

The national program for unrelated stem cells transplant – present and perspectives.

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Executive Summary

This document sets out the NRHSCVD Strategic Plan for 2013-2014. The plan is based on the consultation of the Scientific Council of NRHSCVD, staff consultation network of healthcare facilities that performing activities coordinated by NRHSCVD (HSC Donor Centers, HLA Laboratories, Collection centers and Transplant centers HSC). It is aimed at implementing the NRHSCVD Mission and Vision, in compliance with standards and policy of World Marrow Donor Association (WMDA) (<http://worldmarrow.org/>), which envisages:

- 1) To assure efficient provision of the hematopoietic progenitor cells for patients in need of a stem cell transplantation and to undertake the intervention in one of the Transplant Centres in the country.*
- 2) To increase public and professional awareness of donation of hematopoietic stem cells as means to help patients;*
- 1) To implement the international quality standards and procedures through education and studies;*
- 3) To develop the governance structure for effective and accountable implementation of the mission and;*
- 4) To maximize the available resources.*

Present situation and the actual results after the first 6 months of implementation, difficulties identified and lessons learned were taken into account to determine future prospects for achieving the targets.

Key words: standards and policy, unrelated donors, unrelated stem cell transplantation.

GENERAL CONTEXT

Each year, thousands of people are diagnosed with severe, life-threatening conditions, like leukemia and other hematologic diseases. In some case, the only chance of saving these patients' lives is performing a hematopoietic stem cells transplant from a compatible donor. Some patients have a matching donor in their own family, but most patients rely on unrelated donors. The demand for unrelated hematopoietic stem cells donors has tripled in the last decade alone and might continue to increase during the next decade as well, as a consequence of smaller families. It is known that the interval from diagnosis to transplantation affects the patient's results in a negative way, providing unrelated donors being the main cause of these delays. Delays in finding unrelated donors are caused by: delays in referring the diagnosed patient to a transplant center as a result of waiting for results in the case of sibling typing; the lack of a matching donor (especially for ethnic minorities and/or in the case of rare HLA phenotypes); time and high expenses for checking the donor-patient compatibility if possible donors are HLA-typed at a lower or intermediate resolution; registered donor depreciation; donor ineligibility for health reasons and difficulties encountered with HSC transplants across international borders¹.

Because finding a compatible donor in the population group or the geographic area of the patient is

more likely, most countries have established volunteer hematopoietic stem cells donor's registries. Registries worldwide share donors via an international database administered by Eurodonor - Bone Marrow Donor Worldwide, which now **counter over 22 million of volunteer hematopoietic stem cells donors**. Each of these donors represents a chance at life for patients worldwide.

NRHSCVD is a public institution subordinated to the Ministry of Health. Its mission is to identify and ensure matched hematopoietic stem cells donors for all Romanian patients that need a transplant and don't have related compatible donors.

As of April of this year, the Romanian registry is recognized by the international community and it works according to the standards established by World Marrow Donor Association. It is in permanent contact with similar registries worldwide, registries that have common standards and work procedures. The World Marrow Donor Association represents 71 HSC donor registries, 140 cord blood banks, 350 collection centers and 1,259 transplant centers over 48 countries.

The Romanian registry is small: on September 1st 2013, in the NRHSCVD were 3,450 **HSC donors recruited**. The search database for potential donors matched with patients in need of transplants is incomparably larger due to the fact that it is interconnected with other international registries: the

¹ WMDA Strategic Plan for 2013 till 2017 (20130626-WBRD-Strategic Plan)

European Marrow Donor Information System and Europdonor - Bone Marrow Donor Worldwide.

As members of The European Group for Blood and Marrow Transplant, the Registry and the country's HSC Transplant Centers ensure European-level quality and security standards.

Furthermore, as a medical institution newly established in full swing of the global financial crisis, NRHSCVD's mission, of developing new healthcare services, is rendered even more difficult by the economic difficulties. As of April of 2013, when Government Decisions no. 124/2013 regarding the approval of national health programs for 2013 and 2014, was implemented, and the Ministry of Health order no.422/2013 regarding the technical norms of putting into practice national health programs for 2013 and 2014, the unrelated hematopoietic stem cells transplant program was approved. As a Management and Technical Assistance Unit of unrelated hematopoietic stem cells transplant program no.3.2, to ensure financial support, the Registry must raise to the challenge of identifying and selecting a matching donor for a patient, while maintaining efficiency and performance standards.

For NRHSCVD, the challenge lies with the **ethnic diversity of the available donors**, with improving HLA-typing resolution for Romanian donors and with carefully **monitoring the total costs of providing the HCS product for unrelated HSC allotransplant**.

Another challenge is **the continuous updating of quality standards and standard operational procedures** compliant with the international WMDA standards and **trains the staff** of Registry and the Registry network. The actual and exact knowledge regarding clinical benefits and economic consequences, facilitate the discussions of Registry with the transplant centers for selection of more suitable donors out of available options, such as the discussions with the Ministry of Health and other health authorities regarding **establishing the functional legal framework** for applying the international quality standards from Registry and all the health entities working with Registry.

1. Ensuring efficient supplying of HSC for patients in need of a transplant and carrying out transplant procedures in one of the country's Transplant Centers

One of the main activities of the Registry is to organize and maintain a complex database comprising both volunteer HSC donors and patients in need of a transplant. This database is secured according to all international standards and allows for the processing of HSC donation requests and HSC providing requests, both nationally and abroad.

The registry network includes 18 donor centers, 6

HLA laboratories, 3 collection/apheresis centers, and 3 transplant centers. With all the entities there are a written agreement and all of them have been implemented a minimum WMDA standards.

The Romanian software Prometheus allows the online connection with the EMDIS registries and a national virtual private networking between the head office, located in Bucharest, and keys locations of facilities that work with Romanian Registry. After the extension of the functionality of Prometheus IT system to the network of all the donor centers, laboratories, harvest centers and transplant centers, the virtual private networking allows the following functionalities:

- The 18 donor centers can register new donors. Blood samples of new donors will be sent to the HLA laboratory.
- The 3 partners transplant centers can register new patients. Blood samples of new patients will be sent to the HLA laboratory. The existing patient data and any modification are done by the registry staff on behalf of the request coming from the transplant center.
- The safe communication network is assured through VPN solution with the access (developed under the agreements with IRGHET - International Research Group on Unrelated Hematopoietic Stem Cell Transplantation, and with STS - Special Telecommunication Service).

During first nine months of the year 2013, the Registry performs searches in the local database for 17 foreign patients and 52 national patients with indication for unrelated hematopoietic stem cells transplant. One national HSC adult donor donated for an international patient (from Russia) and for two Romanian patients will carrying out transplant procedures in one of the country's Transplant Centers, with the donors provided by Romanian Registry. The transplant dates for those are fixed in October 2013 and the work-up of donors is ongoing.

The status for the national patients in need for an unrelated hematopoietic stem cells compatible donor is the following:

- **10 Romanian patients were transplanted** with stem cells from unrelated international donors provided by foreign registries: 1 Belgium (1), Poland (2) and Germany (7). The transplant procedures have been performed in all 3 transplant centers (3 in Timisoara, 5 in Bucharest and 2 in Targu Mures).

- Out of **32 active searches** performed for national patients, there are a number of 15 patients for which a compatible donor was identified and confirmed. For 7 patients the transplant plans have been set-up. There are 8 patients for which the Registry is coordinating the communication between the transplant centers of patients and the donor centers of the donors, for fixing

the most appropriate transplant plans and respectively work-up plans.

- **For 10 patients the search have been canceled** (they lost the indication for unrelated transplant, or without finding out an appropriate compatible donor they were transferred in other countries for alternatives therapy – haplo-transplant or genic therapy)

The activities performed for the recorded patient's means a good coordination with HLA laboratories, donor centers, collection centers, transplant centers, and transport providers. This years the Registry coordinated related activities:

- 11 hand carry transports of HSC products (one was shipped by Romanian Registry and ten was transported from foreign Registries to national transplant centers).
- Over 50 international donors was extended HLA-typed
- 29 verification/confirmatory HLA-typing were performed by HLA laboratories in the country (1 - HLA laborator of District Emergency Hospital No.1 Timisoara, 7 - HLA laborator of Clinic Institute Fundeni Bucharest and 21 - HLA laborator of national Institute of Transfusion and Hematology Bucharest)

From the beginning of year 2013, 16 out of 18 donor centres started the recruitment of donors. The number of registered donors by donor centers is presented in the Table No.1.

The total number of recorded donor is 3,450, out of each less than half have been minimum HLA-ABDR typed (1,636 HSC donors), and are ready to be selected for a transplant (the detailed data are presented in the Table no.2). One third of the donors are registered by the centres located in Bucharest. 75% of registered HSC donors are also the blood donors. The age of recorded donors is equal distributed from 18 to 45 ages old (see the Figure No.1).

Perspectives:

- Improve the collaboration with international bodies and Registries: in the next year we plan to have on-line connection with all the EMDIS Registries, including the American (NMDP) and Brazilian where is special request to be fulfill (including the last two years of allotransplant history of all the transplant centers collaborated with Registry)
- To develop strategies to speed up the donor provision and to move to an efficient search
- Implementation a customised IT systems plan and improve performance and service: data of existing donors will be modified and validate and by the donor centers; data of existing patients will be modified and validate TC; the further integration of the software systems of the partner HLA laboratories and stem cell processing facilities.

- Implementation of ISBT 28 barcode for Romanian Registry
- Improving the performance of Registry by establishing resources to support the audit/accreditation activities
- Increase funding for core activities (performing the IDM and HLA typing, transport of blood sample and HSC products, work-up and monitoring of donors post-donation, monitoring of patients post-transplants)
- Increase the capacity of transplant centers
- Assuring sufficient specialize staff and the training according with up-date of standars and procedures.
- Improving the training and developing the education program for all the staff involved in the activities coordinated by the Registry (recruitment, testing, collection and transplant).
- To develop and implement a reporting system able to analyze the economics of hematopoietic stem cell donation of volunteer donors

2. Raising public and professional awareness regarding hematopoietic stem cells donation as a means of helping patients.

The Registry specific goals are to promote the interests of donors and to create public awareness for stem cell donation. In this respect, the Registry established a series of routines, procedures, safety measures, and insurance policies to protect the donors and to ensure proper conduct of the registry and its donor centers.

Start with 2009 when was issued the Governmental Decision for creating the Registry, the politicians recognize the global nature of issues. In June 2013 the Ministry of Health launched an information and communication campaigns "Donate a chance for life!". During 10 days in Bucharest and 4 in Constanta district, over 500 persons were registered in the Registry as hematopoietic stem cells donors. In addition, few hundreds of people contact us (by mail or telephone) and express their willing to become donors.

For promotion of HSC donation, Registry develops a communication strategy. The main activities for implementing the strategy are:

- A set of information materials for donors was developed (brochure, leaflets, flyers)
- On the websites www.rndvcsh.ro and www.registru-celule-stem.ro are published useful information regarding donor centers, steps to became donor, etc.
- For the donors or the persons interested to became donors, a greenline is available - TelVerde 080088 STEM (7836).

Perspectives:

- To work with health authorities and specialist for develop and implement the communication strategy
- To have the necessary agreements and affiliations with national health authorities and health insurance authorities, concerning donor safety and insurance. These should include, without be limited series of routines, procedures, safety measures, and insurance policies to protect the donors and to ensure proper conduct of the registry and its donor centers, HLA laboratories, harvest centres and transplant centers (according with WMDA recommendations for donor workup and stem cell collection, it is therefore recommended that a national registry and harvest center are responsible, unless all legal and administrative aspects of donor workup, cell collection and donor insurance to be in place)
- To coordinate all the regulation and policies promoted with other bodies working in the field of cells, tissues and organs (including accreditation of National Agency of Transplant).

3. Implementation of the international quality standards and procedures through education and studies

All registries receive the WMDA qualification based on adherence to the benchmark standards². For getting into the WMDA qualification process, the NRHSCVD should fulfil at least the following conditions:

- Compliance for all applicable standards, not just benchmark standards;
- Compliance with all of the WMDA standards labeled “must” or “shall” is required for approval of qualification.
- All the entities from the Registry network should comply with relevant WMDA standards (it is the responsibility of the Registry to ensure that).
- The Transplant Centers affiliated with the Registry and requesting a donor from another country meet standards designed to insure that donation of hematopoietic stem cells will only be requested for patients for whom transplantation is a medically acceptable procedure.
- The duties and responsibilities of each entity of Registry network must be documented in a written agreement
- Written policies and protocols for all procedures performed in the Registry (including standard operating procedures, guidelines and report forms).
- A mechanism like physician readily available to assist with routine medical decisions regarding donor

selection and donation, and direct daily access to expert consultants in the areas pertinent to the operation of the registry to assist the registry in establishing policies and procedures.

- The staff of the Registry and network must be trained and knowledgeable about their duties. The Registry must conduct and document staff training and maintain training records and reference manuals.
- Sufficient communication links to facilitate searches
- Ensuring the confidentiality and protection of the identity of donors.
- Fully informed and legally valid written consent obtained from all adult volunteer donors at the time of workup.
- Signed consent obtained initially at the time of recruitment.
- Consent obtained if donor blood or other biological material or information is stored and/or used for the purpose of an ethically approved research project.
- Assuring the accuracy of tests (HLA, infectious disease markers, and other blood group markers). The histocompatibility testing of donors must include identification of HLA loci considered essential for transplant success.
- The Registry must maintain records of its activities and must maintain a database of volunteer donor information.
- All patient and donor communications and records must be stored to ensure confidentiality and to allow for traceability of the donors and steps of the donation process.

Perspective:

- HLA loci tested at intermediate resolution for HLA- A, -B, -C, -DR typed on volunteer donors at the time of recruitment, and a clear plan for change to antigen recognition site and single allele HLA loci tested.
- Plan to change your donor typing technology uses for donor registration from mostly PCR-SSO to PCR-SSP, within the next 5 years.
- Improve and standardize the typing technology use as a secondary method for donor testing (e.g. ambiguity resolution, primary technology failure, etc.)
- Increase the dedicated staff working with the Registry
- Develop the reference manual for staff training and assure the financial sustainability for cost of training (transport, accommodation, etc.)
- Increase the security level of database of Registry with electronic signature for all the

² WMDA Application and Review Packet for Qualification and Accreditation of Registries - 20120101-ACCR-Checklist

documents/information

4. The legal in the Context of the European Union, WHO, WMDA and other regulatory bodies

The development of governance structure for efficient and responsible implementation of NRHSCVD mission should be compliant with the European rules and with the regulations of other international bodies.

In this respect, in the first 18 months from the establishment of NRHSCVD, with the consultation of Scientific Comities, were initiated few regulations or have been proposed changes or completion of existing ones, regarding the following aspects:

- Issues the import/export authorization for stem cells products; define the traceability according with European Directives for covering the donated HSC product and the facilities in charge with donation, testing, collection, preservation, processing, transportation and transplant; accreditation of the health units from the Registry network (transplant centers, harvest centers, HLA laboratories) according with quality and safe requests of European Directives (law no95/2006 – Title VI)
- Approving the membership taxes payable by the NRHSCVD in order to be interconnected with international bodies in the field; defining the NRHSCVD responsibilities' in auditing and authorizing all the formal documents regarding WMDA qualification/accreditation; implementation of ISBT 128 as unique codification and labelling system according with the requests of European Directives (Governmental Decision No.760/2009)
- Establishing the structure of Scientific Council of NRHSCVD (Order of Ministry of Health no. 474/2011)
- Approval the eligibility criteria for a health facility for applying to organized a donor Center, HLA Laborator, Harvest Center or Transplant Center for unrelated stem cells transplant (Order of Ministry of Health no. 6/2013)
- Nomination of the health units which fulfil the conditions to be part of Registry network (Order of Ministry of Health no. 92/2013)
- Annual approval of expenditure with membership taxes (WMDA, BMDW, EBMT) and accreditation fees for HLA laboratories (Governmental Decision No.123/2013)
- Approval of unrelated stem cells transplantation program for years 2013-2014 (Governmental Decision no.124/2013 and order of Ministry of Health no.422/2013)

- Nomination of members of four regional commissions for evaluation of unrelated stem cells transplant indication

Perspective:

- The Registry must assume responsibility and establish procedures 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. The registry is responsible for all reasonable expenses incurred by the donor³.
- Health insurance for the volunteer donors

Conclusions

Implementing the NRHSCVD Mission and Vision, in compliance with standards and policy of WMDA need a strategic plan, agreed by the health authorities and keys professionals in the field of stem cells transplant.

The strategic plan should be shared with the transplant physicians and general public, in the interest of patients in need for an unrelated stem cells transplant.

The NRHSCVD should implement recommended principles in its standards, working procedures, forms, etc. requested by WMDA in order to fulfil them and to apply for and eventually obtains WMDA qualification/accreditation.

References:

1. WMDA Strategic Plan for 2013 till 2017 (20130626-WBRD-Strategic Plan)
2. WMDA Application and Review Packet for Qualification and Accreditation of Registries – (20120101-ACCR-Checklist)

³ According with 10.5 WMDA standards – Financial and legal liabilities

Figure No.1: The group age of recruited donors

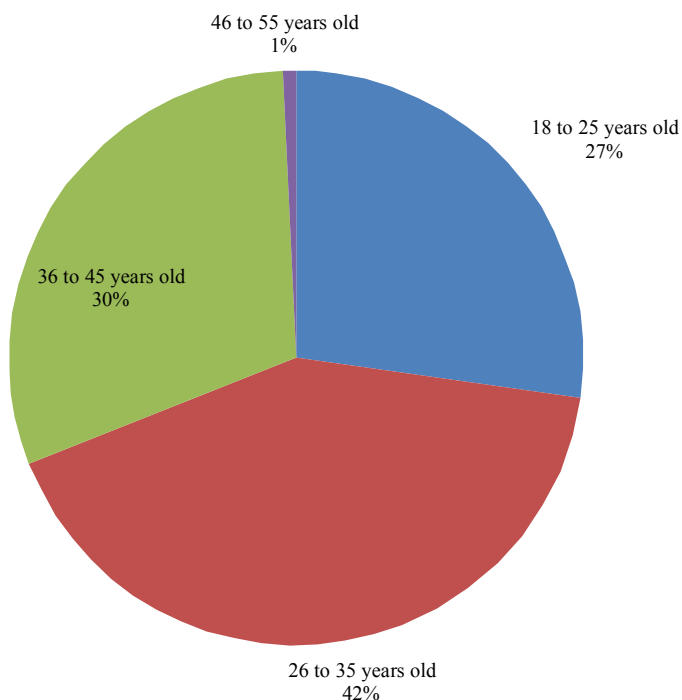


Table No.1: Total number of registered HSC donors and % of blood donors from total

DC ID	Name of Donor Center	Quarter 2			Quarter 3			Total 2013		
		Total count donors	Blood donors	% Blood donors	Total count donors	Blood donors	% Blood donors	Total Count Donors*	Blood donors	% Blood donors
RO1011	CTS Craiova	0	0	0%	0	0	0%	0	0	0%
RO1012	CTS Galati	92	63	68%	155	149	96%	247	212	86%
RO1017	CTS Slobozia	29	28	97%	148	147	99%	177	175	99%
RO1020	CTS Targu Mures	1	1	100%	19	14	74%	20	15	75%
RO1022	CTS Ploiesti	432	381	88%	26	23	88%	458	404	88%
RO1026	CTRS Timisoara	23	18	78%	85	85	100%	108	103	95%
RO1034	CTS Arad	0	0	0%	13	11	85%	13	11	85%
RO1035	CTS Bucuresti	504	448	89%	521	94	18%	1,025	542	53%
RO1036	CTS Olt	103	92	89%	266	261	98%	369	353	96%
RO1037	CTS Satu Mare	0	0	0%	0	0	0%	0	0	0%
RO1040	CRTS Cluj	2	1	50%	2	0	0%	4	1	25%
RO1041	CTS Oradea	84	74	88%	201	199	99%	285	273	96%
RO1044	CTS Braila	68	66	97%	39	37	95%	107	103	96%
RO1045	CTS Brasov	0	0	0%	97	88	91%	97	88	91%
RO1056	Institutul Clinic Fundeni Bucuresti	14	0	0%	1	1	100%	15	1	7%
RO1057	Spitalul Clinic de Urgenta Floreasca Bucuresti	19	14	74%	97	85	88%	116	99	85%
RO1058	Spitalul Universitar de Urgenta Bucuresti	6	0	0%	2	0	0%	8	0	0%
RO1018	Institutul Regional de Oncologie Iasi	5	1	20%	5	0	0%	10	1	10%
RO1001	NRHSCVD - TL	391	196	50%	0	0	0%	391	196	50%
	Total NRHSCVD	1,773	1,383	78%	1677	1194	71%	3,450	2,577	75%

*11 recruited donors was deleted due to medical or personal reasons

Table No.2: HLA donor status report at 1 of September 2013

Donor Status*	Count total	% per DC	RO 1012	RO 1017	RO 1020	RO 1022	RO 1026	RO 1034	RO 1035	RO 1036	RO 1040	RO 1041	RO 1044	RO 1045	RO 1056	RO 1057	RO 1058	RO 1018	RO DC
Not typed (just IDM)	1,717	49.93%	115	177	18	19	114	11	488	342	4	207	39	57	3	106	4	10	3
A typed	2	0.06%	0	0	0	1	0	0	0	0	0	0	0	0	1	0	0	0	0
B typed	2	0.06%	1	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0
C typed	3	0.09%	0	0	0	3	0	0	0	0	0	0	0	0	0	0	0	0	0
DR typed	2	0.06%	0	0	0	1	0	0	0	0	0	1	0	0	0	0	0	0	0
AC typed	4	0.12%	0	0	0	1	0	0	0	0	0	1	0	1	0	1	0	0	0
BDR typed	9	0.26%	0	0	0	2	0	0	3	0	0	0	0	1	0	1	0	0	2
CDR typed	2	0.06%	0	0	0	1	0	0	0	0	0	1	0	0	0	0	0	0	0
ADR typed	2	0.06%	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	1
BC typed	3	0.09%	0	0	0	0	0	0	0	0	0	3	0	0	0	0	0	0	0
ACDR typed	12	0.35%	2	0	0	1	0	0	5	0	0	2	0	1	0	0	0	0	1
ABCDQ typed	1	0.03%	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
AB typed	7	0.20%	0	0	0	1	0	0	1	0	0	1	0	1	0	0	0	0	3
ABC typed	26	0.76%	2	0	1	1	0	0	11	0	0	2	4	4	0	1	0	0	0
BCDR typed	11	0.32%	3	0	0	1	0	0	3	0	0	2	0	2	0	0	0	0	0
ABDR typed	743	21.61%	29	0	0	120	0	0	252	5	0	5	19	0	7	2	4	0	300
ABCDR typed	739	21.49%	74	0	1	300	0	2	184	22	0	59	44	30	1	9	0	0	13
ABDRDQ typed	46	1.34%	0	0	0	0	0	0	24	0	0	0	0	0	0	0	0	0	22
ABCDRDQ typed	108	3.14%	3	0	0	3	0	0	73	0	0	1	1	0	2	0	0	0	25
TOTAL	3,439	100.00%	230	177	20	456	114	13	1,044	369	4	285	107	97	15	120	8	10	370

*This report shows only active donors and temporarily unavailable for transplant (not typed HLA)