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Recruitment of Marrow Donors in the Non-governmental Sector of the Republic of North Macedonia, 2022

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Abstract

BACKGROUND: Bone marrow transplantation is a well-established lifesaving treatment procedure for many patients with various diseases, such as blood cell cancers (leukemia), some severe hematological diseases (aplastic anemia) and some rare diseases, as well as immune deficiency disorders. Allogeneic hematopoietic stem cell transplantation (HSCT) represents a potentially curative therapy for various hematologic disorders and even the only curative treatment for some diseases (e.g., myelodysplastic syndromes). As an alternative donor strategy, in patients lacking a human leukocyte antigen-matched donor or haploidentical donor, mismatched unrelated donors offer the option of using HSCT in this group of patients. Since the establishment of the first registry in the world for recruitment of unrelated bone marrow donors, the number of newly formed registries has increased over the years. In our country, in addition to the government-funded registry, housed at the Institute of Immunobiology and Human Genetics, Faculty of Medicine in Skopje, an additional non-governmental registry was established, Scientific Foundation SPIROSKI - Marrow Donor Registry (MK-SFSMDR). This will contribute to the increase of the number of newly registered donors in the Republic of North Macedonia and will be a great benefit for the patients searching for a bone marrow transplantation.

AIM: We aimed to present the establishment of the first MDR in the non-governmental sector of the Republic of North Macedonia and the recruitment strategies of new donors.

METHODS: The core activity was the creation, realization, and implementation of the Marrow Donors Recruitment Program. The constructed program for increasing the awareness of the population about HSCT and the importance of becoming a marrow donor encompasses the following activities: (1) creation of a web portal for bone MDR in English, Macedonian, and Albanian language; (2) application of standards from the World Marrow Donor Association for educational material preparation and informed consent creation; (3) composing printed and electronic materials for recruitment activities; (4) organization of public debates for marrow donation in governmental and non-governmental sectors; (5) inclusion of students and other non-governmental organizations for recruitment and registration of marrow donors; and (6) submission the obtained results from Macedonian donors and the donors from other communities (Albanians, Roma, Serbs, Turks, Vlachs, and others) in the database for marrow donors.

RESULTS: In 2022, 988 submissions from marrow donors were registered, from which 678 (68.62%) were females and 310 (31.37%) were males. The biggest number of submissions for marrow donors are in the age group of 26–40 years (567 or 57.38%), followed by the age group of 18–25 (270 or 27.32%) and the age group of 41–55 (151 or 15.28%). The most efficient method for new submissions was through social networks, 538 or 54.45% out of 988 registered donors. The second was through word of mouth (200 or 20.24%), the third was onsite marrow donor recruitment actions (145 or 14.68%), followed by information from the websites (19 or 1.92%), and other (86 or 8.70%). From the total Macedonian population (2,062,044), we were able to recruit 988 marrow donors, which is 0.048% of the population. The biggest recruitment percentage was in the Skopje region (0.067%), followed by the Pelagonia region (0.059%) and the Southwest region (0.043%). The lowest participation was in the Polog region (0.011%). The biggest percentage of recruited marrow donors (988) were Macedonians (94.13%), and the rest of them were from the minorities: Albanians (1.92), Turks (0.71%), Roma (0.1%), Croats (0.2%), Bosniaks (0.51%), Vlachs (0.81%), Serbs (1.21%), Macedonian Muslims (0%), and others (0.4%).

CONCLUSION: With the establishment of the SFS-MDR (MK-SFSMDR), one of the goals of SFS was achieved, which, together with the publication of scientific journals, enables and contributes to the scientific research in the field of the main tissue-compatible complex and transplantation of cells, tissues, and organs. The results will be used by patients who need bone marrow treatment in our country, in neighboring countries, and around the world.

Introduction

Bone marrow transplantation has become a well-established lifesaving treatment procedure for many patients with various diseases, such as blood cell cancers (leukemia), some severe hematological diseases (aplastic anemia) and some rare diseases, as well as immune deficiency disorders [1], [2]. For that purpose, bone marrow donors should have, if possible, completely identical, semi-identical, or partially identical human leukocyte antigens (HLA). The best and most common bone marrow donors are siblings (when identical), but recently, the decreasing number of children has rapidly reduced the opportunity to treat severe hematological diseases with bone marrow transplantation [3].

Allogeneic hematopoietic stem cell transplantation (HSCT) represents a potentially

curative therapy for various hematologic disorders and even the only curative treatment for some diseases (e.g., myelodysplastic syndromes) [4]. As an alternative donor strategy, in patients lacking a HLA-matched donor or haploidentical donor, mismatched unrelated donors (MMUD) offer the option of using HSCT in this group of patients. A recent literature study evaluating the reported outcomes after MMUD-HSCT indicated that MMUD-HSCT has shown rather successful results with a sustainable toxicity profile. Moreover, it can increase the HSCT accessibility to underrepresented racial and ethnic populations. A systematic review and meta-analysis study on polled data from comparative studies of the results of unrelated donor bone marrow transplantation (UBMT) and unrelated donor cord blood transplantation (UCBT) in patients requiring HSCT confirmed that UCBT in children and adults had consistently equivalent survival outcomes compared with UBMT despite greater donor–recipient HLA disparity with UCBT [5].

The Anthony Nolan Registry in London, England, was the first established registry in the world for recruitment of the unrelated bone marrow donors. The registry was founded by Shirley Nolan in 1974 after her son, Anthony Nolan, had been diagnosed with Wiskott–Aldrich syndrome and needed a transplant. Following her example, the number of newly formed registries has increased over the years [6].

In 1994, the World Marrow Donor Association (WMDA) was founded. WMDA includes organizations and individuals who promote global collaboration and best practices for the benefit of blood stem cell donors and transplant patients. One of WMDA's main aims is to provide a global platform that facilitates access to the most suitable stem cell source for patients in need of transplantation [7].

In our country, the Macedonian Bone Marrow Donor Registry (MDR) is housed at the Institute of Immunobiology and Human Genetics, Faculty of Medicine in Skopje MK-MDR (MBMDR). This government-funded registry is fully covered by the National Health Insurance Fund. However, no non-governmental organizations have established any form of marrow donor organization in the country [8], [9]. The establishment of our Scientific Foundation SPIROSKI MDR (MK-SFSMDR) in the non-governmental sector aims to increase the opportunities for patients with malignant hematological diseases to find an appropriate marrow donor match. The need to establish an additional non-governmental donor registry arose from the low number of registered donors in our country. Current data shows that only 0.12% of the population in the Republic of North Macedonia is registered as potential marrow donors, in contrast to other countries such as Cyprus's 13% (108 times more), Israel's 12% (100 times higher), Germany's 9.0% (75 times higher), Croatia's 1.5% (12.5 times higher), and Slovenia's 1.0% (8.3 times higher) [10] (Table 1).

Table 1: Comparison of the percentage of the population registered as potential bone marrow donors in the Republic of North Macedonia to Cyprus, Israel, Germany, Croatia, and Slovenia

Country	Percentage of population registered as potential marrow donors	Times higher than Macedonia
Republic of North Macedonia	0.12	-
Cyprus	13	108
Israel	12	100
Germany	9.0	75
Croatia	1.5	12.5
Slovenia	1.0	8.3

The Western Balkan countries include Albania, Bosnia and Herzegovina, Kosovo, Montenegro, the Republic of North Macedonia, and Serbia. The European Union (EU) has implemented a policy to support the gradual integration of these countries into the EU. Montenegro, Serbia, the Republic of North Macedonia, and Albania are official candidates and accession negotiations and chapters have been opened with Montenegro and Serbia. Bosnia and Herzegovina and Kosovo are potential candidate countries [11]. Of the six countries of the Western Balkan region, only two marrow donor registries are included in the WMDA (North Macedonia and Serbia), with an additional one currently in preparation (North Macedonia) [10].

We aimed to present the establishment and creation of the first non-governmental MDR in the Republic of North Macedonia as an additional activity to the governmental bone MDR (MK-MBMDR).

Methods

SFS founded the SFS-MDR in 2021 as the first non-governmental donor register in the Republic of North Macedonia. The core activity was the creation, realization, and implementation of the Marrow Donors Recruitment Program which is partially financially supported by Civica Mobilitas as part of the bone marrow donation program project [12]. The constructed program for increasing the awareness of the population about HSCT and the importance of becoming a marrow donor encompasses the following activities: (1) creation of a web portal for bone MDR in English, Macedonian, and Albanian language; (2) application of standards from WMDA for educational material preparation and informed consent creation; (3) composing printed and electronic materials for recruitment activities; (4) organization of public debates for marrow donation in governmental and non-governmental sectors; (5) inclusion of students and other non-governmental organizations for recruitment and registration of marrow donors; and (6) submission the obtained results from Macedonian donors and the donors from other communities (Albanians, Roma, Serbs, Turks, Vlachs, and others) in the database for marrow donors. We

created a website containing the general information about donors, patients, and families with the possibility of donor's online application [13].

All preparations were completed during the year 2021 (printing materials, making educational materials, videos, websites, webinars, and others). Signed agreements with the Macedonian Post, HistoGenetics, Steiner, DHL, and other institutions were completed, and the submission for accessing into WMDA was prepared. SFSMDR was accepted and included in the database with the ION-2285 and WO-2117. The short code of SFSMDR was defined as MK-SFSMDR [14].

The recruitment of marrow donors started on January 15, 2022, and through a collection of buccal swabs and written consent, the realization of the Marrow Donors Recruitment Program in the non-governmental sector of our country has begun. Two main routes were defined: (1) online submissions through the newly created website (https://www.sfsmdr.mk/) [13] for the MDR and (2) marrow donor recruitment actions. All of the online submissions, buccal swab sets, and written consent were sent by post. Marrow donors were instructed to use four sticks of buccal swabs, to fulfill and sign the marrow donor consent, as well as the written request for HLA genetics testing outside the country, and send back the materials by post. At the same time, we organized six marrow donor public recruitment actions where we gave a short lecture emphasizing the importance of becoming a bone marrow donor and personally onsite we collected the buccal swabs samples, as well as the written consent. The diagram representing the MK-SFSMDR Marrow Donors Recruitment Program is represented in Figure 1.

Samples from the buccal swabs from the online submissions and marrow donor recruitment actions were anonymized using a GRID number, barcode labeled, and sent for molecular analysis at HistoGenetics, USA (CMV, ABO, Rh, HLA, and KIR). The obtained molecular analysis results and the marrow donor's personal data were stored in the Prometheus Light software for marrow donor registries (Steiner, s.r.o). These results can be transferred to the WMDA for listing as well as to the marrow donors for their personal or familial use (not for other marrow donor registries) (Figure 1).

At the same time, all donors received a marrow donor card with the GRID number, other useful information, and detailed explanations. The marrow donor card was prepared in Macedonian, English, and Albanian language (Figure 2).

According to the recent census on the resident population in the Republic of North Macedonia (in 2021), 58.44% of the population declared themselves as Macedonians, 24.30% as Albanians, 3.86% as Turks, 2.53% as Romani, 1.30% as Serbs, 0.87% as Bosniaks, 0.06% as Muslims, 0.47% as Aromanians (Vlachs), 0.19% as Bulgarians, 0.12% as Croats, 0.06% as Montenegrins, 0.02% as Yugoslavs, and the rest were other/unspecified (predominantly Macedonians as per registries) (Table 2) [15]. In order to cover the minorities in our country, we have included the most frequent ethnicities in the marrow donation written consent.

Table 2: Population of the Republic of North Macedonia according to ethnic groups 2021 [15]

Ethnic group	Census 2021, n (%)
Macedonians	1,073,299 (58.44)
Albanians	446,245 (24.30)
Turks	70,961 (3.86)
Romani	46,433 (2.53)
Serbs	23,847 (1.30)
Bosniaks	16,042 (0.87)
Muslims	1187 (0.06)
Aromanians	8714 (0.47)
Bulgarians	3504 (0.19)
Croats	2145 (0.12)
Montenegrins	1023 (0.06)
Yugoslavs	344 (0.02)
Other/unspecified (predominantly Macedonians as per registries)	142,969[a] (7.78[a])
Total	1,836,713

[a]Ashkali 2,406 or 0.13%, Torbeshi 4,174 or 0.2%. Regionally affiliated: 110 or 0.01%, Non-declared: 450 or 0.02%, Citizens for whom the data are taken from administrative sources, not included directly in the census (without ethnic declaration) 132,260 or 7.20%.

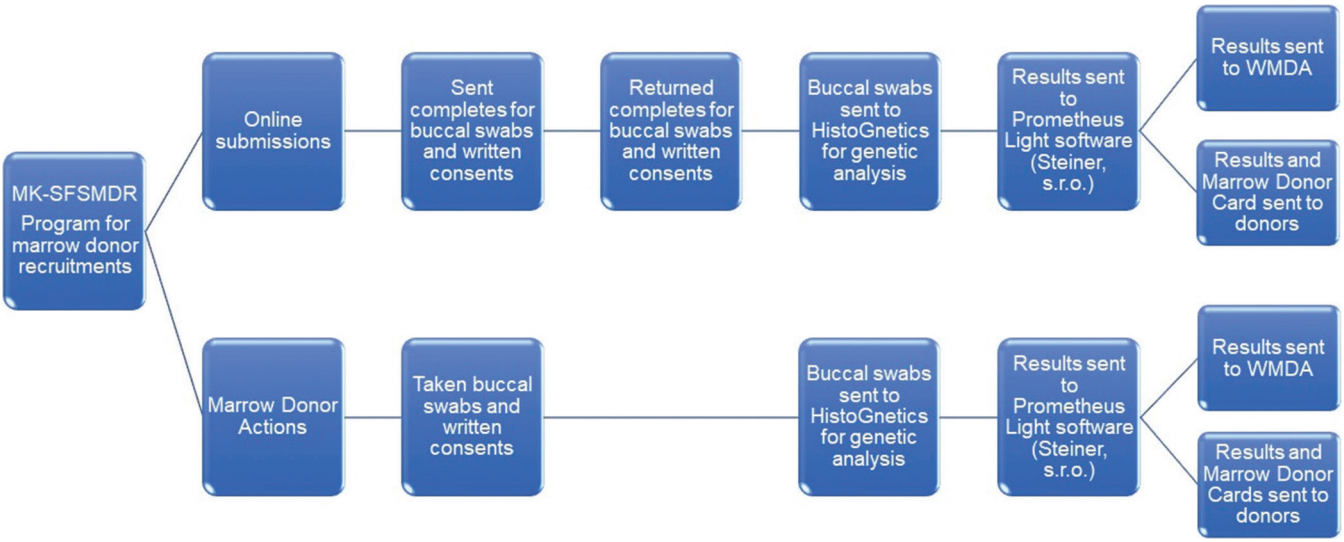

Figure 1: Flow diagram of the MK-SFSMDR Marrow Donors Recruitment Program

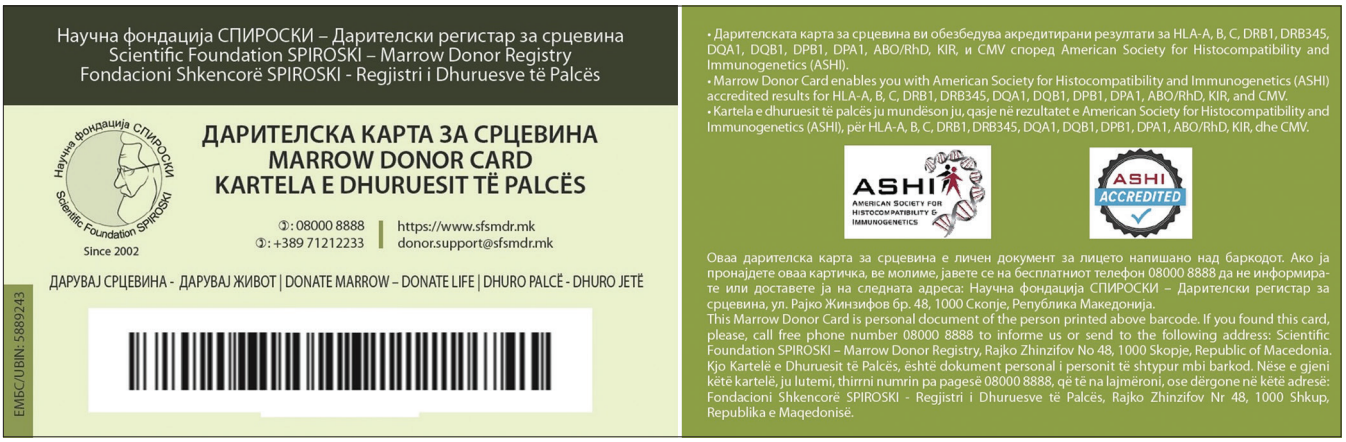

Figure 2: Marrow donor card for each marrow donor including the molecular analysis results and personal data

Results

In 2022, we registered 988 submissions from marrow donors, of which 678 (68.62%) were females and 310 (31.37%) were males. Females submitted 2.19 times more frequently to be marrow donors than males. The biggest number of submissions for marrow donors are in the age group of 26–40 years (567 or 57.38%), followed by the age group of 18–25 (270 or 27.32%) and in the age group of 41–55 (151 or 15.28%) (Table 3).

Table 3: Registered submissions for marrow donors according to age and gender (the year 2022)

Age (years)	Females, n (%)	Males, n (%)	Recruited, n (%)
18–25	170 (62.96)	100 (37.03)	270 (27.32)
26–40	395 (69.66)	172 (30.33)	567 (57.38)
41–55	113 (74.83)	38 (25.16)	151 (15.28)
Total	678 (68.62)	310 (31.37)	988 (100.00)

We used several strategies for the submission of marrow donors. The most efficient method was using the social networks (Facebook, Instagram, and LinkedIn) which contributed with more than half of the marrow donor's registrations and sample submissions (538 or 54.45%). In second place, with 200 marrow donor registrations was the word-of-mouth method (200 or 20.24%), in third place were the organized onsite marrow donor recruitment actions (145 or 14.68%), followed by information from the websites (19 or 1.92%), and other (86 or 8.70%) (Table 4).

Table 4: Methods for marrow donor submissions in MK-SFSMDR (the year 2022)

Method of submission	Social networks	Through word of mouth	Marrow donor actions	Web site	Others	Total submissions
n (%)	538 (54.45)	200 (20.24)	145 (14.68)	19 (1.92)	86 (8.70)	988 (100)

From the total Macedonian population (2,062,044), we were able to recruit 988 marrow donors, which is 0.048% of the population. The biggest recruitment percentage was in the Skopje region (0.067%), followed by the Pelagonia region (0.059%) and the Southwest region (0.043%). The lowest participation was in the Polog region (0.011%) (Table 5).

Table 5: Regional distribution of submission for marrow donors in the Republic of North Macedonia (the year 2022)

Region	Total number of citizens	Submitted in MK-SFSMDR, n (%)
Polog	317,003	38 (0.011)
Skopje	609,140	410 (0.067)
Northeast	175,442	33 (0.018)
Southwest	220,840	96 (0.043)
Vardar	153,659	166 (0.108)
East	178,814	57 (0.031)
Pelagonia	232,959	138 (0.059)
Southeast	173,187	59 (0.028)
Total	2,062,044	988 (0.048)

MK-SFSMDR: MK-SFS-Marrow Donor Registry.

The biggest percentage of recruited marrow donors (988) were Macedonians (94.13%), while the rest of them were from the minorities: Albanians (1.92), Turks (0.71%), Roma (0.1%), Croats (0.2%), Bosniaks (0.51%), Vlachs (0.81%), Serbs (1.21%), Macedonian Muslims (0%), and others (0.4%) (Figure 3).

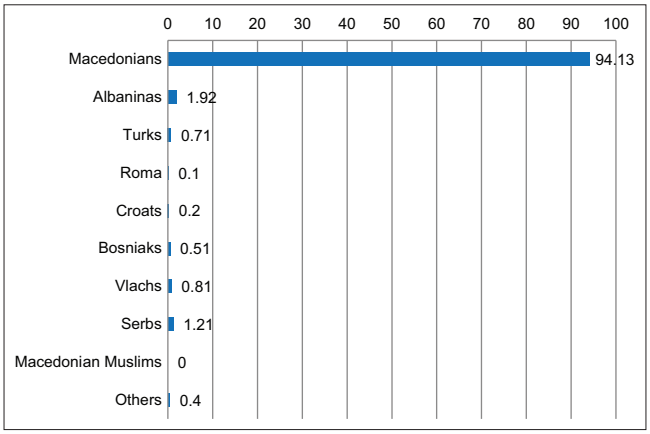

Figure 3: Percentages of marrow donors with an ethical background in MK-SFSMDR

Discussion

In this paper, we presented the 1st-time results of the marrow donors' recruitment in the non-governmental sector of the Republic of North Macedonia in 2022. We have registered 988 marrow

donors' submissions, of which 68.62% were females and 31.37% were males. Females submitted 2.19 times more frequently for marrow donors than males. The largest number of submissions is in the age group of 26–40 years (57.38%). The most efficient methods for the recruitment of marrow donors were social networks (Facebook, Instagram, and LinkedIn) with more than half of the marrow donor's registrations and submissions (54.45%). The number of recruited bone marrow donors is equal to 0.048% of the population. The biggest percentage was in the Skopje region, followed by the Pelagonia region and Southwest region. The lowest participation was in the Polog region. The biggest percentage of recruited marrow donors were Macedonians (94.13%), while the rest of the marrow donors were from the minorities: Albanians, Turks, Roma, Croats, Bosniaks, Vlachs, Serbs, Macedonian Muslims, and others.

A study, performed in our neighboring country Greece, identified the factors that influence the Greek decision to register as potential bone marrow donors using a multivariate logistic regression [16]. Their findings correspond with our results. Moreover, they point out the more frequent gender bone marrow registration (females more frequently than males) that having a friend or a family member requiring a bone marrow transplantation and hearing and learning about the bone marrow transplantation were the main factors contributing to a successful registration recruitment. Interestingly, another study analyzing the rational versus emotional appeals in bone marrow donor registrations showed that 85% of individuals receiving the emotional appeal and only 49% of the participants receiving the rational appeal agreed to register as a bone marrow donor [17].

Investigations identifying and reviewing the transplant physician preference for male donor selection (in a multiple donor option) revealed that the donor registries around the world should develop a program and well-defined strategy to target potential male donor recruits [18]. Even though the number of recruited female donors is increasing, which is also a case in our results (female donors are 2.19 times more frequent than males), it is necessary to educate the stuff involved in the donor recruitment as well as the potential target group to raise the awareness and the importance of the recruitment program.

It is a well-known fact that ethnic minorities have difficulties in finding a matching bone marrow donor, mainly due to the lack of participation by minorities in the donor registries [19]. The need for people from different racial and ethnic backgrounds to volunteer as donors is widely recognized and it has become a part of a significant strategy program for the donor registries worldwide. A phylogenetic analysis study of the HLA allele frequencies performed by the Bulgarian Bone Marrow Donors Registry described that Bulgarians have close genetic resemblance to Macedonian, Greeks, Romanians, Cretans, and Sardinians in comparison to the other investigated European and Mediterranean populations. However, the second largest ethnical group – the Roma – has been genetically most similar to the other Roma populations and North Indians [20].

Another study analyzing the healthy individuals enrolled in the MK-MBMDR showed that in the sample of 1541 bone marrow donors, 50.87% were females and 49.13% were males. One thousand two hundred and eighty-three donors declared themselves as Macedonians (Orthodox), 128 Albanians, 76 Macedonian Muslims, 21 Turks, 6 Roma, 4 Bosnians, 1 Serbian, and 22 did not declare any nationality [9]. Our results of the ethical composition of recruited marrow donors, published in this paper, are different, probably due to the smaller number of recruited marrow donors and the usage of a different recruitment tool and/or different cohorts.

The recruitment of a larger number of voluntary bone marrow donors increases the likelihood of finding an identical donor and performing a transplantation in patients. However, due to the minimal distribution of some HLA genes, it is necessary to include the results in the WMDA in which potentially identical bone marrow donors can be found in another country around the world. The inclusion of a larger number of donors from our country in the WMDA will give a greater chance to our patients, and will significantly contribute to finding an identical donor from our country, which is especially important and needed in the smaller communities and ethical groups (Albanians, Roma, Vlachs, and others) [10].

HLA allele and haplotype frequencies have population-specific patterns, and because of that, there are limitations in the number of obtained different phenotypes by recruiting new donors. In 2019, the WMDA reported a submission of 50 different phenotypes per thousand new adult unrelated donors and core blood units. According to their findings, it is necessary to aim toward a larger recruitment number among the ethnic minority groups, as well as in the parts of the world with a wider genetic diversity, e.g., Africa [6].

Therefore, the next strategy of the MK-SFSMDR is to recruit as many male potential donors and members of ethnic minority communities as possible. This is planned to be achieved by performing specifically targeted marrow donor public recruitment actions, developing a cooperation with non-governmental organizations supporting different ethnic groups in our country and organizing different educational activities emphasizing and clarifying the importance and significance of becoming a marrow donor.

Conclusion

With the establishment of the SFS-MDR (MK-SFSMDR), one of the goals of SFS was achieved,

which, together with the publication of scientific journals, enables and contributes to the scientific research in the field of the main tissue-compatible complex and transplantation of cells, tissues, and organs. The results will be used by patients who need bone marrow treatment in our country, in neighboring countries, and around the world.

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