

DKMS OPERATIONAL USER GUIDE

Version 2.1 as of 2022-09-01

Content

1	Preamble.....	3
2	Abbreviations	3
3	Quality Standards for Transplant Centers.....	4
3.1	Transplant Center Evaluation according to WMDA Criteria	4
4	Donor Search Process and Requirements	4
4.1	Transplant Indication (Diagnosis)	4
4.2	Patient Age	5
4.3	Limit of Mismatch Level.....	5
4.4	Required Information about the Patient	5
4.5	Matching Algorithm	7
4.6	Search Service for Transplant Centers.....	7
4.7	(Preliminary) Donor Search by International Registries	7
4.8	Cancellation / End of Donor Searches.....	8
5	Pre-Workup Requests	9
5.1	Typing Request.....	9
5.2	Infectious Disease Markers Testing (IDM Testing)	9
5.3	Health and Availability Check (HAC)	10
5.4	Confirmatory Typing Request.....	11
5.5	Research Studies at CT Level.....	11
5.6	CCR5 Verification at CT	12
5.7	Donor Reservation	12
6	Workup (HSC Apheresis, HSC Bone Marrow, MNC Apheresis)	12
6.1	Workup Process.....	12
6.2	Maximum Number of Donations for DKMS Donors	14
6.3	Interval between Donations	15
6.4	Cell Count Requests	15
6.5	Simultaneous Confirmatory Typing and Workup.....	16
6.6	Number of Donors Requested for one Patient at the same Time.....	16
6.7	Replacement Donor Search at Workup	17
6.8	Research Studies at Workup Level	17
6.9	Cryopreservation of Stem Cell Products.....	17

6.10	Partial Cryopreservation of Excess Cells of Stem Cell Products.....	18
6.11	Cryopreservation of MNCs	19
6.12	Unavailability of a Donor for One Product Type.....	19
6.13	Additional Testing Requests by the Transplant Center	20
6.14	Maximum Amount of Blood to be drawn at Physical Examination (Pre-Collection Samples)	20
6.15	Transplant Center Acceptance of Formally Ineligible Donors	20
6.16	Donor Reservation after Donation	21
7	Transport.....	21
7.1	Transport Arrangements to be made by International Registries and Transplant Centers.....	21
7.2	Transport Arrangements to be made by DKMS	21
8	Donor Follow-Up	22
8.1	Post-Donation Follow-Up	22
8.2	Adverse Events and Reactions Reporting (SEAR/SPEAR)	22
9	Donor-Patient Contacts	23
9.1	Anonymity Criteria for DKMS Donors and / or Patients of DKMS Registry.....	23
9.2	Patient Follow-Up Information	24
9.3	Release of Personal Information between Donor and Recipient	24
10	Finance.....	24
10.1	Fee Schedule	24

1 Preamble

This operational user guide is enforced at DKMS Registry gGmbH and the DKMS donor centers DKMS gemeinnützige GmbH in Germany (DKMS DE), Fundacja DKMS in Poland (DKMS PL), DKMS Foundation in the United Kingdom (DKMS UK), Fundación de Beneficencia Pública DKMS in Chile (DKMS CL), DKMS BMST Foundation India (DKMS BMST IN), DKMS Foundation NPC in South Africa (DKMS Africa) and DKMS in the United States of America (DKMS USA) - together referred to as DKMS. It describes the rules and procedures in place that have to be followed by transplant centers, search units and international registries using services of DKMS.

This operational user guide may be amended by DKMS from time to time to take account of changes in medical practice, in operational or administrative procedures. DKMS will announce any change to this operational user guide on the DKMS Professionals' Platform (<https://professional.dkms.org/>) 30 days before coming into effect.

2 Abbreviations

Abbreviation	Meaning
BM	Bone Marrow
CBU	Cord Blood Unit
CCR5	C-C Chemokine Receptor type 5
CT	Confirmatory Typing (donor request)
CVC	Central Venous Catheter
DLI	Donor Lymphocyte Infusion
DNA	Deoxyribonucleic Acid
EMDIS	European Marrow Donor Information System
GRID	Global Registration Identifier for Donors
HLA	Human Leukocyte Antigen
HAC	Health and Availability Check
HHQ	Health History Questionnaire
HIV	Human Immunodeficiency Virus
HSC	Hematopoietic Stem Cell
HSCT	Hematopoietic Stem Cell Transplantation
IDM	Infectious Disease Marker
MM	Mismatch
MNC	Mononuclear Cell
NGS	Next Generation Sequencing
PE	Physical Examination
PBSC	Peripheral Blood Stem Cell
SAA	Severe Aplastic Anemia
SCID	Severe Combined Immunodeficiency Syndrome

TC	Transplant Center
T-cell	T Lymphocyte Cell
TNC	Total Nucleated Cell
WHO	World Health Organization
WMDA	World Marrow Donor Association
WU	Workup (preparation for stem cell donation)

3 Quality Standards for Transplant Centers

3.1 Transplant Center Evaluation according to WMDA Criteria

DKMS Registry acts as a patient registry for transplant centers in Chile, Colombia and India, likewise, DKMS Africa supports transplant centers in South Africa. Additionally, DKMS Registry - as a donor registry - may be in direct contact with transplant centers if no established national registry exists.

Transplant centers cooperating directly with DKMS Registry are evaluated according to the WMDA transplant center evaluation criteria before any donor can be requested. The transplant centers are asked to provide specific details which are reviewed and eventually approved by the DKMS Review Board. In case two reviewers come to different conclusions about the acceptability of the transplant center, the case is reviewed and decided by the Chief Medical Director of DKMS.

A reassessment of the evaluation takes place every three years.

4 Donor Search Process and Requirements

4.1 Transplant Indication (Diagnosis)

DKMS is responsible for donor safety and must thus ensure that stem cell products are only provided to patients for whom an unrelated hematopoietic stem cell transplantation (HSCT) is an acceptable medical treatment.

Each patient for whom a DKMS donor is being considered as a potential unrelated donor must satisfy DKMS Registry's requirements regarding diagnosis. Diagnoses that are standard indications for HSCT do not need to fulfill further requirements. The classification into standard or rare indications is based on WHO's guidelines:

Arber *et al.* (2016), `The updated WHO classification of hematological malignancies – The 2016 revision to the World Health Organization classification of myeloid neoplasms and acute leukemia` In: BLOOD, 127:20, pp. 2391-2405.

If the indication for which the transplant center or registry is requesting a donor is not a standard indication for HSCT, DKMS Registry will consult its medical advisor and ask for an assessment of the case. In order to get a decision by the advisor, DKMS Registry may request further clinical information, e.g. an ethics committee vote, the study protocol or relevant case studies, from the transplant center or registry.

4.2 Patient Age

Each patient for whom a DKMS donor is requested for workup, must satisfy DKMS Registry's requirements regarding age. If the age of the patient for whom the transplant center or registry is requesting a donor is above 80 years, DKMS Registry will consult a medical advisor and ask for an assessment of the case. In order to get a decision by the advisor, DKMS Registry may request further clinical information from the transplant center or registry.

4.3 Limit of Mismatch Level

An approval by DKMS' medical advisor is required when HLA matching is $<8/10$. In order to decide on an approval or non-approval, the medical advisor will need information about the patient's health status, whether the patient is participating in a medical trial, the outcome of the evaluation of alternatives to an unrelated stem cell transplantation (e.g. haploidentical transplantation or CBU), and whether the case has already been discussed in a review/tumor board or by the national medical society of the patient's country of origin.

Matching lists for donors with $\leq 8/10$ matching are only provided upon request via email and may not be received via EMDIS or other systems.

4.4 Required Information about the Patient

To search for unrelated donors at DKMS Registry, a donor search has to be initiated by sending relevant patient information. While a preliminary search request only provides match list results on potential stem cell donors, an active search must be started to perform donor requests (e.g. Confirmatory Typing).

1. Patient HLA typing

- **Requirements for preliminary search:**

Minimum: HLA-A, -B, -C, -DRB1 low resolution DNA typing.

Recommended: High resolution HLA typing is highly recommended for HLA-A, -B, -C, -DRB1, -DQB1, -DPB1 before starting an unrelated donor search.

This level of typing accelerates the search process. Low resolution HLA typing decelerates the search procedure by initially only identifying potentially matched

donors. Additional parameters (e.g. CMV status, blood group, ...) can further enhance donor selection.

- **Requirements for search activation (needed to start requests):**

Minimum: HLA-A, -B, -C, -DRB1 high resolution DNA typing.

Recommended: High resolution typing for HLA-A, -B, -C, -DRB1, -DQB1, -DPB1.

Additional parameters (e.g. CMV status, blood group, ...) can further enhance donor selection.

"A high-resolution typing result is defined as a set of alleles that encode the same protein sequence for the region of the HLA molecule called the antigen binding site [...]" (Nunes E *et al.* (2011), `Definitions of histocompatibility typing terms` In: Blood, 118 (23): e180–e183).

The antigen binding site is encoded by exon 2-3 for class I and by exon 2 for class II HLA alleles.

Before requesting a workup at DKMS, verification of patient HLA typing results from an independent sample is recommended. It is the obligation of the transplant center to ensure that verification typing of the patient is performed at the latest before the donor starts mobilization or the collection procedure or before patient starts conditioning, whichever comes earlier.

2. Medical and personal data for donor search and donor request initiation

The following information of the patient must be provided by the transplant center or patient registry at the preliminary and active search stage:

- Patient's HLA typing results: Minimum HLA-A, -B, -C, -DRB1 low resolution DNA typing
- Patient ID
- Patient's name
- Patient's sex
- Patient's date of birth
- Patient's diagnosis

The following additional information must be provided by the transplant center or patient registry at the time of a pre-workup request for a specific donor:

- Patient HLA typing results: Minimum HLA-A, -B, -C, -DRB1 high resolution DNA typing
- GRID of the requested donor

An active donor search must be performed before starting a donor request. Specific information required for a workup request is further defined in the workup section below (chapter 6).

4.5 Matching Algorithm

1. Algorithm

DKMS Registry's search algorithm Hap-E Search® uses a probabilistic donor-recipient matching algorithm based on haplotype frequencies:

Urban, C., Schmidt, A. H., & Hofmann, J. A. (2020), 'Hap-E Search 2.0: Improving the Performance of a Probabilistic Donor-Recipient Matching Algorithm Based on Haplotype Frequencies', *Frontiers in medicine*, 7:32. <https://doi.org/10.3389/fmed.2020.00032>.

2. Ranking of matching list

- 10/10 matching list:
 - 10/10 matching probability
 - Younger donor before older donor
 - Male before female

- 9/10 matching list:
 - 9/10 matching probability
 - 8/10 matching probability
 - Mismatch loci: HLA-DQB1 mismatch before HLA-A, -B, -C or -DRB1 mismatch
 - Younger donor before older donor
 - Male before female

4.6 Search Service for Transplant Centers

DKMS Registry offers a special search support program to transplant centers in Chile, Colombia and India, DKMS Africa support transplant centers in South Africa likewise. This service is not limited to transplant centers in these four countries. It applies to all transplant centers in need of access to unrelated donors. DKMS Registry thereby assists the transplant centers with their national and international unrelated donor and cord blood unit searches. All transplant centers using these services are evaluated according to WMDA criteria (see chapter 3). If you want more information about this program, please contact services@dkmsregistry.org.

4.7 (Preliminary) Donor Search by International Registries

All searches, preliminary and active, are free of charge. Searches for donors from DKMS DE, PL, UK, CL, DKMS BMST IN and DKMS Africa at DKMS Registry can be initiated in three different ways:

1. Via the European Marrow Donor Information System (EMDIS)

DKMS Registry (hub code = DR) is connected to several registries via EMDIS. Donor search requests as well as typing requests (TYP_REQ), sample requests for Confirmatory Typing (SMP_REQ), infectious disease marker request (IDM_REQ) and donor reservation requests (RSV_REQ) can be received via EMDIS. See also our EMDIS National Rules available at WMDA or via our website (<https://professional.dkms.org/services/dkms-services/dkms-registry-services/emdis-connection-to-dkms-registry>) for further information.

2. Via E-Mail/Fax using WMDA forms

DKMS Registry also accepts requests by fax (Fax No. +49 7071 943 2299) or email (services@dkmsregistry.org) for all services. For requests by fax or email, we recommend the use of WMDA forms (<https://wmda.info/professionals/optimising-search-match-connect/wmda-forms>), but we also accept other forms as long as they contain the information needed to perform the requested task (see chapters 1, 4, 5, 6.)

DKMS Registry will send a search report, consisting of DKMS donor (DE, PL, UK, IN, CL, ZA) matching results, usually within one business day after receipt of the search request.

3. Via Donor Navigator® Software

International registries and transplant centers that are registered users of DKMS Registry's web application *Donor Navigator®* can and are encouraged to initiate their donor searches and all subsequent requests through *Donor Navigator®* in case no EMDIS connection is available.

- The registration is free of charge and includes an online introduction to *Donor Navigator®* and its features. Access to *Donor Navigator®* requires a two-factor authentication provided by DKMS Registry.
- The additional benefits for registered *Donor Navigator®* users comprise an overview of all cases of their registry, search unit or transplant center, access to the updated progress tracking of each request and a user-specific notification system via email and within the software. Also, the system allows digital workup requests. Existing data such as contact information, patient as well as donor information is automatically populated in the forms.

4.8 Cancellation / End of Donor Searches

DKMS Registry expects the requesting registry to stop donor searches with DKMS Registry in case a donor is no longer needed for the patient. Reason for status change should be provided via EMDIS or other communication according to the EMDIS semantics

(<https://share.wmda.info/x/BYC7BQ>). DKMS Registry reserves the right to deactivate a donor search after a reasonable time of inactivity.

5 Pre-Workup Requests

5.1 Typing Request

Most DKMS donors are typed in HLA-A, -B, -C, -DRB1- DQB1 in high resolution, allowing easy identification of 10/10 matches. In case donors do not fulfill these requirements or if additional information is needed before confirmatory typing to identify the best matching donor, extended typing can be requested.

The range of results being requested varies between the whole set of HLA genes (HLA-A, -B, -C, -E, -DRB1, -DRB3/4/5, -DQA1, -DQB1, -DPA1, -DPB1), as well as KIR, CCR5 and MICA/B. It is also possible to request only single genes, e.g. in search of a permissive/non-permissive mismatch of HLA-DPB1, a request only for HLA-DPB1 is possible.

Included in a typing request is:

- Health History Questionnaire (HHQ) and first assessment of donor suitability. The transplant center will be notified about medical details if relevant.
- DNA typing from stored samples or fresh sample (blood or buccal swab) in the EFI accredited DKMS Life Science Lab.

5.2 Infectious Disease Markers Testing (IDM Testing)

In case of a pre-selection of multiple potentially matching donors, it might be helpful to know the infectious disease markers or the CMV status to determine the best matching donor(s). IDM requests can be filed in parallel to a typing request, but can also be requested separately. Besides our standard set of IDMs, it is also possible to request individual markers separately.

Included in an IDM testing request is:

- Health History Questionnaire (HHQ) and first assessment of donor suitability. The transplant center will be notified of medical details if relevant.
- Donor blood sample for IDM testing and shipment to DKMS partner lab.
- IDM testing profile: IDM testing includes testing for diseases thought to be important to consider in hematopoietic stem cell transplantation. The detailed composition of markers to be tested differs according to the country of origin of the DKMS donor. A list of standard markers per DKMS entity included in the respective request can be found in our *Specification of Services*.

An example of our *Specification of Services* is available on our website. The current *Specification of Services* valid for your country can be requested at services@dkmsregistry.org.

5.3 Health and Availability Check (HAC)

As most DKMS donors are typed at high resolution for HLA-A, -B, -C, -DRB1, -DQB1, and -DPB1 by NGS, the error rate is very low (see Baier, D.M., Hofmann, J.A., Fischer, H. *et al.* Very low error rates of NGS-based HLA typing at stem cell donor recruitment question the need for a standard confirmatory typing step before donor workup. *Bone Marrow Transplant* 54, 928–930 (2019)). Therefore, identification of a fully matched donor is often possible at the start of a search. Further, some of our donors already have confirmed typing results from previous requests. However, the availability of the donor and medical information might not be up-to-date. DKMS offers transplant centers the possibility to request a HAC instead of CT, in order to speed up donor screening and proceed faster to workup as HLA verification typing is only performed on the donor selected for workup. The typing will then be performed during workup from blood collected with the pre-collection samples, taken from the donor on the day of physical examination. The HLA verification typing results must be provided before the donor's clearance and thus before the donor starts with G-CSF application or before patient conditioning is initiated.

The following criteria need to be fulfilled to request a HAC:

- DNA-based high resolution typing for at least HLA-A, -B, -C, -DRB1 and -DQB1 must be available for this donor. Otherwise, a HAC is only possible in case of confirmed urgency e.g. based on the specific diagnosis and the desired time frame for transplantation (< 6 weeks to transplantation).

Included in a HAC request is:

- Detailed information session with the donor by phone.
- Health History Questionnaire (HHQ) and assessment of donor suitability. The transplant center will be notified of medical details if relevant.
- After a successful completion of a HAC request, the donor is reserved for three months.

Important note: A HAC can be performed **instead of**, but not in advance of, a CT request. It is not allowed that the transplant center request a CT shortly after a completed HAC. The information session and Health History Questionnaire included in a HAC are the same as performed during a CT request. If the transplant center requires the donor's IDM testing results for donor selection, a CT must be requested directly as the initial request.

5.4 Confirmatory Typing Request

HLA verification typing of donor and recipient is always required before a recipient can receive a stem cell product from an unrelated DKMS donor and must be performed either before or during workup. HLA verification typing must be performed from a fresh sample of the potential donor.

When Confirmatory Typing is requested and processed before workup, it includes the following elements:

- Detailed information session with the donor by phone.
- Health History Questionnaire and assessment of donor suitability. The transplant center will be notified of medical details if relevant.
- IDM testing
- Donor blood sample for HLA verification typing.
- Shipping of samples to the lab designated by the requesting transplant center.
- Donor reservation for three months after the estimated date of blood draw was set.

The maximum amount of blood to be drawn at CT must not exceed 50 ml.

An example of our *Specification of Services* is available on our website. The current *Specification of Services* valid for your country can be requested at services@dkmsregistry.org.

5.5 Research Studies at CT Level

Research studies to support donor selection may be important for the transplant outcome of the patient. DKMS generally supports studies if they can result in a benefit for patient care or increase safety of donors and the additional burden on the donor is acceptable.

- All studies have to be approved by DKMS.
- DKMS allows only one study per case.
- For any research studies, transplant centers have to provide the full study synopsis, approval of the ethical review board, as well as translated information and consent form for donors (English or language of involved DKMS donor center).
- Any genetic testing must be approved by DKMS and thus specified in the study synopsis.
- Without approval for the study request, the transplant centers are not allowed to perform any tests with donor material (blood) which exceed the regular tests for donor selection.

5.6 CCR5 Verification at CT

About 1% of the Northern European population carries the $\Delta 32$ mutation of the CCR5 gene homozygously. Homozygous carriers of this mutation are resistant to M-tropic strains of HIV-1. Therefore, CCR5 testing can be performed for patients with a hematological disease who are also HIV-1 positive. DKMS has performed CCR5 tests for all donors at donor recruitment since 2014.

- In cases when CCR5 is relevant for donor selection, CCR5 testing has to be confirmed before donation, e.g., at the Confirmatory Typing step. DKMS can provide access to laboratories that can perform CCR5 testing.

5.7 Donor Reservation

- Without any previous request, a reservation of one of our donors is not possible.
- Donors are **not** reserved after completed Typing Request or IDM Testing.
- Donors are reserved for three months after a CT request or after a completed HAC.
- When the reservation after a CT request or HAC has expired, an extension of reservation for an additional three months is possible without reason.
- After six months reservation period, a justification is required if a further extension of three months is desired.
- After the nine months reservation period, we expect the workup request to be sent.
- In exceptional cases, a new HAC request can be placed to extend the donor's reservation period one more time. A new reservation without a new request is not possible, because the information about the availability and the medical suitability of the donor should be verified again after 9 months at the latest.

6 Workup (HSC Apheresis, HSC Bone Marrow, MNC Apheresis)

6.1 Workup Process

After the workup request form is received, it is checked for completeness and correctness. The following information must be provided by the transplant center at the time of a formal request for a stem cell donation:

- Patient ID
- Patient HLA typing results: Minimum HLA-A, -B, -C, -DRB1 high resolution DNA typing
- Patient's name
- Patient's sex

- Patient's date of birth
- Patient's diagnosis
- Patient's weight
- Patient's blood group and rhesus factor
- Transplant Center name
- GRID of the requested donor
- Product preference
- Required date of clearance
- Duration of the conditioning
- Pre-collection samples requirement
- (Pre-collection samples shipping address)
- Prescription for HSC collection, detailing desired cell dose, additives, and anticoagulants
- Collection day samples requirement
- Transport temperature
- HLA verification typing results (DNA-based typing results for HLA-A, -B, -C, -DRB1 and -DQB1) from the requested donor.

If the workup request form contains all necessary information, it is assigned to a case manager. The case manager will then contact the donor as soon as possible to discuss all details and coordinate the collection.

The following details will be discussed with the donors during the workup procedure:

- Different methods of blood stem cell donation and the transplant center's preferred stem cell product type
- Information about the risks and side effects of the donation
- Willingness of the donor to proceed with the donation
- Availability of the donor for the requested dates and donation method as well as time commitment
- Time frame of medical examination and donation
- Location of the collection center
- The physical examination procedure incl. the requirement of further tests and blood samples before donation
- Anonymity of the donor and patient and confidentiality of personal data
- Whether the donation is part of a clinical trial for the patient
- The donor's right to withdraw consent and consequences of withdrawal after patient conditioning has begun
- Possibility of request for subsequent donation of hematopoietic stem cells or blood products
- Reimbursement and provision of expenses
- Insurance coverage

6.2 Maximum Number of Donations for DKMS Donors

Glossary	
Subsequent Donation of HSC	After the completion of an HSC collection, the same donor is requested for the same patient again: HSC Apheresis or HSC Bone Marrow
Subsequent Donation of Blood Products	After the completion of an HSC collection, the same donor is requested for the same patient again: MNC Apheresis or requests for additional blood samples for further testing (e.g. virus specific T-Cells)
Multi-Donation	The respective donor completes more than one HSC collection for different patients.
Second Transplant	The respective patient receives a second HSC product from a donor different from the previous donor.
Subsequent Transplant	The respective patient receives a second HSC product from the same donor.

If patients have a relapse or a graft failure, a subsequent donation of HSC from the same donor can become necessary. This happens in approximately 2-3 % of our cases.

A donor can also be requested as best match for a different recipient (<1% of cases).

To protect donors, the number of donations for HSC Apheresis or HSC Bone Marrow is limited to two collections per donor for each product type.

There is no defined maximum number of donations for MNC Apheresis. However, when the donor is requested for MNC Apheresis the third time, a medical advisor will be contacted to evaluate the indication.

Subsequent Donation:

- The transplant center must provide a written reason to justify the need for a subsequent donation and the WMDA F20 form (Previous Transplant History) or equivalent
- Subsequent donations of HSC for the same patient have to be approved by the medical advisor of DKMS. After a completed workup for the same patient, only a subsequent workup or MNC Apheresis request is accepted. HAC requests are not accepted in between.

Multi-Donation:

- Transplant centers will already be informed at the time of pre-workup request, if a donor has donated before, as the donor will only be available for the same stem cell product type one more time.

6.3 Interval between Donations

After an HSC donation the donor may suffer from side effects for some time. Therefore, there is a defined minimal interval between two donations.

- The interval between two PBSC donations should be at least 4 weeks as a graft failure cannot be diagnosed earlier.
- In urgent cases, e.g. poor mobilization, it might be possible to shorten the interval between donations, and switching the cell source (PBSC to BM / BM to PBSC) if not contraindicated.
- The interval between two BM donations should be at least 4 weeks. A PBSC donation should be considered for the second request, if possible.
- There is no defined minimal interval for MNC Apheresis. However, the donor blood count must be in normal range.
- A subsequent donation can only occur if the donor has fully recovered.
- All decisions have to be made after individual consideration.
- DKMS BMST Foundation India only provides PBSC products. DKMS BMST donors in India are not allowed to undergo any type of second donation (including MNC Apheresis) within 6 months after a peripheral stem cell harvest due to Indian law. Consequently, we recommend to request a higher cell count for the first donation, if possible, and to cryopreserve a part of the product for a potential subsequent transplant.

6.4 Cell Count Requests

We observe a huge range in requested CD34⁺ cell counts for HSC Apheresis from 1.5 x 10⁶ / kg to 50 x 10⁶ / kg body weight of the recipient. Generally, a CD34⁺ cell count of 5 x 10⁶ / kg recipient body weight is considered sufficient. However, there are protocols in use that require higher numbers of CD34⁺ cells.

For HSC Bone Marrow, the requested TNC usually is within a range of 3-5 x 10⁸ / kg body weight of the recipient. For children with rare diseases (e.g., SCID, other congenital disorders or metabolic diseases) as well as for patients with SAA, a higher cell count may be reasonable, as there is a higher possibility of graft failure.

- For HSC Apheresis, the transplant center must justify requests for CD34⁺ cell counts exceeding 5 x 10⁶ / kg recipient body weight. Requests exceeding 5 x 10⁶ / kg recipient body weight without a plausible explanation cannot be accepted.
- For HSC Bone Marrow the collection of TNC is limited, as only 20 ml bone marrow / kg body weight of the donor may be collected. Usually, a maximum volume of 1,500 ml is collected.
- Transplant centers should thus consider donor's weight when requesting a BM product.
- If the HSC product is being cryopreserved, a higher number of cells might be approved provided that it is still feasible for the donor.

6.5 Simultaneous Confirmatory Typing and Workup

As nowadays HLA results from donor registry typing are very accurate, a transplant center can very often identify a match for a patient immediately on the search results list. Therefore, in urgent cases or in cases where the donor was already requested multiple times for CT, the HLA verification typing can be shifted to the workup process. In these cases, it is possible to request CT and workup at the same time. The transplant center has to consider that CT unavailability varies between 20-40% depending on the DKMS entity. For this reason, it is recommended that a Health and Availability Check (HAC) has been completed before a simultaneous CT and workup is requested to verify the donor's availability and medically suitability. A HAC does not include IDM testing which will be performed only during workup in these cases.

- DKMS accepts workup requests without preceding CT request. The blood draw for HLA verification typing takes place at the time of physical examination and the transplant center has to confirm that HLA verification typing has been performed at the time of donor clearance. Results should be reported to DKMS before the donor receives G-CSF or is admitted for bone marrow harvest.
- Note: If the transplant center requires that the blood samples for HLA verification typing are drawn before physical examination, CT and workup must be requested separately.

6.6 Number of Donors Requested for one Patient at the same Time

At DKMS, the workup unavailability rate is approximately 15 % globally, including temporary reasons.

- DKMS accepts that a transplant center requests more than one donor for WU. However, the requesting transplant center / registry **must** inform DKMS which donor is the primary or backup donor. This also applies if one of these donors is not a DKMS donor but a donor from another donor registry.
- The primary donor will be contacted as usual and will not be informed that there is another donor requested for workup.
- If the DKMS donor is the backup donor, he/she will be contacted and informed that he/she is a backup donor and therefore might not be requested to donate, if the primary donor is able to proceed in the requested time frame. The information session will be performed with the backup donor to assess willingness and availability **but no collection slots will be blocked in the collection center facilities.**

If there is an increased risk that the primary donor will be unavailable, DKMS may, in exceptional, plan collection dates with both donors simultaneously. Further exceptions can

be made in individual cases, e.g. if several donors have already failed for a patient and the urgency is given.

6.7 Replacement Donor Search at Workup

With a global DKMS donor pool of more than 11 million donors, many patients have more than one potential DKMS donor.

In case a donor becomes unavailable for the patient during workup, DKMS starts a replacement donor search within all DKMS donors.

- As soon as we learn that a donor might be unavailable for the patient (e.g. donor is unavailable for the requested period or the stem cell source the transplant center is requesting), a replacement donor search is started.
- Transplant centers are informed about the outcome of the replacement donor search.
- In addition to the manually triggered replacement donor search, an automated replacement donor search is running at the start of the workup. If there are no other matching donors available, DKMS types potentially matching donors who are not fully typed at own costs.

6.8 Research Studies at Workup Level

Research studies for better treatment or outcome of the patients are important. DKMS therefore supports studies if they can result in a benefit for patient care or increase safety of donors and the additional burden on the donor is acceptable.

- All study requests have to be approved by DKMS.
- DKMS allows only one study per case.
- The study request has to be sent to DKMS with the workup request.
- Study requests received after physical examination of the donor cannot be accepted.
- For any research studies, transplant centers have to provide the full study synopsis, approval of the ethical review board, as well as translated information and consent form for donors (English or language of involved DKMS donor center).
- Any genetic testing must be approved by DKMS and thus specified in the study synopsis.
- Without approval for the study request, the transplant centers are not allowed to perform any tests with donor material (blood, BM, PBSC, MNC products or data) which are not standard requirement for either donor selection or transplantation.

6.9 Cryopreservation of Stem Cell Products

Stem cell products from unrelated donors are normally transplanted fresh, once the product has arrived in the transplant center and the quality assessment at the transplant center has

been performed. Under certain circumstances, a cryopreservation of the product can become necessary.

- DKMS has to approve any cryopreservation request. To be able to approve the request, DKMS needs a detailed justification for the cryopreservation request.
- DKMS wants to avoid cryopreservation of stem cell products. Therefore, a postponement of the transplant date before collection is generally preferred.
- Cryopreservation of bone marrow products is associated with higher cell losses. DKMS will approve such requests when excessive TNC counts are expected.
- The donor is contacted by the workup case manager and informed about the cryopreservation request. The donor has to agree to the cryopreservation of his/her product and give consent.
- A clear timeline for start of conditioning and date of transplantation must be communicated before cryopreservation can be approved.
- Infusion should be scheduled as soon as possible and pre-transplant conditioning should start immediately after safe arrival of the product or, in case of recipient related cryopreservation, once health status is appropriate.
- In addition, the transplant center must confirm with a formal cryopreservation request form to assess the feasibility of immediate transplantation prior to the beginning of the donation procedure (1st dose of G-CSF or hospital admission for BM collection).

If the required information about the planned cryopreservation has not been provided before the start of the mobilization, the collection center, donor center or the donor may not proceed with the donation.

- DKMS will follow-up with the transplant center as long as the cells are cryopreserved and not infused. The transplant center needs to inform DKMS when they have infused the cells. If the cryopreserved product will not be used for the intended patient, the transplant center must also inform DKMS and explain why the product cannot be used.
- If the cells will definitely not be infused, some DKMS entities may ask transplant centers to keep unused PBSC products cryopreserved for the time being and / or initiate retrieval of those cells to be stored at DKMS Stem Cell Bank.
- As unrelated stem cell products are directed to a single patient, it is not allowed to use cells for another purpose, e.g. science, studies or validation processes without approval from DKMS and a specific donor consent.
- DKMS has to give final approval before cells are destroyed.
- Donors will always be kept updated about the infusion or non-infusion of their stem cells.

6.10 Partial Cryopreservation of Excess Cells of Stem Cell Products

If the stem cell product contains more cells than needed, the transplant center should cryopreserve residues of the HSCs or MNCs for a later use.

- Donors agree on the consent form, that portions of the stem cell product can be cryopreserved if the stem cell product contains more cells than needed. Excess cells can only be used as a subsequent transplant for the same patient.
- If remains of the stem cell product are no longer needed for the patient, the transplant center must discard the cells. A specific information to DKMS is not required.

It is not allowed to use the product for research or any other purposes without approval of DKMS and the donor.

6.11 Cryopreservation of MNCs

Donor MNC products usually are portioned and most parts are cryopreserved. One portion should be infused freshly.

- A transplant center needs to inform DKMS if they plan to cryopreserve the complete product and not infuse at least one fresh portion within 14 days. A reason and the plan for infusion should be communicated so that the donor can be informed correctly.
- If the transplant center wants to cryopreserve the lymphocytes for longer than 14 days before administering the first dose, the cryopreservation of MNC products is also subject to approval by DKMS and the donor.
- If an infusion seems very unlikely, the transplant center should consider postponing the MNC Apheresis.
- DKMS will follow-up with the transplant center some days after the planned date of the first infusion and inform the donor accordingly. Any changes of plans or delays should be communicated by the transplant center actively and in a timely manner.

6.12 Unavailability of a Donor for One Product Type

For recipient safety, transplant centers can request approval for cryopreservation of the stem cell product if a donor is only available for one stem cell source (HSC Apheresis or HSC Bone Marrow).

- HSC Apheresis: If the donor is only available for HSC Apheresis, the transplant center can request approval to cryopreserve the stem cell product in case the donor is a poor mobilizer and no sufficient cell count can be collected. If the donor does not give his/her consent to a cryopreservation, the transplant center will be informed accordingly.
- HSC Bone Marrow: If the donor is only available for HSC Bone Marrow, cryopreservation of the product can also be approved. However, the expected cell counts have to meet the minimum requirement of TNC cells by the Transplant Center.
- Even in these cases, the transplant center must request approval for cryopreservation from DKMS. A scheduled transplantation date is a prerequisite for approval.

DKMS recommends to infuse cells fresh wherever possible and to have a backup plan for each transplantation (e.g. other donor or therapeutic cell source).

6.13 Additional Testing Requests by the Transplant Center

In some countries, transplant centers have to perform additional tests, which are not relevant for donor clearance in the donor's country.

- Transplant centers have to inform DKMS of any additionally required tests in good time before the donor's physical examination. DKMS checks if it is possible to perform the tests in the laboratory of the collection center and informs the transplant center about the additional costs.
- The transplant center then decides if they want to perform the additional test themselves out of the pre-collection samples or if they want DKMS to perform the test and agree to pay the additional costs.
- If DKMS performs the test, results are communicated together with the donor final clearance.

6.14 Maximum Amount of Blood to be drawn at Physical Examination (Pre-Collection Samples)

Pre-collection samples of donors are often requested as part of the workup request. Transplant centers can perform specific tests required before transplantation.

- Pre-collection samples are drawn at the time of physical examination (PE).
- The maximum amount of blood for pre-collection samples to be drawn at PE is 50 ml.
- Exceptions can be taken into consideration on a case-by-case basis.
- For NMDP requests, 35 ml cannot be exceeded as additional blood tubes have to be drawn for FDA-approved infectious disease marker testing.

6.15 Transplant Center Acceptance of Formally Ineligible Donors

If the physical examination reveals that donation bears no increased risk for the donor but the potential transmission of a condition or disease to the recipient as specified in the respective official guidelines of the donor's country, such a donor may only be cleared after written acceptance by the transplant center.

Examples: travel history, sexual high-risk behavior, enzyme deficiency (G6PDH).

6.16 Donor Reservation after Donation

As subsequent donations for the same patient occur in about 10% of all our cases (HSC Apheresis or Bone Marrow: 2.8% and MNC Apheresis: 7.8%), donors are reserved for the patient for whom they donated.

- All DKMS donors are reserved for the patient for whom they have donated for a period of two years (starting from the first day of collection).
- Transplant centers can ask for a prolonged reservation in case they may consider a subsequent donation from the same donor in the near future.
- DKMS informs the transplant center within 5 years after the first transplantation if the donor will be no longer available for subsequent donations.

7 Transport

7.1 Transport Arrangements to be made by International Registries and Transplant Centers

Once the date of collection is confirmed, the DKMS case manager sends a form to the respective registry or transplant center to fill in the required information.

For international transport arrangements, the applicable DKMS or WMDA forms must be submitted.

DKMS needs to be informed about the following information:

- Name of the courier
- Courier's date of birth
- Passport number including expiration date
- 24/7 mobile phone number of the registry or transplant center
- Date and time of arrival at the location of the collection center including the name of the hotel and a travel plan containing all transport information

7.2 Transport Arrangements to be made by DKMS

DKMS can organize the stem cell courier on behalf of the transplant center. This service is charged in addition.

In case the transplant center asks DKMS to provide a courier, DKMS contacts a courier company to arrange the transport of the HSC / MNC product. The courier company forwards all relevant information about the courier including a main and an alternative travel plan to DKMS. These courier details are sent to the respective registry or transplant center. They may provide DKMS with additional forms that need to be forwarded to the courier in charge.

8 Donor Follow-Up

8.1 Post-Donation Follow-Up

Donor follow-up will be initiated after the first injection of a mobilizing agent, the administration of anesthesia, or the beginning of apheresis (in case of MNC Apheresis), independently of completion of the collection.

The donor's health must be assessed to monitor the recovery process, long-term health effects after the donation and the availability for further donations.

- All DKMS donors have a minimum of 10-year post-donation follow-up.
- Follow-up questionnaires are sent out to the donor 1 month, 6 months, 1 year, and then annually until 10 years post-donation.
- For non-US donors a blood test is done 1 month post-donation.
- If there are abnormal findings, timely controls will be arranged with the donor upon the physician's / medical advisor's decision.

8.2 Adverse Events and Reactions Reporting (SEAR/SPEAR)

To ensure donor's and recipient's health and safety, all adverse events and reactions of unrelated donors or patients have to be reported to WMDA to gain insight in the occurrence of health incidents or risks. This also applies to MNC Apheresis.

SEAR Reporting

- The DKMS donor center affected by the SEAR submits the report to the registry it is associated with or directly to WMDA and to national authorities accordingly if required.
- At the end of the year a negative report is sent to WMDA in case there was no adverse event.
- If there is a risk of disease transmission to the recipient (e.g. infectious disease, malignancy), the transplant center will be informed.
- Any SEAR is documented in a way that allows tracking and analysis.

SPEAR Reporting

- Reporting product or patient adverse events / reactions is primarily within the responsibility of the transplant center and the associated patient registry.
- DKMS Registry has implemented the following procedure to ensure that all adverse events and reactions are reported to WMDA for cases where DKMS Registry is the patient registry.

- Transplant centers that use the search service of DKMS Registry must agree during the evaluation of their center that serious events will be reported to DKMS Registry within 2 weeks after occurrence.
- Once per year, DKMS Registry asks all transplant centers that have received stem cell products via DKMS Registry in the previous year to fill a SPEAR questionnaire.

9 Donor-Patient Contacts

9.1 Anonymity Criteria for DKMS Donors and / or Patients of DKMS Registry

Donor and recipient information are confidential for at least two years post-donation (1 year for US donors). The goal of maintaining donor and recipient anonymity is to ensure privacy for both, donor and recipient. In some countries, no contact between donor and recipient is allowed. If regulations differ between donor and patient country, the stricter rule applies (e.g., if no contact between donor and patient is allowed in the donor or patient country, there will be no contact). If no laws of the donor or patient country conflict, the following applies:

- Anonymous correspondence between donor and recipient is allowed immediately after the transplantation.
- In case of DKMS donors, all correspondence is checked by DKMS employees to ensure confidentiality guidelines are met. The correspondence is documented in DKMS' software.
- The exchange of photos showing people or recognizable locations / landscapes is generally not permitted. In particular, photos of donor, recipient or family members may not be exchanged.
- Post cards with clear indication of the donor's or recipient's residence are not allowed.
- Anonymous letters between relatives of deceased patients and their donors (or the patient and relatives of a deceased donor) are possible.
- One gift – meeting anonymity criteria – is allowed per side. The gift
 - should not be more expensive than 20 EUR / 20 USD.
 - should not contain anything fragile.
 - should not contain food items, including beverages or sweets.
 - should not contain audio files.
 - should not include gift certificates or money.
- In case of patients of DKMS Registry, messages from the patient can be handed to the transplant center to send it on to the registry of the donor directly without involvement of DKMS Registry.

9.2 Patient Follow-Up Information

Stem cell donation is an altruistic act. Most donors are interested to know if the donation was successful and the patient has recovered after stem cell donation. In addition, engraftment data have to be obtained for the collection centers to prove their quality and fulfill requirements for JACIE accreditation.

- DKMS requests patient follow-up information usually three months after stem cell donation including engraftment data. The engraftment data will be sent to the collection center for their quality management and JACIE accreditation.
- Donors will be informed about the outcome of the patient's transplantation but only basic and anonymous information is given to the donor.
- Upon a donor's request, DKMS asks for further updates after 1 year and / or annually.

9.3 Release of Personal Information between Donor and Recipient

If no laws of the donor or patient country conflict, two years after transplantation (for DKMS US donors 1 year), personal information of donor and recipient can be exchanged. If it is possible, the following applies:

- DKMS allows exchange of personal information between donor and recipient.
- The release of personal information between donor and relatives of their deceased recipient (or vice versa) is also possible. The anonymity period of 2 years is lifted once the patient is deceased.
- A subsequent donation or MNC Apheresis within the second year after transplant may prolong the confidentiality period. Another year of anonymity adds from the day of the second transplant date (for HSC donations) or three months from the day of infusion of the first portion of MNCs, respectively.
- Either recipient (via the transplant center) or donor has to request the release of personal information.
- Donor and recipient have to sign a consent form to release personal information.
- The recipient's written consent to release personal information to the donor should be already on file when the request is sent to DKMS.
- Once DKMS has received the consent form from donor and recipient, the personal information can be exchanged.

10 Finance

10.1 Fee Schedule

The current fee schedule of DKMS Registry can be requested at services@dkmsregistry.org.

Any changes are communicated 30 days prior to becoming effective.

Each transplant center or registry is accountable for the payment of the fees according to DKMS Registry's fee schedule. **The accruing costs refer to the fee schedule that is valid at the time of request initiation.** The invoice will be issued by the DKMS entity that performed the request, usually soon after service delivery. Payment term is 30 days.