the Ministry of Health (art. 13 Decree 2/12/2016). However, due to the importance of the biological samples, everything must be in place in order to:

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

21.2 Careful attention is required in the labelling of the blood sample tubes. Only the unique identification code must be used to track the donor.

21.3 Transport, import and/or export of biological samples intended to diagnostic tests, do not need a prior authorisation from the Ministry of Health.

21.4 The courier for the biological sample shipment is chosen by Galliera Hospital.

21.5 Packaging

The tubes containing blood samples/DNA:

a) must be hermetically sealed and be preferably made of unbreakable material;
b) must be labelled with the donor GRID, anticoagulant used and volume, DC physician signature (readable), collection date and time.
c) when hermetically sealed, there must be no external traces of the content;
d) 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 in sufficient quantity to absorb all the content in the event of leakage;
e) the second container must be placed in a rigid container with insulating properties in order to avoid damages by external agents.

21.6 Documentation:

- the **Attachment M**, stating the content of the samples and IDM results 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 **Attachment N**, must be affixed on items potentially containing infectious products;

- in order to send potentially infectious diagnostic samples, the international agreements request that a specific label stating: "UN3373 BIOLOGICAL SUBSTANCE CATEGORY B" is affixed on the external packaging.

HPC/LYMPHOCYTES

21.7 Authorization for HPC import/export is released by the Italian Ministry of Health, case by case, in accordance with the a*rt. 11 and 12 of the Decree of 10 October 2012* **Min 401 - Min 402 Form**.

21.8 The imported/exported product which is not compliant with the criteria defined by the National regulation, could be imported/exported in derogation according to the *art 13, Decree of 10 October 2012* **Min 403 Form**.

21.9 The HPC/lymphocytes must be transported by a courier designated by the IBMDR, following the requirements of the **Attachment T.**

21.10 The courier has sole responsibility for the safe and timely transport of HPC from the collection centre to the transplant centre. The courier must:

- take care of the accuracy and safety of the transport;
- be responsible of the safety, conservation and preservation of the HPC/lymphocytes from the CC/TE or CBB to the TC;
- choose the most suitable type of transportation for carrying the HPC;
- select the best itinerary and travel plan for performing the delivery of the product within the indicated timing (standard 21.20);
- select the proper isotermal container and cooler of hand carry dimension.

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

Severe (Product) Event Avverse Reactions

21.11 Severe and adverse events affecting donor or product (collection, processing and transportation included) and potentially the patient's health 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 way, will be transmitted to the WMDA SPEAR committee.

21.12 Serious Adverse Reactions occurring due to registry operations and impacting the health and safety of donors or patients must be identified, documented and reported to the relevant Competent Authority. These data, in an anonymous way, will be transmitted to the WMDA SPEAR committee.

21.13 HPC/lymphocyte Import:

- 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.
- the TC must request to the IR providing the HPC all the laboratory tests that must accompany the shipped product.
- in case the IR is not able to perform the requested tests, the TC must request an additional blood sample with the purpose of performing the necessary tests.

21.14 HPC/lymphocyte Export

- the IBMDR must inform the DC, 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.
- the DC must provide all the laboratory test results, which must accompany the HPC shipment.
- in case the DC is not able to perform the requested tests, the DC must send an additional blood sample to the requesting centre through the coordination of the IBMDR, with the purpose of performing the necessary tests.

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

21.15 Each bag must be labelled with the following:
- the specification of the content:
  a) "HPC, Marrow"
  b) "HPC, Apheresis"
  c) "TC, Apheresis"
- SEC and UNI identification code or product code (in case it is not feasible, the code must be written in the accompanying documentation);
- Donor GRID (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 (readable) signature;
- the type and volume of anticoagulant used and total volume collected;
- collection date and time, including time zone;
- recipient's identification code;
- a biohazard label if the donor's product could transmit infectious diseases in case the product:
  a) has not yet been tested for IDMs;
  b) has been collected from a donor who has declared a risk factor for a transmissible disease;
  c) has a positive result in an IDM test.

21.16 Each bag must 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.

21.17 The second container must be placed in a rigid container with insulating properties in order to avoid damages by external agents.

21.18 The outer container must be labelled with the "*Delivery note*" **TE200 Form** and **TE201 Form**.

21.19 HPC 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 communicated by the TC. Dry ice must never be used.

21.20 Due to the importance of the transported product, the transport must be planned in order to ensure the HPC delivery at recipient's TC as soon as possible: every effort must

be done to complete the infusion within 24 hours from the collection, and possibly no more than 48 hours after collection.

21.21 In case HPC /blood components are transported by flight, they must never be X-rayed when going through the airport security area. The HPC bag may be shown to the custom officials and eventually handled with extreme care, **CNC-C2 Form**. The isothermal container can be X-rayed only if the product bag is not contained inside.

21.22 The courier must remain in possession of the HPC product at all times. The product can never be boarded in the air cargo.

Labelling, packaging, documentation and transport of the CBU HPC from CBB to TC

21.23 Procedures for transport of cryopreserved CBUs shall be designed to protect the integrity of the CBU and health and safety of personnel.

21.24 The shipment time between the CBB and the TC facilities should be minimal. Plans for alternative emergency transportation must be available.

21.25 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.

21.26 The dry shipper must contain a device (data logger) that continuously monitors temperature for all the shipping.

21.27 The CBU bag must be labelled at least (partial label) with:

- the product name "*HPC-Cord Blood";*
- SEC and UNI identification code or product code and CBB specification (in case it is not feasible, the code must be written in the accompanying documentation);

Any bag bearing a partial label shall be accompanied by the complete information (attached securely to the CBU on a tie tag or enclosed in a sealed package that accompanies the unit) that comprehends:

- date of CBU collection;
- name and volume of any additives including anticoagulant and cryoprotective agents.
- volume or weight of the CBU;
- product manipulation description;
- ABO group and Rh type;
- HLA typing;
- number of nucleated cells;
- gender of CBU infant donor;
- recommended storage temperature in Celsius degrees;
- recipient's identification code.

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

21.29 The shipping methods must comply with the existing regulations and procedures related to the shipment of such devices (e.g. dry-shipper must be kept in vertical position), **Attachment T-CBU.**

22 UNRELATED DONOR SEARCH COSTS AND FEES

Following the *Law n. 52 of 6 March 2001 art. 3*, the cost of the tests performed for the enrollment of the donors in the IBMDR Registry is covered by the Italian Regional administrations. The costs for HLA typing, blood samples shipment, the donor medical evaluation, HPC or other blood components collection and transport are covered by the patient's health system coverage, 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;

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

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

Patient covered by the Italian national Health System -SSN *(a,b)*

22.3. The services requested by the IBMDR are covered by the regional health system according to the patient's residence.

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

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

International patients (*c*)

22.6. The services performed on behalf of international patients are invoiced to the TC/ IR according to the established IBMDR fee schedule.

22.7. IBMDR is responsible for refunding the pertinent Italian structures (DC, RR, CC, CBB) for the services provided according to the established IBMDR fee schedule.

Patients in the charge of an Italian TC, but not covered by the Italian National Health System (SSN)

22.8. Before activating search procedures, the TC must clearly establish who has the responsibility to cover the costs of the search procedures and of the transplant. If the patient is not covered by the NHS, he/she should pay for the medical services received, following the IBMDR indications.

Table III

Required criteria to activate a UD search and a Work up according to the disease and the disease stage *(GITMO Review – May 2024).*

ACQUIRED DISEASES

Age limit for activating the search:

a) ≤ 65 years for SAA and EPN with marrow failure;
b) ≤ 75 years for all other neoplastic diseases or

DISEASE	Disease STAGE and CHARACTERISTICS	SEARCH ACTIVATION	WORK UP
ACUTE MYELOID LEUKEMIA (AML) > 18 years			
Low risk, MRD positive Intermediate-high risk	CR1	YES	YES
Any class of risk	≥ CR2	YES	YES
Resistant	Resistant	YES	YES
ACUTE MYELOID LEUKEMIA (AML) <18 years			
High risk	CR1	YES	YES
Any class of risk	≥ CR2	YES	YES
Resistant	Resistant	YES	YES
ACUTE PROMYELOCYTIC LEUKEMIA	≥ CR2	YES	YES
MYELODISPLASTIC SYNDROME > 18 years			
IPSS, IPSS-R score, IPSS-M	≥ Int	YES	YES
MYELODISPLASTIC SYNDROME <18 years			
Resistant cytopenia in pediatric patient	-Transfusion-dependent disease; -ANC≤1000/mmc; -Complex kariotype; -Chromosome 7 monosomy	YES	YES
Advanced MDS Therapy-related MDS/AML		YES YES	YES YES
MYELO-MONOCYTIC JUVENILE LEUKEMIA		YES	YES

CHRONIC MYELOID LEUKEMIA			
	Blast crisis	YES	CP/AP[2]
	FA FC ≥2 FC1 resistant to ≥ 2 TKI	YES	YES
MYELOFIBROSIS (primary/secondary)			
DIPSS or IPSS score, DIPSS plus, MIPSS70, MIPSS70 plus	≥ Intermediate	YES	YES
MYELOID and LYMPHOID neoplasms with eosinophilia Rearrangement of FGFR1/ PCM1-Jak2		YES	YES
CHRONIC MYELOMONOCYTIC LEUKEMIA CPSS, CPSS-mol	≥ Int	YES	YES
MYELODYSPLASTIC/MYELOPROLIPHERATIVE neoplasm with SF3B1 AND TROMBOCYTOSIS	Disease progression (persistent cytopenias, new cytogenetic alterations)	YES	YES
MDS/MPN WITH NEUTROPHILIA		YES	YES
MDS/MPN NOT FURTHER SPECIFIED		YES	YES
MYELOID/LYMPHOID NEOPLASIES WITH EOSINOPHILIA AND:			YES
FGFR1 or PCM1-Jak2 rearrangement		YES	YES
SEVERE APLASIA ANEMIA		YES	YES
PAROXYSMAL NOCTURNAL HEMOGLOBINURIA	with bone marrow failure	YES	YES
LANGHERHANS CELLS HISTIOCYTOSIS			
multi-systemic resistant disease		YES	YES
ACUTE LYMPHOBLASTIC LEUKEMIA > 18 years			
Ph neg	CR1 -MRD positive or other high-risk indicators	YES	YES
Ph pos	CR1	YES	YES

Any class of risk	CR2	YES	YES
Resistant	Resistance	YES [1]	IBMDR GITMO Committee[1]
ACUTE LYMPHOBLASTIC LEUKEMIA <18 years			
Any high risk ALL	CR1	YES	YES
Ph pos	CR1-MRD positive	YES	YES
Any class of risk ALL	≥ CR2	YES	YES
Resistant ALL	Resistance [1]	YES [1]	IBMDR GITMO Committee[1]
CRONIC LYMPHOCYTIC LYMPHOMA	High risk CLL (immunotherapy and "pathway inibitors" resistant	YES	YES
NON-HODGKIN LYMPHOMA > 18 years			
NHL large B cell lymphoma	Relapsed/resistant disease	YES	If ≥ SD[3]
Follicolar lymphoma	Relapsed/resistant disease	YES	If ≥ SD[3]
Mantellar lymphoma	-CR/PR >1 after autologous Tx -CR/PR >1 no autologous Tx -Resistant disease	YES	If ≥ SD[3]
Burkitt Lymphoma	First or further relapse	YES	If ≥ SD[3]
T-Cell peripheral Lymphoma	• chemo-sensitive relapse ≥ CR1; • CR1 • Resistant disease	YES	If ≥ SD[3]
Cutaneous T-Cell Lymphoma	Advanced/IIB-IV stage EORTC/ISCL	YES	If ≥ SD[3]
NON-HODGKIN LYMPHOMA <18 years	(Independently from histological subtypes)		
	≥ CR2 Resistant disease/ persistent disease	YES	If ≥ SD[3]

	after rescue treatment		
HODGKIN LYMPHOMA			
	• First chemo-sensitive relapse after autologous; • Second or further relapse; • Resistant disease	YES	If ≥ SD
WALDENSTROM MACROGLOBULINEMIA			
	High risk disease (immuno-chemotherapy, proteasome inhibitors and immunomodulator agent resistant disease)	YES	YES
MULTIPLE MYELOMA			
	Chemo-sensitive relapse after autologous Tx High risk chemo-sensitive	YES	YES
PLASMACELLULAR LEUKEMIA			
	Chemo-sensitive disease after induction	YES	YES

Definitions/ abbreviations:

CP: chronic phase
AP: accelerated phase
CR1: first complete remission
CR2: second complete remission
CR/PR>1: first complete remission / partial response obtained with one or more rescue treatments after the failure of the standard induction therapy
SD: stable disease

[1] Acute leukemia with not favorable risk at diagnosis, have indication to activate an UD search. In the event of a work-up request for a recipient with ALL not in CR, the IBMDR GITMO Committee opinion must be required.

[2] CML in blast crisis may activate an UD search. In the event of a work-up request for a patient with CML, the blast crisis must be in CP or AP.
The donor selection for work up on behalf of a patient with a CML not CP/AP blast crisis is possible according to the IBMDR GITMO Committee evaluation.

[3] Lymphoma patients may request a donor for work-up in case of a complete response, partial response or stable disease. In case of progressive disease, the evaluation of IBMDR GITMO Committee is required.

INHERITED DISORDERS

1. PRIMARY IMMUNODEFICIENCIES

- Severe Combined Immunodeficiency (SCID)(independently from molecular classification)
- Primary Immunodeficiency disease (PID) based on its clinical, immunological and molecular characteristics.

Combined Immunodeficiency, CID (based on clinic and immunologic evaluations and phenotypic group)
Chronic Granulomatous Disease (CGD)
Wiskott-Aldrich Syndrome
Haemophagocytic familiar histiocytosis (FHL 1-5)
RAB27α Deficiency
Chediak-Higashi Syndrome
Lymphoproliferative Syndrome to X: XLP1, XLP2
Severe Congenital neutropenia
CD40 Ligand Deficiency
CD40 Deficiency
IPEX
CD25 Deficiency
MHC II Class Deficiency
Leucocyte Adhesion Deficiency Type I, LAD I
Haploinsufficiency of CTLA4
LRBA Deficiency
GATA2 Deficiency
DOCK8 Deficiency
DOCK2 Deficiency
Cartilage-hair Hypoplasia
Schimke immuno-osseous dysplasia (SIOD)
PGM3 Deficiency
STAT1-GOF

STAT3- GOF
IL-10 Deficiency
IL-10 receptor Deficiency
NEMO Deficiency
Immunodeficiency associated with DNA repair defects non SCID
ada2 Deficiency

2. HEMATOLOGICAL DISORDERS

- Blackfan Diamond anemia
- Sickle-cell anemia
- Transfusion dependent Talassemia
- Inherited Dyserythropoietic anemia
- Fanconi Anemia
- ShwachmanDiamond Syndrome
- Inherited Dyscheratosis
- Glanzmann Thrombasthenia
- Congenital Amegakaryocitosis
- Osteopetrosis

3. METABOLIC DISEASE

<u>Lysosomial disorders</u>

A. MUCOPOLYSACCARIDOSIS
    - Hurler Disease (MPS 1 H)
    - Scheie Disease (MPS 1 S)
    - Hunter Disease (MPS II)
    - Maroteaux-Lamy Disease (MPS VI)
B. SFINGOLIPIDOSIS
    - Metachromatic Leukodystrophy
    - Krabbe Disease
    - Farber Disease
C. GLICOPROTEINOSIS
    - α-Mannosidosis
    - Fucosidosis

<u>Perossisomialis disease</u>

- Adrenoleukodistrophy

Table IV

Minimum criteria needed to request a subsequent donation for Donor Lymphocyte Infusion (DLI)

DLI purpose	Indication	Timing	Maximum CD3/kg dose which can be requested
Prophylaxis	Clinical experimental GCP protocol needed and approval of IBMDR GITMO Committee	I HPC request	
Pre-emptive (MRD or mixed chimerism)	Standard	Start tapering IS Collection 1 month after IS conclusion	<=9/10 = 5 10x107 10/10 = 20 x107
Hematological relapse	Standard	After rescue in case of complete remission *	<=9/10 = 10x107 10/10 = 20 x107

*It is possible to forward the request before the start of rescue therapy