DKMS
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DKMS TRANSPLANT CENTER OPERATIONAL USER GUIDE

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Content

1 Background

1.1 About DKMS Group and DKMS Registry

DKMS Group gGmbH (hereinafter DKMS) comprises several departments and affiliate organizations providing various services towards enabling unrelated Donor hematopoietic stem cell transplantations. A detailed list of these can be found on the DKMS Professionals' platform (https://professional.dkms.org/)
The DKMS Registry gGmbH (referred to as DKMS Registry here onwards) began its operations as a subsidiary of DKMS in Germany on August 1, 2020. It operates as an international registry and works in close cooperation with transplant centers, search centers and other international registries.
DKMS Registry is World Marrow Donor Association (WMDA) qualified since 2021 and is moving towards full standard certification in 2025. Services provided by DKMS Registry follow standards and guidelines provided by WMDA (https://wmda.info/ensuring-quality/).

1.2 Scope of the document

This document describes the search and request support offered by DKMS Registry and the associated obligations/requirements that both DKMS Registry and its cooperative transplant centers need to fulfill in order to ensure patient and Donor safety - in compliance with WMDA standards and DKMS Group policies.
In addition to the terms described in this document, those described in the DKMS operational user guide (https://professional.dkms.org/services/operational-user-guide) and other cooperation policies must be observed in applicable cases.

1.3 Document control

DKMS Group policies and external regulations and guidelines like the WMDA Standards may be amended from time to time to take account of changes in medical practice, in operational or in administrative procedures. DKMS Registry will announce any change to this transplant center operational user guide on the DKMS Professionals' Platform (https://professional.dkms.org/services/dkms-services/dkms-registry-services/search-support-for-transplant-centers) 30 days before coming into effect.

2 Glossary of terms and abbreviations

Term/Abbreviation	Definition
ADCU	Adult Donor cryopreserved units
BM	Bone marrow

CBU	Cord blood unit
DLI	Donor lymphocyte infusion
Donors	Persons who have declared their willingness to donate hematopoietic stem cells for a patient suffering from a life-threatening disease of the hematopoietic system for which HSCT is an adequate treatment option and that are registered in a Donor Registry
Donor registries/ Donor centers	Organizations that register Donors for the purpose of matching them with patients and that take over the organization of a stem cell donation from a matching Donor
DKMS Donors	Donors recruited by affiliated entities of DKMS Group gGmbH, except DKMS US. DKMS US Donors are listed by the US-NMDP Registry and for the purpose of this document do not fall under the category of DKMS Donors
GRID	Global registration identifier for Donors
Hap-E Search	DKMS Registry web-application that lists Donors and ADCUs from the DKMS Donor pool as well as search results from the worldwide Donor pool of the WMDA Search & Match Service (https://new.hapesearch.org)
HLA	Human leukocyte antigen
HAC	Health and availability check
HSC	Hematopoietic stem cell
HSCT	Hematopoietic stem cell transplantation
IDM	Infectious disease marker
MNC	Mononuclear cell
PBSC	Peripheral blood stem cell
SEAR	Serious events and adverse reactions
SPEAR	Serious product events and adverse reactions
TC	Transplant center
VT	Verification typing, also known as confirmatory typing (CT)
WHO	World Health Organization (https://www.who.int/)
WMDA	The World Marrow Donor Association comprises organizations and individuals that promote global collaboration and best practices for the benefit of blood stem cell Donors and transplant patients (www.wmda.info)

3 Search and request support service

Transplant centers without access to a national patient registry or with limited access to worldwide unrelated Donors can utilize the DKMS Registry's search and request support. As part of this service, cooperative centers receive:

- Education and training on processes needed to successfully obtain stem cell products for HSCT from the worldwide Donor pool.
- Access to Hap-E Search, an in-house, browser-based free Donor search and case management tool (Urban C et al. (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. doi: 10.3389/fmed.2020.00032).
- Support from a dedicated search coordination team guiding the Donor search process, selection of best matched Donor(s) - including verification typing - and Donor workup up to product transportation to the transplant facility and potential follow-ups.

Recruitment, training and educational requirements of the search coordination team complies with the recommendations provided by the WMDA Registries Working Group (https://wmda.info/publications/). DKMS Registry's search and request support is currently offered to transplant centers located in Belarus, Chile, Colombia, India, Pakistan, and South Africa.

4 Service affiliation requirements

A transplant center interested in collaborating with DKMS Registry for the purpose of unrelated Donor search and request must be appropriately registered, licensed, or accredited by its national government (if applicable) and/or another agency relevant to HSCT. The center must have a medical director and at least one additional physician with sufficient experience in allogeneic HSCT, including at least one year in unrelated transplantation.
The transplant center must have sufficient resources to perform HSCT with adequate outcomes for their patients. These resources include but are not limited to:

- Access to an accredited lab for high-resolution HLA typing of patients (DKMS Registry may support if needed)
- Access to an accredited stem cell processing lab to perform product testing
- A transplant team that includes nurses with training and experience in the care of transplant patients
- Physician coverage 24 hours per day, seven days per week
- Coordinator or other key personnel proficient in English and available to provide daily and emergency communication for Donor search coordination and product procurement

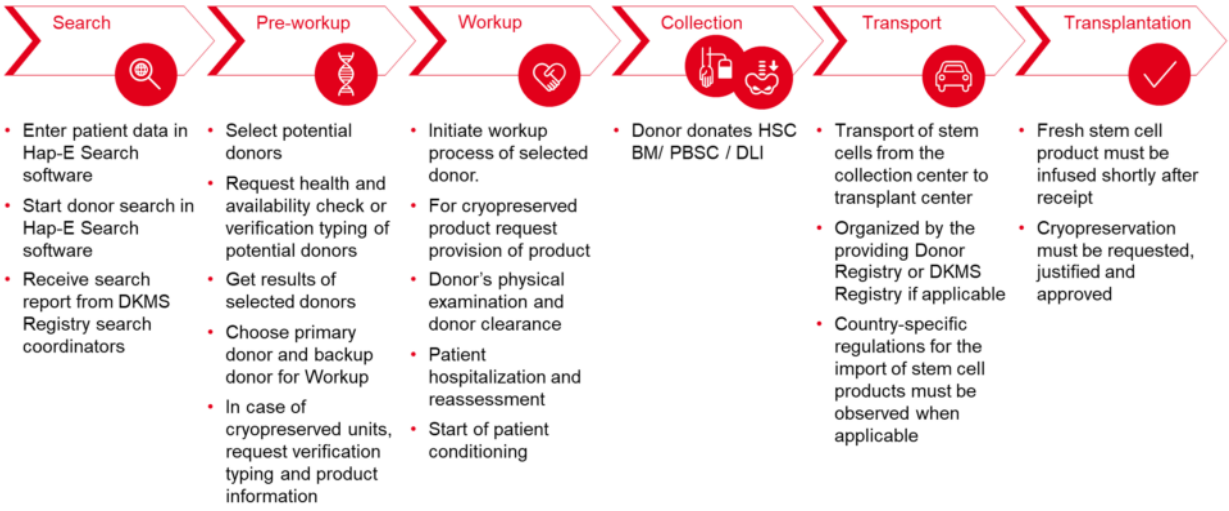
The transplant center must successfully pass evaluation by DKMS Registry. The evaluation process follows WMDA criteria and may be amended from time to time. Evaluation forms are available online and provided upon request. Re-evaluation is performed every 3 years and must be completed by the center without delay. A transplant center accredited by FACT-JACIE

is exempt from this evaluation due to the associated compliance with the WMDA criteria and may only provide administrative information. Any changes to staff members, substantial changes to the facility, as well as changes to accreditation status must be promptly communicated to DKMS Registry.

5 Unrelated Donor process overview

The process for obtaining unrelated stem cell Donor products starts with a search initiation, followed by potential Donor(s) or cryopreserved product(s) selection, initiation of pre-workup requests to confirm Donor or product availability and compatibility, and subsequently initiation of workup, i.e., product request. Figure 1 provides on overview of the major steps involved in the international Donor search and request process as facilitated by DKMS Registry. The stipulations for the various steps are described in detail in the ensuing sections.

Figure 1: **From unrelated Donor search to transplantation - process overview**



6 Donor search initiation process and requirements

6.1 Informed consent

Patient informed consent for unrelated Donor search: If required DKMS Registry can provide a template for transplant centers that must be adapted by the transplant center as required by local laws and regulations.

6.2 Patient diagnosis criteria and age

Each patient for whom a Donor is being considered as a potential unrelated Donor must satisfy requirements regarding diagnosis and age. Patients less than 80 years of age and with 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 (Khoury JD *et al.* (2022), The 5th edition of the World Health Organization Classification of Haematolymphoid Tumours: Myeloid and Histiocytic/Dendritic Neoplasms. *Leukemia*. 36:1703–19. doi: 10.1038/s41375-022-01613-1)
If the indication for which the transplant center is requesting a Donor is not a standard indication for HSCT and/or the patient is older than 80 years of age, 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 transplantation center.

6.3 Search initiation

Relevant patient information accompanied by their HLA report must be submitted via Hap-E Search to initiate the search for a suitable Donor. Once initiated, the search runs automatically on the DKMS Donor database and WMDA's Search & Match Service (https://wmda.info/optimising-search-match-connect/). While a preliminary search request only provides match list showing search results on potential stem cell Donors, ADCUs and – if requested - CBUs, an active search must be started to perform Donor or cryopreserved product requests (e.g. HLA VT request).
The following data must be submitted at the time of search initiation:

Patient HLA typing

- **Requirements for preliminary search:**
  Minimum: HLA-A, -B, -C, -DRB1 low resolution DNA-based typing.
  Recommended: high resolution DNA-based typing for HLA-A, -B, -C, -DRB1, -DQB1, and if available -DPB1. This level of typing accelerates the search process. Low resolution HLA typing decelerates the search procedure by including potentially matched Donors that may have one or more mismatches in the final high-resolution match.

- **Requirements for search activation (needed to start requests):**
  Minimum: HLA-A, -B, -C, -DRB1 high resolution DNA-based typing.
  Recommended: High resolution DNA-based 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. *Blood*, 118 (23): e180–e183). doi: 10.1182/blood-2011-05-353490)

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

Patient's medical and personal data for Donor search and Donor request initiation

- Patient ID at transplant center
- Patient's name
- Patient's sex
- Patient's date of birth
- Patient's diagnosis

In addition to the above information, transplant centers can indicate search preferences such stem cell product of choice (BM, PBSC, or CBU), Donor mismatch level (if 9/10 matched Donors are accepted), and Donor CMV status at the time of search initiation. Furthermore, other supplementary information may be requested depending on the providing Donor Registry.

6.4 Search results and report

The results of the worldwide Donor search are displayed directly on the Hap-E Search Software. Together with the top 200 Donors listing, a search report is provided within one working day. Transplant centers may choose to receive a detailed or basic search report, the former contains a detailed recommendation of best-fit Donors according to the Donor preferences specified by the transplant centers and up-to-date Donor selection criteria. Transplant centers must have sufficient experience working in an international setting and importing stem cell products to receive basic search reports.

6.5 Cancellation / End of Donor Searches

DKMS Registry expects the transplant centers 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 Hap-E Search - DKMS Registry reserves the right to deactivate a Donor search after a reasonable time of inactivity. Deactivating in this context means that we will stop providing daily Donor updates for this search. DKMS Registry will close, archive and/or delete searches according to applicable data retention and deletion requirements.

7 Pre-workup and workup request process and requirements

7.1 Informed consent

Patient informed consent for stem cell transplantation must be obtained before initiating requests with unrelated Donors.

7.2 Facilitation of requests

Types of requests
Pre-workup and workup requests for unrelated Donor stem cell products can be requested via DKMS Registry for most WMDA-listed international registries.
The spectrum and conditions of pre-workup requests and workup requests vary amongst Donor Registries. For DKMS Donors, these are detailed in the DKMS operational user guide document (https://professional.dkms.org/services/operational-user-guide). Please refer to our specifications of services for available Donor-related requests and services. The specification of services are provided by DKMS Registry upon request.

Ensuring Donor and patient safety
Ensuring the safety of both Donors and patients is of highest priority for DKMS Registry. Consequently, requests shall be facilitated for Donor Registries that are certified by WMDA. Exceptions might be granted if the unrelated Donor and the patient are from the same country and thus fall under the same regulations. Furthermore, should an unrelated Donor be available at a Donor Registry that has not been certified by WMDA and the Donor is the only worldwide Donor listed for the patient, DKMS Registry will facilitate requests for the non-certified Donor Registry when explicitly commissioned by the transplant centers accepting the risk.

7.3 Placing requests

Requests pertaining to DKMS Donors can be placed directly on the Hap-E Search software by authorized, trained personnel from the transplant centers, while requests for Donors from other registries are facilitated by assigned search coordinators through registry-to-registry communication channels. Forms required to facilitate the requests are provided directly on Hap-E Search or via E-Mail, depending on the Donor Registry of interest.

7.4 Backup Donors

Transplant centers may request more than one Donor for HAC/VT to save time in cases where there is more than a single suitable Donor listed. This ensures that backup Donors are available for the patient at the time of workup. The number of Donors accepted for HAC/VT

requests vary from Donor Registry to Donor Registry. For DKMS Donors, these are detailed in the operational user guide document (https://professional.dkms.org/services/operational-user-guide). Transplant centers must provide information on Donor ranking (primary, secondary, etc.) if requested by the Donor Registry.
Workup is facilitated by DKMS Registry usually for only one unrelated Donor at a time, i.e., the primary Donor. A secondary Donor may be requested in case of problems / delays with the primary Donor causing a risk to the patient in compliance with providing Donor Registry policies.

7.5 Patient VT before workup

To ensure the accuracy of the HLA typing and to prevent potential complications for the patient and transplant outcome, the patient's HLA typing results must be validated through the analysis of a second, independent sample. Referred to as patient VT, the results of this HLA verification typing must confirm enough HLA loci to respond to the clinical matching requirements. The results should be available prior to workup initiation and are mandatory before Donor mobilization / collection or patient conditioning, whichever occurs first. Although high-resolution HLA typing for both tests is always preferable, patient VT can be acceptable if the patient was initially typed in low resolution and subsequently in high resolution. We recommend a minimum of HLA-A, -B, -DRB1 for one typing and HLA-A, -B, - C, -DRB1 and -DQB1 at high resolution for the other typing. It is however of utmost importance that the typing results have been confirmed at least once from independent samples to avoid fatal results to the patient in case of e.g. samples switches.

7.6 Communication of changes, cancellations and postponements of requests

- Transplant centers must be aware that some communication, specifically during workup require responses within one working day – in urgent cases within few hours.

- Any changes in the patient or search status that impact the reservation or any request of a Donor or cryopreserved product must be communicated by the transplant centers without delay. This is especially important during workup requests, before Donor physical examination, start of Donor mobilization and collection where unnecessary interventions increase the burden of the Donor and carry the risk of harm to the Donor. DKMS provides an emergency phone number for each workup These should be used by transplant centers to communicate patient development after business hours.

- Should the unrelated Donor or cryopreserved product no longer be required, transplant centers must cancel the requests accordingly. Upon cancellation, Donors become available to other patients in need. Moreover, if a donation has to be rescheduled, transplant centers can request postponement of workup. Cancellations and postponements of requests may also occur due to Donor-related reasons and these are promptly communicated to the transplant centers. Transplant centers must ensure

after-hours contacts, i.e., 24/7 emergency numbers are implemented at their institutions which can be used for urgent communications.

8 Follow-up processes

8.1 SPEAR Process

To ensure Donor and recipient health and safety, all serious adverse events and reactions of unrelated Donors or patients have to be reported to WMDA to gain insight on the occurrence of health incidents or risks. This also applies to MNC Apheresis.

Donor or donation related SAR Process

Transplant centers will be informed by the Donor Registries of serious events and adverse reactions that affect the stem cell product and potentially the patient's health. These include for example a risk of disease transmission to the recipient (e.g. infectious disease, malignancy). For DKMS Donors, these are detailed in the operational user guide document (https://professional.dkms.org/services/operational-user-guide).

Patient or product related SAR Process

Transplant centers must report an event or a reaction that may have occurred after stem cell product delivery if they qualify as Serious (Product) Event and Adverse Reaction (SPEAR) to DKMS Registry. DKMS Registry in turn will report that event or reaction to WMDA if relevant. Many Donor Registries also request for information on SPEAR directly after product delivery or as part of their follow-up process (see section 8.2). In which case SPEAR must be promptly reported as well. A SPEAR many include:

- **Any processing, labelling, handling and transport errors/problems, example:**
  - Wrong stem cell product transfused
  - Wrong stem cell product received
  - Serious problems in transportation
  - Damage to bag
  - Inadequate cell dose in the stem cell product
  - Clotting or other loss of product viability
  - Product contamination

- **Any serious unpredicted transmissible infection**, **example**:
  - HIV, Hepatitis B, Hepatitis C

- **Any serious unpredicted non-infectious transmissible disease**, **example**
  - Malignancy, auto-immune disease, congenital anomaly

- **The following do not qualify as SPEAR and need not be reported**:
  - CMV-positivity
  - EBV-positivity
  - Contamination in product without infection in recipient

8.2 Outcome reporting

According to WMDA Standards, transplant centers are responsible for reporting their patients' outcome data to a competent national and/or international authority/organization. Valid informed patient consent must be obtained prior to such reporting, conforming to all data protection policies as warranted by the outcome registry.
In addition, Donor Registries have procedures for short-term and/or long-term follow-up of recipient after donation. Such procedures are in place for quality assurance, to inform Donors of patient status, and collect basic patient outcome data. The Donor Registries contact the transplant centers directly or via DKMS Registry for this follow-up process. The required forms are provided for each patient case and transplant centers should ensure to complete these forms in a timely fashion. Such observational data are highly essential to understanding current trends and thereby improving future practices for unrelated HSCT and encouraging future altruistic donations.

9 Customs requirements

DKMS Registry is located in Germany. We do not offer services to support in any import / export and customs regulations pertinent to the country in which the transplant center is located (e.g. import of saliva and blood samples as well as cellular therapy products). Customs regulations vary greatly from country to country and transplant centers should contact their relevant airport and/or customs authorities promptly and comply with regional and national laws.

Cellular therapy products or samples may be subject to import duties and taxes, which are levied once the goods reach the designated destination.

10 Finance Requirements

10.1 Invoicing Process

Transplant centers are invoiced for the services procured through the DKMS Registry. The invoicing is carried out by the providing DKMS Donor Center or DKMS Registry in case of all other Donors from international Donor Registries. The invoices contain protected information, such as the Donor identifier (GRID) that must not be shared with patients and their family.
Prices for pre-workup requests, workup requests, postponement and cancellation depend on the providing Donor Registry. In case of DKMS Donors, the fee schedules are accessible on the Hap-E Search software at all times and all prices are stated at the time of request initiation. Pro-forma invoice (upon request) and final invoice are issued by the corresponding DKMS Donor Centers during workup.
For requests pertaining to other Donor Registries, DKMS Registry will issue a cost estimation form detailing all applicable fees. Upon acceptance of the estimate, a pro-forma invoice is issued to the transplant center. A final invoice then follows after successful completion of the

request(s), detailing all services received. DKMS reserves the right to demand advance payment in the event of payment irregularities. This may also be requested by the transplant center if needed for their processes.

10.2 Payment

Please refer to our fee schedules for details on payments. Fee schedules will be provided upon request.

11 Confidentiality requirements

According to WMDA Standards, transplant centers must maintain confidentiality of Donors and thus must not share the following with patients, relatives, and other unauthorized personnel:

- Information regarding the Donor, specifically GRID number, date of birth, and Donor Registry at which they are registered
- Contact information of Donor Registry, DKMS Group, and DKMS Registry offices and employees
- Invoices

12 Periodic news and alerts communication

DKMS Registry periodically shares unrelated HSCT relevant latest news, alerts and guidelines relevant to transplant centers using its services. This communication is undertaken to notify cooperative transplant centers on requirements and procedures and does not constitute a newsletter.