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SPECIAL REPORT

Unrelated adult stem cell donor medical suitability: recommendations from the World Marrow Donor Association Clinical Working Group Committee

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The World Marrow Donor Association (WMDA) fosters collaboration between international registries to facilitate the exchange of hematopoietic stem cell products for unrelated stem cell donor transplantation. As indications for hematopoietic SCT grow, the movement of products across the world will increase. Although competent authorities may regulate products within their country, there is a need to protect the best interests of donors and recipients by identifying universal donor medical suitability criteria. Within this report the WMDA provides a background to unrelated adult donor and recipient safety, recommends a common framework for assessing the health of unrelated adult donors at each stage of the donation pathway and presents a novel mechanism for sharing international consensus criteria for individual medical and lifestyle conditions. Wherever possible, these criteria are evidence-based. By establishing a donor medical suitability working group, the WMDA has developed a process through which donor centers and registries may request a consensus opinion on conditions not already listed, as well as challenge existing criteria. Guidance from the WMDA is intended to complement, not supersede, guidance from national competent authorities and international regulatory bodies.

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INTRODUCTION

The mission of the World Marrow Donor Association (WMDA) is to foster collaboration between international registries to facilitate the exchange of hematopoietic stem cell products for the purpose of unrelated hematopoietic SCT (HSCT).[1]

As cellular therapy and HSCT have advanced over the past 10–20 years, so too has the field of transplantation grown.[2] By necessity, the development of regulatory oversight of the use of cellular products has been implemented, or is in the process of being implemented, by national competent authorities around the world. Although individual countries may regulate these products differently (for example, as biological drugs, blood or tissue products, or in some instances as organs), there is a common theme in the approaches used by regulatory bodies to assure donor suitability. This approach is one that seeks to protect the unrelated adult donor from harm while ensuring that a safe and effective product is made available to the recipient in need.

To this end, assessment of donor medical suitability is designed to identify and limit the risk of transmitting infectious, genetic or malignant diseases through the product, both to the recipient and those handling the product. It also aims to ensure a maximum level of safety for the donor, and informs them of the risks of donation. As ~46% of stem cell products cross international borders,[3] it is important that processes designed to determine donor medical suitability, and the definitions used, be harmonized where possible, yet remain flexible enough to accommodate differences required by the national competent authority, institutional policy and the scarcity of the product.[1] In addition, a rigorous assessment of donor medical suitability at each stage of the donation pathway ensures that the least suitable donors are removed from the register, and contributes to reducing donor attrition at a later stage. Ultimately this expedites donor provision, potentially improving recipient outcomes[4–6] and reduces the cost to the registry of registering donors who will never be eligible for donation.[7]

In 2008, the Quality Assurance and Clinical Working Groups of the WMDA authored a special report that recommended procedures and criteria for medical deferral of those wishing to donate.[8] This paper contemporizes those recommendations, and continues to protect the best interests of donors and recipients by: (1) providing a background to the reasons for donor medical suitability criteria; (2) considering all stages of the pathway to donation; and (3) providing a novel mechanism for reviewing new recommendations to ensure they remain current and evidence-based.

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RISKS OF DONATION: DONOR SAFETY

Risks of BM collection

BM was the original source of hematopoietic stem cells (HSC) collection mechanical extraction of liquid BM through a breach in the cortical bone (most commonly from the posterior iliac crest). The procedure is typically performed under general anesthesia. Up to 1500 mL of BM and blood may be removed, depending on the weight of the donor.[9]

This procedure bears a number of risks.[10,11] Bone and soft tissue trauma at the harvest site may cause pain, bleeding, edema or nerve compression. Damage to a lumbosacral nerve root or penetration into the pelvic cavity or internal iliac vessels may cause severe morbidity. Anesthesia carries an unavoidable (albeit very small) risk of life-threatening cardiac or respiratory events, as well as the possibility of allergic or idiosyncratic reactions to anesthetic agents. Removal of large volumes of blood may cause symptoms of hypovolemia or anemia. Some collection centers routinely transfuse autologous blood postoperatively, although evidence to support this practice is weak,[12,13] and many centers use intravenous fluids to support the circulation and may recommend oral iron replacement. Recovery usually takes 1–2 weeks, although a small percentage ($<2\%$) of donors will suffer lower back pain for longer and $<1\%$ may have long-standing problems with pain.[14]

Risks of PBSC and lymphocyte collection

Over the past two decades, PBSC or progenitor cell leukapheresis has become the preferred route of HSC collection for many indications, accounting for ~70% of unrelated adult donations.[3] Donors have subcutaneous injections of G-CSF for 4–5 days, which mobilizes HSC into the circulation. On day 5, donors undergo apheresis, which removes the buffy coat containing HSC and returns red cells, plasma and plts. Where the requisite number of cells is not collected, the donor may be asked to provide a second day of collection.

G-CSF commonly causes flu-like symptoms and (in up to 95% of donors) bone discomfort, and this may cause severe pain in 1–2% of donors.[15] Other symptoms include nausea and vomiting, myalgia, fatigue, insomnia and injection site reactions. Splenic enlargement is well recognized, but splenic rupture is extremely rare.[16,17] Hyperviscosity syndrome has not been described in a healthy adult donor. Anaphylaxis to G-CSF has been documented as case reports in medical literature, but the incidence is estimated to be <1 in 10 000.[18] As a consequence of venipuncture, bruising, bleeding or nerve injury may occur. Should the donor have inadequate peripheral venous access, a central venous catheter may be required, with its incumbent medical risks. The apheresis process itself may cause symptomatic hypovolemia, and hypocalcemia commonly occurs as a result of the use of citrate anticoagulation. A reduction in the plt count is inevitable; however, this rarely drops to a level where bleeding risk is significantly increased.[19]

There has historically been concern over the long-term risks of G-CSF. Studies involving long-term follow-up of either unrelated or related donors to date do not suggest an increased risk of hematological malignancy.[20,21] On a genetic level, Nagler *et al.*[22] suggested that epigenetic changes, characteristic of malignancy, were seen in the lymphocytes of related donors who had received G-CSF. However, Hirsch *et al.*[23] found no evidence of G-CSF-induced chromosomal instability. Further studies are ongoing, and the applicability of these findings to biosimilars has not been established.[24]

Rates of serious adverse events

Miller *et al.*[11] published a comprehensive prospective study of donor adverse events, showing that serious adverse events were rare (1.34% of BM donors and 0.6% of PBSC donors). These findings are in contrast to a study by the European Group for Blood and Marrow Transplantation (EBMT), which suggested a lower rate of serious adverse reactions overall, but a higher rate of adverse events in related PBSC donors compared with BM (10.76 vs 4.32 per 10 000 donors; $P<0.05$).[25] However, this latter study was retrospective, questionnaire based and the very low overall rates of serious adverse events may represent underreporting.

More recently, in a large cohort of 6768 PBSC and 2726 BM donors donating on behalf of the National Marrow Donor Program from 2004 to 2009, rates of serious adverse events were 0.56% and 2.38%, respectively.[26]

Unrelated donor deaths

Deaths in unrelated HSC donors are very rare. Only one death has been reported to the WMDA since the establishment of the S(P)EAR (serious (product) events and adverse reactions) reporting system, which was caused by hemothorax secondary to traumatic jugular central venous catheter insertion.

However, a number of deaths have been reported in related donors, from causes such as subarachnoid hemorrhage, sickle crisis, myocardial infarction and pulmonary embolism.[25,27,28] In many of these donors, preexisting medical conditions were identified postmortem, highlighting the need for stringent medical suitability criteria and assessment of all HSC donors.

RISKS OF DONATION: RECIPIENT SAFETY

Owing to its very nature, transplantation of HSC has the potential to transmit the same range of blood-borne illnesses as blood transfusion itself. In addition, a number of other conditions have the potential for transmission through HSCT.

Infectious diseases

Hepatitis B,[29] hepatitis C,[30,31] human T-lymphotropic virus type I,[32,33] malaria,[34] syphilis,[35] Chagas disease[36] and brucellosis[37] have all been reported to be transmitted by HSC. Although not reported, transmission of HIV through HSC transplantation is thought very likely if the donor is infected. There have been no documented cases of transmission of prion-related diseases by HSC; West Nile virus has not to date been shown to be transmitted by HSC, although this has been reported in recipients of blood and organs (including heart, lung, liver and kidney). It should also be considered that the majority of emerging infections first reported in the past three decades have been, or potentially could be, transmitted through allogeneic HSCT.

Malignancy

Few HSC donor-derived malignancies have been reported, and to date all such cases have been hematological, including AML,[38–40] ALL,[41] T- and B-cell lymphomas,[42,43] Burkitt lymphoma,[41] myelodysplastic syndrome[44] and T-cell large granulocytic leukemia.[45] Reports of synchronous development of the same malignancy occurring in both the donor and a donor-derived clone in the recipient are rare.[46,47]

Autoimmune diseases

The development of an autoimmune condition in a recipient from a donor with the same condition has been well reported following allogeneic HSCT. These include thyroid disease, type 1 diabetes, immune thrombocytopenia, vitiligo and psoriasis.[48–53]

Inherited diseases

It is inevitable that any inherited disease in the donor that is phenotypically dependent on the expression of the affected gene

within the hematopoietic pool will be transferred to a successfully engrafting recipient. This includes hemoglobinopathies such as sickle cell disease and thalassemias, platelet disorders and the inherited BM failure syndromes, to name but a few.

PRINCIPLES IN THE ASSESSMENT OF DONOR MEDICAL SUITABILITY

The main aim of assessing the medical suitability of a donor is to identify those medical conditions that may increase the risk to either the donor or the recipient as a result of donation or transplantation. However, there are key differences in the implications and ethics of risk assessment between donors and recipients.

Donor risk

Donation of HSC is an act of altruism. Although it is recognized that the process of donation carries a small but unavoidable risk of harm to the donor, it is both the ethical and legal responsibility of donor registries and donor centers to minimize any 'avoidable' risk. This includes medical conditions that may increase the risk of harm to the donor before, during and after the collection of HSC.

For this reason, medical criteria governing conditions that may increase donor risk are necessarily stringent, and certainly more so than would be the case if the individual were undergoing a procedure for therapeutic benefit.

In many cases it is difficult to establish a rigorous evidence base as justification for the criteria. In such cases, expert opinion of the underlying physiology of disease should be sought, and combined with knowledge of the known physiological changes associated with donation, as well as the experience gained through several decades of HSC donor follow-up and adverse event reporting. In general, if there is any doubt about the safety of the donor in the presence of a particular medical condition, it is recommended that any donor with that condition be prevented from donating.

Recipient risk

For many patients, allogeneic HSCT represents the only possibility of disease cure or long-term remission. Because of the difficulty in matching histocompatibility antigens and other donor characteristics such as donor age and gender, CMV status and blood group, many patients will have a limited number of potentially matched donors.[54] In such cases, the decision regarding the acceptability of donor medical conditions that present a risk to the recipient alone may be left to the transplant center, who are best placed to make an informed risk–benefit judgment on whether to proceed with that particular donor.

MIMIMUM STANDARDS FOR THE ASSESSMENT OF DONOR MEDICAL SUITABILITY

Timing of assessment and deferral

There are three stages in the typical pathway of an unrelated HSC donor from joining a registry to donation, namely: recruitment; confirmatory/verification typing stage and work-up stage. The intensity of the assessment differs at each stage in the process, and there may be conditions that necessitate deferral at certain stages in the process but not in others. Therefore, it is important to consider the types of questions asked of the potential donor at each stage of the process to ensure that they are appropriate. It is also important to ensure that permanent conditions warranting deferral due to unacceptable donor or recipient risk are identified early.

At recruitment stage

A recommended minimum set of questions required of potential donors at recruitment is set out in Table 1. (For the most contemporary version see the WMDA donor medical suitability website http://www.worldmarrow.org/donorsuitability/index.php/Table_1.)

The primary reason for assessing the potential donor at recruitment is to exclude those with medical conditions or lifestyles that would permanently preclude donation based on a serious risk to the donor or the recipient. Donors must be made aware of the expectations involved with donation and the associated risks so that they do not withdraw at a later stage in the process. Furthermore, it is misleading to allow an individual to join the registry when it is clear that a preexisting permanent condition will thwart their ability to participate at a later stage in the process. Donors should be advised that the screening process at registration is a preliminary assessment of their medical suitability. Further assessments will be performed later should the donor be identified as a possible match for a patient and potentially requested for donation.

The registration process also provides the opportunity to educate the donor of the importance of keeping the registry informed of significant changes to their health; prompting each donor for updates on health status should become part of a registry or donor center's retention policy.

At HLA confirmatory/verification typing stage

When a potential donor/recipient match is identified following a search request, the transplant center may request that the donor be contacted to obtain a sample for confirmatory/verification HLA typing and infectious disease marker (IDM) testing. At this point,

Table 1. Minimum donor information requested at recruitment

Medical history	*Specifically asked about*
Cancer	
Autoimmune disease	
Infectious diseases, including being a sexual partner of an infected individual	HIV, hepatitis B, hepatitis C, HTLV, syphilis
Infectious diseases, others	CJD (including familial risk), Chagas disease, tuberculosis, malaria
Inherited disease	Sickle cell disease, thalassemia, inherited bleeding disorder
Any other medical history	The potential donor should be asked if they have any other past or current medical problems
High-risk sexual behavior	As defined by the registry's national competent authority. However, registries should be aware that sexual practices may change with time and are not necessarily criteria for exclusion
Non-prescription parenteral drug use	
Current medications	
Height and weight	
Allergies	

Abbreviations: CJD = Creutzfeld-Jacob disease; HTLV = human T-lymphotropic virus.

Table 2. Minimum donor history recommended at the confirmatory/verification typing stage

Medical history	*Specifically asked about*
Cancer	
Autoimmune disease	Ankylosing spondylitis; Crohn's disease; ulcerative colitis; myasthenia gravis; rheumatoid arthritis; sarcoidosis; systemic lupus erythematosus; multiple sclerosis; scleroderma/CREST. Any other autoimmune condition
Infectious diseases, including being a sexual partner of an infected individual	HIV, hepatitis B, hepatitis C, HTLV, syphilis
Infectious diseases, others	CJD (including familial and exposure risk, for example, neurosurgery, use of pituitary hormone), Chagas disease, tuberculosis, malaria
Inherited disease	Sickle cell disease (or trait); thalassemia (including trait); inherited bleeding disorder; any other inherited disease
Back problems	Any acute or chronic back complaint, including cause, investigations, duration, medication and impact on activities of daily living
Hypertension	Most recent blood pressure readings; medications; degree of control
Cardiac disease	Coronary artery disease; evidence of valve disease, for example, murmur; arrhythmia
Asthma	Degree of control; medications; use of oral steroids; hospital admissions; intensive care admissions/ventilation
Epilepsy	Medications; date of last seizure
Pregnancy	Number of pregnancies, including miscarriage; current/recent pregnancies; breastfeeding
Blood transfusion	Receipt of a blood transfusion. Ask year and place of transfusion
Any other medical history	The potential donor should be asked if they have any other past or current medical problems
Height and weight	
High-risk sexual behavior	As defined by the registry's national competent authority
Non-prescription parenteral drug use	
Alcohol consumption	
Tattoo, acupuncture or body piercing	When and where. Establish if at an establishment registered according to national regulations
Current medications	
Allergies	

Abbreviations: CJD = Creutzfeld-Jacob disease; HTLV = human T-lymphotropic virus.

Table 3. Donor assessment at the work-up medical stage

Medical history as per Table 2	
Travel history	Identify travel to areas with endemic malaria, Chagas disease and West Nile virus
Sexual history	Identification of high-risk sexual behavior, including within groups associated with a higher prevalence of blood-borne viruses
Examination	General (including height and weight); cardiovascular (including blood pressure); respiratory; gastrointestinal; neurological
Laboratory investigations (see Table 5 for infectious disease markers)	
Hematology	Full blood count; coagulation screen (including PT, APTT and fibrinogen); ESR; blood film; hemoglobin electrophoresis or high-pressure liquid chromatography if indicated
Biochemistry	Urea and electrolytes; liver function tests; LDH; ferritin; random glucose; β-HCG (for females of child-bearing age)
Other investigations	Chest X-ray; electrocardiogram

Abbreviations: ESR = erythrocyte sedimentation rate; HCG = human chorionic gonadotropin; PT = prothrombin time; APTT = activated partial thromboplastin time; LDH = lactate dehydrogenase.

a further medical history is obtained and a more extensive assessment of the potential donor is performed. A recommended minimum questionnaire is shown in Table 2. (For the most contemporary version see the WMDA donor medical suitability website http://www.worldmarrow.org/donorsuitability/index.php/Table_2.)

As IDM testing and confirmatory typing may take several weeks, and may have significant associated costs, it is recommended that the medical suitability of the donor be established before requesting a sample for testing. In addition, any donor medical information that suggests an increased risk to the recipient must be identified early on and reported to the transplant center, as this may influence the decision of the transplant team to either proceed with further testing or to evaluate another potential donor.

A significant time period may have elapsed between registration and HLA confirmatory/verification typing, and since the potential donor may progress to provide a stem cell product, they should be reminded of the risks associated with donation at this stage.

At work-up stage

Once the donor proceeds to work-up, they must be assessed in a face-to-face interview by an appropriately qualified licensed medical practitioner. This gives the opportunity for a thorough assessment to identify any medical conditions that might have been missed at an earlier stage. A travel history should be obtained to prompt extended IDM testing if appropriate. The interview also gives an opportunity to take an in-depth sexual

Table 4. Schedule for repeating donor assessments in the event of delayed donation

Time from work-up medical assessment to collection date	*Repeat assessments required*
⩽30 days	None
>30 days, ⩽90 days	Infectious disease markers only
>90 days, ⩽12 months	Donor history and examination, all laboratory tests excluding hemoglobinopathy screening, Infectious disease markers
>12 months	Donor history and examination, all laboratory tests excluding hemoglobinopathy screening, Infectious disease markers Chest X-ray and ECG

Abbreviation: ECG = electrocardiogram.

Table 5. Minimum recommended donor infectious disease marker testing

Stage	*Infectious disease*	*Recommended validated assay*
Recruitment	Nil	Nil
CT/VT stage	HIV	HIV-1,2 antibody
	Hepatitis B	Hepatitis B surface antigen
	Hepatitis C	Hepatitis C antibody
Work-up	HIV	HIV-1,2 antibody, p24 antigen, HIV RNA
	Hepatitis B	Hepatitis B surface antigen and antibody Hepatitis B core antibody, hepatitis B DNA
	Hepatitis C	Hepatitis C antibody, hepatitis C RNA
	HTLV I+II	HTLV I+II antibody
	Syphilis	Validated serological testing algorithm

Abbreviations: CT/VT = confirmatory/verification typing; HTLV = human T-lymphotropic virus.

history that allows the assessing physician to share an informed opinion on the possibility of an increased risk of transmission of blood-borne infections. A thorough examination of the donor should be performed, along with laboratory testing for key hematological and biochemical parameters, an electrocardiogram and a chest X-ray if indicated. A recommended minimum assessment is detailed in Table 3. (For the most contemporary version see the WMDA donor medical suitability website http://www.worldmarrow.org/donorsuitability/index.php/Table_3.)

Occasionally, a medical condition is identified that does not warrant immediate deferral, but may require further investigation (for example, the presence of a heart murmur). As any delay to transplantation may adversely affect patient outcome, such issues should be assessed in a prompt manner so that the transplant clinician's decision on whether to accept the donor or not can be made in a timely manner. Both donor risk and recipient risk are important in this assessment. It should be noted, however, that responsibility for donor safety rests with the medical personnel who assess the donor before collection and not with the transplant clinician.

Ideally, the donor medical assessment should be performed as close to the collection event as logistically possible, to allow for the most up-to-date information on patient and donor risk. By keeping this time frame short, the risk of acquisition of an infectious disease or other medical condition that might compromise donation is minimized. If the transplant is delayed, then part or all of the assessment may need to be repeated. A recommended schedule for this is set out in Table 4. (For the most contemporary version see the WMDA donor medical suitability website http://www.worldmarrow.org/donorsuitability/index.php/Table_5.).

IDM testing

In general, testing for infectious diseases is governed by national competent authorities and international regulatory systems, such as FACT-JACIE; donor registries and centers are obliged to conform with this guidance as part of their license to practice. In addition, however, registries are responsible for screening for globally prevalent transmissible infectious diseases such that the community can have faith in the quality of the donors on each WMDA member registry, and expect that, where reasonable, donors wouldill have been screened appropriately. To assist in this global exchange of stem cells, the WMDA has made recommendations for a minimum standard of donor IDM testing, which are detailed in Table 5. (For the most contemporary version see the WMDA donor medical suitability website http://www.worldmarrow.org/donorsuitability/index.php/Table_4.)

Donor registries should be aware of additional transmissible diseases that are endemic within their geographic region, and have a responsibility to develop local screening policies appropriate to these diseases.

WMDA CRITERIA FOR DONOR DEFERRAL AND EXCLUSION

The WMDA has established a set of online criteria appropriate to donor medical suitability assessment, which can be found at www.worldmarrow.org/donorsuitability. Within this website is guidance on decision making for the more common medical conditions likely to be encountered by registry and collection center staff, as well as for those having more serious consequences for donor or recipient. Where possible, supporting evidence is provided in the form of medical literature citations.

To create and support this resource, the WMDA has established the donor medical suitability working group, which is a WMDA Executive Board committee. Members of the committee represent all major regions in the world, and are themselves overseen by numerous competent authorities within their country of practice. Committee members are actively involved in donor center and/or registry operations with experience in matters concerning unrelated donor medical suitability.

The website also provides users with a mechanism for requesting the committee to review a condition not currently listed, as well as an opportunity to give feedback on existing guidance. Requests for new guidance, and feedback on existing guidance, are submitted to the committee chair/designate and reviewed by the committee members. Comments and justifications for the committee decision are documented, including justification for the decision. Regardless of the outcome, a formal response to the query is provided to the author of each submission in order to inform the registry/donor center of the outcome of the discussion. Recommendations that are approved are posted to the donor medical suitability pages of the WMDA website. Any controversies pertaining to the recommendations are added to the discussion section on the relevant page.

Owing to the variances between legal authorities, comments regarding medical suitability are offered as recommendations only, and the discussions of each meeting are recorded. Donor registries are reminded that the WMDA guidance does not at any point supersede that of their national competent authority, or similar legislative body. Terms of reference for this committee as well as recommendations concerning donor medical eligibility can be found at www.worldmarrow.org/donorsuitability.

CONCLUSION

The ultimate responsibility for determining medical suitability of the donor with regard to donor safety rests with the medical personnel assessing the donor's health before donation, but responsibility for recipient safety is shared by the requesting transplant center. A donor's wish to provide stem cell products without remuneration is a wonderful, altruistic act. The role of the registry/donor center must be to ensure that the unrelated adult donor is adequately assessed to ensure his/her medical suitability to provide a quality product in the safest manner possible. International registries and donor centers should establish procedures using the recommendations of the WMDA to ensure harmonization of donor medical suitability standards throughout the world.

The WMDA strongly recommends that registries and donor centers establish formalized policies and standards that outline the roles and responsibilities of both the registry and its partners to support timely searches, donor selection and collection. Registries should obtain and share knowledge of regulations governing the country where the registry operates with domestic and international partners, and serve as a resource for that information. Consistent with requirements of the national competent authorities, registries should develop recommendations and/or guidelines for obtaining a current donor health history and assessment. Risk must be evaluated at each stage in the process; however, the information or data used may differ.

Finally, the WMDA would like to stress that these recommendations are largely based on consensus between the donor registries represented in the committee. Owing to the relatively rare event of donation in the context of medical comorbidity, many of the guidelines are not supported by published literature.

Subcommittee recommendations

- Registries should maintain a current and well-characterized list of medically suitable, unrelated adult stem cell donors available for search and possible donation.
- Registry practices should provide opportunities for periodic donor contact so that donors remain engaged and are able to provide demographic and/or health/medical updates that might impact their availability for donation.
- Registry/donor center policies should be developed to prevent the listing of donors who are permanently unsuitable because of donor or recipient safety risk.
- Assessment of the registrant/donor should be appropriate for the stage in the process so as to facilitate early detection of problems that may lead to donor deferral.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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