Ezer Mizion Operations Manual

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EZER MIZION

Bone Marrow Donor Registry

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WMDA FULL STANDARDS

Receive international requests | Coordinate national patient search process | Volunteer Adult Cells | Cord Blood

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

1.1.1.8 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.

1.1.1.8.1 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 Maintain a database of donors in pseudonymous form, which may be searched as appropriate.

1.1.2.3 Upon request activates a donor search within the registry's donors and provide a list of HLA compatible donors in pseudonymous form according to the current state of the scientific and technical knowledge to the requesting organization without delay.

1.1.2.4 Accepts requests for further typing and shipment of blood samples

1.1.2.5 Reports incoming test results to the relevant institutions

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

1.1.2.7 Responsible for billing of all services within the donor search

1.1.2.8 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 Chapter 10.

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 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. A cooperative agreement between the Ezer Mizion BMDR and the affiliated external entities must be in place.

1.2.2 Laboratories

1.2.2.1 Any tissue-typing laboratory that serves the Ezer Mizion BMDR must gain an accreditation approval by the European Federation for Immunogenetics (EFI) 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 A laboratory that performs ABO/Rh typing and/or IDMs testing (including NAT tests) must be authorized by the Israeli MOH and certified by the Israel Laboratory Accreditation Authority or another authorized accreditation body. The laboratory must obtain a valid certificate and deliver a copy of the certificate to the Ezer Mizion BMDR.

1.2.3 Transplant Centers

1.2.3.1 National Transplant Center

1.2.3.1.1 Ezer Mizion BMDR is affiliated with and oversight national transplant centers in Israel. The centers must be authorized by the Israeli Ministry of Health, possess all licenses required by law, and comply with relevant WMDA standards and Ezer Mizion criteria for transplant centers. A service level agreement between the Ezer Mizion and the transplant center must be in place.

1.2.3.1.2 National transplant centers must report all consecutive transplants to either EBMT or CIBMTR to ensure that donation of hematopoietic stem cells will only be requested for patients for whom transplantation is a medically acceptable procedure.

1.2.3.1.3 Ezer Mizion BMDR does not facilitate search requests of international donors on behalf of its affiliated national transplant centers.

1.2.3.2 Cross-border Transplant Center

1.2.3.2.1 Ezer Mizion BMDR may affiliate with transplant centers in countries without an established national registry. In such cases, search will be performed in Ezer Mizion database, as well as in international registries on behalf of the transplant center. The cross-border transplant center must possess all licenses required by law and observe all applicable local regulations. Cross-border transplant center must comply with relevant WMDA standards and the Ezer Mizion criteria for transplant center. No request can be initiated before the Ezer Mizion BMDR accredits and approves the Transplant center. The nature of the affiliation between Ezer Mizion and a cross-border transplant must be included in a service level agreement.

1.2.3.2.2 Ezer Mizion BMDR requests donors on behalf of its affiliated cross-border transplant center from international organizations certified by WMDA. If the requested donor is registered with a non-WMDA certified organization, Ezer Mizion must ensure that the safety and well-being of both the HSC source and the intended recipient are protected.

1.2.3.3 In instances where Ezer Mizion receives a donor request from an international transplant center that is not affiliated with a WMDA-certified registry or has not been assessed by its national registry in accordance with WMDA criteria, Ezer Mizion will require the transplant center to complete the *WMDA Transplant Center Evaluation Form*. Ezer Mizion will then evaluate the submitted information to determine whether the transplant center meets the necessary criteria.

1.2.3.4 Ezer Mizion BMDR criteria for 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 associates with national collection centers to perform donor's medical evaluation, collection of hematopoietic stem cells and follow-up of donors for the sake of patients in need.

1.2.4.1.1 Ezer Mizion Collection center serves as the main collection center of the registry for peripheral blood HSC and lymphocyte collection.

1.2.4.2 Collection centers under Ezer Mizion BMDR oversight collecting, manufacturing and distributing hematopoietic stem cell products from peripheral blood or bone marrow must be authorized by the Israeli MOH to perform hematopoietic stem cell collection, and hold a valid certificate of the Institute for Standardization and Control of Pharmaceuticals.

1.2.4.3 Collection centers must comply with Ezer Mizion BMDR criteria for HSC collection and the relevant WMDA standards. It is recommended that collection centers work towards obtaining a JACIE accreditation.

1.2.4.4 The nature of the affiliations and the duties and responsibilities of each entity must be documented in a written agreement. Collection centers must inform the Ezer Mizion BMDR of any substantial change in their professional accreditation or authorization.

2. DONOR RECRUITMENT

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 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 and it is a volunteer act performed with the free will of the new conscripts.

2.2.2.3 The recruitment center 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 of a registration kit. 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 Ezer Mizion BMDR initiates donor-drives that are focused on a specific targeted population. 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 The upper age limit for prospective donors selected to donate hematopoietic stem cells should not exceed sixty (60) years. Donors' status in the registry's database will be changed to close and they will not be available for search once they reach their 60th birthday.

2.3.4 It is mandatory that all potential donors complete a donor questionnaire at recruitment that 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.

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

2.3.5.1 Severe cardiovascular disease

2.3.5.2 Severe pulmonary disease

2.3.5.3 Severe kidney and liver disease

2.3.5.4 Severe neurological disorder or sever neck, back or spinal disease

2.3.5.5 Infections with HIV, hepatitis B or C, HTLV, Syphilis

2.3.5.6 Systemic autoimmune or metabolic diseases, or other severe chronic illnesses

2.3.5.7 Severe illness of the blood or immune system

2.3.5.8 Severe psychological disorders

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

2.4 Donor Information and Consent

2.4.1 Donors must receive comprehensive information on the donation process upon recruitment to the registry and express their consent by signing the designated *Informed Consent forms (FRM_IC11/FRM_IC10).* Information may be given through literature or in person by recruitment staff. The information must contain the following items:

2.4.1.1 Reasons for the search for voluntary blood stem cell donors.

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

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

2.4.1.4 The identity of the donor must be protected to ensure the confidentiality and anonymity of donation

2.4.1.5 The donor is a volunteer member of the Ezer Mizion registry and can withdraw consent at any time.

2.4.1.6 The donor is not remunerated for the donation. However, all expenses incurred during the donation process will be reimbursed.

2.4.1.7 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

2.4.1.8 Information regarding the donor potential role in the donation of HSC, methods of blood stem cell donation, the risks involved in the donation and possible side effects.

2.4.1.9 Information about the use of any medical intervention and its known risks and/or side effects.

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

2.5 Donor Typing at Recruitment

2.5.1 New donors are registered at Ezer Mizion using the internationally recognized GRID (Global Registration Identifier for Donors).

2.5.2 Donors should be typed by molecular technique at registration for HLA–A, HLA-B, HLA-C, HLA-DRB1, HLA-DQB1, and HLA-DPB1 in ASHI or EFI accredited laboratories.

2.5.3 ABO and Rh factor typing using molecular technique is performed for new recruits that joined the registry since 2017.

2.5.4 Uploading 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 upload of HLA data to the registry database.

3. DONOR TESTING

3.1 General

3.1.1 In the case of adequate HLA-compatibility of the patient and a potential donor, further testing will be performed by Ezer Mizion BMDR according to the patient's transplant center request.

3.1.2 HLA typing must be applied in an HLA testing laboratories that can carry out DNA–based intermediate and high-resolution HLA-typing and are accredited by EFI or ASHI. Donor samples should be typed according to the HLA typing requirements and resolution levels as defined by EFI or by ASHI.

3.1.3 If a discrepancy 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, a definite resolution of the discrepancy must be obtained by the HLA lab. In case repeat testing of a fresh donor sample is performed all organizations involved must be informed about the result of the repeat testing. All discrepancies in HLA typing of donors shall be reported to WMDA HLA discrepancy survey.

3.1.4 ABO/Rh typing, IDMs testing, and any other blood tests will only be performed in laboratories that have been authorized by the Israeli MOH and accredited 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 Additional Typing

3.2.1 Additional Typing (Extended 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.

3.2.2 Additional typing may be requested by the transplant center and may include any combination of the genes: A*, B*, C*, DRB1*, DQB1, DPB1* or DRB3/4/5* at low or high resolution by molecular methods. High resolution typing results of all loci requested are recommended to be reported together rather than in a stepwise fashion.

3.2.3 Extended typing will be performed on a fresh buccal swab sample collected from the donor. If the donor does not respond within seven (7) calendar days, Ezer Mizion will contact the transplant center or requesting registry to establish whether to continue with the request. If the transplant center or requesting registry wishes to cancel, email confirmation will be required to confirm formal cancellation of the request.

3.2.3.1 The donor must receive information about the process and sign the *Additional Typing Informed Consent form (FRM_IC21).* In addition, *Donor Health History Questionnaire (FRM_IC40)* must be completed. The donor 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.

3.2.4 A donor requested for Extended Typing test must be placed on a "reserved" status for the patient for 45 days from the time of extended typing request. The donor will be released after 45 days into the available donor pool unless other specific requests are received in writing from the Transplant center.

3.2.5 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. Typing results should be reported to the requesting transplant center or registry within 14 days.

3.3 Verification Typing

3.3.1 HLA verification typing of the potential donor and recipient must be performed by the transplant center's HLA laboratory to confirm the identities of the individuals.

3.3.1.1 The HLA typing of the potential donor and the recipient should be at high resolution and include at a minimum typing of HLA-A, -B, -C, -DRB1, -DQB1 loci to allow the evaluation of the pair matching appropriate for the clinical application.

3.3.1.2 All specimens requested by the transplant center for verification HLA typing of the donor should be tested accordingly and results provided to the Ezer Mizion BMDR in a timely manner. If not tested, the transplant center should inform the Ezer Mizion BMDR as to the status of that donor request.

3.3.1.3 The HLA typing results of the potential donor and recipient should be reported to Ezer Mizion prior to requesting a specific donor for workup and at the latest must be available before the donor begins mobilization or proceeds to collection, or the patient begins with the preparative regimen, whichever is earliest.

3.3.2 Verification typing 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.

3.3.3 A health screening including infectious disease testing must be performed at the time of verification typing. Testing must monitor infection with human immunodeficiency virus (HIV), hepatitis B virus (HBV), hepatitis C virus, cytomegalovirus (CMV), Treponema pallidum (syphilis). If a transplant center requires additional infectious diseases testing, the Ezer Mizion BMDR will send the donor samples to the appropriate transplant center.

3.3.4 ABO blood group and Rh factor (AB0, RhD) testing by serology methods is performed at verification typing stage if the donor's blood group has not previously determined.

3.3.5 A donor information session must be performed before providing the samples and include the following:

3.3.5.1 The donor identity must be verified.

3.3.5.2 The donor counseling must be performed by Ezer Mizion coordinator. The major points can be discussed by phone and various information materials are provided.

3.3.5.3 Donor counseling must cover the following aspects: 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.

3.3.5.4 Information on the number of pregnancies (including all pregnancies, whether or not a child was born) and history of other prior sensitizing events such as transfusion must be obtained from donors.

3.3.5.5 The donor must complete *Health History Questionnaire (FRM_IC40)* and sign a designated *Informed Consent form (FRM_IC20).*

3.3.6 No part of the samples collected at verification typing stage can be used for research.

3.3.7 The volunteer donor has the right to receive the results of the health screening.

3.3.8 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.

3.3.9 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.

3.3.10 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.

3.3.11 The Ezer Mizion registry organizes donor blood sample collection and the accompanying tests as well as the transport of the blood samples to the respective appropriately accredited laboratories. Ezer Mizion registry must respond in a timely manner to requests for donor samples and make utmost efforts to provide the samples within a time period consistent with WMDA metrics.

3.3.12 Blood sample collection is performed at designated medical clinics that have a service level agreement with the registry.

3.3.13 Blood samples test tubes collected at the verification typing stage, and/or at any other stage of the donation process, must be labeled and indicate the GRID, the patient number, and the collection date. 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.

3.3.14 The maximum blood sample volume shipped to the transplant center for verification typing is 50mls. Additionally, up to 15 ml blood is sent for ABO/Rh typing and IDM testing. 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.

3.3.15 A donor selected for a specific patient must be placed on a reserved status from the time of verification typing test until the transplantation date is reached. This period 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. In justified cases the donor's reservation may be extended to accommodate the patient's medical status upon a written request from the transplant center.

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

3.4 Health and Availability Check

3.4.1 Ezer Mizion BMDR permits a Health and Availability Check (HAC) request in place of verification typing test under certain conditions:

3.4.1.1 In case of transplant urgency and a need to expedite a patient's timeline to transplant.

3.4.1.2 Only on case of an urgent search where the donor is considered a backup donor.

3.4.1.3 Donor h0as previously been requested for verification typing.

3.4.2 The typing of a donor requested for HAC should have at minimum, high-resolution (allele or antigen recognition domain level) DNA-based typing at HLA-A, -B, -C, and -DRB1. If the donor's HLA quality does not meet these criteria, HAC may still be permitted in cases of extreme patient urgency.

3.4.3 A donor information session must be conducted while performing a HAC. The *Health History Questionnaire (FRM_IC40)* is used to determine medical eligibility and donor consent. Additionally, donor availability is checked. Further results and applicable transplant relevant information are reported to the requesting registry via the *Health Availability Check Result Form (FRM_CT20).*

3.4.4 The donor will remain reserved for 4 weeks after HAC results are provided. In justified cases the reservation may be extended at the request of the transplant center.

3.4.5 If the donor is subsequently requested to donate, the required verification typing must be performed in parallel to workup. The transplant center must provide the verification typing result to Ezer Mizion BMDR before the donor begins mobilization or proceeds to collection, or the patient begins with the preparative regimen, whichever is earliest.

4. FACILITATION OF SEARCH REQUEST

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. To initiate an unrelated search, the request should be entered into the registry software.

4.1.2 Main communications between the Ezer Mizion BMDR and international registries or transplant centers must be in writing.

4.1.3 Requests from International registries are mainly made through EMDIS system. In case an international registry does not retain access to EMDIS system, a search request must be obtained by sending the Ezer Mizion BMDR *Preliminary Search Request form (FRM_S20)* or equivalent search request form via fax/e-mail. National preliminary search requests should be obtained by sending Ezer Mizion form of *Preliminary Search Request (FRM_S20).*

4.1.4 Ezer Mizion BMDR accepts search requests for donors registered at Ezer Mizion from national and international centers. Ezer Mizion also accepts search requests for international donors on behalf of its affiliated cross-border transplant center. In this case Ezer Mizion shall use the WMDA Search & Match Service (WSMS) to perform a worldwide search for suitable international donor. Ezer Mizion shall perform a worldwide Cord Blood Unit search on WSMS only if the cross-border transplant center specifically requires this.

4.1.5 The policy for the minimum criteria needed to allow a specific donor to be available for a specific patient should be accessible to national/international organizations authorized to provide HSCT.

4.2 Patient Acceptance

4.2.1 Patient characteristics permissible for initiation of donor search are those described in the EBMT recommendations published in the latest report of indications for hematopoietic cell transplantation for haematological diseases, solid tumors and immune disorders. If the indication for which the patient's transplant center is requesting a donor is not a standard indication, Ezer Mizion may request further clinical information according to the discretion of the medical director of the registry.

4.2.2 The following patient's information must be provided to Ezer Mizion BMDR to initiate a search request: Patient ID, Gender, Date of birth, Diagnosis and status of patient, HLA typing (minimum HLA-A, -B, -C, -DRB1, -DQB1), TC/Registry reference, Invoice address. Patient name is optional.

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 results of an Ezer Mizion donor search requested via EMDIS will be returned to the searching organization via EMDIS. For non-EMDIS users, a search report list consisting of the Ezer Mizion BMDR's Donors will be sent within one business day after the receipt of the search request by secured email. Donors that are not active or not available will not appear in the preliminary search report. The status of the donor will be clearly indicated on the search report.

4.3.3 International donor search results performed via WSMS on behalf of cross-border transplant center will be sent by secures email within three business days of receipt of the request.

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

4.3.5 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.

4.3.6 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 GRID will be utilized in all correspondence between the Ezer Mizion BMDR office and representatives and the patient's registry/transplant center.

4.3.7 Verification typing of potential donors must be performed according to the HLA typing requirements and resolution levels as defined in section 3.3. Donor verification typing result, at a minimum of HLA-A, -B, -C, -DRB1 DNA based typing at high resolution, must be forwarded to Ezer Mizion BMDR and indicate if the donor is to be reserved for the patient concerned according to Ezer Mizion donor reserving policy (section 3.3.14).

4.3.8 The results of HLA compatibility tests of the patient and donor should be provided by the HLA laboratory to the attending physician of the transplant center. Ezer Mizion can provide advice on matching donors and patients but the decision for the final donor selection is always the responsibility of the transplant center physician (either national or international) or international registry.

4.3.9 Under certain conditions a verification typing test can be performed after a health and availability check (section 3.4) or parallel to a workup request (section 5.1.9). Similarly, in exceptional cases where donor blood is not available for IDM testing, at the time of verification typing, the IDM testing could be delayed until workup. The registry must inform the transplant center of the reason for the delay and the potential for risk to the patient should the donor prove to be ineligible.

4.3.10 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. Any changes in the patient or search status that impact the reservation of the donor, should be communicated to the Ezer Mizion BMDR in a timely manner.

4.4 Termination of a Search

4.4.1 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.

4.4.2 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.

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

5. COLLECTION AND PROCESSING OF HSC

5.1 Work-up Request

5.1.1 Workup 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.

5.1.2 The procedure must take place at Ezer Mizion associated collection centers. The information, medical evaluation and informed consent sessions are to be carried at the collection center.

5.1.3 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. In case the donor workup is being held in the same medical center where the patient is admitted, the donor examination must be performed by a physician who is not the treating physician overseeing the care of the patient.

5.1.4 The registry must be informed of the proposed date(s) of transplant at the time a specific donor is requested for workup for a specific patient. The transplant center must specify the latest date by which the registry must provide donor clearance. To request a workup for HSC collection the following forms, or their international equivalent, must be completed and forwarded by the transplant center or international registry to Ezer Mizion BMDR:

5.1.4.1 *Donor HLA Verification Typing Results (WMDA form: S60),* or an equivalent WMDA based form completed by the tissue typing laboratory associated with the Transplant center.

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

5.1.5 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 Ezer Mizion medical director. This applies to both national and international patients.

5.1.6 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 donor will be inquired about his/her preference for type of stem cell harvest and for any other donor-specific issues that may affect the donation (e.g. availability for subsequent donations). 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 donors must be free to change his mind at a later date.

5.1.7 The transplant center will be notified in a timely manner about the stem cell collection date/s using the Ezer Mizion form *Workup 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. The transplant center must complete and return the Confirmation of *Workup*

Schedule form to Ezer Mizion BMDR.

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

5.1.9 Ezer Mizion will accept workup requests without prior verification typing of the respective patient/donor pair only under the following conditions:

5.1.9.1 Particular transplant urgency is documented for example: donor deferral during a workup, primary or secondary graft failure, failure of induction therapy, known high-risk Leukemia, and relapse.

5.1.9.2 The patient must be registered with high resolution HLA at the 5 loci (HLA-A, -B, -C, -DRB1, -DQB1) and the donor's HLA must have been tested at high resolution at the HLA-A, -B, -C, -DRB1 loci.

5.1.9.3 A donor health and availability check has already been performed.

5.1.9.4 HLA verification typing test must be performed in parallel to workup by means of pre-collection. The typing results must be available before the donor begins mobilization or proceeds to collection, or the patient begins with the preparative regimen, whichever is earliest.

5.2 Backup Donor

5.2.1 Ezer Mizion will accept requests for a **backup donor** at workup stage only under the following terms and conditions:

5.2.1.1 Ezer Mizion will approve only one backup donor per recipient.

5.2.1.2 A backup donor must be known to be of acceptable HLA match with the intended recipient and have demonstrated suitability through verification typing (preferred) or HAC (minimum). Ezer Mizion will not approve a request for backup donor unless either VT or HAC have been completed. A backup donor must be placed on reserved status according to Ezer Mizion policy at either VT stage (see section 3.3.14) or HAC (see section 3.4.5).

5.2.1.3 The transplant center is required to inform Ezer Mizion whether the requested donor is the primary or backup donor, regardless of whether the primary donor was selected from Ezer Mizion or another registry. If the primary donor is not from Ezer Mizion registry, the transplant center must notify Ezer Mizion of the schedule for the primary donor's donation, any changes to the backup donor priority, and when the donor can be released.

5.2.1.4 Backup donors must be counselled and informed that they have been selected as the backup for donation. Where possible, the preferred product and transplant timeline must be communicated to the backup donor. Obtaining consent for donation, physical examination or other workup-related preparative activities such as scheduling collection and pre-collect sample acquisition, will not be initiated unless the backup donor was requested for active workup.

5.2.1.5 The backup donor should only be requested for active workup under exceptional circumstances. If the transplant center actively requests that a backup donor proceed to workup in parallel to the primary donor's workup, it must maintain clear communication with Ezer Mizion and provide timely update regarding the workup status to avoid accidental and unnecessary preparation of the backup donor. Cancellation of a backup donor must be communicated as soon as it becomes evident that a collection will not be needed. Under no circumstances should a donor initiate G-CSF or proceed to collection if they are not the primary donor.

5.3 Cryopreservation

5.3.1 Stem cell products collected from unrelated donors are intended for direct distribution and the immediate transplantation in a specific patient. The blood stem cell product should be completely used, if possible. Parts of the preparation can be cryopreserved for later therapeutic use for the same patient. The cryopreservation of the complete cell product or a portion thereof can only be performed if the donor consents. Ezer Mizion BMDR is to be informed in detail of the use and/or cryopreservation of the product.

5.3.2 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 informed of the consequences of cryopreservation.

5.3.3 After collection of a product, and upon request of the registry, the transplant center is to provide information as to if and when a cryopreserved product was infused.

5.4 Donor Information

5.4.1 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.

5.4.2 Donor's identity must be verified and documented.

5.4.3 Prior to donation, donors must meet with a physician at the collection center for an 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.

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

5.4.5 In case the donor has doubts regarding the peripheral blood HSC collection procedure, or if he/she is not eligible for it, the donor should be informed that conventional bone marrow donation might 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 wait for its confirmation to proceed with bone marrow collection.

5.4.6 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.

5.4.7 The donor must sign a further consent if 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.

5.4.8 Issues to be discussed and fully explained to the donor during the Collection center physician counseling are:

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

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

5.4.8.3 The product preference of the transplant center.

5.4.8.4 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.

5.4.8.5 Personal information that will be collected and how this information will be protected.

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

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

5.4.8.8 The possible duration of absence from work and physical activities.

5.4.8.9 The donor center and hospital general liability insurance coverage for the workup and collection procedures.

5.4.8.10 Non-remuneration of donation.

5.4.8.11 Reimbursement of reasonable expenses incurred during the donation process.

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

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

5.4.8.14 Requirement of bone marrow HSC donation if the G-CSF mobilization is unsuccessful or must be interrupted.

5.4.8.15 Risks and side effects of anesthesia, marrow donation, administration of G-CSF and peripheral blood HSC donation and other blood product donations.

5.4.8.16 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 workup.

5.4.8.17 In case of bone marrow collection the donor should be informed that an autologous blood unit may be collected before the procedure.

5.4.8.18 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 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.

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

5.4.8.20 The policy regarding anonymity between donor and patient.

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

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

5.4.8.23 The donor must be informed if the transplant center may request product's cryopreservation prior to the beginning of the recipient conditioning therapy. In addition, the donor should be informed that a portion of the product may be cryopreserved at the transplant center for a subsequent treatment of the patient if excess HSC were collected.

5.4.8.24 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.

5.5 Donor Medical Evaluation and Testing

5.5.1 All donors are assessed at the collection center during workup by a qualified physician who decides if the donor should be cleared for collection or deferred. The physician who determines the donor's eligibility for the donation must not be a member of the transplant team, or directly involved in the patient's care. The results of the examination must be recorded in writing.

5.5.2 *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 workup. The Collection center physician is required to evaluate and review the donor questionnaire and witness the donor's signature on the consent form.

5.5.3 The Work-up assessment tests of the donor must include:

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

5.5.3.2 Blood tests: complete blood count, full biochemistry screening of the blood, basic coagulation functions, and ABO and Rh blood type by serology method.

5.5.3.3 Other tests may be performed according to the discretion of the collection center physician, applicable regulation or incidences. Donors who have recently travelled outside their country should be evaluated for infectious diseases prevalent in the areas of travel.

5.5.4 The transplant center should be informed regarding the infectious disease markers that will be routinely tested, those that may be available upon request, and those for which a sample can be provided for testing.

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

5.5.6 Pregnancy is a contraindication for donation. Female adult volunteer donors of childbearing age must have a pregnancy test performed during the workup 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.

5.5.7 The donor's peripheral veins must be assessed. In case of peripheral blood HSC collection particular care should be taken regarding venous assessment. The collection center designee who will undertake the apheresis procedure should ideally perform this assessment.

5.5.7.1 Autologous blood unit: In case of PBSC collection, a backup autologous blood unit is not routinely recommended. In case of bone marrow aspiration, 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 bone 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.

5.5.8 Full IDMs testing must be performed within thirty (30) days prior to the transplant date. The IDMs results, 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 results of infectious disease markers performed at workup should be reported no later than five (5) working days after testing.

5.5.9 In the event of postponement of the transplant, IDM testing must be repeated within thirty (30) days prior to transplant date. If more than thirty (30) days but less than six months

have passed since the donor 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 (6) months or more have passed since donor's clearance, a full donor workup must be repeated including hematological and blood chemistry tests, physical assessment and IDMs.

5.5.10 If pre-collection samples are required, no more than 50 mL of peripheral blood should be requested in addition to the blood samples collected for the blood tests at the collection center.

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

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

5.5.13 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 IDM tests 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 on the *Donor Final Clearance (FRM_WU50)*.

5.5.14 The recipient conditioning therapy must not be initiated until donor clearance for blood stem cell donation including the results of the donor IDM tests 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.

5.6 Abnormal Finding and Donor Deferral

5.6.1 Any abnormal findings at verification typing or workup, 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 by the Ezer Mizion BMDR. The transplant physician or his designee should reply to the Ezer Mizion BMDR with written acknowledgement that they have been informed of the abnormal findings and indicate whether they wish to proceed or release the donor from the search process. A record of the reply must be kept in the donor file.

5.6.2 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).

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

5.6.4 Donors with abnormal finding during workup:

5.6.4.1 The collection center physician shall determine whether an abnormal finding constitutes unacceptable risk to the donor. The collection center physician should inform the donor about the abnormal results, notify the registry office and refer the donor to either the

registry's medical director or his authorized representative, or for appropriate medical follow-up elsewhere.

5.6.4.2 Documentation of the counseling regarding abnormal finding shall be maintained as follow:

5.6.4.2.1 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.

5.6.4.2.2 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 center via Ezer Mizion form *Abnormal Donor Finding (FRM_WU52).*

5.7 G-CSF Administration

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

5.7.2 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.

5.7.3 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.

5.7.4 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.

5.7.5 G-CSF will be administered subcutaneously at a dose of 10-12 micrograms (µg) per Kg per day (10-12µg/Kg/Day).

5.7.6 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.

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

5.7.8 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.

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

5.7.10 On day 5, after the day 4 G-CSF injection, 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).*

5.8 Collection Procedure

5.8.1 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 workup which ensures the plans for the collection are considered acceptable and verified by collection center physician, registry office and transplant center.

5.8.2 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.

5.8.3 The transplant center should be encouraged to send feedback information to the Ezer Mizion BMDR on whether the product met transplant center criteria using the Ezer Mizion form *Transplant Report (FRM_WU74).*

5.8.4 Peripheral Blood HSC Collection Procedure

5.8.4.1 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).

5.8.4.2 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 (2).

5.8.4.3 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. Heparin may also be added according to the collection center procedures.

5.8.4.4 Because of the potential complications involved, a central venous catheter (CVC) must be avoided. If during the medical evaluation it becomes evident that a CVC insertion may be needed, the donor should only be cleared for bone marrow HSC donation, or a different donor should be searched for. If an insufficient venous access for a peripheral donation becomes apparent on the day of apheresis, an arterial line may be placed following an approval of the medical director of the collection center. A physician who is qualified and experienced in this procedure must perform an arterial line insertion.

5.8.4.5 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 $5x10^6$ CD34+ cells/kg 'ideal' patient body weight. No further collections should take place if $5x10^6$ (or greater) CD34+ cells/kg 'ideal' patient body weight are collected in the first collection procedure.

5.8.4.6 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; (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.

5.8.4.7 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 bone 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 6 of this manual. If a bone 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.

5.8.4.8 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.

5.8.4.9 *The Collection Report form (FRM_WU71*) should accompany the HSC product to the transplant center and also sent to Ezer Mizion BMDR.

5.8.5 Marrow HSC Collection Procedure

5.8.5.1 Bone 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.

5.8.5.2 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.

5.8.5.3 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.

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

5.8.5.5 After aspiration, the bone 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.

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

5.8.5.7 The total number of nucleated cells collected must be tabulated and reported on the *Collection Report form (FRM_WU71).* Wherever possible, the collection centers should perform analysis for 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.

5.9 Product Processing after Collection

5.9.1 General

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

5.9.1.2 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.

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

5.9.2 Cultures and Viability

5.9.2.1 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

5.9.2.2 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 bone marrow HSC product a sample of the marrow collection should be cultured under aerobic and anaerobic conditions.

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

5.9.3 Processing

5.9.3.1 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.

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

5.9.4 Storage and Transport of Peripheral Blood HSC

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

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

5.9.4.3 For long distance transportation and storage of product, the final concentration of nucleated cells in the collection is important for viability. Unless the transplant center requested otherwise, the concentration of nucleated cells should be reduced in the processing laboratory to less than $3x10^8$/ml by the addition of donor plasma or 5% HSA (Human Serum Albumin saline). Request for 150-200 mL of plasma should be indicated on the prescription for the product.

5.9.4.4 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.

5.9.4.5 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.

5.9.5 Storage and Transport of Bone Marrow HSC

5.9.5.1 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.

5.9.5.2 For transport over eight (8) hours marrow should be diluted in ACD–A incase the cell counts are above $2x10^8$/ml. No other additives must be injected into the bags of marrow during the transport of the marrow unless requested by the Transplant center.

6. SUBSEQUENT DONATIONS

6.1 Introduction

6.1.1 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..

6.1.2 A single donation may include more than one procedure. For example, a failed peripheral blood HSC collection followed by a bone marrow collection or two days peripheral blood HSC collection is equal to one donation.

6.1.2.1 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.

6.1.3 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.

6.1.4 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.

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

6.1.6 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.

6.1.7 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.

6.2 Request and Approval Procedure for Subsequent Donations

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

6.2.2 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 *Formal Request and Prescription for HPC, Marrow, HPC, Apheresis and for MNC, Apheresis (WMDA form: 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.

6.2.3 All requests for a second or subsequent donation are examined by the Ezer Mizion BMDR 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.

6.2.4 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:

6.2.4.1 The possibility of a subsequent donation of stem cells must be discussed at the original donor workup and be explicitly indicated in the consent forms.

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

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

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

6.2.4.5 The procedures donor information, medical evaluation and collection are as for the first donation (section 5). The results of the medical evaluation within the normal range are a basic requirement for a subsequent donation.

7. TRANSPORT

7.1 General

7.1.1 Bone marrow, peripheral blood HSC and donor lymphocytes must be hand carried during the whole transport by an authorized courier whose details have been conveyed to the Ezer Mizion BMDR, collection center and transplant center.

7.1.2 The transplant center is generally 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.

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

7.1.4 Non-cryopreserved HSC are transported at a temperature of 2°-8°C unless otherwise specified by the transplant center . The courier must supply the transport container.

7.1.5 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.

7.1.6 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 Ezer Mizion BMDR, there needs to be a SLA in place between the transport company and Ezer Mizion BMDR. 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 and must be trained in all policies and procedures required for the transportation of HSC.

7.2.1.2 The courier must not be related to the donor or patient.

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

7.2.1.4 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 checkpoints. If security staffs 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 checkpoints 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, printed using waterproof ink labels, and must contain the following information using the designated format according to the ISBT 128 standard:

Donation Identification Number (DIN); GRID; Recipient name and unique identification code; product name; product code and product information; product warnings regarding irradiation and leuco-reduction; donor ABO/Rh group; collection date; collection time and time zone at end of collection; product volume and anticoagulant; product storage conditions; address and location of the transplant center.

7.6 Product Accompanying Documentation

7.6.1 *Collection Report form (FRM_WU71)* that contains the following: product name; cell count and, if applicable, processing information; product code; recipient Id code; recipient name (optional); GRID; donor AB0/Rh group; date and time of collection, transplant center name 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 *Donor Final Clearance (FRM_WU50)* which contains results of donor infectious disease markers testing

7.6.4 *Verification of Prescription for Cell Product form (FRM_WU30)*

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

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

7.7 Product Packaging

7.7.1 Packaging and shipping containers must be rigid, shatterproof thermally insulated transport box qualified for the transport of HSC and lymphocytes 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 must be arranged as specified by transplant center for adequate temperature control over the estimated transit time into the cooler. Bags of HSC must be thermally insulated from frozen coolant packs to avoid spot freezing. Dry ice must never be placed in the cooler with non-cryopreserved HSC.

7.7.3 Electronic Data loggers for recording, monitoring and documentation of the transport temperature must be used during transport. In case of transport of a cryopreserved cellular product, the dry shipper must contain a data logger that continuously monitors temperature throughout the transportation or shipping period.

7.7.4 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.

7.7.5 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:

7.7.5.1 MEDICAL SPECIMEN – HANDLE WITH CARE

7.7.5.2 DO NOT X-RAY

7.7.5.3 WARNING: Contains human tissue for transplantation

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

7.7.5.5 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.

7.7.6 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 (*Product Labeling Checklist form 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 affecting 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 RECIPIENT 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-term 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 the *Donor Assessment Post Stem Cell donation form (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 the *Annual Donor Assessment Post Stem Cell Donation form (FRM_FU22).* The donor should also be assessed according to this form after two (2), five (5) and ten (10) years post donation to ensure appropriate care for any conditions related to the hematopoietic 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 HSC and bone marrow donors, and subsequent donations of HSC or Lymphocytes 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.

8.1.6 Donor health issues post-donation potentially affecting the health of the recipient must be reported to the transplant center. The Ezer Mizion BMDR 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.

8.2 Serious Adverse Events and Reactions

8.2.1 Serious Adverse Events and Reactions affecting donors undergoing collection of stem cells and lymphocytes occurring during and/or after administration of G-CSF, during the actual donation, and in the short term and/or long-term as a consequence of the donation must be reported by the Collection center to the Ezer Mizion using the *Donor Incident Report form (FRM_RP20).* Ezer Mizion should document and investigate Serious Adverse Events and Reactions and remedial and/or corrective action should be taken.

8.2.2 Serious Adverse Events and reactions during and after a donation (HSC and lymphocytes) or during mobilization of stem cells, as well as events which resulted in the risk of such a reaction, must be submitted to the WMDA S(P)EAR Committee.

8.2.3 Serious Adverse Reactions occurring during collection, processing, transport, or at/post-transfusion of cells, as well as events that resulted in the risk of such a reaction, and impacting the health and safety of donors or patients must be identified, documented, investigated and remedial and/or corrective action taken. The Serious Adverse Reactions must be submitted to the WMDA S(P)EAR Committee.

8.2.4 Ezer Mizion is responsible for informing the transplant centers or international registries, and the WMDA S(P)EAR Committee about any relevant long-term donor abnormal findings which may affect the patient treatment or transplant outcome. Likewise, cases must be reported if the transplant center diagnoses a serious illness of the patient, which may have been transmitted by the donor.

8.2.5 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 (or during previous procedure regarding the collection) in which the donor was injured or damaged, should be reported to MOH within 24 hours.

8.3 Donor-Recipient Communication post Transplantation

8.3.1 Donor and recipient may share anonymous correspondence and gifts post-transplant. Any correspondence must be reviewed by the Ezer Mizion BMDR to ensure all personally-identifying information is removed before it is forwarded.

8.3.2 Direct contact between donor and recipient is not permitted until one year after the first transplant date at the earliest. Before any direct contact is permitted, both the donor and the recipient or his legal guardian (if the patient is under the age of 18 years) must sign the corresponding consent form (*Patient/Donor consent to Release Personal Information form* (*FRM_IR10/11).* Should the patient receive a further transplant from the same donor, direct contact is possible one year after the second transplantation at the earliest. The date of the second transplantation does not shorten the initial required period of one year. Identities of donor and recipient will not be exposed eternally to the other party or family in case the patient has died.

8.4 Recipient's Condition Post Transplant

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

8.4.2 The Ezer Mizion BMDR will contact the transplant center 12 months after the donation in order to collect information about the recipient's condition. The *Stem-Cell Transplantation Follow-Up* form *(FRM_FU31)* or any equivalent form should be used for this purpose.

8.4.3 In case Ezer Mizion registry requests a product on behalf of its affiliated cross-border transplant center, basic patient outcome data should be shared with the registry providing the product.

8.4.4 If the cell product is not infused, Ezer Mizion BMDR, must be informed about the disposition of the preparation. In the case of cryopreserved products, the transplant center is to provide information in case the cryopreserved product was not infused. The donor is to be informed accordingly.

8.4.5 Upon the donor request, the Ezer Mizion BMDR will provide information about the recipient's condition only one year after the donation date. Medical data is not to be communicated to the donor, rather only general information is to be provided (e.g. alive, good general condition, patient is able to work again). The recipient must be informed and provide his consent before the transplant center transmits or uses any medical follow-up data. The Ezer Mizion BMDR coordinator must ensure the confidentiality of the donor and the patient information.

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

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 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.

9.1.4 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.

9.1.5 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.

9.1.6 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 (30) 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 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.

9.4.2 Donor Expenses

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

9.4.2.2 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 earnings, incidental expenses and accommodations will be reimbursed to the donor and companions (in special circumstances) by Ezer Mizion BMDR.

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

9.4.2.4 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.

9.4.2.5 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.

9.4.2.6 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.

9.4.3 Donor Insurance

9.4.3.1 All Collection centers must provide appropriate medical 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.

9.4.3.2 Ezer Mizion BMDR maintains medical liability and malpractice insurance.

10. INFORMATION TECHNOLOGY AND INFORMATION MANAGEMENT

10.1 Records and Record Retention

10.1.1 Ezer Mizion BMDR maintains electronic and hard copies records generated through the entire donors and patients' procedures. Appropriately interpreted, the regulations in this section apply likewise to electronic, paper based or otherwise manual processes.

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

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. Records of donors who have donated HSC products or have been pretreated for this purpose must be maintained at a minimum for thirty (30) years following donation.

10.1.5 Records must be preserved and protected from accidental un-authorized access, destruction or modification.

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 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 Ezer Mizion BMDR 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.

10.3 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 donors related information that is communicated externally must not contain names but only pseudonymous codes. The registry must assign a unique and anonymous Identifier, GRID, according to WMDA guidelines to each adult volunteer donor.

10.3.1.3 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.

10.3.1.4 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.

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. The searchable database available for donor selection should be updated every day.

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 the registry web site and at the registry's page on WMDA Share. National transplant centers and international registries that do not maintain EMDIS connections with the registry receive match lists that are generated by the registry own data system.

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
CVC	Central Line Catheter
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
HBV	Hepatitis B Virus
HBsAg	Hepatitis B Surface Antigen
HBc	Hepatitis B core antibodies
HCV	Hepatitis C Virus
HIV	Human Immunodeficiency Virus
HLA	Human Leukocyte Antigen
HPC	Hematopoietic Progenitor Cells
HSC	Hematopoietic Stemדקרש דיסורג 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
IC21	Confirmatory 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
S22	Regulatory Questionnaire for Transplant center
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
IR10/11	Patient/Donor consent to Release Personal Information form

Appendix 2: List of Changes between Version 9 and 10

Section	Change	Rational
1.1.1.18	Deleted	The section was merged with section 1.1.1.17
1.2.3	Revised	The entire paragraph was revised to comply with Std 1.07 in the new WMDA standards version 2024
1.2.4	Revised	The entire paragraph was revised to comply with Std 1.08 in the new WMDA standards version 2024. The specific criteria for collection centers were deleted since they appear in SOP-Q-21 – Ezer Mizion Criteria for collection center.
2.2.4.2	Deleted	The section was combined with section 2.2.4.1
3.2.4	New	A donor requested for Extended Typing test must be placed on a "reserved" status for the patient for 45 days from the time of extended typing request.
3.3.11	Added	Ezer Mizion registry must respond in a timely manner to requests for donor samples and make utmost efforts to provide the samples within a time period consistent with WMDA metrics
3.4.4	Added	The donor will remain reserved for 4 weeks. In justified cases the reservation may be extended at the request if the Transplant center
3.5	Deleted	The information was removed to SOP-REC-28
3.6	Deleted	The information was removed to SOP-REC-28
4.1.3.1	Deleted	The section was deleted to avoid redundancy with Std 1.07
4.1.4	Added	The section was added to include search procedures for cross-border TC
4.2.1	Revised	The wording was further clarified
4.2.2	Revised	Patient name is optional
4.3.2	Deleted	Removed to chapter 10
4.3.3	Added	The section was added to include search procedures for cross-border TC
4.3.9	Added	In exceptional cases where donor blood is not available for IDM testing, at the time of verification typing, the IDM testing could be delayed until workup.
4.3.10	Revised	The wording of this section was amended to comply with WMDA standards: Donor verification typing results at a minimum of HLA-A, -B, -C, -DRB1 DNA based typing at high resolution **MUST** be provided to Ezer Mizion BMDR prior to a hematopoietic stem cell donation for a specific patient
5.1.9	Revised	The entire paragraph was revised to comply with Std 6.04 in the new WMDA standards version 2024
5.1.10	Revised	Backup donor policy was revised to comply with new WMDA recommendations for BUD
5.4.3.6	Revised	The paragraph was revised to comply with Std 3.24.2 in the new WMDA standards version 2024
5.4.4	New	In accordance with Std 3.24.2 in the new WMDA standards version 2024
5.7.4	Revised	Central Line Catheter is not permitted
7.7.3	Revised	In case of transport of a cryopreserved cellular product, the dry shipper must contain a data logger that continuously monitors temperature throughout the transportation or shipping period.
8.4.4	Revised	a policy for sharing basic patient outcomes data with donors
9.4.3.2	Deleted	Ezer Mizion BMDR provides a comprehensive medical insurance to all its donors
10.1.5	Deleted	The registry keeps hard copy and electronic records for every donor file in verification typing and workup stage
10.5.3	Added	The searchable database available for donor selection should be updated every day

Approved By

Name	Position	Date of Approval	Signature
Dr. Bracha Zisser	Director of Bone Marrow Division	14.06.2024	
Prof. Isaac Yaniv	Medical Director of Bone Marrow Division	13.6.2024	

Annual Review

Version Number	QA Manager	Date	Registry Manager	Date