Ezer Mizion Bone Marrow Donor Registry

Operations Manual

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EZER MIZION

Bone Marrow Donor Registry

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1. ORGANIZATION

1.1 Ezer Mizion Bone Marrow Donor Registry

1.1.1 General

1.1.1.1 Ezer Mizion is the largest non-profit organization in Israel offering an extensive range of medical and social support services to any person in need. Ezer Mizion is an official recognized legal entity listed by the Israeli Ministry of Justice as a non-profit organization no. 580079978 (enlisted May 1985). The Ezer Mizion Bone Marrow Donor Registry (BMDR) operates as one of the services offered and operated by the Ezer Mizion health support organization.

1.1.1.2 Ezer Mizion BMDR provides hematopoietic stem cells (HSC) obtained from individuals recruited as volunteer donors to patients in need in Israel and in any other country worldwide.

1.1.1.3 Ezer Mizion BMDR operates as a national organization according to the Bone Marrow Donor Registry act, 2011 and in compliance with the Israeli MOH guideline which regulates bone marrow registries in Israel (39/2012. Dec 2012).

1.1.1.4 Ezer Mizion BMDR operates from one central national office and maintains both donor registry and donor center functions:

1.1.1.4.1 Donor registry – serving as a national organization whose responsibility is to process requests originating from within Israel and emanating from abroad for hematopoietic stem cells from volunteer donors unrelated to the patient. The registry maintains a database of donors, which may be searched as appropriate.

1.1.1.4.2 Donor center – responsible for recruiting, consenting, counseling, tests coordinating and Work-up of prospective donors.

1.1.1.5 Ezer Mizion BMDR should be an organizational member accredited by the World Marrow Donor Association (WMDA) and must review its recommendations.

1.1.1.6 Changes to the status of the registry (such as change in legal status, change in physical location, change in key personnel, and change in national laws) must be brought to the attention of the WMDA and to the relevant collaborating entities in a timely fashion. These notifications shall be provided in writing with the signature of the registry director.

1.1.1.7 Ezer Mizion BMDR must provide an organizational chart, on which name, task and position of all employees within the organization can be seen.

1.1.1.8 Ezer Mizion BMDR maintains written policies and protocols, including all relevant forms, in the Ezer Mizion BMDR Operations Manual.

1.1.1.9 All procedures applied by the Ezer Mizion BMDR central office and its descendant entities must be detailed in the Operations Manual and SOPs which must be available where these procedures are carried out. Each procedure must be annually reviewed and written evidence of this review must be recorded.

1.1.1.10 Any change in the Operations Manual must be approved by the registry director. The registry must assure that the relevant person(s) or entity influenced by these changes will be informed in writing.

1.1.1.11 Ezer Mizion BMDR must maintain a quality management system at least corresponding to the definition of WMDA standards. It must ensure and document compliance with these standards comprising especially document management, records, staff training and further education, complaint management and traceability. The registry maintains written policies and protocols for all the processes performed in the registry. The registry quality policy and management system is described in the Quality Manual.

1.1.1.11.1 The registry should have a plan to provide crisis response, business continuity and disaster recovery.

1.1.2 Tasks

1.1.2.1 Registration, selection and recruitment of potential donors

1.1.2.2 Maintains a database of donors in pseudonymous form, which may be searched as appropriate. The registry does not facilitate search requests of international donors on behalf of national transplant centers.

1.1.2.3 Provides lists of HLA compatible donors in pseudonymous form according to the current state of the scientific and technical knowledge to the requesting organizations (search units, foreign registries, transplant centers) without delay.

1.1.2.4 Upon request activates a donor search within the registry's donors.

1.1.2.5 Accepts requests for further typing and the shipment of blood samples.

1.1.2.6 Reports incoming test results to the relevant institutions.

1.1.2.7 Guarantees immediate handling and forwarding of all important processes within the donor search and donor procurement.

1.1.2.8 Responsible for billing of all services within the donor search.

1.1.2.9 Ensures documentation of all essential processes within the donor search.

1.1.3 Location and Resources

1.1.3.1 The central office of the Ezer Mizion BMDR is located at the Oranit Center in Petah Tikva, Israel. An additional facility of the Ezer Mizion BMDR is the volunteer-donor-recruitment booth located in the Israeli Defense Forces (IDF) military base where new soldiers are enlisted to the army.

1.1.3.2 The physical space and electronic infrastructure shall match the volume requirements for the registry operations.

1.1.3.3 The Ezer Mizion BMDR office can be contacted by phone, fax and e-mail. The registry must guarantee continuous occupation of all essential functional units during regular office hours, adequate in number and qualification. A 24 hour emergency telephone number is available outside office hours and in case of emergencies.

1.1.3.4 The registry contact details are made public in letterheads, email signatures, forms and the Ezer Mizion BMDR website.

1.1.3.5 There must be adequate equipment in data system technology. Data protection and security must be guaranteed according to Section 10 "Information Technology and Information Management".

1.1.4 Staff

1.1.4.1 Ezer Mizion BMDR must have a managing and administration director who has the necessary professional skills in this field of activity. The registry director is responsible for ensuring the registry's compliance with the WMDA standards. The authorized official of the the registry is responsible for ensuring the registry's compliance with the WMDA Standards. The authorized official must authorize all official documents related to WMDA qualification/accreditation.

1.1.4.2 Ezer Mizion BMDR must have a medical advisory committee which will be available to assist the registry with medical issues and various related procedures.

1.1.4.3 Ezer Mizion BMDR must have a medical director who is licensed physician with the necessary professional skills in this field of activity. The medical director is available to assist with routine medical decisions regarding donor selection and donation.

1.1.4.4 Ezer Mizion BMDR must have external medical advisors and consultants with expertise in human histocompatibility and HSC transplantation.

1.1.4.5 The registry will maintain sufficient staff that would allow it to carry out its tasks within reasonable time frame based on WMDA metrics for unrelated donor search. It must be ensured that at least one staff member who has a good spoken and written command of English language is always available. Position descriptions, roles, experience, time allocation are documented for all staff members.

1.1.5 Ezer Mizion BMDR requires that all staff is trained and knowledgeable about their duties. The registry will facilitate continuous training opportunities for its staff in the fields required for their work and maintain training records.

1.2 External Entities

1.2.1 Ezer Mizion BMDR relies on external entities to perform some of the duties described in these standards. It is the responsibility of the registry to ensure that these entities comply with WMDA standards and national Israeli regulations. The nature of these affiliations and the duties and responsibilities of each entity must be documented in a written agreement.

1.2.2 Laboratories

1.2.2.1 Immunogenetics Laboratories: Any tissue typing laboratory that serves the Ezer Mizion BMDR must gain an accreditation approval by the European Federation for Immunogenetics (EFI) and/ or the American Society for Histocompatibility and Immunogenetics (ASHI) to provide histocompatibility testing services essential for stem cell transplantation. This includes accreditation to perform HLA typing for Class I and Class II, both at low and high resolution, by molecular methods. The laboratory must hold a valid certificate of accreditation and should deliver a copy of the valid certificate to the Ezer Mizion BMDR.

1.2.2.2 Laboratory for Blood Group and Infectious Disease Marker (IDMs) Testing: A laboratory that performs ABO/Rh typing and/or IDMs testing (including NAT tests) must be authorized by the Israel Laboratory Accreditation Authority or another authorized accreditation body. The laboratory must obtain a valid certificate and deliver a copy of the valid certificate to the Ezer Mizion BMDR.

1.2.3 Transplant Centers

1.2.3.1 Blood stem cell transplantations of unrelated Ezer Mizion BMDR donors may only be performed in transplant centers that possess the required expertise and authorized by the Israeli MOH and report all consecutive transplants to either EBMT or CIBMTR designed to ensure that donation of hematopoietic stem cells will only be requested for patients for whom transplantation is a medically acceptable procedure.

1.2.3.2 The transplant center must be in possession of all licenses required by law and must observe all applicable regulations, laws and guidelines.

1.2.3.3 The criteria for affiliated transplant center should be clearly defined. The nature of these affiliations, the duties and the responsibilities of these entities must be documented in a written agreement.

1.2.3.4 Affiliated transplant centers should present to the Ezer Mizion BMDR prior to the initiation of a search: Valid authorization/accreditation to perform hematopoietic stem cell transplantation and a letter from the patient's physician detailing the indication for transplant.

1.2.3.5 The registry's standards for Israeli transplant centers are available to other registries as written document sent upon request.

1.2.4 Collection Centers

1.2.4.1 Ezer Mizion BMDR relies on local Collection centers to perform donor's medical evaluation, collection of hematopoietic stem cells and donor's follow up for the sake of patients in need.

1.2.4.2 Ezer Mizion Collection Center serves as the main collection center of the registry for Peripheral blood HSC collection.

1.2.4.3 Israeli collection centers must be authorized by the Israeli MOH to perform hematopoietic stem cell collection, and should meet international standards (EBMT/FACT-JACIE or equivalent) and Ezer Mizion BMDR standards for HSC collection.

1.2.4.4 The center must have experience in the collection of hematopoietic cellular products by Apheresis or Bone Marrow aspiration. Center must have adequate and appropriate resources to support its collection and associated management activities.

1.2.4.5 Center must have a medical director who is a licensed physician qualified and experienced to supervise the collection procedures. The physician is responsible to perform the medical evaluation, supervise the collection process and be available for direct telephone discussions.

1.2.4.6 Center shall have staff experienced in the management of HSC collection and processing of cellular components, and shall designate a coordinator to work with the registry.

1.2.4.7 Stem cell processing laboratories and IDM laboratories that perform the medical evaluation must obtain an accreditation certificate from a recognized organization. It is recommended that the collection center works towards JACIE accreditation.

1.2.4.8 Center shall maintain written procedures and policies for donor evaluation, mobilizing agent administration, and management of adverse events, and for the collection, testing, storage, labeling, and transport of hematopoietic cells and for the maintenance of Apheresis equipment.

1.2.4.9 Collection center must comply with the WMDA standards. The nature of the affiliations and the duties and responsibilities of each entity must be documented in a written agreement. Collection centers are expected to inform the Ezer Mizion BMDR of any substantial change in their professional accreditation or authorization.

2. DONOR RECRUITMENT AND CONSENTING

2.1 Recruitment Staff

2.1.1 The recruitment of stem cell donors must be performed under the direction of individuals who are experienced in recruitment of donors and management activities including education, consenting, counseling, confidentiality and medical screening.

2.1.2 All the personnel involved in the registration of the volunteers may have diverse backgrounds but all should receive adequate training and educational background material.

2.1.3 Personnel who are not a part of the routine recruiting team but participate in recruitment of donors during special donor-drives must be adequately trained.

2.1.4 The donor recruitment personnel must have a good knowledge of counseling new donors, confidentiality issues, basic medical screening, and receive an introductory briefing at the Ezer Mizion BMDR general office.

2.2 Donor Recruitment Setting

2.2.1 A donor may join the Ezer Mizion BMDR in several different settings as detailed below:

2.2.2 IDF Recruits

2.2.2.1 Since 2005, new soldiers being recruited to the Israeli Defense Force (IDF) may join the Ezer Mizion BMDR during the process of their enrollment to the army. The recruitment takes place at the Ezer Mizion BMDR booth at the military base where new soldiers are enlisted.

2.2.2.2 Joining the registry on the day of recruitment to the army is not compulsory but rather it is a volunteer act performed with the free will of the new soldier.

2.2.2.3 The booth in the military base is an integral part of the Ezer Mizion BMDR and is being operated by staff that complies with all the regulations and SOPs of the registry.

2.2.2.4 The Ezer Mizion BMDR sees great importance in the recruitment of volunteer donors through their enlistment to the IDF. This endeavor enhances the genetic diversity of the registry and lowers the average donor age of the registry through the recruitment of these young healthy donors of mixed ethnic origins.

2.2.3 Routine Recruitment of Donors

2.2.3.1 Routinely, people who are willing to join the registry may contact the Ezer Mizion BMDR office in order to coordinate a date for sample collection or shipment. This recruitment does not have to be a part of a donor-drive, but is always performed under the regulations and SOPs of the registry detailing issues of confidentiality, consent etc

2.2.4 Targeted Population Donor Drive

2.2.4.1 On occasion Ezer Mizion BMDR will initiate a donor-drive that is focused on a specific targeted population. This drive may be initiated following the request of a specific patient's family. In case no related donors were found for a patient, the registry may initiate a donor-drive that would be focused on recruiting new donors that belong to the same ethnic origin as the patient.

2.2.4.2 Family members over the age of 18 years who have already been tissue typed may be asked to join and have their details transferred to the registry at any time up to the age of sixty (60).

2.2.4.3 Before initiating a population targeted donor drive, the registry will consult with the HLA advisors in order to plan the drive to be optimally focused on the potential population of interest.

2.3 Recruitment Terms

2.3.1 At the time of recruitment, the following information about the donor will be collected: age, gender, ethnic origin, date of birth, ID number, weight, contact details and medical background.

2.3.2 Donors will be enrolled by the Ezer Mizion BMDR only between the ages of 18 and 45 years. There may be exceptions in the upper age limit in specific ethnic groups after discussion with the director of the registry.

2.3.3 Donors will be retired from the registry at the age of 60. The donor is deleted from the registry's database at his 60st birthday.

2.3.4 The donor must assure to be healthy to the best of his knowledge and not to suffer from any of the following diseases/conditions:

2.3.4.1 Cancer other than minor skin cancer or carcinoma in situ of the cervix

2.3.4.2 Leukemia, lymphoma, myeloma or related blood disorders

2.3.4.3 A risk or confirmation of HIV 1/2 or Hepatitis B or Hepatitis C or the confirmation of HTLV I/II

2.3.4.4 Creutzfeldt–Jakob Disease (CJD), Gerstmann Straussler Scheinker Syndrome (GSS), Fatal Familial Insomnia (FFI), or at risk of developing CJD, GSS or FFI

2.3.4.5 Sever conditions such as: severe cardiovascular diseases, severe pulmonary diseases, systemic autoimmune diseases, multiple sclerosis, severe metabolic diseases, severe neurological disease, severe allergies and severe psychological disorders

2.3.4.6 Myeloproliferative diseases including polycythemia vera, thrombocytopenia and myelofibrosis, or other evidence of serious bone marrow dysfunction (e.g. refractory anaemia, chronic neutropenia)

2.3.4.7 Thalassaemia major and severe coagulopathy

2.4 Donor Information and Consent

2.4.1 Donors must receive comprehensive information on the donation process and express their consent by signing the proper forms. This must take place in three stages:

2.4.2 Recruitment

2.4.2.1 The donor's consent to join the registry must be documented in designated forms (FRM_IC11/FRM_IC10). Comprehensive information must be provided to the donor prior to registration. Information may be given through literature or in person by recruitment staff. The information must contain the following items:

2.4.2.1.1 Reasons for the search for voluntary blood stem cell donors

2.4.2.1.2 Methods of sample collection for HLA sampling; the donor must be advised that further sample collections and testing may be necessary in the future

2.4.2.1.3 Information about possible storage of donor samples

2.4.2.1.4 Information that a medical examination will be performed prior to blood stem cell donation

2.4.2.1.5 Anonymity of donation

2.4.2.1.6 The donor is a volunteer member of the Ezer Mizion registry and is not remunerated for the donation. However, all expenses incurred during the donation process will be reimbursed

2.4.2.1.7 Donor must be willing to donate on behalf of any patient in need in any part of the world. The Donor's HLA information will be anonymously registered in the Search & Match database

2.4.2.1.8 Methods of blood stem cell donation, their risks and possible side effects

2.4.2.1.9 Donor must be conscious of the Ezer Mizion BMDR policy on encounters between patients and donors and the reasons for that policy

2.4.2.1.10 Donor must be informed that he/she can withdraw consent at any time

2.4.3 Additional typing and Verification typing

2.4.3.1 If donors are selected for additional or Verification typing (VT) they must be provided with the information referred in section 2.4.4. The major points can be discussed by phone and information materials are provided to the donor via information sheet or the Ezer Mizion web site. Counseling must include anonymity of the donor and patient, requirement for further blood samples before donation, requirement for infectious disease and other testing, risk of donation, possible duration of inability to conduct normal activities, location of the collection, the potential for collection of autologous blood, donor's right to withdraw consent and consequences for the patient, details of insurance coverage, possible subsequent donations of HSC or blood products and alternative collection methods.

2.4.3.2 If blood samples need to be collected for additional typing - Additional Typing Informed Consent form (FRM_IC21) needs to be completed. At the time of VT the Ezer Mizion Donor Health History Questionnaire form (FRM_IC40) must be completed in conjunction with the Verification typing Informed Consent form (FRM_IC20).

2.4.3.3 Donors should be contacted no later than twelve (12) weeks after a confirmatory testing sample is drawn to give them an update on the progress of the compatibility testing.

2.4.3.4 Donor identity must be verified.

2.4.4 Donor Work–up

2.4.4.1 The Ezer Mizion BMDR coordinator should provide the donor preliminary information regarding the donation. The collection center physician and designees are ultimately responsible for providing comprehensive information, disclosure of any risks and the physical assessment of the donor at this stage.

2.4.4.2 Donor's identity must be verified and documented.

2.4.4.3 Prior to donation, donors must meet with a physician at the collection center for a final information session, and physical examination. The donor must be given the opportunity to discuss this information and to have any questions explained by the collection center physician before signing the Informed consent form.

2.4.4.4 Donors must be given the opportunity to have an advocate or third party (family member) present at the pre-collection physical and information session and during the collection.

2.4.4.5 If the donor is in doubt about the procedure or unsuitable for peripheral blood HSC collection he should be informed that conventional Bone Marrow donation may be possible. If the donor chooses not to donate peripheral blood HSC but is willing to donate bone marrow, the registry must inform the transplant center and accept its confirmation to proceed with Bone Marrow collection.

2.4.4.6 Consent for the HSC collection must be obtained and documented by the collection center in compliance with all applicable legislations. The donor confirms in writing that he has understood the information provided and that all his questions have been fully answered. Donors that have agreed to follow the procedure must sign the designated Informed Consent forms (FRM_IC31 / FRM_IC32). By signing the consent form the donor confirms to be informed of the preparations for the procedures of collection, and the associated risks including the consequences for the recipient if he withdraws his consent to donate after the beginning of the recipient conditioning therapy. A copy of this document must be provided to the donor and delivered to the Ezer Mizion BMDR office.

2.4.4.7 The donor must sign a further consent if blood or other biological material is stored and/or used for research projects or different purposes. The principal investigator must provide the study number, the title of the study, a synopsis and the approval of the ethics committee. Clinical studies are being conducted in compliance with the Israeli MOH guideline for clinical trials in human beings.

2.4.4.8 Issues to be discussed and fully explained to the donor during the collection center physician counseling are:

2.4.4.8.1 Therapeutic value of blood stem cell donations and possible benefit for the recipient

2.4.4.8.2 Donation methods and procedures of peripheral blood and marrow HSC collection.

2.4.4.8.3 The product preference of the transplant center

2.4.4.8.4 Required blood samples collection before the donation date, pre-collection samples, tests for infectious disease markers (IDMs) and other clinical parameters, and the donor's right to receive the results of this screening

2.4.4.8.5 Personal information that will be collected and how this information will be protected

2.4.4.8.6 Information regarding the risk of infectious disease transmission to the recipient by blood stem cell transplantation

2.4.4.8.7 Physician's general duty to inform the donor in case of abnormal finding during the medical examinations

2.4.4.8.8 The possible duration of absence from work and physical activities

2.4.4.8.9 The donor center and hospital general liability insurance coverage for the Work-up and collection procedures

2.4.4.8.10 Reasonable expenses incurred during the donation process will be reimbursed.

2.4.4.8.11 Non-remuneration of donation

2.4.4.8.12 The location of the collection center and an emergency telephone number

2.4.4.8.13 Instructions for the timing of Granulocyte Colony Stimulating Factor (G-CSF) injections and availability of contact information of the physician on duty

2.4.4.8.14 Requirement of Marrow HSC donation if the G-CSF mobilization is unsuccessful or must be interrupted

2.4.4.8.15 Risks and side effects of anesthesia, Marrow donation, administration of G-CSF and peripheral blood HSC donation and other blood product donations

2.4.4.8.16 In case of peripheral blood HSC donation the donor should be informed that this protocol will only allow the use of peripheral venous access for collection except special circumstances, such as inadequate access identified on the day of collection despite the donor being cleared for peripheral blood HSC collection at Work-up

2.4.4.8.17 In case of Marrow collection the donor should be informed that an autologous blood unit may be collected before the procedure

2.4.4.8.18 If the donor is female, she must be informed that pregnancy is a contraindication to donate and adequate contraception may need to be discussed. A full disclosure of the risks involved should be given to the woman with regard to the possibility of fetal malformation and/or miscarriage. Women who are breastfeeding must be willing and able to interrupt breastfeeding during the days of G-CSF administration

2.4.4.8.19 The possibility of and possible procedures involved with a subsequent donation and the risks involved.

2.4.4.8.20 The policy regarding anonymity between donor and patient

2.4.4.8.21 The donor should be prepared for the eventuality that for a variety of reasons the transplant may not be successful

2.4.4.8.22 Information regarding whether blood will be collected and reserved for research purposes

2.4.4.8.23 The donor has a right to withdraw consent at any stage however the donor must be informed of and understand the risk including the possibility of death for the recipient should the donor withdraw after the beginning of the recipient conditioning therapy

2.4.4.8.24 In exceptional cases, the option of product cryopreservation prior to the beginning of the recipient conditioning therapy subjected to the donor consent

3. TISSUE TYPING, HEALTH SCREENING & IDM TESTING

3.1 HLA Typing Standards

3.1.1 This standard outlines the minimal HLA typing requirements for tissue typing laboratories providing donors from the Ezer Mizion BMDR for unrelated HSC transplantation and distinguishes these requirements from additional ones deemed important by individual transplant centers.

3.1.2 Recruitment

3.1.2.1 HLA–A, HLA-B, HLA-C, HLA-DRB1, HLA-DQB1, and HLA-DPB1 typing by Next Generation Sequencing (NGS) technique at registration.

3.1.2.2 HLA typing must be applied in an HLA testing laboratories that are capable of carrying out DNA–based intermediate and high-resolution HLA-typing and are appropriately accredited by ASHI or EFI.

3.1.3 Additional Typing

3.1.3.1 Additional typing requests may be requested by the transplant center and may include any combination of the genes: A* or B* or C* or DRB1* or DQB1* or DRB3/4/5* at low or high resolution. HR typing results of all loci requested are recommended to be reported together rather than in a stepwise fashion.

3.1.3.2 Usually typing tests are being performed with stored DNA samples. In the event that the laboratory reports to the registry that there is not enough DNA from the donor in order to perform the additional typing request, the donor will be contacted and invited for a collection of an additional blood sample.

3.1.3.3 Additional typing results turnaround times: high resolution typing results should be received at the registry no later than 14 working days after a standard typing request was sent to the laboratory. The discovery of new HLA alleles and some complicated new ambiguities may result on occasions in the 14 day turnaround time to be exceeded.

3.1.3.4 All officially named alleles are to be resolved to the four digit level so that either one (homozygote) or two (heterozygote) alleles are reported. With the following exceptions noted:

3.1.3.4.1 Due to the rapidly increase in HLA nomenclature, alleles officially named during the preceding six months may not be included for analysis/assignment purposes. Laboratories must update typing libraries at least every six months.

3.1.3.4.2 Ambiguous allele combinations which lie outside of the region of interest are acceptable without further resolution. The region of interest is defined as exon 2 for HLA class II and exon 2 and exon 3 for HLA class I. Performing further typing at other exons to increase resolution is not precluded. Reported results must be accurate and if exon 3 of HLA class II or exon 4 of HLA class I is not typed, ambiguities unable to be resolved must be included in the result.

3.1.4 Verification typing

3.1.4.1 Additional tests performed by the laboratory serving the transplant center determine the degree of donor/recipient compatibility and confirm the appropriate donor. The results must be provided prior to donor work-up to determine the degree of donor/recipient compatibility and to confirm the donor identification. The transplant center must report the Verification HLA typing results of the donor and the recipient back to the Ezer Mizion BMDR.

3.1.4.2 Verification typing at a minimum of HLA-A, -B, -C, -DRB1 must be performed prior to donation/shipment for a specific patient.

3.1.5 Standards for Allelic DNA Assignments

3.1.5.1 All HLA data of donors shall be recorded in the registry database only in the format given by the current WHO nomenclature and standards or requirements of respective professional organizations such as EFI, ASHI or WMDA.

3.1.5.2 Information on new alleles can be obtained from the International Immunogenetics Information Systems (IMGT) web site or from the World Health Organization (WHO) Nomenclature Committee report which is published in Human Immunology and Tissue Antigens. Both sources are updated regularly.

3.1.5.3 NMDP codes are accepted and entered in the database providing that the typing laboratory provides them with the result of typing.

3.1.5.4 New sequences should be incorporated into generic and allele specific typing strategies and all ambiguous allele combinations from this point onwards are to be documented in each laboratory. High resolution strategies should as far as possible provide unambiguous typing for the alleles.

3.1.5.5 Where more than one donor meets the minimum matching criteria HLA C, DRB3, DRB4, DRB5 and DPB1 may be used to select the best matched available donor.

3.1.6 Quality Assurance of Samples and Tests Results

3.1.6.1 All blood samples collected at the verification typing stage and/or at any other stage of the donation process must be labeled and identified according to the regulations of the Laboratories department of the Israeli MOH procedure: CL11004/3 - registration and labeling of laboratory samples (2014). This procedure must be fully adhered to without jeopardizing the anonymity of the donor.

3.1.6.2 All HLA typing of donors will always be performed in a tissue-typing laboratory that is accredited by EFI or ASHI. Quality control of a specific laboratory typing the donors is ensured by the EFI/ASHI accreditation of the laboratory and annual verification of validity of the accreditation.

3.1.6.3 Entering HLA data of a newly recruited donor should be performed in an automated form directly from the primary data delivered by the typing laboratory. A designated worker is primarily responsible for the correct entry of HLA data in the registry database.

3.1.6.4 Any ambiguity or uncertainty or misunderstanding in the interpretation or comprehension of HLA typing results must be reported in writing to one of the HLA consultants of the registry in order to receive their feedback.

3.1.6.5 If a discordance is found in the HLA typing of a donor – i.e. the result of the primary typing of the donor is different from the result of the consequent typing, such discordance shall always be clarified by the HLA laboratory. All discordances in HLA typing of donors shall be reported to WMDA HLA discrepancy survey.

3.1.6.6 The IT database system of the Ezer Mizion BMDR does not allow input of 'illegal' allele or antigen assignments. Any attempt to enter entries that are not acceptable - will not be allowed and will be alerted by the database software.

3.2 Health Screening and Infectious Disease Testing

3.2.1 Donors must be screened for infectious disease markers (IDM) and other risk factors prior to donation of stem cells. Screening can take place at three stages: donor recruitment, donor selection, and donation processes. Screening is not mandatory at all stages: donors may be screened at recruitment but must be screened at VT and Work-up.

3.2.2 ABO/Rh typing, IDMs testing and any other blood tests will only be performed in laboratories that have been approved by the Israeli Laboratory Accreditation Authority or other authorized accreditation body and obtained a valid certificate. The laboratory must provide an annual verification of validity of the accreditation.

3.2.3 Recruitment

3.2.3.1 It is mandatory that all potential donors complete a donor questionnaire at recruitment which includes basic information about the donor's health status, age and gender. Any risks identified in a questionnaire will be discussed with the registry medical director and the decision will be made whether to accept or disqualify this donor. A donor's Body Mass Index (BMI) can fluctuate over the course of their time in the registry so no BMI limit is imposed at recruitment.

3.2.3.2 ABO and Rh factor typing using NGS method is performed for new recruits that joined the registry since 2017.

3.2.4 Verification typing

3.2.4.1 The Ezer Mizion registry organizes donor blood sample collection for verification typing (VT) and the accompanying tests as well as the transport of the blood samples to the respective appropriately accredited laboratories.

3.2.4.2 At the time of a VT sample request, a donor information session must be performed (see section 2.4.3). Furthermore, the donor must complete Health History Questionnaire (FRM_IC40) and signe the consent form (FRM_IC20).

3.2.4.3 Sample collection for VT is commonly performed in the Ezer Mizion BMDR central office. The Health History Questionnaire form may also be posted to the donor at the time of request for VT, completed by the donor and then returned to the registry, at the time the blood samples are shipped.

3.2.4.4 IDMs testing must monitor infection with human immunodeficiency virus (HIV), Human T-cell lymphotropic virus I and II (HTLV), Hepatitis B virus, Hepatitis C virus and Cytomegalovirus (CMV). If a transplant center requires additional infectious disease testing the registry will ship the donor samples to the appropriate transplant center.

3.2.4.5 The ABO blood group and Rh factor testing of donors must be done at the VT stage if the donor's blood group has not been previously determined. The test must be performed in a certified blood-banking laboratory.

3.2.4.6 Abnormal IDMs results are evaluated by the registry's medical director. The medical director or his/her authorized representative must inform the donor of abnormal infectious disease marker results and possible follow-up testing.

3.2.4.7 In addition to the Health History Questionnaire evaluation form, any abnormal findings that do not lead to donor deferral must be reported to the transplant center.

3.2.4.8 Any donor that has a BMI less than 20 or greater than or equal to 35 must be discussed with the registry's medical director as to whether the donor should be deferred temporarily or permanently from the registry.

3.2.4.9 The volunteer donor has the right to receive the results of his or her health screening.

3.2.5 Work-Up

3.2.5.1 Health History Questionnaire form (FRM_IC40) must be completed. The questionnaire will be provided to the donor at the collection center during the information session as part of the Work-up. The collection center physician is required to evaluate and review the donor questionnaire and witness the donor's signature on the consent form.

3.2.5.2 All donors are assessed at the collection center during Work-up by a qualified physician who decides if the donor should be cleared for collection or deferred. A physician who must not be a member of the transplant team or the team directly in care of the recipient determines the donor eligibility for the donation. The results of the examination must be recorded in writing.

3.2.5.3 The Work-up assessment tests of the donor include:

3.2.5.3.1 <u>IDMs tests</u>: HIV 1 & 2; HTLV I/II; Hepatitis B (HBsAg and Anti-HBc) Hepatitis C; EBV; CMV; Toxoplasma; Treponema pallidum (syphilis test); Nucleic Acid Testing (NAT) for HIV, HBV, HCV and West Nile Virus.

3.2.5.3.2 <u>Blood tests</u>: complete blood count, full biochemistry screening of the blood, ABO and Rh blood type.

3.2.5.3.3 Other tests may be performed according to the discretion of the collection center physician.

3.2.5.4 The tests results are evaluated by the collection center physician. The physician assessing donor´s health eligibility can indicate other necessary examinations based on the information regarding the donor´s health condition.

3.2.5.5 Pregnancy is a contraindication for donation. Female adult volunteer donors of childbearing age must have a pregnancy test performed during the work-up stage, within thirty (30) days prior to transplant date. Within 7 days prior to the initiation of the recipient conditioning therapy or within 7 days prior to the first donor G-CSF injection (if it starts sooner than the recipient conditioning therapy) the pregnancy test should be repeated to exclude pregnancy.

3.2.5.6 The donor's peripheral veins must be assessed. In case of Peripheral blood collection particular care should be taken regarding venous assessment, as central venous access is not routinely permitted. The person who will undertake the collection procedure should ideally perform this assessment.

3.2.5.7 In case of HSC marrow collection, the collection center physician will decide if autologous red cells units should be collected from the donor. The number of units collected will depend on the amount of marrow required for the patient. Collection of autologous donor blood must be performed at a blood collection center that fulfills national guidelines of the Israeli MOH. The decision whether to transfuse red blood cells, the donor's hemoglobin level, although important, should not be the sole deciding factor. Signs and symptoms of hypoxia, ongoing blood loss, the risk to the donor of anemia and the risk of transfusion should be considered.

3.2.5.8 Full IDMs testing must be performed within thirty (30) days prior to the transplant date. The IDMs results and blood type and supplementary donor information must be recorded in writing and must be completed and checked by the collection center physician once the laboratory results and the Health History Questionnaire have been reviewed. The donor's blood type and supplementary donor information can be completed by the donor center coordinator or authorized representative. The results of infectious disease markers performed at Work-up should be reported no later than seven (7) working days after testing.

3.2.5.9 In the event of postponement of the transplant, IDM testing must be repeated within thirty (30) days prior to transplant date. If more than 30 days but less than six months have passed since donor's clearance, the Health History Questionnaire must be reassessed by the collection center physician and a repeat physical assessment may be performed at the physician's discretion. If six months or more have passed since donor's clearance, a full donor Work-up must be repeated including hematological and blood chemistry tests, physical assessment and IDMs.

3.2.5.10 If pre-collection samples are required, no more than 50 mL of peripheral blood should be requested.

3.2.5.11 The volunteer donor has the right to receive the results of his or her health screening.

3.2.5.12 The donor medical suitability assessment is determined according to the WMDA Recommendations for Donor Medical Suitability and the NMDP donor assessment tool.

3.2.5.13 If the examining collection center physician determines that the donor is eligible for donation and the donor has signed the consent to donate, the collection center must report the donor clearance for collection and the results of the donor infectious disease testing on the appropriate Ezer Mizion form Donor Final Clearance (FRM_WU50). The transplant center must confirm in writing the collection date, the start date of the recipient conditioning therapy and the transplant date in the Donor Final Clearance Form.

3.2.5.14 The recipient conditioning therapy must not be initiated until donor clearance for blood stem cell donation including the results of the donor infectious disease testing have been reported in writing to the transplant center. In case of peripheral blood HSC donation, G-CSF injections must not begin until the transplant center has confirmed the collection date.

3.2.6 Abnormal Finding and Donor Deferral

3.2.6.1 A number of questions in the Ezer Mizion Donor Health History Questionnaire relate to the donor's general health and well-being. In part, these questions are designed to obtain information on possible infectious diseases that the donor may have or may have had but that are not addressed in specific questions. In case of infectious diseases that are not referred to in this document should be referred to the Ezer Mizion BMDR medical director for a decision on deferral periods.

3.2.6.2 Any abnormal findings at VT or Work-up, either with the Health History Questionnaire form or donor IDMs results that do not lead to donor deferral must be reported to the transplant center via the Ezer Mizion BMDR office. The transplant physician or his/her designee should reply to the Ezer Mizion BMDR with written acknowledgement that they have been informed of the abnormal findings and wish to proceed or wish to release the donor from the search process. A record of the reply must be kept in the donor file.

3.2.6.3 In case of a serious infectious disease identified during the health screening, the collection center must report the abnormal results to the Israeli MOH and proceed according to the MOH guideline for an immediate report of serious diseases (2006).

3.2.6.4 In case that a donor abnormal finding is identified during VT, the registry medical director, or his designee, informs the donor of the abnormal findings and arranges possible follow-up testing and counseling.

3.2.6.5 Donors with abnormal finding during Work-up:

3.2.6.5.1 The medical director and collection center examining physician shall determine whether an abnormal finding constitutes unacceptable risk to the donor.

3.2.6.5.2 The collection center physician informs the donor about the abnormal results, notifies the registry office and refers the donor to either the registry's medical director or his authorized representative, or for appropriate medical follow up elsewhere. Documentation of the counseling regarding abnormal finding shall be maintained.

3.2.6.5.3 *Abnormal findings increasing the risk of donation*: Final clearance of the donor is not granted if according to the discretion of the collection center physician the donor is ineligible. The collection center must send the Ezer Mizion form *Declaration of Ineligible Donor (FRM_WU53)* that will be sent to the transplant center. The transplant center must confirm this form in writing.

3.2.6.5.4 *Abnormal finding increasing the risk for the recipient*: Although positive results for any of the IDMs will not necessarily exclude a donor from donating, the transplant center must be made aware of any positive results so a decision can be made whether to proceed with the transplant. An increased risk product should be released by exception only when there is a documented clinical need for the product and when approved by the physician of the transplant centre via Ezer Mizion form *Abnormal Donor Finding (FRM_WU52)*.

4. FACILITATION OF SEARCH REQUESTS

4.1 Preliminary Donor Search

4.1.1 When an immediate or extended family search does not provide a suitable donor, a search can be undertaken in Ezer Mizion BMDR for an unrelated donor. In order to initiate an unrelated search the request should be entered into the registry software.

4.1.2 Main communications between registries or between registry and transplant center must be in writing. National preliminary search requests should be obtained by sending Ezer Mizion form of *Preliminary Search Request (FRM_S20).* International requests for a search of Ezer Mizion BMDR are mainly made through EMDIS system. In case an international registry does not possess access to EMDIS system a search request may be obtained by sending the form *FRM_S20* or equivalent via fax/e-mail.

4.1.3 Preliminary international searches can be initiated by:

4.1.3.1 Registries who are WMDA members acting on behalf of transplant centers in their country.

4.1.3.2 International transplant centers that are members of an international hematopoietic stem-cell transplantation association or accredited by their national governmental authorities. New applying centers must submit a signed letter of authorization from the relevant national authority or the international authority that accredits their status as a transplant center.

4.2 Patient Acceptance

4.2.1 Ezer Mizion BMDR will accept patients that require Bone Marrow Transplant from national or international centers. However, in certain cases, additional information may be required and additional processes followed.

4.2.2 Patient characteristics permissible for initiation of donor search are those described in the EBMT special report "Indications for all- and auto-SCT for haematological diseases, solid tumors and immune disorders: current practice in Europe 2019" (Duarte et al., Bone Marrow Transplantation 2019), and in rare situations following the approval of the medical director of the registry.

4.2.3 When a donor search on behalf of a patient is initiated the patient details are manually checked. If all patient characteristics are within Ezer Mizion BMDR standard requirements, no further action is required.

4.2.3.1 If the Ezer Mizion criteria are not met, the search will not be executed until further clarifications are received from the transplant center and approved by the registry's medical director. Should specific criteria or patient characteristics require further information or results that do not meet the registry's minimum criteria, this must be communicated via EMDIS or e-mail to the requesting registry/transplant center.

4.2.4 The Ezer Mizion BMDR medical director or a person authorized by him verifies the indication for the unrelated donor search.

4.2.5 For non-standard diagnosis a copy of the clinical study protocol and its approval by the responsible ethical committee must be provided for review by the medical director.

4.3 Search Procedure

4.3.1 The exchange of data on the national and international level must take place via Ezer Mizion BMDR.

4.3.2 Preliminary search results will be sent automatically via EMDIS, or by fax/e-mail on the next working day following receipt of the request.

4.3.3 Preliminary search request must include all donors that are potential 6/6 alleles match to the patient. Additional donors presenting different degrees of mismatches may also be included in the search results.

4.3.4 Donors that are not active or not available will not appear in the preliminary search report.

4.3.5 All searches may be repeated on request. Routine repeat searches are performed upon request.

4.3.6 Donor and patient identity must remain confidential in accordance with the country's privacy laws. Only appropriate registry personnel have access to the search data. It is never allowed for any person who is not a member of the registry main office staff to hold or read or use or have access to information regarding donor and patient identity.

4.3.7 Reports and/or information and/or any files sent to the transplant center or registry will never include any information regarding identity of donors except for gender and age data. Only the unique donor identifier code will be utilized in all correspondence between the Ezer Mizion BMDR office and representatives and the patient's registry/transplant center.

4.3.8 Ezer Mizion BMDR must inform the transplant center or the requesting registry in writing of any change in the donor's availability that occurs after a search process was initiated and that may influence this process. This written notification must be sent to the transplant center or to the requesting registry immediately as this change may bring about modifications in their search strategy for the specific patient.

4.4 Testing

4.4.1 Additional Typing

4.4.1.1 Typing requests can be submitted by EMDIS or fax/e-mail by using Ezer Mizion form HLA Typing Request (FRM_S30), WMDA form or equivalent.

4.4.1.2 High resolution typing results should be reported to the requesting transplant center or registry within 14 days.

4.4.2 Verification Typing

4.4.2.1 VT requests can be submitted by EMDIS or fax/e-mail by using WMDA form *Blood Sample Request for Verification Typing (S40)*, or an equivalent WMDA based form.

4.4.2.2 A donor selected for a specific patient must be placed on a "reserved" status from the time of VT until the transplantation date is reached. This period of time will not exceed three (3) months. It is expected that all confirmatory matching be made within this time and the selection of a donor can be made if appropriate. After three months the donor will be released into the available donor pool unless other specific requests are received in writing from the transplant center.

4.4.2.3 Donors should be contacted no later than twelve (12) weeks after a confirmatory (or third stage) testing sample was drawn, to give them an update on the progress of the compatibility testing.

4.4.2.4 The total quantity of blood samples provided to a transplant center for VT must not exceed 50mL per donor. Ezer Mizion BMDR cannot guarantee that blood samples are provided exactly as requested. This may refer to the number and volume of tubes and in rare cases to minor variations concerning the anticoagulant.

4.4.2.5 Blood samples test tubes collected at the verification typing stage, and/or at any other stage of the donation process, must be carefully labeled and indicate the donor and patient unique identifier, date and time of collection. A declaration of content and proforma invoice should be affixed to the container. Packaging and shipment must meet the regulations of the Israeli MOH, Department of Laboratories, procedure: CL11004/3 – "registration and labeling of laboratory samples" (2014) and according to the regulations of the International Air Transport Association (IATA) regarding shipment of dangerous goods. The registry should notify the transplant center regarding the VT sample arrival date.

4.4.2.6 No part of these samples can be used for research.

4.4.3 Work-up

4.4.3.1 The Ezer Mizion BMDR must be informed of the proposed date(s) of transplant at the time a specific donor unit is requested for stem cell donation on behalf of a specific patient.

4.4.3.2 The registry must be notified in writing using WMDA form - *Formal Request and Prescription for HPC, Marrow, HPC, Apheresis and for MNC, Apheresis* (F10) or an equivalent WMDA based form where details of the required stem cell product are to be described.

4.4.3.3 The transplant center must specify the latest date by which the Ezer Mizion BMDR must approve the eligibility of a donor for donation of hematopoietic stem cells for a specific patient (i.e., provide donor clearance).

4.4.3.4 The registry office will notify the donor by telephone that he was chosen to voluntarily donate stem-cells for a patient in need.

4.4.3.5 Ezer Mizion BMDR will not provide donors for transplantation if there are more than two mismatches at HLA Class I or II at the allelic level (two fields). Any exceptions to this can be reviewed by the registry's medical director. This applies to both national and international patients.

4.4.3.6 Prior to transplant the registry will contact the prospective donor in order to inquire about the donor's preference for type of stem cell harvest and for any other donor-specific issues (e.g. availability for subsequent donations) that may impact the donation. Any relevant information (such as a harvest method that is in contradiction to the transplant center's preference) must be rapidly reported in writing to the transplant center. The donor must be free to change his mind at a later date.

4.4.3.7 For registry policy regarding counseling the donor in the case of positive identification of donor health risk please refer to Section 3.

4.4.3.8 An increased risk product should be released by exception, only when there is a documented clinical need for the product and when approved by physician of the transplant center (Ezer Mizion form Abnormal Donor Finding (FRM_WU52).

4.5 Termination of a Search

4.5.1 Once a patient is on the search list, removal is an active process. Thus, registries/transplant centers are requested to notify Ezer Mizion BMDR when a donor search should be cancelled.

4.5.2 Failure to follow up at any of these stages can result in significant delays in the treatment of individual patients. This scheme is designed to prevent delays and ensure that adequate documentation is obtained for all patients.

4.5.3 The decision to terminate a search may only be made by the (1) patient, (2) referring physician, with the agreement of the patient, and (3) transplant center, with the agreement of the referring physician and the patient.

4.5.4 Searches will remain in progress until a signed notification regarding cancellation of search has been received to Ezer Mizion BMDR or until the date of a transplant has passed.

5. SUBSEQUENT DONATIONS FOLLOWING INITIAL STEM CELL DONATIONS

5.1 Introduction

5.1.1 This policy pertains to requests for second and subsequent HSC donations, Marrow, Peripheral blood or Lympcytes from an Ezer Mizion BMDR donor for the same patient. The policy does not cover requests for platelets or granulocytes.

5.1.2 It should be noted that a single donation may include more than one procedure. For example, a failed Peripheral blood HSC collection followed by a Marrow collection or two day Peripheral blood HSC collection is equal to one donation.

5.1.2.1 If a donor fails to mobilize and insufficient cells are collected after two Peripheral blood HSC collections ($<2x10^6$ CD34+ per Kg ideal patient body weight) a Marrow collection may be necessary. This must only occur after CD34+ analysis indicates that the Marrow collection is needed and after a review of the donor's fitness to donate post Peripheral blood HSC collection.

5.1.3 The minimum time intervals between donations should be one month. In urgent cases and upon the medical director discretion the interval between donations may be shorter.

5.1.4 After the first donation the donor is asked whether he is available for a subsequent donation for the same recipient if needed. The donor will be reserved for three (3) years for the initial recipient in order to be available for a subsequent donation. During this time the donor is not available for another patient.

5.1.5 The results of the medical evaluation in the normal range are a basic requirement for a subsequent donation.

5.1.6 A donor may be able to donate a subsequent donation to a new patient in case he expressed his free wish to return to the registry pool. Also, a subsequent donation to a new patient is approved if the patient for which the donor gave donation has deceased, and it is the donor free wish to return to the registry pool. In this case the donor is to be banned for a year after donation.

5.1.7 A donor may generally donate twice, either for one patient or for two different patients. After a donor has donated twice, it is recommended not to make him available for further donations. A further stem cell donation shall only be permitted in cases of urgent medical need, and reviewed by the medical director.

5.2 Request and Approval Procedure for Subsequent Donations

5.2.1 A written request using the WMDA form *Previous Transplant History (F20)* is required from the transplant physician clearly outlining the clinical justification for the request accompanied by *WMDA form Formal Request and Prescription for HPC, Marrow, HPC, Apheresis and for MNC, Apheresis (F10)*, or an equivalent WMDA based form. The transplant center must outline in writing the clinical justification for a further stem cell donation for a patient who already received an allogeneic transplant. The medical director of the registry must review the request. This regulation is valid regardless of whether the previous transplantation was carried out with stem cells from the same or a different donor. The written request must

include: proposed time frame for transplantation, recipient's preparative therapy plan if applicable, data from previous transplant and the current clinical condition of the recipient.

5.2.2 All requests for a second or subsequent donation are examined by the registry medical director, the physician responsible at the collection center and the registry senior coordinator. Their approval is required to approach the donor for subsequent donations. Decisions made on such requests are processed within forty eight (48) hours if at all possible.

5.2.3 If the request is approved, the Ezer Mizion BMDR is responsible for approaching the donor. The donor must be free to decline a subsequent donation at the time that it is requested. In addition to the above guidelines, it is emphasized that with respect to subsequent donations:

5.2.3.1 A clear cut division between donor and transplant centers must be maintained especially where the donor and patient are both in Israel.

5.2.3.2 All requests for subsequent donations must go through the Ezer Mizion BMDR.

5.2.3.3 The possibility of a subsequent donation of stem cells must be discussed at the original donor Work-up and be explicitly indicated in the consent forms.

5.2.3.4 A full disclosure of the procedure and risks must be made as with any donation.

5.2.3.5 The donor must be given ample time to make his/her decision and be free to ask any questions to which all answers must be freely given.

5.2.3.6 No pressure can be placed on the donor for any form of subsequent donations. The donor must feel free to decline.

5.2.3.7 The procedures donor information, medical evaluation and collection are as for the first donation (section 8). The results of the medical evaluation within the normal range are a basic requirement for a subsequent donation.

6. COLLECTION AND PROCESSING OF HSC

6.1 Work-up Request

6.1.1 A Work-up is the process a selected donor goes through to make sure that she/he is healthy enough to donate. After the availability of the results of donor's Verification typing, IDMs and other transplant-relevant data, the transplant center decides if the donor is acceptable.

6.1.2 The procedure must take place at Ezer Mizion BMDR affiliated collection centers. The information, medical evaluation and informed consent sessions are to be carried at the collection center as detailed in sections 2.4.4 and 3.2.5 of this manual.

6.1.3 The collection center must ensure the identity, safety and privacy of the donor and the confidentiality of the donor. Particular care should be taken that the donor does not meet the patient.

6.1.4 The registry must be informed of the proposed date(s) of transplant at the time a specific donor is requested for transplantation for a specific patient. The transplant center must specify the latest date by which the registry must provide donor clearance. To request a Work-up for HSC collection the following forms, or their international equivalent, must be completed:

6.1.4.1 Final patient HLA typing - unrelated donor transplant and confirmation of donor HLA typing. These forms must be completed by the tissue typing laboratory associated with the transplant center.

6.1.4.2 WMDA form - *Formal Request and Prescription for HPC, Marrow, HPC, Apheresis and for MNC, Apheresis* (F10) or an equivalent WMDA based form completed by the patient's physician at the transplant center.

6.1.4.3 The documentation must be forwarded by the transplant center or international registry to Ezer Mizion BMDR.

6.1.5 After the request has been reviewed and approved, the registry's coordinator will contact the donor and the collection center to schedule the collection procedure dates. The transplant center will be notified in a timely manner about the stem cell collection date/s using the Ezer Mizion form *Work-Up Schedule (FRM_WU20).* The schedule will be finally confirmed after the donor is considered suitable and consent has been obtained. The transplant center will be notified in case any changes in the collection schedule are required.

6.1.6 For non-standard procedure or diagnosis, a copy of the clinical study protocol and its approval by the responsible ethical committee must be provided for review by the medical director of the registry.

6.1.7 Parallel Work-up requests of different donors for the same recipient are generally not allowed. If parallel Work-up requests should become necessary in justified exceptional cases Ezer Mizion BMDR and the donors involved must be informed and must agree.

6.1.8 In exceptional cases, cryopreservation of a blood stem cell product at the transplant center prior to the beginning of the recipient conditioning therapy may be requested. If it is intended that cryopreservation is to be undertaken, an application, in advance is to be made. The registry director will review the application for consideration of any special circumstances which may be relevant in each individual case. Prospective donors must be made aware of the facts surrounding the circumstances and the risks and consequences of cryopreservation.

6.2 G-CSF Administration

6.2.1 The term "G-CSF" in this document refers specifically to Filgrastim for mobilization of Ezer Mizion donors with trade names being Neupogen® or TEVAGRASTIM®.

6.2.2 G-CSF will be prescribed by the collection center physician and the coordination of its administration will be conducted by the collection center in liaison with the registry office.

6.2.3 After the donor has agreed to participate, an appointment will be made by the collection center for administration of the first dose of G-CSF (Day 1) under supervision. This can take place at the collection center or with a local health professional. The coordinator should ensure that the donor has a clear understanding about the G-CSF commencement date, time and place and the collection date. This should be communicated in writing as well as verbally.

6.2.4 A letter must be provided to the medical or nursing staff who may be asked to administer G-CSF. This letter will detail the dosage and the schedule and contain information on G-CSF administration.

6.2.5 G-CSF will be administered subcutaneously at a dose of 10-12 micrograms (µg) per kg per day.

6.2.6 Following the administration of the first dose of G-CSF the donor will remain under the supervision of the collection center or a local health professional for a period of one hour in case of any adverse reactions. The donor must be provided with a contact name and telephone number in case of any concerns.

6.2.7 Self-administration may be appropriate for the remaining G-CSF injections (Day 2 onwards) at the discretion of the collection center in collaboration with the registry. If self-administration is undertaken, the collection center or health professional must train the donor in self-injection.

6.2.8 G-CSF is given as a subcutaneous injection, once a day for a period of four (4) days with collection usually being possible on the fifth day. If necessary, a second collection may be required the next day after an additional injection on day five.

6.2.9 Donors will be advised to avoid any strenuous physical activity during the 4 or 5-day period of G-CSF treatment.

6.2.10 On day 5, after the 4-day G-CSF treatment period, the donor will arrive to the collection center for review prior to the first collection, undertaken that day. In order to follow up on any adverse event during the injections the collection center will fill out the form *Donor Assessment Injection and Symptoms (FRM_FU10)*.

6.3 Collection Procedure

6.3.1 The transplant center must be informed as early as possible if the requested cell dose is not feasible based on the experience at the collection center. The Ezer Mizion form *Verification of Cell Product (FRM_WU30)*, must be completed at the time of donor Work-up which ensures the plans for the collection are considered acceptable and verified by collection center physician, registry office and transplant center.

6.3.2 If the collection or transplant is cancelled, the transplant center and the registry respectively must ensure that the cancellation request has arrived at the appropriate center.

6.3.3 It is recommended to encourage the transplant center to send feed-back information to the Ezer Mizion BMDR on whether the product met transplant center criteria.

6.3.4 Peripheral blood HSC Collection Procedure

6.3.4.1 The pre-collection test of complete blood count (CBC) should be performed prior to the apheresis procedure, for both day 1 and day 2 of the collection (if a second collection is required). The platelet count should be in excess of $100x10^9$/L to allow collection to commence for both day 1 and day 2 of the collection (if a second day collection is required).

6.3.4.2 Collection will normally commence on day 5. It is suggested that a minimum of two (2) blood volumes should be processed with a maximum of 4.5 blood volumes. It is anticipated that one or two procedures will normally be performed. The maximum number of collection procedures in any donor will be two.

6.3.4.3 Addition of anticoagulants: ACD-A will be added to the HSC product during collection on the cell separator as programmed by the Apheresis machine and according to the collection center operation procedures (final concentration of ACD-A in the product bag is 1:10 to 1:15). Heparin may also be added according to the collection center procedures.

6.3.4.4 If during the medical evaluation it becomes evident that a central venous catheter (CVC) insertion may be needed, the donor should only be cleared for Marrow HSC donation, or a different donor should be searched for. In documented exceptions, an apheresis with a CVC may be planned at the time of medical evaluation if the donor gives his written consent and upon approval of the registry's medical director.

6.3.4.5 If an insufficient venous access for a peripheral donation becomes apparent on the day of apheresis, a CVC may be placed under clinical conditions as a documented, justified exception, following approval by the medical director of the registry. The donor's written informed consent for this procedure is obligatory. Counseling and CVC insertion must be performed by a physician who is qualified and experienced in this procedure.

6.3.4.6 Yield of CD34+ cells: The collection center should attempt to achieve the yield of CD34+ requested by the transplant center. If this is not possible, an acceptable yield after the first collection will be $4.5x10^6$ CD34+ cells/kg 'ideal' patient body weight. No further collections should take place if $4.5x10^6$ (or greater) CD34+ cells/kg 'ideal' patient body weight are collected in the first collection procedure.

6.3.4.7 An exception to the above policy can only be made under specific criteria that must be indicated by protocol and clearly detailed on or attached to the prescription for stem cells. These criteria are subject to prior approval both by the registry and the donor:(1) Active residual disease in recipient; (2) The patient has a non-malignant diagnosis; (3) The prescription requests T cell depletion, CD34+ selection or other T cell selection techniques.

6.3.4.8 Failure to mobilize: CD34+ counts must be obtained in order to determine whether another collection procedure is required the following day. If after two collection procedures the cell count is less than $2x10^6$ CD34+ per kg 'ideal' patient body weight, it may be necessary to proceed to a Marrow HSC collection. In this case, it is mandatory for the donor to sign an informed consent for marrow collection. After agreement between the collection and the donor, this option can be offered to the transplant center at a time to be arranged and after a review of the donor's fitness to donate post Peripheral blood HSC. For more information refer to section 7 of this manual. If a Marrow HSC collection is required, a yield of 2×10^8 mono-nucleated cells (MNCs) per kg 'ideal' patient body weight count should be the target.

6.3.4.9 The total nuclear cell count, CD34+ count and CD3+ count of each product should be monitored and recorded by the collection center. Red cell depletion should not be required, although plasma depletion may be performed, depending on the donor and patient's ABO blood groups.

6.3.4.10 A back up autologous blood unit is not routinely recommended. If autologous donor blood is to be collected - it must be collected at a blood collection center that is approved by the Israeli MOH.

6.3.4.11 The Ezer Mizion form Collection Report (FRM_WU71) is to be completed after the stem cell collection by a senior member of the collection team. The form should accompany the hemopoietic stem cells to the transplant center and also faxed to Ezer Mizion registry BMDR.

6.3.5 Marrow HSC Collection Procedure

6.3.5.1 Marrow will be collected under general anesthesia in an operating room. It must only be extracted from the posterior iliac crests. Only in exceptional circumstances should spinal anesthesia be considered. This would be a decision made by the anesthetist in consultation with the donor.

6.3.5.2 The volume of marrow taken at each aspiration should be kept to a minimum (usually 5–10 mL) to reduce the dilution of marrow with peripheral blood.

6.3.5.3 The amount of marrow to be aspirated will be guided by the weight of the donor, donor's and patient's ABO blood types, and by the expected manipulation of the marrow.

6.3.5.4 To ensure that an appropriate number of nucleated cells are collected, cell counts should be taken half way through the collection procedure to estimate the final collection volume. In general, 10–20 mL of marrow should be aspirated for every kilogram of patient weight with a target of $3x10^8$ nucleated marrow cells per Kg of patient weight. The total volume of marrow aspirated should not exceed 20 ml per Kg of donor weight.

6.3.5.5 After aspiration, the marrow should be collected into an anticoagulant solution based on ACD-A or heparin according to procedures validated at the collection center. Any solution or additive that can adversely affect the quality of the transplant may not be used. It is recommended that bone marrow collected for adults and large pediatric recipients should be divided into at least two blood collection/ transfer packs.

6.3.5.6 The marrow must be filtered prior to final transfer to the storage bag in order to eliminate debris.

6.3.5.7 The total number of nucleated cells collected must be tabulated and reported on the Ezer Mizion form Collection report (FRM_WU71). Wherever possible, the collection centers should perform analysis for CD34+ and CD3+ cells in the marrow. A copy of this form must be sent in conjunction with the product to the transplant center and a copy sent to the Ezer Mizion BMDR office and filed in the donor's file.

6.4 Product Processing after Collection

6.4.1 General

6.4.1.1 The collection center oversees the processing of the collection, quality control, production of products, and their release and distribution.

6.4.1.2 Processing of HSCs and any other collected cell products intended for therapeutic use prior to the delivery to the transplant center must be performed at a cell processing unit that fulfills standards established by the Israeli MOH and accredited by international authorities.

6.4.1.3 Sterility of equipment: All tubing, containers and other equipment and fluids that come into contact with the donations during processing or storage must be sterile and approved for clinical use in Israel.

6.4.2 Cultures and Viability

6.4.2.1 To confirm the lack of microbial contamination, the sterility of the product should be confirmed. Abnormal cultures results should be reported to the transplant center via the Ezer Mizion BMDR office as soon as they are available

6.4.2.2 The sterility of Peripheral blood HSC product should be ascertained using liquid and/or semi-solid culture medium for full bacteriological and fungal cultures. To assess the sterility of Marrow HSC product a sample of the marrow collection should be cultured under aerobic and anaerobic conditions

6.4.2.3 Analysis for viability of the cells should be performed by a validated procedure.

6.4.3 Processing

6.4.3.1 The only manipulation allowed at the collection center on a standardized basis is adjusting the volume of the aphaeresis product to ensure an optimal concentration of cells in the product for storage and transport. No other manipulation (depleting erythrocytes, immunoselection, etc.) is allowed unless the transplantation center requires it in writing in advance.

6.4.3.2 Product may be processed at the transplant center in various ways (e.g. volume reduction, red cell reduction, CD34 positive selection) for various reasons (e.g. ABO incompatibility and the prevention of graft versus host disease).

6.4.4 Storage and Transport

6.4.4.1 Peripheral blood HSC,

6.4.4.1.1 Non-manipulated cells may be stored unfrozen up to 72 hours at 2-8°C.

6.4.4.1.2 It is not mandatory to reduce cell concentration if receipt of the product in the cellular laboratory is within five (5) hours of collection.

6.4.4.1.3 For long distance transportation and storage of product the final concentration of nucleated cells in the collection is important for viability. The concentration of nucleated cells should be reduced by the addition of donor plasma (or 5% HSA saline) in the processing laboratory to less than 3 $x10^8$/ml or as requested by the transplant center. Please note that a request for 150-200 mL of plasma should be indicated on the prescription for the product.

6.4.4.1.4 Transport of Peripheral blood HSC product in Israel: If two collections are required, the first can be stored at 2-8°C overnight and transported fresh with the second collection the next day.

6.4.4.1.5 Transport of Peripheral blood HSC to international transplant centers: If two sessions of collections of cells are required, arrangements must be made for a late collection on day 5 and early on day 6. The first can be stored at 2-8°C overnight and transported fresh with the second collection the next day.

6.4.4.2 Marrow HSC

6.4.4.2.1 Storage limit: Every effort should be made to transfuse non–cryopreserved marrow within eight (8) hours of collection for Israeli patients and within 48 hours of collection for international patients.

6.4.4.2.2 For transport over eight (8) hours marrow should be diluted in ACD–A. No other additives must be injected into the bags of marrow during the transport of the marrow unless requested by the transplant center.

7. TRANSPORT

7.1 General

7.1.1 The transplant center is responsible for the transport. It authorizes a courier to perform the hand carried transport of the product. The courier must be informed about the product and the transport conditions.

7.1.2 The courier has sole responsibility for the safe and timely transport of HSC from the collection center to the transplant center.

7.1.3 Non-cryopreserved HSC are transported cooled at a temperature of 2°-8°C unless otherwise specified by the transplant center. The product must be transported in a shatterproof and temperature insulating container that is labeled as described in section 7.5. The courier must supply the transport container.

7.1.4 Policies and procedures for training and qualification of individuals acting as couriers and documenting the transport process should follow WMDA guidelines. The entity providing the courier is responsible for ensuring that the transport takes place according to WMDA guidance and Ezer Mizion BMDR operation procedures.

7.1.5 Upon the transplant center request, the Ezer Mizion BMDR will facilitate the product transport by a courier. If a commercial courier company is used by the registry to perform the transport, there needs to be a direct committed relationship between the transport company and Ezer Mizion registry. The company must be able to customize the service they provide to meet with Ezer Mizion BMDR requirements and to be able to provide trained couriers that meet the registry's guidelines

7.2 Couriers

7.2.1 Couriers Requirements

7.2.1.1 The Courier must understand the significance of the product.

7.2.1.2 The Courier must be trained in all policies and procedures required for the transportation of HSC.

7.2.1.3 The Courier must not be related to the donor or patient.

7.2.1.4 The courier must not have other obligations until after the HSC have been delivered.

7.2.1.5 For international transport the courier must be an experienced independent traveler, have a reasonable amount of cash or credit card for expected expenses, have adequate command of English and be covered by travel insurance for international destinations.

7.2.2 Couriers Responsibilities

7.2.2.1 The courier is responsible for ensuring that the HSC is transported safely from the collection to the transplant center in the shortest possible time and at the temperature requested by the transplant center.

7.2.2.2 The courier must remain in possession of the HSC product at all times.

7.2.2.3 The courier must carry documentation relating to transportation of the HSC product.

7.2.2.4 The courier must verify accuracy of information on HSC labels.

7.2.2.5 The courier must place the product bags and samples properly in the cooler

7.2.2.6 The courier must deliver the HSC directly to the designated person at the transplant center or processing laboratory.

7.2.2.7 The courier must inform the transplant center of possible delays.

7.2.2.8 The courier must not consume alcohol or sedative drugs while transporting the HSC.

7.2.2.9 For international transport, the courier must ensure that the HSC does not pass through X-ray screening at security check points. If security staff insist upon opening the shipper or performing other security checks, couriers are to request this to be done under the supervision of the courier.

7.2.2.10 For international transport, the courier must ensure carry-on luggage is within airline restrictions to allow passage of HSC container. The courier must ensure that the HSC product never be placed inside checked luggage or inside the courier's personal cabin baggage.

7.2.2.11 The courier must always maintain patient and donor confidentiality. Couriers must not disclose to the recipient's family or staff of the transplant center or collection center, details that could result in identification or location of the donor or recipient

7.3 Courier Accompanying Documentation

7.3.1 For couriers traveling by air the courier must carry documentations for security and custom check points that may consist of:

7.3.1.1 Airline ticket or electronic ticket information

7.3.1.2 Passport

7.3.1.3 Visa/ entry permits

7.3.1.4 Information on reservation of accommodation

7.3.1.5 Travel insurance

7.3.1.6 Foreign currency as needed

7.3.1.7 Phone card or mobile phone with international roaming

7.3.1.8 Import/export permits for HSC as required by local authorities

7.3.1.9 Courier & Emergency Contact Information during Stem Cell Transplantation form (FRM_TR11).

7.3.1.10 Letters for security at departure and transit airports or train stations

7.4 Flights

7.4.1 Flights must be booked with minimum stopovers.

7.4.2 The courier must be aware of alternative modes of transport if substantial delays arise.

7.4.3 Backup flights should be arranged if permitted by the airline.

7.4.4 Notification of airline and security staff at airports, by the registry organizing the shipment, is required at some airports.

7.4.5 For long haul flights the courier must make contact with the collection center at least one day prior to the scheduled collection.

7.4.6 All changes in original transport arrangements must be communicated immediately to the transplant center and requesting registry.

7.5 Product Labeling

7.5.1 Labeling should adhere to IATA (International Air Transport Authority) and national regulations concerning the safe handling and transport of biological material at all times.

7.5.2 Labeling of the HSC and accompanying blood samples must comply with the Israeli national regulatory/legal requirements and with the ICCBBA, ISBT 128 international standard to ensure the identity of product. Labels must be legible and printed using waterproof ink labels and must contain the following information using the designated format according to the ISBT 128 standard:

7.5.2.1 Donation Identification Number (DIN)

7.5.2.2 GRID

7.5.2.3 Recipient name and unique identification code

7.5.2.4 Proper product name, code, and product information

7.5.2.5 Product warnings regarding irradiation and leucoreduction

7.5.2.6 Donor ABO/Rh group

7.5.2.7 Collection date, time and time zone at end of collection

7.5.2.8 Product volume and anticoagulant

7.5.2.9 Product storage conditions

7.5.2.10 Address and location of the transplant center

7.6 Product Accompanying Documentation

7.6.1 Results of preliminary testing (cell counts as appropriate for product release) or Collection Report form (FRM_WU71) that contains the following:

7.6.1.1 product name

7.6.1.2 cell count and, if applicable, processing

7.6.1.3 product code

7.6.1.4 name and recipient number

7.6.1.5 donor identifier

7.6.1.6 donor AB0/Rh group

7.6.1.7 date and time of collection

7.6.1.8 name and address of the transplant center and contact details

7.6.2 Name, address and 24 hour phone contact numbers of the registry, collection center, processing lab and transplant center including contact names

7.6.3 Results of donor infectious disease markers testing

7.6.4 Verification of Prescription for Cell Product form (FRM_30)

7.6.5 Date and time of product handover to the courier (Transport of Stem Cell Product Audit form FRM_TR20)

7.6.6 Name and signature of collection center coordinator who hands over the product to the courier (Product Labeling Checklist FRM_TR50)

7.7 Product Packaging

7.7.1 Packaging and shipping containers should be shatterproof and qualified to hold at the required temperature for in excess of the anticipated transit time, under the expected range of external temperatures.

7.7.2 Pre-chilled cooler bags, pre-frozen coolant packs and any insulating material should be arranged as specified by transplant center for adequate temperature control over the estimated transit time into the cooler.

7.7.3 Data loggers or thermometers with a protected probe and exterior temperature display should be used to record the temperature of the HSC during transport.

7.7.4 Bags of HSC must be thermally insulated from frozen coolant packs to avoid spot freezing.

7.7.5 Dry ice must never be placed in the cooler with non-cryopreserved HSC.

7.7.6 Additional peripheral blood or bone marrow specimens should be placed inside specimen transport containers or plastic bags prior to placing in cooler or isothermal transport box with the HSC.

7.7.7 Transport cooler containers must be clearly and unambiguously identified using labels that remain intact under the storage conditions used. The label wording should include for example:

7.7.7.1 MEDICAL SPECIMEN – HANDLE WITH CARE

7.7.7.2 DO NOT X-RAY

7.7.7.3 WARNING: Contains human tissue for transplantation

7.7.7.4 Do not place near heat / Do not freeze / Do not delay delivery

7.7.7.5 Address labels of the transplant center including institution, address, contact details and phone numbers should be affixed to the cooler ensuring donor/ recipient confidentiality during transportation.

7.7.8 Before releasing the shipment from the collection center/processing lab to the courier – it is the responsibility of the physician in charge or the processing lab director or designee to verify the correctness of all documentation (Ezer Mizion form Product Labeling Checklist (FRM_TR50)).

7.8 Couriers Tasks during Assignment on the Day of Collection

7.8.1 Arrive at collection center at arranged time and location.

7.8.2 Make contact with designated contact person.

7.8.3 Carry personal identification and the documentation required for the transport.

7.8.4 Crosscheck with the collection center representative, the type, number and labeling of bags containing HSC, the cell count and the addition of anticoagulant against the request for HSC.

7.8.5 Pack HSC and additional specimens into the cooler according to instructions provided by the transplant center.

7.8.6 Collect and check all accompanying paperwork.

7.8.7 Declare the HSC on all customs/ immigration and quarantine forms for inspection as required.

7.8.8 Supervise any visual inspection of the HSC

7.9 Couriers Tasks on Arrival at the Transplant Center

7.9.1 Travel immediately to the transplant center or processing laboratory according to instructions.

7.9.2 Contact the designated staff member at the transplant center for hand over.

7.9.3 Record the time of delivery and temperature of the HSC upon arrival.

7.9.4 Cross check the HSC and specimen tubes against the details provided by the collection center and the request for HSC.

7.9.5 Record any events or incidents during transport.

7.9.6 Sign for delivery of the HSC to the transplant center.

7.9.7 Alert transplant center staff regarding documents requiring completion and return to the collection center post-delivery and/ or post-transplant.

7.9.8 Transplant center should send feedback information to the Ezer Mizion registry on whether the product met transplant's center criteria using the Ezer Mizion form Transplant Report (FRM_WU74).

7.10 Serious Adverse Events

7.10.1 Serious adverse events impacting the product or that occurred throughout the transportation and delivery of the cellular product must be reported immediately to the central office of the Ezer Mizion BMDR (see section 9 for further details).

7.10.2 It is the responsibility of the courier to report the incidence of such a serious adverse event to the registry office. Serious adverse events that occurred after the product has been delivered to the transplant center should be reported by the transplant center staff. The registry central office will see to it that this event be submitted to the WMDA sponsored international centralized database of such events (SPEAR).

8. FOLLOW-UP OF PATIENT AND DONOR

8.1 Donor Follow-Up after Donation, Short & Long Term

8.1.1 Following the donation the collection center physician is responsible for the evaluation of the donor's well-being. The donor's health should be checked and when appropriate the donor will be formally discharged from the collection center by the harvest team physician.

8.1.2 The collection center should follow the donor weekly from 1 week until donor's recovery and must keep records of all corresponding donor contacts and initiated examinations or therapies.

8.1.3 The registry is responsible for the donor short and long term follow-up after the donor's discharge from the collection center.

8.1.3.1 The registry coordinator must contact the donor by telephone within 48 hours post donation to evaluate his physical and emotional well-being.

8.1.3.2 One week post donation the registry coordinator should contact the donor and provide him by phone/post/e-mail the short form Assessment post stem cell donation_ (FRM_FU20). It must be documented if the coordinator is unable to reach the donor.

8.1.3.3 One year post donation the registry coordinator should contact the donor and provide him by phone/post/e-mail the long form - Assessment post stem cell donation_ (FRM_FU22). The donor should also be assessed according to this form after two, five and ten years post donation to ensure appropriate care for any conditions related to the hemopoietic stem cell donation. It must be documented if the coordinator is unable to reach the donor.

8.1.4 This process must be followed for Peripheral blood and BM HSC donors, and second or subsequent donations of HSC for the same or different patient.

8.1.5 The Ezer Mizion BMDR coordinators are responsible for ensuring this procedure is carried out. Donor follow-up forms and information must be kept in the donor file permanently.

8.1.6 Donor health issues post-donation potentially affecting the health of a patient having received a hematopoietic stem cell donation from that donor must be reported to the transplant center. The Ezer Mizion senior coordinator must report this information in writing to the transplant-center and confirm that this information was indeed received. Records of this report will be maintained in the donor records file permanently.

8.2 Donor Removal after Donation

8.2.1 After donation, donors will be removed from the registry permanently.

8.2.2 In case donors are requested for repeated donation for the same patient for whom they donated - they will be contacted and asked if they wish to proceed with the repeated donation. A request for a second or subsequent donation for the same patient must be evaluated by the registry's medical director on a case by case basis.

8.2.3 One year after the donation, if the donor has expressed his explicit will to return to be listed in the registry, this can be made possible after approval from the registry's senior coordinator and the medical director.

8.3 Adverse Events and Adverse Reactions

8.3.1 Adverse events are any donor health incidents that potentially can affect the health of the donor or the patient receiving a HSC donation and also any adverse findings that can affect a subsequent donation.

8.3.2 Serious Adverse Events affecting donors undergoing collection of HSC and occurring as a consequence of the donation must be identified, documented, investigated and remedial and/or corrective action taken. Similar actions must be taken for adverse reactions occurring due to registry operations and impacting the health and safety of donors or patients.

8.3.3 In order to report any serious adverse events and reaction that occurred during and/or after administration of G-CSF, the actual donation, and or occurring long-term as a consequence of the donation, the Ezer Mizion form *Donor Incident Report (FRM_RP20)* should be completed by the designated personnel at the collection center and sent to the registry office.

8.3.4 According to the Israeli MOH guideline for operation of bone marrow donor registry (39/2012) every serious adverse event occurring during the HSC collection process in which the donor was injured or damaged (or previous procedure regarding the collection), should be reported to MOH within 24 hours.

8.3.5 Ezer Mizion is responsible for informing the transplant centers or international registries for Israeli and international patients about any relevant abnormal findings which may affect the patient treatment or transplant outcome.

8.4 S(P)EAR

8.4.1 S(P)EAR: The Serious (Product) Events and Adverse Reactions of WMDA or "SEAR" and "SPEAR" are a central reporting system of the WMDA member organizations to the WMDA S(P)EAR Committee. The reports are collected and analyzed by the S(P)EAR committee to obtain insight in the occurrence of serious events and adverse effects in relation to HSC donation by unrelated donors. Comprehensive and confidential reporting is fundamental to success of this scheme.

8.4.2 All Serious Events and Adverse Reactions (SEARR), and Serious Product Events and Adverse Reactions (SPEAR) as defined by WMDA must be reported by the collection centers as soon as the donor's condition has resolved. In case of long lasting, uncertain outcome, the report can be completed and a follow-up report can be submitted later using the WMDA S(P)EAR form. The form used for reporting to the S(P)EAR is issued by the WMDA. A copy of the current version of the form can be obtained by contacting the registry's senior coordinator or it can be downloaded from WMDA website.

8.4.3 The report shall be completed by the most appropriate person, sent to the registry's senior coordinator who will then forward to medical director who will then forward the information to the WMDA office.

8.4.4 SEAR Report

8.4.4.1 If an event/reaction is deemed to be one of the following it should be reported: serious/unexpected/medically relevant/previously unknown.

8.4.4.2 In addition to these general principles, the following specific events are given as indicators of what should be reported:

8.4.5 Any serious potential risk during anesthesia should be reported. Even when resolved completely, these should be reported e.g. profound bradycardia during anesthesia requiring emergency treatment, laryngospasm during anesthesia, severe adverse reactions to drugs or IV fluids etc.

8.4.6 Any serious cardiac complication should be reported during or in close proximity to stem cell donation.

8.4.7 Any serious infection should be reported e.g. infections beyond local infections of site of marrow collection or minor line infections, sepsis, osteomyelitis etc.

8.4.8 Any serious mechanical injury should be reported e.g. nerve damage from marrow collection or IV lines, damage to SI (sacroiliac) joint, fractures of iliac crest, retroperitoneal hematoma or injuries etc.

8.4.9 Any serious incident in hemostasis should be reported e.g. thrombosis, embolism, after Marrow or Peripheral blood HSC harvest, abnormal bleeding secondary to thrombocytopenia complicating Peripheral blood HSC harvest.

8.4.10 Any serious (late) effect of Marrow or Peripheral blood HSC donation should be reported e.g. a flare of a systemic disease after marrow donation, hematological disease reported following growth factor administration etc.

8.4.11 Any donor death (from initiation of donation until day 30 post donation; or at any time of donation is implicated.

8.4.12 Reports of adverse events affecting a donation must be submitted to the Registry or transplant center involved in the transplantation if the event might affect an initial or subsequent donation. Other individuals or groups should be notified as appropriate.

8.4.13 SPEAR Report

8.4.13.1 Issues that should trigger a report to SPEAR:

8.4.14 Inadequate cell dose in the stem cell product.

8.4.15 Any serious impairment of the quality of the stem cell product including coagulation and contamination.

8.4.16 Serious problems in transportation.

8.4.17 Wrong stem cell product transfused.

8.4.18 Any serious unpredicted transmissible infection e.g. HIV, Hepatitis B, Hepatitis C.

8.4.19 Any serious unpredicted non-infectious transmissible disease e.g. hematologic/ oncologic diseases discovered in the donor HSC after administration of the product

8.5 Donor-Recipient Communication after Transplantation

8.5.1 The Ezer Mizion BMDR approves communication between donor and recipient after transplantation and regulates guidelines under which such communication may be facilitated.

8.5.2 Identities of donor and recipient will not be exposed one to the other at least in the first year after the transplant.

8.5.3 Identities of donor and recipient will not be exposed eternally to the other party or family in case the patient has died.

8.5.4 If at least one year has passed from the date of transplant Identities of donor and recipient may be exposed to the counterpart side only after written consent has been received from the donor and the recipient.

8.5.5 If the patient is under the age of 18 years, the patient's parents may serve as his representatives for this purpose.

8.5.6 Anonymous gifts or letters may be delivered between the two parties even before the first year has passed from the day of transplant. Anonymous gifts or letter exchange must be facilitated through the Ezer Mizion central office.

8.6 Patient Follow Up

8.6.1 The Ezer Mizion registry seeks to follow-up on the condition of the recipients who were transplanted from its donors.

8.6.2 The registry office will contact the transplant center at 6 months and 12 months after the donation in order to collect information about the patient's condition.

8.6.3 The Ezer Mizion form *Stem-Cell Transplantation Follow-Up (FRM_FU30)* or any equivalent form should be used for this purpose.

9. FINANCIAL AND LEGAL LIABILITIES

9.1 Responsibilities

9.1.1 Ezer Mizion is a non-profit organization in Israel offering an extensive range of medical and social support services to any person in need in Israel.

9.1.2 Ezer Mizion is an official recognized legal entity in the State of Israel listed by the Israeli Ministry of Justice, The Corporate Authority as non-profit organization no. 580079978 (enlisted May 1985).

9.1.3 The Ezer Mizion BMDR operates as one of the services offered and operated by the Ezer Mizion health support organization.

9.1.4 Ezer Mizion BMDR keeps complete and accurate financial records for all services provided and requested according to national laws and regulations as well as international standards - all in coordination with the central accounting office of the general Ezer Mizion charity organization.

9.1.5 The registry has a designated staff member that is dedicated to perform all accounting duties, in collaboration with the financial desk at the general Ezer Mizion organization.

9.1.6 Being affiliated with the general Ezer Mizion charity organization, the registry participates in the annual financial reports and accounts being submitted to the Israeli Ministry of Finance.

9.1.7 The registry's finance supervisor together with the central finance office of the Ezer Mizion charity organization will guarantee the settlement of all invoices in due course according to the agreements between the registry and its counterparts.

9.2 Fee Structure

9.2.1 Ezer Mizion BMDR has a clear fee schedule detailing payment terms for HLA testing, infectious disease marker testing, harvest and other related services that is available upon request. Changes in the fee schedule are provided to interested parties thirty days prior to implementation.

9.2.2 Any cost not standardized or, for any reason, not accessible through the official fee schedule (e.g. courier charges) may be estimated and communicated in advance to the requesting registry and/or the transplant center.

9.2.3 If the harvest procedure is cancelled after the final donor selection, the Ezer Mizion BMDR will be entitled to charge for services performed prior to notice of cancellation. This practice is clearly noted on the fee schedule.

9.3 Billing

9.3.1 Ezer Mizion BMDR providing donor stem cells or any other requested service will bill to and request payment from the registry or transplant center requesting the donor stem cells or service.

9.3.2 Billing should occur within sixty (60) days of service completion.

9.3.3 If the requesting registry or transplant center cancels the request, the Ezer Mizion BMDR will try to withdraw and call-off the execution of the request within a reasonable time frame. The registry shall expect full payment provided that the services are completed and reported within 30 days of the cancellation date.

9.3.4 It is the responsibility of the requesting registry/ transplant center to collect funds from any person or institution ultimately covering these expenses. If it is unable to collect funds from the originating institution, the registry/ transplant center shall be liable for expense incurred.

9.4 Donor Expense and Insurance

9.4.1 Ezer Mizion BMDR, in line with WMDA standards, recruits volunteer donors. The volunteer nature of a donor means that donors won't be paid for their donation but expenses incurred during the process may be reimbursed.

9.4.2 Ezer Mizion BMDR assumes responsibility for all donor medical expenses including the pre-collection physical examination, the collection procedure and all post-collection medical expenses that are directly related to the donation. No donor should assume financial liability for any portion of the follow up testing and/or stem cell harvest/procurement process.

9.4.3 Donor Expenses

9.4.3.1 The registry is responsible for all reasonable expenses incurred by the donor.

9.4.3.2 Donor expenses are defined as those costs generated at different stages during the search process and paid by the donor. All reasonable expenses including travel, meals, loss of earning, incidental expenses and accommodations will be reimbursed to the donor and companions (in special circumstances) by Ezer Mizion BMDR.

9.4.3.3 Ezer Mizion BMDR is responsible for ensuring the donor receives appropriate medical care and /or referral if required as a result of the donation.

9.4.3.4 Ezer Mizion BMDR is responsible for the reimbursement of all reasonable expenses incurred by the donor during routine follow-up visits and assessments post-donation.

9.4.3.5 Any expense that exceeds the reasonable amount should not be reimbursed until reviewed on a case by case basis by the registry. On those occasions consideration will be given to the total amount for reimbursement, not just the excessive expense in isolation.

9.4.3.6 A properly completed expense claim form including receipts should be submitted for payment except for low incidental expenses. Claims forms should be authorized by the registry designee.

9.4.4 Donor Insurance

9.4.4.1 All collection centers must provide appropriate general liability and malpractice insurance. In most cases this will be under the accepted government insurance scheme covering public hospitals to insure against the event of donor death or disability.

9.4.4.2 Donors should be encouraged to seek advice from their insurance company with regard to any personal insurance cover. Donors' insurance companies seeking advice from Ezer Mizion BMDR or any of the centers involved in the donation process can be provided with the same information received by the donor.

9.4.4.3 Ezer Mizion BMDR provides a comprehensive medical insurance to all its donors. The registry is responsible to inform the insurance company of every new donor that was asked to perform donation in order to include his/ her name in the list of insured donors.

10. INFORMATION TECHNOLOGY AND INFORMATION MANAGEMENT

10.1 Records and Record Retention

10.1.1 Ezer Mizion BMDR maintains paper and computerized database of donors and patients records which include search requests, search results, consent forms, documentation of information sessions and medical measures, health history questionnaires, all records documenting HLA typing and examination results

10.1.2 Appropriately interpreted, the regulations in this section apply likewise to electronic, paper based or otherwise manual processes.

10.1.3 Electronic and paper records shall be legible, indelible, complete and retrievable in a reasonable period of time.

10.1.4 The requirements of record retention must be in compliance with the regulations for record retention of the Bone Marrow Donor Registry act 2011. Donors' records are maintained indefinitely. All documentation relevant to donors who were included in an initiated search process but eventually were not worked up and their file was closed, will be kept for ten (10) years.

10.1.5 Records must be preserved and protected from accidental un-authorized access, destruction or modification. The registry keeps hard copy and electronic records for every donor file in Verification typing and Work-up stage.

10.1.6 All records and communications relating to patients, recipients, donors or potential donors shall be kept strictly confidential. The access to donor and patient data information in the registry as well as the transmission of this information to and from the registry is organized in a way that accidental or unauthorized access, destruction or modification is prevented and confidentially is guaranteed.

10.1.7 Donors' paper records are archived in a dedicated archive facility that is authorized by the Israel`s State Archive.

10.1.8 The retention of all the registry records is under the responsibility of the Ezer Mizion organization, which in the event of termination of the registry's operations must ensure that all the records are maintained and protected.

10.2 Data Protection

10.2.1 The Ezer Mizion BMDR must assign a data protection officer.

10.2.2 A written Information Security Policy must be documented and maintained.

10.2.3 The registry personnel must be informed about the regulations of data protection and must commit themselves in writing to observe the data protection regulations.

10.2.4 Data security must be ensured. All patient and donor communications and records are stored to ensure confidentiality and to allow for traceability of the donors and steps of the donation process. The spacious condition in particular must ensure that only authorized staff has access to donor and patients records.

10.2.5 The protection of an individual against unlimited data collection, recording, use and transfer of his personal data must be guaranteed according to the national laws (The act for protection of privacy 1981; The act for genetic information 2000; The act for the patient's rights 1996; MOH guideline for IT security of bone marrow donor registry (39/2012. Dec 2012 part 8) and ISO 27001 standard.

10.2.6 The registry must maintain evidence of compliance to the requirements for data protection for a minimum of six (6) years.

10.3 Anonymity

10.3.1 In the course of all processing steps and manufacturing processes the anonymity of donors and patients must be strictly maintained and protected. For the protection of anonymity, the following applies:

10.3.1.1 Access to personal data of donor and patient must be limited to authorized institutions, and coordinated in a way that accidental or unauthorized access, destruction or modification is prevented.

10.3.1.2 All donor related information that is communicated externally must not contain names but only pseudonymous codes. The registry assigns, a unique and anonymous Identifier, GRID, according to WMDA guidelines to each adult volunteer donor. A unique and anonymous Identifier is assigned for each donor cellular product according to ISBT128 standard. It is impossible for one identifier to designate two separate people. This identifier will permanently provide the traceability of donor information and procedures during the participation in the entire donation process.

10.3.1.3 The transplant center is responsible for ensuring that all necessary measures are taken to prevent donor data (e.g. donor ID, date of birth) from becoming accessible to patients.

10.4 System Administration

10.4.1 The key components of a registry's hardware, software and network architecture and external connections must be adequately documented.

10.4.2 Ezer Mizion BMDR obtains EMDIS connection with most of the international registries and is using the Prometheus information system by Steiner, Ltd to operate the communication system with EMDIS. All other database and software programs used by the registry are developed by Ezer Mizion own IT department.

10.4.3 The software and hardware responsibilities are being conducted by the Ezer Mizion IT department.

10.4.4 All communication regarding definition, specification, implementation, validation and authorization of IT systems (software, hardware, network) must be documented. Any such system installed must be accompanied with adequate documentation for its maintenance (in particular detail if developed in house), administration and operation.

10.4.5 The registry database and application are hosted on industry-standard cluster of physical servers which make the system tolerant to single point of failure of the hardware. All the registry data elements are backed-up onto magnetic tape on regular basis and restoration test are performed. The back-up tapes are kept in a data security service facility located off-site. Backups are validated by data restoration tests to ensure their ability to re-build databases should the need arise. These activities must be documented.

10.5 Functionality of IT System

10.5.1 Data entry to the system must designed to prevent errors in input of information.

10.5.2 Search algorithms must provide lists of suitability matched donors in a reasonable time frame.

10.5.3 All donors recruited to the Ezer Mizion BMDR must be listed in the Search & Match database and will be made available to any patient in need.

10.5.4 International registries that maintain EMDIS connections with the registry receive match lists through this system. The basic information to international registries or transplant centers outside Israel on how to access Ezer Mizion BMDR donors is documented and available on EMDIS and the registry web site. National transplant centers and/or international registries that do not maintain EMDIS connections with the registry receive match lists that are generated by the registry own data system. The system's algorithm is considering the Loci HLA-A, B, DR. Lists of suitably matched donors are created immediately, under the parameters dictated by the search coordinator.

10.5.5 Any HLA-related information stored, presented or communicated by the registry must follow WHO nomenclature and WMDA guidelines for the use of HLA nomenclature.

10.5.6 When transferring electronic data from the registry to another establishment, there must be a validated protocol for the transfer of data. Both the transferring establishment and the receiving establishment must have policies to validate data.

10.5.7 Search reports will never contain any information about the donors except for age, gender and HLA typing. Donors that are not active or not available - will not appear in the search report.

10.5.8 Each printed report is always dated. Preliminary search results will be sent via EMDIS system or by fax/e-mail on the next working day following receipt of the request.

10.5.9 Each step in the search process (e.g. patient registration and any request, result or update) is always documented with all relevant attributes including date and staff-person name. The unique donor identifier will always accompany all information relating to a specific donor. All search steps are always recorded.

11. LIST OF ABBREVIATIONS

ABO, Rh	Major human blood groups (A, B, O) / Rh refers to Rh D antigen
ACD-A	Anticoagulant Citrate Dextrose-Solution A
AIDS	Acquired immune deficiency syndrome
Anti-HIV-1,2	Anti-human immunodeficiency virus 1 and 2 antibodies
Anti-HBc	Hepatitis B Core Antibody
ASHI	American Society for Histocompatibility and Immunogenetics
BM	Bone Marrow
BMDR	Bone Marrow Donor Registry
BMI	Body Mass Index
CMV	Cytomegalovirus
DLI	Donor Lymphocyte Infusion
EBMT	European Group of Blood and Marrow Transplantation
EBV	Epstein Barr Virus (family of herpes virus)
EFI	European Federation of Immunogenetics
EMDIS	European Marrow Donor Information System
G-CSF	Granulocyte Colony Stimulating Factor
GRID	Global Registration Identifier for Donors
HBsAg	Hepatitis B Surface Antigen
HCG	Human Chorionic Gonadotrophin
HCV	Hepatitis C Virus
HIV	Human Immunodeficiency Virus
HLA	Human Leukocyte Antigen
HPC	Hematopoietic Progenitor Cells
HSC	Hematopoietic Stem Cells
HTLV	Human T-Lymphotropic Virus
ICCBBA	International Council for Communality in Blood Banking Automation
IDMs	Infectious Disease Markers
JACIE	Joint Accreditation Committee – ISCT and EBMT
MOH	Ministry of Health
NAT	Nucleic Acid Testing
NMDP	National Marrow Donor Program
PBSC	Peripheral Blood Stem Cells
SEAR	Serious Events and Adverse Effects Registry
SEAR	Serious events and adverse events
SOP	Standard Operating Procedures
VT	Verification typing
WMDA	World Marrow Donor Association

Appendix 1: List of Forms and Questionnaires

Form no.	Form name
IC10	Recruitment Informed Consent
IC20	Additional Typing Informed Consent
IC30	Informed Consent for BM Donor
IC31	Informed Consent for PBSC Donor
IC32	Informed Consent for DLI Donor
IC33	Informed Consent CVC
IC40	Donor Health History Questionnaire
S20	Preliminary Search Request
S30	HLA Typing Request form
WMDA form S40	Blood Sample Request for Verification Typing
WU30	Verification of Cell Product
WU50	Donor Final Clearance
WU52	Abnormal Donor Finding
WU53	Declaration of Ineligible Donor
WU71	Collection Report
WU74	Transplant Report
WMDA form F10	Formal Request and Prescription for HPC, Marrow, HPC, Apheresis and for MNC, Apheresis
WMDA form F20	Previous Transplant History
FU10	Donor Assessment Injections & Symptoms
FU20	Donor Assessment Post Stem Cell Donation_Short
FU22	Donor Assessment Post Stem Cell Donation_Long
FU30	Stem Cell Transplantation Follow Up
TR11	Courier & Emergency Contact Information During Stem Cell Transplantation
TR20	Courier Information for CC
TR 50	Courier Information for Security
RP20	EM Donor Incident Report

Appendix 2: List of Changes between Version 6 and 7

Section	Change	Rational
1	Revised	Chapter 1 was merged with chapter 2 and the sections numbering were changed appropriately.
1.1.2.2.	Added	"..The registry does not facilitate search requests of international donors on behalf of transplant centers in Israel"
1.1.2.3	Added	"..in pseudonymous form according to the current state of the scientific and technical knowledge to the requesting organizations (search units, foreign registries, transplant centers) without delay"
1.1.3.5	Added	"..There must be adequate equipment in data system technology. Data protection and security must be guaranteed according to Section"
1.2.4.2	Added	Ezer Mizion Collection Center serves as the main collection center of the registry for HSC, Apheresis.
1.2.4.3	Deleted	"..Located within public hospitals, or medical centers"
2	Deleted	Chapter 2 was merged with Chapter 1 and the sections numbering were changed appropriately.
2.2.2	Revised	Search and Match
2.3.3	Added	The donor is deleted from the registry's database at his 60st birthday
2.4.4.8.23	Added	In exceptional cases, the option of product cryopreservation prior to the beginning of the recipient conditioning therapy subjected to the donor consent
3	Revised	Chapter 3 was amend to be Chapter 2 and the sections numbering was changed
3.1.2.2.	Revised	HLA typing must be applied in an HLA testing laboratories that are capable of carrying out DNA–based intermediate and high-resolution HLA-typing and are appropriately accredited by ASHI or EFI
3.1.4.2	Revised	Verification typing at a minimum of HLA-A, -B, -C, -DRB1 must be performed prior to donation/shipment for a specific patient
3.2.5.3	Added	West Nile Virus
4	Revised	Chapter 6 was amended to be Chapter 4 and the sections numbering were changed appropriately.
4.2.2	Revised	"Indications for all- and auto-SCT for haematological diseases, solid tumors and immune disorders: current practice in Europe 2019" (Duarte et al., Bone Marrow)
4.2.3.1	Added	"If the Ezer Mizion criteria are not met…. communicated via EMDIS or e-mail to the requesting registry/transplant centre"
4.4.2.4.	Added	according to the regulations of the International Air Transport Association (IATA) regarding shipment of dangerous goods
5	Revised	Chapter 7 was amended to be Chapter 5 and the sections numbering were changed appropriately.
5.1.3	Added	In urgent cases and upon the medical director discretion the interval between donations may be shorter
5.1.4	Revised	After the first donation the donor is reserved for three years
5.1.5	Added	The results of the medical evaluation in the normal range are a basic requirement for a subsequent donation
5.2.1	Added	" The transplant center must outline in writing … with blood stem cells from the same or a different donor (informal justification).

6	Revised	Chapter 8 was amended to Chapter 6 and the sections numbering were changed appropriately.
6.1.4.2	Revised	WMDA form - Formal Request and Prescription for HPC, Marrow, HPC, Apheresis and for MNC, Apheresis (F10) or an equivalent WMDA based form
6.4.1	Deleted	High resolution typing of DRB1* should be accompanied with C* in at least low resolution
7	Revised	Chapter 8 was split and the section regarding product transport was extracted to become new separate chapter no 7. The sections numbering were changed appropriately.
7.5.2.2	Deleted	and/or Donor unique identification code
7.7.1	Revised	qualified
8	Revised	Chapter 9 was amended to be Chapter 8. The sections numbering were changed appropriately.
9	Revised	Chapter 10 was amended to be Chapter 9 The sections numbering were changed appropriately.
10	Revised	Chapter 5 was amended to be Chapter 10. The numbering of the sections in this chapter was changed appropriately.
10.1.8	Added	The retention of all the registry records is under the responsibility of the Ezer Mizion organization, which in the event of termination of the registry's operations must ensure that all the records are maintained and protected
10.2.1	Added	The Ezer Mizion BMDR must assign a data protection officer
10.2.2	Added	A written Information Security Policy must be documented and maintained
10.2.3	Added	The registry personnel must be informed about the regulations of data protection and must commit themselves in writing to observe the data protection regulations.
10.2.4	Added	The spacious condition in particular must ensure that only authorized staff has access to donor and patients records
10.2.6	Added	The registry must maintain evidence of compliance to the requirements for data protection for a minimum of six (6) years.
10.3.1.1	Added	"..and coordinated in a way that accidental or unauthorized access, destruction or modification is prevented"
10.3.1.2	Added	".. A unique and anonymous Identifier is assigned for each donor cellular product according to ISBT128 standard"

Approved By

Name	Position	Date of Approval	Signature
Dr Bracha Zisser	Registry Director		
Prof Isaac Yaniv	Medical Director		

Annual Review

Version Number	QA Manager	Date	Registry Director	Date