DKMS
WE DELETE BLOOD CANCER

DKMS OPERATIONAL USER GUIDE

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Contents

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 in the United Kingdom (DKMS UK), Fundación de Beneficencia Pública DKMS in Chile (DKMS CL), DKMS BMST Foundation India (DKMS BMST IN) and DKMS in the United States of America (DKMS USA). It describes the rules and procedures in place that have to be followed by Transplant Centers (TCs), 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 give their partners a thirty days' notice by email of any change to this user guide.

2. Abbreviations

Abbreviation	Meaning
BM	Bone Marrow
CCR5	C-C Chemokine Receptor type 5
CT	Confirmatory Typing (Verification Typing)
CVC	Central Venous Catheter
DLI	Donor Lymphocyte Infusion
EMDIS	European Marrow Donor Information System
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
MDRI	Marrow Donor Registry India
MNC	Mononuclear Cell
NGS	Next Generation Sequencing
PE	Physical Examination
PBSC	Peripheral Blood Stem Cell
SAA	Severe Aplastic Anemia
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 Partner TCs

TC Evaluation according to WMDA Criteria

DKMS Registry acts as a patient registry for TCs in Chile, India and Sri Lanka. Additionally, DKMS Registry as a donor registry may be in direct contact with TCs if no established national registry exists.

Transplant Centers cooperating with DKMS Registry are evaluated according to WMDA TC evaluation criteria before any donor can be requested. The TCs 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 TC, the case is reviewed and decided by the Chief Medical Director of DKMS.
A reassessment of the evaluation takes place every three years.

Transplant Centers in the rest of the world also need to fulfill WMDA TC evaluation criteria. If the requesting registry is neither WMDA qualified nor confirms in written form that affiliated TCs are evaluated according to WMDA criteria, DKMS Registry will seek for information about the requesting Transplant Center and ask the Transplant Center to fill in the TC evaluation form (in accordance with WMDA criteria). No request can be initiated before the DKMS Review Board approved the Transplant Center.

4. Donor Search Process and Requirements

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 possible unrelated donor, must satisfy DKMS Registry's requirements regarding diagnosis. Diagnoses that are a standard indication 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.

Patient Age

Each patient for whom an unrelated donor search is started at DKMS Registry 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.

In case of search initiation via EMDIS, the assessment takes place before the first donor request is completed, i.e. when it is clear that a DKMS donor might be of interest for the patient.

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).

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, HLA-E, …) can further enhance donor selection.

- **Requirements for search activation:**
  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, HLA-E, …) 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.

Confirmation of patient HLA typing results from an independent sample is recommended before requesting a workup at DKMS to exclude sample switch.

Medical and personal data for search initiation
The following information must be provided in a preliminary search request from an international registry or Transplant Center:

- Patient's name (required)
- Patient's sex (required)
- Patient's date of birth (required)
- Patient's ethnicity (optional)
- Patient's weight (optional, required for workup)
- Patient's blood group (optional, required for workup)
- Patient's HLA typing (Minimum as defined above required)
- Patient's diagnosis (required)
- Transplant Center (optional, required for workup)

Matching Algorithm

a) 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

b) Ranking of matching list

10/10 matching list:
1. 10/10 matching probability
2. Younger donor before older donor
3. Male before female

9/10 matching list:
1. 9/10 matching probability
2. 8/10 matching probability

3. MM loci: HLA-DQB1 mismatch before mismatch at HLA-A, -B, -C or -DRB1
4. Younger donor before older donor
5. Male before female

Limit of Mismatch Level

An approval by DKMS medical advisor is required when matching is <8/10.
8/10 matching results will be provided upon request via email (not via EMDIS).

Search Service provided to Transplant Centers in Chile, India and Sri Lanka

DKMS Registry offers a special search support program to Transplant Centers in Chile, India, and Sri Lanka. DKMS Registry thereby assists Transplant Centers in these countries 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.

(Preliminary) Donor Search by International Registries

All searches, preliminary and active, are free of charge. Searches for donors from DKMS UK, DKMS CL and DKMS BMST IN 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 (SMP_REQ), infectious disease marker request (IDM_REQ) and donor reservation requests (RSV_REQ) can be received via EMDIS.

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 usage 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.

   DKMS Registry will send a search report, consisting of DKMS donor (UK, IN, CL) matching results and donor details of the most relevant donors, usually within one business day after receipt of the search request.

3. **Via Donor Navigator® Software**

   International registries 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.
   - The additional benefits for registered *Donor Navigator*® users comprise an overview of all cases of their registry, 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 that can be filled by the requesting Transplant Center affiliated to the registry.

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 by EMDIS or other communication according to the EMDIS Semantics. DKMS Registry reserves the right to deactivate a donor search after a reasonable time of inactivity.

5. Donor Requests

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 standard typing profile for extended HLA typing is HLA-A, -B, -C, -DRB1, -DQB1, -DPB1. Non-standard markers can be typed up on special request.

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

Included in a typing tequest is:

- Short Health History Questionnaire (HHQ) and first assessment of donor suitability. TC will be notified about medical details if relevant.
- Buccal swab sample from donor for DNA typing.
- Typing results from our ASHI and EFI accredited DKMS Life Science Lab.

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 the whole set of IDMs, it is also possible to request only ABO, rhesus factor and CMV status - combined or separately.

Included in an IDM request is:

- Short Health History Questionnaire and first assessment of donor suitability. TC will be notified of medical specificities if required.
- Donor blood sample for IDM testing
- 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 markers included in the respective request can be found in our *Specification of Services*.

The current *Specification of Services* can be requested at services@dkmsregistry.org.

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 donors screening and proceed faster to workup as confirmatory HLA typing is only performed on donor selected for workup. Confirmatory HLA typing (verification 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.

Included in a HAC request is:

- Detailed information session with the donor by phone
- Detailed Health History Questionnaire and assessment of donor suitability. TC will be notified of medical specificities if required.

Confirmatory Typing (not parallel to Workup)

Confirmatory HLA 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 typing must be performed from a fresh sample of the potential donor and recipient.

When confirmatory typing is requested and processed before workup, it includes the following elements:

- Detailed information session with the donor by phone
- Detailed Health History Questionnaire and assessment of donor suitability. TC will be notified of medical specificities.
- IDM testing
- Donor blood sample for HLA typing
- Shipping of samples

Please see our DKMS Registry *Specifications of Services* for detailed information on IDM markers tested per DKMS Donor Center. The current *Specification of Services* can be requested at services@dkmsregistry.org.

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

Research Studies at CT level

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

- All studies have to be approved by the DKMS Clinical Trials Unit (CTU).
- DKMS allows only one study per case.
- Transplant Centers are not allowed to perform any tests with donor material (blood) which exceed the regular tests for donor selection.

- 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).

CCR5 Verification at CT

About 1 % of the Northern European population carries the Δ32 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.

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

Workup Process

After the workup request form is received, it is checked for completeness and correctness. If it contains all necessary information, the workup request 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 donor:

- Methods of blood stem cell donation, their risks and possible side effects
- Preferred donation method
- Time frame of medical examination and 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
- Possible collection center
- Anonymity of donation
- Non-remuneration of donation, but refunding of expenses incurred by the donation and loss of earnings including coverage by an accident, life and disability insurance.

- Voluntary nature of the donation and right of withdrawal at any time. However, the donor will be informed about the risk of death of the recipient in case the donor should withdraw after the beginning of the recipient´s conditioning therapy.

Maximum Number of Donations for DKMS Donors

Subsequent Donation	After the completion of an HSC collection, the same donor is requested for the same patient again (HSC apheresis, HSC bone marrow or MNC apheresis).
Second/Multi Donation	The respective donor completes more than one HSC collection for different patients.
Second Transplant	The respective patient receives a second HSC product by a donor different from the one of the first product.

If patients have a relapse or a graft failure, a subsequent donation (HSC apheresis or HSC bone marrow) of the same donor can become necessary.
A donor can also be requested as best match for a different recipient; this happens in approximately 2-3 % of our cases. To protect donors, stem cell collections per donor are limited.

- HSC apheresis or HSC bone marrow are limited to two collections per donor for each product. This would theoretically mean that a donor can donate bone marrow twice and PBSC twice.
- Subsequent donations of HSC apheresis or HSC bone marrow for the same patient have to be approved by the medical advisor of DKMS.
- Transplant Centers will already be informed at confirmatory typing stage, if a donor has already donated before, as the donor will only be available for the same stem cell product type one more time.
- There is no defined maximum number of MNC apheresis. However, when the donor is requested for MNC apheresis the third time, a medical advisor will be contacted to evaluate the indication.

Interval between Donations

After an HSC donation (the donor can 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.
- The interval between two BM donations should be at least 4 weeks. A PBSC donation should be considered for the second request, if possible.
- The interval between HSC donations should also be at least 4 weeks.

- There is no defined minimal interval for MNC apheresis. However, the donor blood count must be in normal range.
- A subsequent or second 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 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 possible second transplant.

Cell Count Requests

We observe a huge range in requested CD34+ cell counts for HSC apheresis from 1.5 x 10^6 / kg to 50 x 10^6 / kg bodyweight of the recipient. Generally, a CD34+ cell count of 5 x 10^6 / kg recipient bodyweight 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 10^8 / kg bodyweight 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 CD34+ requests above 5 x 10^6 / kg recipient bodyweight. Requests above 5 x 10^6 / kg recipient bodyweight without a plausible explanation cannot be accepted.
- For HSC bone marrow the collection of TNC is limited, as only 20 ml bone marrow / kg bodyweight of the donor and max. 1500 ml can be collected.
- Transplant Centers should thus consider donor's weight when requesting a BM product.

CT and Workup in Parallel

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 list. Therefore, in urgent cases or in cases where the donor was already requested multiple times for confirmatory typing, the confirmatory typing can be shifted to the workup process. In these cases, it is possible to request CT and workup in parallel. The Transplant Center has to consider that CT unavailability varies between 20-40% depending on the DKMS entity. A health and availability check (HAC) should be requested instead of a CT to assure the donor's availability and medically suitability. HAC does not include IDM testing which will be performed during workup in these cases.

- DKMS accepts parallel requests of CT and workup in urgent cases. The blood draw for confirmatory typing takes place at the time of physical examination and the

Transplant Center has to confirm that confirmatory HLA 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 TC requests that the blood samples for confirmatory typing are drawn before physical examination, a separate confirmatory typing request must be sent.

Number of Donors Requested for one Patient at the Same Time

At DKMS the workup unavailability rate is approximately 15% globally.

- DKMS accepts that a Transplant Center requests more than one donor for WU. However, the TC/registry **must** inform DKMS which donor is the primary or backup donor.
- The preferred donor will be contacted as usual and will **not** be informed that there is another donor requested for workup.
- The backup donor will be contacted and will be informed that he/she is a backup donor and therefore might not be requested to donate, if the preferred donor is able to proceed in the requested timeframe. 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, in urgent cases, there is an increased risk that the preferred donor will not be available, DKMS may, in exceptional cases, plan with both donors simultaneously.

Replacement Donor Search at Workup

With a DKMS donor pool of more than 10 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 from start of the workup. If there are no matching donors available, DKMS types potentially matching donors who are not fully typed at own costs.

Research Studies at Workup Level

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

- All study requests have to be approved by the DKMS Clinical Trials Unit (CTU).
- In addition, research studies have to be approved by the ethical review board responsible for the Collection Center.
- 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.
- Transplant Centers are not allowed to perform any research with donor material (blood, BM, PBSC, MNC products or data) which is not standard requirement for either donor selection or transplantation.
- For any research studies, Transplant Centers have to provide the full study synopsis, approval of the ethical review board, as well as a translated information and consent form for donors.

Cryopreservation of Stem Cell Products

Stem cell products from unrelated donors are normally transplanted fresh, immediately after the product has arrived in the Transplant Center. 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.
- A clear timeline for 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 TC must confirm 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).

  This includes:
  - Recent health status: recipient's health status allows for transplantation (the recipient must have been examined by a physician shortly prior to the start of donation, not only when the request was initiated)
  - Extended and verification typing of the recipient performed
  - Donor verification typing performed
  - Insurance covering or other financial resources for transplant expenses
  - Capacity in the Transplant Center
  - Recipient's consent for immediate start of therapy

  If the information stated above 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 kept cryopreserved and until they are either infused or destroyed. The Transplant Center needs to inform DKMS when they have infused the cells or if they want to destroy a cryopreserved product. Donors will be kept updated about the infusion.

- As unrelated stem cell products are directed to a single patient, it is not allowed to use cells for another purpose, e.g. science without specific donor consent.

Cryopreservation of MNCs

Donor MHC 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 a fresh portion within 14 days. A reason and any plans for infusion should be communicated so that the donor can be informed correctly.

If an infusion seems very unlikely, the Transplant Center should consider postponing the MHC apheresis.

DKMS will follow-up with the Transplant Center on the date of the first infusion and inform the donor accordingly.

Partial Cryopreservation of Stem Cell Products

If the stem cell product contains more cells than needed, the Transplant Center can cryopreserve residues of the HSCs or MHCs 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. Product can only be used as a subsequent transplantation for the same patient.
- If the stem cell product is 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.

Discarding Cryopreserved Stem Cell Products

In cases in which DKMS agreed to cryopreservation of a stem cell product and the product cannot be used for the intended patient, the stem cell product usually has to be discarded.

- DKMS has to be informed about the reason why the product cannot be used for the patient before the product is discarded.
- It is not allowed to use the product for research or any other purposes without approval of DKMS and the donor.

Unavailability of a Donor for One Product

For recipient safety, Transplant Centers can cryopreserve the stem cell product after arrival and before patient conditioning 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 TC is allowed 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, the TC can request approval for cryopreservation of the product.
- In any case, the Transplant Center must have a transplant date scheduled and inform DKMS accordingly.

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

Manipulation of Stem Cell Products

T-cell or red cell depletion is a common manipulation method before stem cell transplantation. Transplant Centers are usually responsible to perform T-cell or red cell depletion.

- In case a Transplant Center cannot perform this type of manipulation, DKMS may be able to organize this in the country of the collection (not necessarily in the Collection Center).
- Cost of the manipulation has to be covered by the Transplant Center.

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 country.

- Transplant Centers have to inform DKMS about the additional tests. 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 by their own out of the pre-collection samples or if they want DKMS to perform the test.
- If DKMS performs the test, results are communicated together with final donor clearance.

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

Pre-collection samples of donors are often requested in a workup request. Transplant Centers can perform specific tests required before transplantation.

- Pre-collection samples are drawn at time of physical examination (PE).
- The maximum amount of blood for pre-collection samples to be drawn at the 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 tests.

TC 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

responsible official guidelines of the donor country, such a donor may only be cleared after written acceptance from the Transplant Center.
Examples: travel history, sexual high-risk behavior, enzyme deficiency (G6PDH)

Donor Reservation after Donation

As subsequent donations occur in 10.5% of all our cases (HSC apheresis or bone marrow: 2.5% and MHC apheresis: 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 two years.
- Transplant Centers can ask for a prolonged reservation in case they may consider a subsequent donation of the same donor in the future.
- If DKMS receives a CT request from a different Transplant Center within 5 years after the first donation, DKMS will contact the primary Transplant Center to check if the donor can be released for the new patient.

7. Transport

Transport Arrangements to be made by International Registries and Transplant Centers

Once the date of the 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

Transport Arrangements to be made by DKMS

In case the Transplant Center asks DKMS to provide a courier, DKMS contacts a courier company to arrange the transport of the HSC product. The courier company forwards all relevant information on 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

Post Donation Follow-Up

After a stem cell collection, the donor's health must be assessed to monitor the recovery process and long-term health effects after the donation.

- All DKMS donors have a minimum of 10-year post-donation follow-up.
- 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.
- Follow-up questionnaires are sent out to the donor 6 months, 1 year, then annually until 10 years post-donation.

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 MHC apheresis.

SEAR Reporting

- The DKMS Donor Center affected by the SEAR, submits the report to the registry it is associated with.
- When DKMS Registry is the responsible registry, it checks and submits SEAR reports to the WMDA.
- 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 recipient (e.g. infectious disease, malignancy), the TC 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 cases have to be reported to DKMS Registry within 2 weeks after occurrence.
    - Once per year, DKMS Registry asks all Transplant Centers that use the search service of DKMS Registry and that have received stem cell products of DKMS donors in the previous year to fill a SPEAR Questionnaire.

9. Donor-Patient Contacts

Anonymity Criteria for DKMS Donors

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.
- All correspondence is checked by DKMS employees to ensure confidentiality guidelines are met.
- Exchange of donor or recipient pictures are not allowed.
- Postcards with clear indication of the donor's or recipient's residence are not allowed.
- Anonymous letters between relatives of deceased patients and their donor are possible.
- One gift – meeting anonymity criteria – is allowed per side. The gift
    - should not be more expensive than 20€/20$.
    - 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.

Patient Follow-Up Information

Stem cell donation to an unrelated patient is an altruistic act. Many 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 3-6 months after stem cell donation including engraftment data. The engraftment data will be sent to the collection center for their quality management.
- Upon the donor's request, DKMS asks for further updates after 1 year and then annually.
- Donors will be informed about the outcome of the patient (only very basic and anonymous information is given to the donor).

Release of Personal Information between Donor and Recipient

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

- DKMS allows exchange of personal information between donor and recipient.
- The release of personal information between donors and relatives of their deceased recipients is also possible. The anonymity period of 2 years is lifted once the patient is deceased.
- A subsequent donation or MHC apheresis within the second year after transplant may prolong the anonymity period. Another year of anonymity adds from the day of the second transplant date.
- Either recipient (may be represented by 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

Fee Schedule

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

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 Donor Center that performed the donor request.