

EZER MIZION PROCEDURES FOR TRANSPLANT CENTERS AND COOPERATIVE REGISTRIES



EZER MIZION **Bone Marrow Donor Registry**

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1. Purpose and Scope

This guide sets out the procedures to be followed by Transplant Centers (TC) and Cooperative Registries using Ezer Mizion services. It also provides an overview on our business processes and the resulting expectations we have when requesting services abroad for our patients.

The document addresses experienced staff of registries and TCs involved in hematopoietic stem cell transplantation and gives references regarding certain aspects of the search process and the access to our donors in general. This document is not intended to provide comprehensive or detailed insight into registry activities. Further information on requirements of our registry can be found in the Ezer Mizion Operation Manual:

(<https://share.wmda.info/display/WMDAREG/Documents+ION-4987>).

2. Introduction

Ezer Mizion is the Israel's largest health support organization offering a diverse array of services, which includes the Ezer Mizion Bone Marrow Donor Registry (<https://www.ami.org.il/bone-marrow-registry/>). The Ezer Mizion BMDR was created in 1998 and has been WMDA accredited since 2011. Ezer Mizion operates both as bone marrow donor registry and as donor center. It is responsible for the recruitment and maintenance of a current panel of donors, maintains contact with and providing information to donors, collections centers and to the search coordinators units in the national transplant centers.

Ezer Mizion BMDR provides suitably matched unrelated voluntary donors for national and international patients in need of transplantation.

National Transplant centers: national centers requesting an Ezer Mizion donor must be in possession of all licenses required by Israeli law and must observe all applicable regulations, laws and guidelines.

International Transplant centers: The registry operates directly with most established registries worldwide and maintains relations with some TCs in countries where no established registry exists. Registries that request an Ezer Mizion donor on behalf of a TC must be participating registry of the World Marrow Donor Association (WMDA) and ensure that their member TCs meet Ezer Mizion standards, regulatory requirements and WMDA Standards. International transplant centers that are not affiliated with local registry needs to fulfill a *Transplant Center Evaluation* form (FRM_S22). No request can be initiated before the Ezer Mizion BMDR approved the TC.

All Communication must go through Ezer Mizion - All users of services provided by Ezer Mizion agree that any and all communication relating to donors (this includes but is not limited to search, selection, typing services, provision of donors and follow up, both domestic and international), shall be made via Ezer Mizion.

3. Contact Information

Ezer Mizion Bone Marrow Donor Registry

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Friday to Saturday: Mrs. Sigal Manor: +972-52-9580039

Secondary Emergency Contact: Prof. Isaac Yaniv: +972-50-4057147

Web page: Eng - www.ezermizionis.org.il; Heb - www.ami.org.il/bone-marrow-registry/

EMDIS hub: IL2

4. Procedure for Search

- Each patient for whom a search is requested must be recommended by a physician for a stem cell transplant and must satisfy Ezer Mizion requirements regarding diagnosis, age and any other factors, which Ezer Mizion may consider relevant.
 - **Diagnosis** - When considering the diagnosis of a patient, Ezer Mizion will use the recommendations set out in the latest European Society for Blood and Marrow Transplantation (EBMT) Handbook. If the indication is not a standard indication, Ezer Mizion may request further clinical information from the TC/Registry.
 - **Age** - The TC/Registry physicians may exercise their discretion about whether a patient is of a suitable age for a transplant, if such physicians follow the relevant national and international standards and ethically approved protocols.
- **Procedure for Requesting a Search** - The TC/Registry may request a search by using the European Marrow Donor Information System (EMDIS). If EMDIS is not used, a *Preliminary Search Request* form (Ezer Mizion/WMDA or equivalent) should be sent to Ezer Mizion either by fax or e-mail.

All of the following information must be contained in an electronic or fax search request:

- Patient's full name
 - Patient's gender
 - Patient's date of birth
 - Diagnosis and current status of patient
 - HLA typing of patient (It is recommended that the HLA typing is performed to second field level for HLA-A, -B, -C, -DRB1 and -DQBQ1)
 - Registry reference
 - Invoice Address
- **Search upon request** - On receipt of a search request via EMDIS for Ezer Mizion donor, Ezer

Mizion system will automatically provide search report within 24 hours. In case search was requested through fax or email, Ezer Mizion will prepare a search report consisting of the Ezer Mizion donor listings. Ezer Mizion will send the report to the TC/Registry within two business days of the receipt of the search request. Ezer Mizion shall use the WMDA Search & Match Service to perform a worldwide search for a suitable international donor on behalf of a Transplant Centre upon request.

- **Activation of Search** - Searches performed electronically via EMDIS must be set to active before requests can be accepted. For patients with EMDIS-activation, automatic repeat searches are performed every night. All non-EMDIS searches are activated when the first request is made on behalf of a patient. New match lists are provided upon request.
- **Matching of Patients and Donors** - The matching list includes the HLA-A, -B, -C, -DRB1, and -DQB1 typing data. Where ambiguities exist, resulting in intermediate resolution results, the allele codes developed by the National Marrow Donor Program are utilized to enter data onto the computer. If required, Ezer Mizion will extend searches to look for donors with a single mismatch at any loci.
- **Cancellation of Search** - To cancel a search, the TC/Registry shall email Ezer Mizion with details of, and the reason for, the cancellation.
- **Search Termination** - Search request should be cancelled either by EMDIS or by e-mail/fax. There is no need to cancel a search that has never become active. For activated searches, Ezer Mizion expects a formal cancellation of the donor search. This is usually performed when a suitable donor has been identified and/or the patient proceeds to transplant, when the patient is no longer interested in or eligible for a transplant or when the requesting center loses contact with the patient. Ezer Mizion suggests that a search can be cancelled after three months of no activity for a patient.

5. Typing Request

- **Extended Typing** - the TC/Registry may request an extended typing of a donor by using EMDIS or by sending *Request for Extended Donor HLA Typing* form (Ezer Mizion/WMDA or equivalent) via fax or e-mail. Typing is performed by molecular methods in EFI/ASHI accredited laboratory for the loci indicated in the table below. Extended typing test will NOT be performed on stored DNA sample. Ezer Mizion will contact the donor to discuss the proposed typing, donation procedures, health and availability, and will obtain fresh buccal swab sample. Ezer Mizion will inform the Transplant Centre if Ezer Mizion has been unable to contact the donor or if the donor is not eligible and shall request new instructions before proceeding further. If the TC requests extended typing of an international donor, Ezer Mizion will pass the request for extended typing to the appropriate international registry but cannot guarantee that such donor will be available to provide a further sample, because the policies of other registries about providing further samples vary. Ezer Mizion shall endeavor to keep the TC informed about the progress of the extended typing and will pass on the results of extended typing which it receives from

international registries to the TC as soon as Ezer Mizion receives the results itself.

Locus	Low	Intermediate	High
A	X	X	X
B	X	X	X
C	X	X	X
DRB1	X	X	X
DQB1	X	X	X
DQA1, DRB3, DRB4, DRB5*, DPA1*, DPB1*,			X

*Not routinely performed, but can be performed in request. Time to result can vary

▪ **Cancellation of Typing Request -**

A TC/Registry may cancel requests for further typing at any time. Ezer Mizion requires at least 2 (two) business days' notice to allow time for the donor to be contacted and for the procurement of the sample from the donor to be cancelled. Every effort is made to cancel a test but if tissue typing has commenced before the cancellation notice the typing results will be sent.

6. Verification Typing Request

- **Request for Verification Typing** - On identifying potential donor matches to the patient, further Verification typing by the TC laboratory is necessary to ensure that the donor's initial HLA-typing results and level of matching with the patient are correct and still fulfill the medical requirements for donation. A TC/Registry may request Verification typing by using EMDIS or sending *Blood Sample Request for Verification Typing* form (Ezer Mizion / WMDA or equivalent). The patient must be registered in the Ezer Mizion BMDR database with high resolution data for HLA-A, -B, -C, -DRB1 and preferably -DQB1 at the time of Verification typing request.
- **Contact with Donors** - Ezer Mizion shall contact the donors to arrange the Verification typing and the donor will be asked to provide fresh blood samples. If an Ezer Mizion donor will be selected, Ezer Mizion will discuss donation procedures, health and availability with the donor. The total quantity of blood samples for Verification typing must not exceed 50mL per donor. No part of these samples must be used for research. Ezer Mizion 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.

If an international donor is selected, Ezer Mizion shall, as requested by the TC, facilitate shipment of the international donor blood sample to the designated Transplant Centre laboratory for verification typing.

- **Notification of Transplant Center** - The packaging and shipment of blood samples test tubes collected from an Ezer Mizion donor must meet the regulations of the Israeli MOH and the regulations of the International Air Transport Association (IATA) regarding shipment of dangerous goods. Ezer Mizion shall ship blood samples via the Fedex International Priority® service unless the TC requested otherwise. Once arrangements have been made, Ezer Mizion will notify the

TC/Registry of when to expect the blood sample from the donor together with details of donor availability and medical issues which could affect the donation. If Ezer Mizion has been unable to contact the donor within ten (10) calendar days, Ezer Mizion will contact the TC/Registry to establish whether to continue with the request. The TC/Registry will be required to confirm its decision by email/EMDIS.

- **IDM screening for donors** - A screening for Infectious disease markers (IDM) is always performed when requesting a blood sample. The results are sent about 1 week after blood drawing. IDM includes HBs-Ag, Anti-HBc, Anti-HCV, Anti-HIV-1/2, Anti-Treponema pallidum, Anti-CMV.
- **ABO blood group and Rh factor** - testing of donors must be done at the verification typing stage if the donor's blood group has not been previously determined.
- **Verification Typing Results** – TC/Registry must return the results of donor's typing to Ezer Mizion as soon as possible, by fax or email, indicating whether the donor should be released or reserved. Discrepancies in HLA typing results should be sent to Ezer Mizion.
- **Release of Donors** - If the TC/Registry does not instruct Ezer Mizion to reserve a donor, Ezer Mizion will hold the donors for 90 days after the date on which the Verification Typing samples were shipped and then release them. In the case of an international donor, if the TC does not instruct Ezer Mizion to reserve such a donor, Ezer Mizion will give instructions to the international registry to release the international donor.
- **Cancellation of Blood Sample Procurement** - A TC/Registry may cancel requests for blood sample procurement or blood sample shipment, at any time. Ezer Mizion requires at least two business days' notice to allow time for the donor to be contacted and for the procurement of the blood sample from the donor/blood sample shipment to be cancelled. If notice of cancellation is received by Ezer Mizion when the typing, sample procurement or sample shipment has begun, the TC shall still be required to pay the full charge for such typing or sample. Search cancellation automatically cancels all pending requests.
- **Reporting of Discrepancies in HLA Typing Results** - The Transplant Centre must report all discrepancies in HLA typing results to Ezer Mizion as soon as possible.
- **Concurrent Verification Typing Sample and Work-up Request for an Ezer Mizion Donor** - TCs can request concurrent Verification typing/work-ups for urgent patient cases where there is insufficient time to perform the Verification typing of the donor separately to work-up. Ezer Mizion will process concurrent Verification typing/workups for Ezer Mizion donors who have not yet been typed in the Laboratory associated with the patient's TC. In such cases, the TC must provide high resolution verification typing results of the donor to Ezer Mizion prior to the patient starting conditioning, or before the donor begins G-SCF, whichever happens first, along with a written statement confirming that they wish to proceed with the work-up.

7. Facilitating the Collection of PBSC or Bone Marrow from Ezer Mizion Donor

- **Work-up Request** - A Transplant Centre which requires Peripheral Blood Stem Cells (PBSC) or Bone Marrow (BM) from a donor on Ezer Mizion registry must send a [Formal Request and Prescription for Blood Stem Cell Collection](#) form (Ezer Mizion/WMDA or any equivalent compliant forms). The requesting registry/TC must have submitted confirmatory typing results at least for the loci HLA-A, -B, -C, -DRB1 and -DQB1 demonstrating at least a 9/10 match at high resolution level. Lower than 9/10 high resolution matches are subject to review.
- **Source of Cells** - The TC/Registry should specify whether it requires PBSC or BM derived stem cells.
- **Patient's Pre Collection Samples** - If the TC/Registry requires Pre collection tests it should be indicated in the prescription.
- **Cells Dose** - Requests for high cell doses (i.e. PBSC request above 5×10^6 / kg donor's body weight or above 20 ml of aspirated BM per Kg donor's body weight) shall be made under specific criteria that must be clearly detailed in the prescription form.

Unless otherwise instructed by the TC on the relevant prescription form, PBSC collections will be diluted with 4.5% Human Serum Albumin (HSA) to get an approximate final concentration of 200×10^6 ml TNC (Total Nucleated Cell). The Transplant center should indicate incase a dilution with autologous plasma or any other diluents is required. Bone Marrow will be diluted with ACD at a dilution of 1:9 vol ACD/vol BM.

- **Confirmation of Receipt of Work-Up Request** – Ezer Mizion will confirm receipt of each work-up request by fax or email to the TC/Registry within one Business Day.
- **Checking of Work-Up Request and Patient Criteria** – Ezer Mizion will check all work-up requests to ensure that the appropriate donor has been selected for the patient, by verifying initial donor eligibility based on HLA requirements, age, and medical status. Ezer Mizion will also check that the patient's criteria comply with Ezer Mizion standards. Ezer Mizion will notify the TC/Registry of the name of the Coordinator responsible for the patient's work-up request.
- **Ezer Mizion Contact with the Donor** – Ezer Mizion shall check with the selected donor that he is still willing to proceed and is available on the dates requested by the TC/Registry. A confirmation on donor availability will be sent in a timely manner and up to 7 calendar days after receipt of work-up request. If the Donor is not available on the requested dates, this information, with alternative dates proposed by the donor, will immediately be relayed to the requesting TC/Registry.
- **Work-Up Schedule** - When the dates for the donation and transplantation have been agreed, Ezer Mizion will book a full medical examination for the donor at one of the Collection Centers. Ezer Mizion will notify the TC/Registry of the confirmed dates for the donor's medical examination (which includes donor's consenting and counseling for the donation procedure), estimated date for the donor's clearance, dates of the G-CSF injections (if the method of donation is PBSC), date(s) of the donation, expected delivery day of the donated PBSC or BM. Ezer Mizion will send the [Verification](#)

of *Cell Product* form to the TC/Registry in order to ensure that plans for the collection are considered acceptable by all parties.

- **Donor Clearance** - When all the donor's tests and reports have been accepted as suitable for the donor to proceed with donation, Ezer Mizion will send the *Donor Final Clearance* form to the TC/Registry. The TC/Registry's designated physician shall sign the forms and return them to Ezer Mizion.
- **Procedure if Donor Fails Medical Evaluation** - If any tests or examination results are not within the accepted range, they will be reviewed immediately by Ezer Mizion. If any condition is uncovered which prevents the donor from donating, Ezer Mizion will immediately notify the TC/Registry that the donor will not donate. Ezer Mizion will not give the TC/Registry any personal information regarding the reasons why the donor has failed his or her medical evaluation.
- **Postponements and Cancellations of Transplants** - The TC/Registry must immediately notify Ezer Mizion of any postponement or cancellation of a transplant.
- **Postponements and Cancellations of Donations** – Ezer Mizion will immediately notify the TC/Registry, both by telephone and in writing, of all postponements or cancellations of scheduled donation. The TC/Registry must provide a 24 hour telephone number for this purpose. In rescheduling a donation, if the last IDM testing was performed on a donor sample taken more than thirty (30) days prior to the donation date, a repeat IDM testing will be performed. If the transplant has been delayed by more than six months, Ezer Mizion will arrange a repeat full medical examination of the donor.

8. Facilitating the Collection of PBSC or Bone Marrow from an International Donor

- **Work-up Request** - Request for Work-up for International donor should be facilitated as indicated in section 7.
- **Contact with International Registry** - Ezer Mizion will forward each request for an international donor to the respective international registry. The international registry will then proceed to contact the international donor and will confirm availability and dates. Ezer Mizion will confirm that the infectious disease markers that will be tested for the international donor's during medical check-up are according to the Transplant Center requirements. Ezer Mizion will forward this to the Transplant Centre for review. If any additional tests are required, the Transplant Centre will need to contact their coordinator requesting additional pre-collection blood samples from the international donor. Ezer Mizion will forward this on to the international registry.
- **Work-Up Schedule** - The time frame for confirmation of dates and availability of an international donor will vary but Ezer Mizion will maintain contact with the international registry and Transplant Centre to ensure that all information is received at the appropriate times to allow the transplant to proceed on schedule. Ezer Mizion will forward information to the Transplant Centre as soon as it

receives it.

The written information which will be passed on to the Transplant Centre by Ezer Mizion will include: the date of the international donor's medical, the date of donation, the date on which blood samples will be delivered to the Transplant Centre (if applicable), the expected date and time(s) of the delivery of the donated PBSC or bone marrow. If the dates do not suit the Transplant Centre, Ezer Mizion will attempt to obtain new dates from the international registry until a mutually acceptable date is found.

- **International Donor Clearance** - When Ezer Mizion receives the International Donor Clearance and results of IDM from the international registry, Ezer Mizion will email these to the Transplant Centre, before the date on which patient conditioning begins.
- **Donors on Reserve, Postponements and Cancellations of Donations** - The various international registries have different reservation policies. The Transplant Centre should ask Ezer Mizion for this information if it is required. Ezer Mizion will immediately notify the Transplant Centre of all postponements and cancellations of the scheduled donation. Likewise, the Transplant Centre must immediately notify Ezer Mizion of any postponement or cancellation.

9. Subsequent Donation

- **Requesting a Subsequent Donation** - If a TC/Registry requires a further donation for a Patient from an Ezer Mizion Donor who has already donated PBSC or Bone Marrow to such Patient, the TC/Registry must complete and send to Ezer Mizion *Previous Transplant History* (WMDA form or equivalent) by email or fax. The TC/Registry shall also send the adequate prescription form. Ezer Mizion medical director will review the request and provide a decision within 2 (two) business days of receipt of the request.
- **Frequency of Subsequent Donations** - Any requests for subsequent donation will be considered on a case by case basis. After the first donation the donor is reserved for three years for the initial recipient. During this time the donor is not available for another patient. The number of subsequent donations by a donor for the same transplanted patient or different patient is limited to two. In certain cases the registry will approve a third donation. Under special circumstances a donor may be able to donate a subsequent donation to a new patient.

10. Transportation of PBSC and Bone Marrow

Provision of Couriers – TCs/Registries usually arrange for the transportation of the products from the Israeli Collection Centre to the appropriate overseas hospital, using their own courier. In case a TC/ Registry requests Ezer Mizion to arrange the transportation of the product, Ezer Mizion must be provided with any specific requirements relating to shipments. Ezer Mizion will transport the product using a third party courier. Ezer Mizion will provide the TC information concerning the transport cost ahead of transport depending on the TC's destination and travel arrangements and confirm the delivery only after the TC approves.

11. Serious Adverse Event/Reaction Reporting

The TC/Registry must report to Ezer Mizion all Serious Adverse Events and Serious Adverse Reactions and any other event which has affected the cell product prior to infusion at the TC and/or the patient outcome by email.

12. Cryopreservation

Infusion and Cryopreservation - The TC/Registry must not cryopreserve the product without the prior written agreement of the Ezer Mizion medical director. The TC/Registry must notify Ezer Mizion when the cryopreserved product is either infused or discarded. Excess material, post transfusion, may be cryopreserved for therapeutic purposes or discarded according to standard protocols without applying to Ezer Mizion for the donor's permission.

13. Procedures after Donation

- **Transplant Report** – After the product infusion the TC/Registry should complete the form *Transplant Report* (FRM_WU74 or equivalent) and send to Ezer Mizion.
- **Updates on Patient's Progress** - Each Donor may request a single update on their patients' progress within the first year after donation.
- **Donor/Patient Contact** – Anonymous patient-donor contact is permitted after the transplantation. Generally, personal contact is possible beginning at least one year after the transplant if the patient and the donor agree and sign a declaration of consent to release personal information.

14. Research

- The TC/Registry may request that an Ezer Mizion donor be involved in a research program. Ezer Mizion will then consider the request. All research studies will require the approval of the Ezer Mizion medical director and Israeli regulations. Such an application must consist of:
 - Covering letter of intent from the principal investigator
 - Evidence of relevant institutional review board approval
 - The research protocol
 - Information for the participant
 - Donor consent form

15. Finance

- **Fee schedule** - The current Schedule of Fees is routinely distributed to the cooperating registries by e-mail thirty days prior to implementation.
 - A Preliminary search and activation of the search process are free of charge.
 - The price for the confirmatory typing sample includes testing for infectious disease markers.

- The procurement fee for bone marrow or peripheral stem cells does not include the courier costs, a separately shipped pre-collection and/or IDM sample. Provision of the courier by the transplant center is encouraged.
- **Cancellation** - Every effort is made to cancel a test but if tissue typing has commenced an invoice is issued on receipt of the results and has to be paid. For provision of blood samples, if an appointment date (blood draw date) has passed and the samples shipped an invoice for the sample collection and freight is raised. If the shipment can be stopped in time, freight is not charged.
- **Terms of Payment:**
 - The total amount is due within 30 days.
 - Payment must be made by a check or a bank draft direct to our business bank, expressed in USD, for the full amount invoiced free of bank charges, drawn to the corresponding business bank, payee Ezer Mizion.
 - Our invoice numbers should be noted on the document.

16. Ezer Mizion Staff

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