German Standards for Unrelated Blood Stem Cell Donations

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Preamble

These standards have been compiled by a Standards Committee, which is composed of representatives from the ZKRD, donor centers, search units, cord blood banks, collection centers and transplant centers. The standards apply to the essential areas of unrelated blood stem cell donor recruitment and care, the procurement and facilitation of the respective therapeutic products and the organizations involved in these processes. The standards adhere in all essential requirements to the standards of the WMDA [1].

These standards shall guarantee a high level of quality and safety as well as a uniform procedure concerning donor recruitment, testing, search, donation and transport of hematopoietic products. This helps to protect the interests of all donors and patients, and creates a better transparency for all national and international organizations involved. The German standards are binding minimum requirements, which may be handled even stricter by individual organizations. Valid laws, guidelines and contracts in the current version will remain unaffected.

These standards are revised and updated if needed at least every three years by the Standards Committee. In doing so, new medical developments and legal regulations and guidelines are to be considered as well as suggestions of the organizations, which are active in the area of donor search and donor procurement.

The organizations mentioned in the following document commit themselves to comply with the standards that apply to them.

In the following text, for reasons of better legibility, the expression “blood stem cells” is used for all hematopoietic stem cells irrespective of their origin or method of collection. If only one source is concerned, this will be expressed by using the terms “bone marrow”, “peripheral blood stem cells” (hereinafter also referred to as “PBSC”) or “cord blood”.

Binding standards have been indicated by using the imperative form or the respective form of the words “must” or “must not”. Standards containing the words “recommended”, “can” or “should” are used for recommendations.

In the whole text the masculine form is used for persons of both genders.

When forms are referred to, generally the name of the respective ZKRD form is used. Forms may be replaced by documents with an equivalent content.
1 Organizations Involved

1.1 Zentrales Knochenmarkspender-Register Deutschland (ZKRD)

1.1.1 Requirements

1.1.1.1 The ZKRD must have an organizational and legal form that guarantees proper financial and administrative operation.

1.1.1.2 The medical director of the ZKRD must be a licensed physician with the necessary professional skill in this field of activity. He must not be subjected to directives in his professional competence.

1.1.1.3 The ZKRD must have an appointed business administration manager, who has the necessary professional skill in this field of activity.

1.1.1.4 The ZKRD must guarantee continuous occupation of all essential functional units during regular office hours\(^1\), adequate in number and qualification. Outside office hours availability must be guaranteed for emergency cases.

1.1.1.5 It must be ensured that at least one person is always available who has a good spoken and written command of the English language.

1.1.1.6 The ZKRD must provide an organizational chart, on which name, task and position of all employees within the organization can be seen.

1.1.1.7 There must be adequate equipment in data system technology.

1.1.1.8 Data protection and security must be guaranteed according to Chapter 10 “Data Protection, Anonymity and Record Retention”.

1.1.1.9 The ZKRD must maintain a quality management system at least corresponding to the definition of the WMDA standards. It must ensure and document compliance with these Standards comprising especially document management, records, staff training and further education, complaint management and traceability.

1.1.2 Tasks

1.1.2.1 The ZKRD is managing a central databank containing transplantation relevant data of unrelated prospective blood stem cell donors in pseudonymous form, which is updated by the German donor centers on a regular basis.

\(^1\)If the term “regular office hours” is used in this document it means Monday-Friday 8.00 a.m. - 4.00 p.m. on working days.
1.1.2.2 Search requests for unrelated blood stem cell donors for patients in Germany and from abroad are accepted and processed by the ZKRD exclusively.\(^2\)

1.1.2.3 The ZKRD provides lists of HLA compatible donors in pseudonymous form according to the current state of the scientific and technical knowledge to the requesting organizations (search units, foreign registries, transplant centers) without delay.

1.1.2.4 The ZKRD must ensure that all its cooperative transplant centers have a corresponding qualification (refer to \(^1\[6.1\])

1.1.2.5 Upon request the ZKRD activates a donor search and obtains, where required, a confirmation from the health insurances to take over the costs for the search, submitting to them auditable documents.

1.1.2.6 The ZKRD accepts requests for further typing and the shipment of blood samples, checks, if they are complete and plausible and forwards the requests to the appropriate donor centers and foreign registries.

1.1.2.7 The ZKRD reports incoming test results to the relevant institutions without delay.

1.1.2.8 The ZKRD does the billing of all services within the donor search with the relevant payers at home and abroad.

1.1.2.9 The ZKRD guarantees immediate handling and forwarding of all important processes within the donor search and donor procurement.

1.1.2.10 The ZKRD ensures documentation of all essential processes within the donor search.

1.1.2.11 The ZKRD enhances cooperation of all institutions involved in the donor search.

1.1.2.12 The ZKRD coordinates and leads the negotiations with the head organizations of the compulsory health insurances in the Project Committee (Projektkommission) \(^23\).

1.1.2.13 The ZKRD fulfills the tasks of a national registry according to the WMDA recommendations. \(^17\), \(^18\), \(^19\), \(^20\), \(^21\).

1.1.2.14 The ZKRD is responsible for all customs declarations for transplants from non-EU countries (third countries) imported into Germany and coordinates these with the transplant centers. The responsibility of the declaration of German transplants being exported into third countries lies with the economic owner at the time of export. The ZKRD holds a license for a simplified import process of transplants for German transplant centers. Regarding export, the ZKRD is classified as a licensed exporter and, therefore, has the right to utilize a simplified export process.

### 1.2 Donor Centers

#### 1.2.1 Requirements

1.2.1.1 The donor center must have an organizational and legal form that guarantees proper financial and administrative operation.

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\(^2\)Existing contracts with the NMDP concluded up to 2000-01-01 remain unaffected.

\(^3\)DRB1 typing performed free of charge by the donor centers upon request of a search unit while a donor search is active via the ZKRD is not affected thereby.
1.2.1.2 The donor center must have a medical director who is a licensed physician with the necessary professional skill in this field of activity. It must have a managing director or administrative director who is responsible for the organizational tasks in the donor center. It is possible that one person holds both the medical and the administrative position.

1.2.1.3 The donor center must appoint a person who is qualified in psychological care and counseling, who counsels the donors as a donor advocate, if required. This person shall not be affiliated with the donor center nor an institution that is caring for patients or be biased by a conflict of interests.

1.2.1.4 The personnel responsible for the education, recruitment and counseling of blood stem cell donors is subject to supervision by the medical director and must be knowledgeable of the essential processes involving donor search and blood stem cell transplantation.

1.2.1.5 The donor center must provide continuous staff coverage with qualified personnel, at least during regular office hours.

1.2.1.6 It must be ensured that during regular office hours at least one person is available, who has a good spoken and written command of the English language.

1.2.1.7 The donor center must have documentation on names, function and position of all employees within the organization.

1.2.1.8 The donor center must guarantee storage of all personal and transplantation relevant donor data as well as the transmission of donor data and test results according to the current state-of-the-art technology. For these purposes the donor center must have adequate IT support.

1.2.1.9 The donor center must have an HLA-A,-B typed file of at least 5,000 donors. Donor centers founded before January 1st, 2006, and which have continuously been operated independently are exempt.

1.2.1.10 Data protection and security must be guaranteed according to Chapter 10 “Data Protection, Anonymity and Record Retention”.

1.2.1.11 The donor center must maintain a quality management system that corresponds to the minimum requirements regarding a quality management system for the respective institution according to the definition of the WMDA standards. It shall particularly comprise standard operating procedures (SOPs) and records, staff training and further education, complaint management and traceability, and it shall document compliance with these Standards.

1.2.2 Cooperation with Other Organizations

1.2.2.1 All organizations (laboratories, collection centers, transplant centers, search units and the ZKRD) cooperating with the donor center must comply with the standards defined for them.

1.2.2.2 A cooperative agreement between the ZKRD and the donor center must be in place.
1.2.2.3 A cooperative agreement must be made between the donor center and the collection centers and the donor center must ensure, that the collection center follows the applicable laws, guidelines and regulations. It is recommended that the collection center works towards a JACIE accreditation.

1.2.2.4 The donor centers cooperate in a constructive way with all organizations involved to achieve common aims.

1.2.3 Tasks

1.2.3.1 The donor center is responsible for the recruitment, education, registration and counseling of the donor, as well as for the organization of HLA typing and further testing.

1.2.3.2 The donor center must update the donor data reported to the central registry on a continuous basis, as well as take suitable measures to keep the donors motivated.

1.2.3.3 The donor center must take suitable measures to safeguard the interests of the donor and to protect him from unjustified demands.

1.2.3.4 The donor center reports to the ZKRD on a continuous basis the performed or cancelled blood stem cell collections, indicating donor and patient numbers, the product type and the collection date. Further information may be necessary according to the current specifications of the WMDA, which the donor center will be notified of in due time.

This data is used by the ZKRD for statistical purposes, summary reporting within existing contracts and cooperations, as well as for the generation of match lists only.

1.2.3.5 Further tasks of the donor center are listed under Chapter 2 to 10.

1.3 Search Units

1.3.1 Requirements

1.3.1.1 As a general rule the search unit is affiliated to a transplant center, university clinic or an institution specialized in transfusion medicine. It must provide sufficient room and staff and be delimited from the other activities.

1.3.1.2 The search unit must have a medical director, who is a licensed physician with the necessary professional skill in this field of activity.

1.3.1.3 The search unit must ensure continuous staff coverage with qualified personnel.

1.3.1.4 During regular office hours at least one person must be available, who has a good spoken and written command of the English language.

1.3.1.5 The search unit must be adequately technically equipped for national and international data exchange.

1.3.1.6 It must coordinate unrelated donor searches for at least 20 patients per annum.

1.3.1.7 Data protection and data security must be guaranteed according to Chapter 10 “Data Protection, Anonymity and Record Retention”.

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1.3.1.8 The search unit must maintain a quality management system that corresponds to the minimum requirements regarding a quality management system for the respective institution according to the definition of the WMDA standards. It shall particularly comprise standard operating procedures (SOPs) and records, staff training and further education, complaint management and traceability, and it shall document compliance with these Standards.

1.3.2 Cooperation with Other Organizations
1.3.2.1 The search unit must maintain regular information exchange with the ZKRD.
1.3.2.2 All organizations cooperating with the search unit must comply with the standards defined for them.
1.3.2.3 A cooperative agreement between the ZKRD and the search unit must be in place.

1.3.3 Tasks
1.3.3.1 The search unit initiates the search for an unrelated donor for patients with an indication for blood stem cell transplantation according to the search request form (attending physician, transplant center) with the aim to identify a suitable donor.
1.3.3.2 It must guarantee a continuous exchange of information in adequate time intervals with the attending physician of the responsible transplant center about the status of the donor search and the continuity of the indication.
1.3.3.3 It must, in consultation with the immunogenetics laboratory, guarantee the storage of cell/DNA samples from donors selected for transplantation and from patients for quality control and scientific analysis for at least five years. In the case of scientific analyses from blood samples, an approval of the ethics committee and the respective informed consents must be in place.
1.3.3.4 Further detailed tasks of the search unit are listed under Chapter 4.

1.4 Cord Blood Banks

1.4.1 Requirements
1.4.1.1 The cord blood bank must have an organizational and legal form that guarantees proper financial and administrative operation.
1.4.1.2 The cord blood bank must meet all requirements of the German Drug Law (AMG) [8] and the German Good Manufacturing Regulation (AMWHV) [14].
1.4.1.3 The cord blood bank must have a manufacturing license according to the German Drug Law (AMG) [8] and a medicine product authorization of the Paul-Ehrlich-Institute (PEI).
1.4.1.4 The spatial, technical and hygienic requirements for the drawing, manufacturing and quality controlling of cord blood units must follow the current state-of-the-art technology. The external collection centres (maternity clinics) must also meet the spatial, technical and hygienic requirements.
1.4.1.5 The cord blood bank must have a medical director, who is a licensed physician with the necessary professional skill in this field. It must have a managing or administrative director, who is responsible for the organizational tasks in cord blood bank. It is possible that one person holds both the medical and the administrative position.

1.4.1.6 The cord blood bank must provide continuous staff coverage with qualified personnel, at least during regular office hours. It must be ensured that during regular office hours at least one person is available, who has a good spoken and written command of the English language.

1.4.1.7 The personnel assigned with the education, recruitment and counselling of cord blood stem cell donors is subject to supervision by the medical director and must be conversant with the essential processes within the cord blood search and blood stem cell transplantation. Job training and further education must be documented.

1.4.1.8 The cord blood bank must have an organisational chart on which all cooperating organizations (maternity clinics, laboratories) and all staff members with name and function are shown. Detailed job descriptions must be available.

1.4.1.9 The cord blood bank must guarantee storage of all personal and transplantation relevant donor data as well as the transmission of donor data and test results according to the current state-of-the-art technology. For these purposes the cord blood bank must have adequate IT support.

1.4.1.10 Data protection and security must be guaranteed according to Chapter 10 “Data Protection, Anonymity and Record Retention”. Cord blood units must be identified in a way that an assignment to donor and patient is possible within 30 years post transplantation.

1.4.1.11 The cord blood bank must maintain a quality management system that corresponds to the minimum requirements regarding a quality management system for the respective institution according to the definition of the WMDA standards. It shall particularly comprise standard operating procedures (SOPs) and records, staff training and further education, complaint management and traceability, and it shall document compliance with these Standards.

1.4.2 Cooperation with Other Organizations

1.4.2.1 All organizations (laboratories, collection centres, transplant centres, search units and the ZKRD) cooperating with the cord blood bank must comply with the standards defined for them.

1.4.2.2 The cord blood bank must have cooperative agreements with all cooperating organizations.

1.4.2.3 A cooperative agreement between the ZKRD and the cord blood bank must be in place. It may be integrated in an agreement between the ZKRD and the respective donor center.
1.4.3 Tasks

1.4.3.1 The cord blood bank must update the data of the cord blood units reported to the central registry on a continuous basis.

1.4.3.2 Before the donation the mother must be informed in writing about the whole process, especially benefits, risks, data-protective aspects and alternatives to cord blood donation. The kind of laboratory tests of the mother and the baby must be discussed. The mother must be informed explicitly about the right to receive the test results and the right to withdraw at any time. The cord blood bank must obtain a written informed consent of the adult mother.

1.4.3.3 A medical examination of the pregnant woman must be performed and documented. The following items must be considered: Process of pregnancy, risk of transmissible diseases of the mother, genetically determined diseases of the hematopoietic system in the family. Abnormalies during birth and diseases or deformities of the child must be documented. A hemoglobinopathy testing must be performed on a CBU sample before releasing the cord blood unit.

1.4.3.4 All laboratory tests on maternal blood must be performed on samples collected within 48 hours of delivery according to the directives of the Paul-Ehrlich-Institute. From fresh blood of the baby the following tests must be performed: blood group testing AB0 group and rhesus type), CMV by molecular biology testing, and HLA-A, -B, -DRB1 by molecular biology testing in an EFI- or ASHI-accredited laboratory.

1.4.3.5 If relevant positive infectious disease marker testing results or other extraordinary results are determined, the mother must be informed and counselled by a physician.

1.4.3.6 The identity of the cord blood unit must be checked using a validated process before shipment.

1.5 Collection Centers

1.5.1 Centers collecting, manufacturing or distributing hematopoietic stem cell products from peripheral blood or bone marrow must possess the respective manufacturing license according to the German Drug Law (AMG) corresponding to §13 or §20b/c, respectively, as well as a permit from the federal authority according to §21a AMG for direct application in a known individual. Furthermore, they must observe the applicable laws, guidelines and regulations in their current versions. [2], [4], [7], [8], [9], [10], [11], [12], [14], [22].

1.5.2 A cooperative agreement between the ZKRD and the collection center must be in place.

1.5.3 Data protection and data security must be guaranteed according to Chapter 10 “Data Protection, Anonymity and Record Retention”.

1.6 Transplant Centers

1.6.1 Transplantation of blood stem cell products from unrelated donors may only be performed in centers that possess the required expertise [2] and report their transplant
data to the DRST. The ZKRD verifies the criteria before starting a cooperation and periodically thereafter. It is recommended to achieve JACIE accreditation[^25] within two years after commencing with these transplant services, at the latest.

1.6.2 A transplant coordinator who is considered as contact person must be appointed and is responsible for contact with the cooperation partners.

1.6.3 The transplant center must annually report to the ZKRD the number of unrelated blood stem cell transplants according to the specifications of the WDMA.

1.6.4 The transplant center must be in possession of all licenses required by law and must observe all applicable regulations, laws and guidelines[^2],[^5],[^9].

1.6.5 A cooperative agreement between the ZKRD and the transplant center must be in place.

1.6.6 Data protection and data security must be guaranteed according to Chapter[^10] "Data Protection, Anonymity and Record Retention”.

### 1.7 Laboratories

#### 1.7.1 Immunogenetics Laboratory

1.7.1.1 A laboratory performing histocompatibility tests in the area of blood stem cell donation (immunogenetics laboratory)

- must be accredited by EFI or ASHI in the category bone marrow and blood stem cell transplant respectively,
- must as a matter of principle be in a position to meet the listed requirements of the current consensus of the DGI and the DAG-KBT[^15],[^16].

1.7.1.2 An immunogenetics laboratory that performs primary testing of patients as well as confirmatory and compatibility tests of donors and patients must in addition to 1.7.1.1 also meet the methodology requirements to identify newly defined and for allogeneic blood stem cell transplant relevant alleles according to the state of the scientific knowledge.

1.7.1.3 An immunogenetics laboratory performing the tests at recruitment must have an EFI or ASHI accreditation in the category “Donor Registry”. If there are additional tests of the donor to be done in this laboratory (HLA-A, -B, -DR, high resolution, etc.), the laboratory must have an EFI or ASHI accreditation for this technical category as well.

1.7.1.4 Data protection and data security must be guaranteed according to Chapter[^10] “Data Protection, Anonymity and Record Retention”.

#### 1.7.2 Laboratory for Blood Group and Infectious Disease Marker Testing

A laboratory that performs ABO/Rh typing and/or infectious disease marker testing
- must meet all criteria of the current guidelines given by the German Medical Association. Applicable are the “Guidelines for the Preparation of Blood and Blood Components and for the Use of Blood Components (Hemotherapy)” [7], as well as the “Guidelines of the German Medical Board for Quality Assurance of Quantitative Medical Laboratory Tests” [3] in the version valid at the time.

- must provide evidence of having regularly and successfully participated (as a rule four times a year) in appropriate external interlaboratory testing for all parameters tested.

- must guarantee data protection and data security according to Chapter 10 “Data Protection, Anonymity and Record Retention”

Infectious disease marker testing required for donor and product release must be performed in a laboratory licensed or accredited for these diagnostics.
2 Donor Registration

2.1 Information

Comprehensive information must be provided to the donor prior to registration. Information may be given through literature or in person by donor center staff. This also applies to the biological mothers prior to cord blood donation.

The information must contain the following items:

2.1.1 Reasons for the search for voluntary blood stem cell donors.

2.1.2 Methods of sample collection, i.e. blood sample collections or buccal swabs for HLA testing; the donor must be advised that further sample collections and testing may be necessary in future.

2.1.3 Information about possible storage of donor samples.

2.1.4 Information that a medical examination will be performed prior to blood stem cell donation.

2.1.5 Methods of blood stem cell donation, their risks and possible side effects.

2.1.6 Anonymity of donation (see Chapter 8.2 and 10.2).

2.1.7 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. The donor is not remunerated for the donation.

2.1.8 Voluntary nature of the donation and right of withdrawal at any time.

2.1.9 Registration with the intention of a directed blood stem cell donation is not permissible.

2.1.10 Transmission of HLA typing results and other data important for donor selection in pseudonymized form to national and international registries and search units.

2.1.11 Avoiding registration with multiple donor centers at the same time.

2.2 Requirements

2.2.1 The donor must be at least 18 years old.

2.2.2 The donor is deleted from the national registry at his 61st birthday. The donors should be informed accordingly by the donor center.
2.2.3 The donor must assure to be healthy to the best of his knowledge and does not suffer from any of the following diseases:

- severe cardiovascular diseases
- severe pulmonary diseases
- severe kidney diseases
- severe neurological diseases
- severe metabolic diseases
- severe tropical diseases and severe chronic infectious diseases
- infections with HIV, hepatitis B or C, HTLV, Syphilis (also of a sexual partner)
- systemic autoimmune diseases or other severe chronic diseases
- cancer
- severe illness of the blood or immune system
- severe psychological disorders

2.2.4 Further conditions for cord blood donations are:

- The biological mother must be able to understand the medical history questionnaire and the information regarding language and content without being distracted by aspects of labor.

- A written medical history by means of a standardized questionnaire must be obtained and carefully evaluated.

2.3 Donor Consent

2.3.1 The consent form signed by the donor must contain the following items:

- Consent to store his personal data in the data bank of the donor center.

- Confirmation of receipt of information on the donation (including items 2.1.1–2.1.10, see above) and confirmation that this information has been understood.

- Consent to forward all data relevant to the search via the ZKRD to national and international registries and search units.

- Confirmation that the exclusion criteria are known.

- Consent to store and possibly test samples at a later date.

- Consent for inquiries at the registration of address office by the donor center.
• Additionally to the first five sub points the following apply to cord blood: The biological mother confirms in writing that she transfers the ownership rights of the collected cord blood to the cord blood bank and that she does not claim it for herself.

2.3.2 A written confirmation of the registration must be given to the donor. It is recommended to give the donor a copy of his signed consent form.

2.4 Further Procedures

2.4.1 The blood collection required for registration and subsequent HLA typing must be carried out by a physician or under the supervision of a physician.

In case of a cord blood donation, the blood samples may also be drawn by an authorized person of the maternity room (e.g. midwife).

2.4.2 The donor center ensures that the samples drawn from the registered donor are normally HLA-A, -B and -DRB1 typed within three months and the donor’s data are forwarded to the ZKRD without delay. All typings must be performed by methods of molecular biology. Within the documentation, serologic data must not be derived from molecular biologic tests or vice versa. When registering cord blood units, the size of the preparation (total nucleated cell count, TNC) must be specified.

2.4.3 It is recommended that the donor is contacted annually, and the return information is documented. Every five years at the latest, the contact data must be checked and documented.

Regular contact with the biological mothers who have agreed to the donation and storage of cord blood units is not required.

2.4.4 The regulations of data protection according to the Federal Data Protection Law must be observed (see Chapter 10 “Data Protection, Anonymity and Record Retention”).
3 Donor Testing

3.1 General

In case of adequate compatibility of the patient and potential donor HLA types the donor center is assigned with the organization of further donor testing via the ZKRD. The reservation concept generally only allows for testing requested with regard to the same patient. The ZKRD system supports this concept through extensive plausibility checks, but currently double registrations of donors cannot be excluded because of the donor data pseudonymisation. As soon as one suspects that a donor might be registered more than once, the ZKRD must be informed immediately. Testing twice for the same patient or parallel CT testing for different patients should be avoided for donor safety reasons.

3.2 Extent and Method of Donor Testing

3.2.1 The donor center must be able to have at least the following tests performed: HLA-class I, HLA-class II, DNA-based testing by molecular biology, at a low- to high resolution level.

3.2.2 If a stored sample is used for testing, the donor must be informed. The donor need not be informed when testing is performed on stored samples during the manufacturing process of cord blood products.

3.2.3 Testing of blood and rhesus types (AB0, RhD) and infectious disease markers (Lues, HBsAg, anti-HBc, antibodies to HIV1, HIV2, HCV and CMV) is performed at CT stage.

3.2.4 Manufacturing and examination of cord blood products is subject to the requirements of the German Medical Association and the Paul-Ehrlich-Institut. They also apply to the diagnostic methods used when examining the infectious disease markers of the pregnant woman and the fetus (cord blood) as well as to haemoglobinopathy testing.

3.3 Confirmatory Typing (CT)

The donor center organizes donor blood sample collection for confirmatory typing (CT) and the accompanying tests as well as the transport of the blood samples to the respective laboratories.

3.3.1 At the time of a CT sample request, a donor information session must be performed. Furthermore, the following must be obtained:
- Donor health history questionnaire (see Appendix B)
- Donor signed consent form (see Appendix B).

3.3.2 A physician should evaluate the donor health history questionnaire. In addition to the CT questionnaire evaluation form from the ZKRD, the WMDA homepage [27] gives detailed information. Any abnormal findings that do not lead to donor deferral must be reported to the search unit via the ZKRD.

3.3.3 ABO/Rh typing and infectious disease marker testing (see 3.2.3) must be arranged by the donor center at the time of CT blood sample shipment. Testing of infectious disease markers must always be performed on fresh blood samples and evaluated by a physician. In case of cord blood units, testing is performed on a stored sample, if possible, on an attached segment.

3.3.4 The maximum blood sample volume that is shipped to the search unit for confirmatory testing is 50 ml. Additionally, up to 10 ml blood is sent to the donor center laboratory for ABO/Rh typing and infectious disease marker testing.

3.3.5 CT blood samples must not be used for research. According to a WMDA recommendation [28], a donor is regarded as a study object if additional data or samples are collected only for research purposes. If a donor shall become a study object, the study number, the title of the study, the synopsis and the approval of the ethics committee as well as the respective informed consent form in German must be provided to the donor centre and the ZKRD. After education, the donor may give his or her written informed consent. If a blood sample is to be used for research purposes, these must be specified and the donor center must be informed via the ZKRD. The donor’s written informed consent must be obtained prior to using blood samples for research. The principal investigator must provide the study number, the title of the study, a synopsis and the approval of the ethics committee.

3.3.6 The blood tubes must be labeled with the donor and patient number and the collection date. Packaging and shipment must meet the regulations of the International Air Transport Association (IATA-DGR) regarding shipment of dangerous goods.

3.3.7 The potential donor is reserved by the ZKRD for 60 days after the date of blood sample collection.

3.3.8 The temporary or permanent unavailability of a donor or a cord blood unit must be immediately reported via the ZKRD to the requesting search unit.

3.3.9 The medical director of the donor center or his/her authorized representative must inform the donor of abnormal infectious disease marker results and possible follow-up testing.

### 3.4 Confirmatory Typing Results

3.4.1 In case of discrepancies between the HLA typing results, a definite resolution of the discrepancy must be obtained. In case of a continuing discrepancy, repeat testing on
a fresh donor sample (e.g. blood sample or buccal swab) and a stored cord blood sample, respectively must be performed. The donor and the cord blood unit, respectively are temporarily deferred during this time. All organizations involved must be informed about the result of the repeat testing.

3.4.2 In case the search unit provides concordant HLA typing results of a higher resolution level, the donor center must upgrade the donor typing accordingly.

3.4.3 When reporting results of confirmative typing, the donor can generally be reserved for a 3-month time period. An extension can be granted by the donor center to accommodate changes in the patient’s medical status.
4 Donor Search

4.1 General

4.1.1 The search request is made by a transplant center or the patient’s attending physician in agreement with a transplant center.

4.1.2 The search unit has to assure itself of the necessity of extending the search to unrelated donors by obtaining documentation of the unsuccessful family search.

4.1.3 Before initiating an unrelated search, two HLA typing results of separately drawn patient blood samples must be available. One of these HLA typings must be performed by an immunogenetics laboratory on behalf of the search unit. These tests must be performed at a level of resolution as defined in the current contracts and agreements.

4.1.4 When initiating the search, the following documentation must be available to the search unit and the ZKRD:

- Medical report on the indication for transplantation
- Patient informed consent including information on patient’s health insurance
- Guarantee of payment form signed by health insurance or patient (submission to the ZKRD only).

The medical report and the patient informed consent may not be older than three months. If the search continues or is resumed, the medical report must be reissued after twelve months and the transplant center must verify that the patient informed consent has been reconfirmed.

4.1.5 The medical director of the ZKRD or a person authorized by him verifies the indication for the unrelated donor search. In case the blood stem cell transplantation is considered a developmental therapy whose efficacy is being assessed in clinical studies, the ZKRD must be provided with the clinical protocol and its approval by the ethical committee. In urgent cases, the latter can be submitted later.

By activating the search for a German patient the ZKRD confirms search cost coverage. This implicates no claim for refunding by the German compulsory health insurances.

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4 At least one HLA-A,-B,-C,-DRB1 and DQB1 testing must have been performed by molecular biology at high resolution level.
4.2 Search Procedure

4.2.1 The exchange of data on the national and international level must take place via the ZKRD.

4.2.2 The search strategy must be agreed upon and documented by the search unit and the responsible physician of the transplant center. It should be known if also cord blood units are to be included in the search.

4.2.3 The responsible physician of the transplant center has to instruct the search unit in writing about search strategy changes.

4.2.4 Confirmatory testing of potential donors must be performed according to the HLA typing requirements and resolution levels as defined in the current consensus of the DGI and the DAG-KBT [15], [16].

When releasing a donor, part of the typings is sufficient. However, one locus must basically be completely typed.

If confirmatory testing of cord blood is done, a complete typing result (HLA-A, -B, -C, -DRB1 and -DQB1, molecular biology, high resolution) is always to be delivered (independent from release or reservation request).

4.2.5 The CT typing result must be forwarded immediately via the ZKRD to the donor center and it must be indicated if the donor is to be reserved for the patient concerned.

4.2.6 The director of the accredited HLA laboratory evaluates the HLA compatibility of donor and patient and provides a written report to the attending physician and the transplant center, respectively.

The transplanting physician is responsible for the final selection of the donor.

4.3 Search Cancellation

The search must be cancelled immediately for the following reasons:

- Patient’s death
- Discontinuation of indication.

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[5] This does not apply for contracts with the NMDP concluded before January 1, 2000.
[6] HLA-A,-B,-C,-DRB1 and -DQB1, HLA-typed by molecular biology at high resolution level.
5 Requesting and Preparing Blood Stem Cell Donations (Donor Work-up)

5.1 Work-up Request

5.1.1 After the availability of the results of donor confirmatory and infectious disease testing and other transplant-relevant data, the transplant center decides if the donor is acceptable. The transplant center requests this donor for blood stem cell donation as described in 5.1.2.

In case of cord blood transplant, the selected cord blood unit is requested and its transport is organized.

5.1.2 It is recommended to send work-up requests including all associated correspondence to the respective cooperative partner via the ZKRD. If the request is sent directly to the donor center, the ZKRD must receive a copy of the request from the transplant center.

5.1.3 The request of a donor work-up including communication of important data is done with the ZKRD forms WU_001 and WU_002. The ZKRD forms WU_003, WU_004 and WU_005 are used as the medical prescription (see Appendix B). Cord blood units are requested using ZKRD form CB_003 as the medical prescription.

5.1.4 The requested cell dose should at least correspond the minimum cell counts mentioned in the current guidelines [2]. The transplant center must justify requests of much higher cell counts.

5.1.5 For non-standard diagnoses (see [6]), a copy of the clinical study protocol and its approval by the responsible ethical committee must be provided. The medical director of the donor center or cord blood bank or their authorized representative must agree.

5.1.6 Parallel work-up requests of different donors for the same recipient are generally not allowed. If parallel work-up requests should become necessary in justified exceptional cases the ZKRD, the donor centers and the donors involved must be informed and must agree.

5.1.7 A blood stem cell request without prior CT testing of the respective patient/donor pair should only be considered if particular urgency is documented or if at least two concordant CT results are on record for the donor. In individual cases, a parallel request is possible if the following conditions are fulfilled:
• The patient’s search must be “active”.

• The patient must be registered with high resolution HLA at all 5 loci, which also applies to foreign patients.

• The donor’s HLA must have been confirmed at high resolution from at least one fresh blood sample (e.g. as CT for a different patient).

• For an especially urgent parallel request, the donor’s HLA at the loci A, B and DR must have been tested using molecular biology testing and the probability for a 9/10 match must be at least 90% in addition to the conditions previously listed. Additionally, further acceptance criteria (e.g. CMV, accepted HLA differences) must be taken into account.

The parallel request of a CT and a blood stem cell donation must be submitted via the ZKRD.

The following reasons may justify a parallel request of a CT and a blood stem cell donation with special urgency:

• donor deferral during a work-up

• primary or secondary graft failure

• urgent need of transplantation due to failure of induction therapy or known high-risk leukaemia

• relapse

In the case of a parallel request of CT and blood stem cell donation, the donor has only a short time to decide about the donation. This fact must especially be taken into consideration during counseling (see chapter 5.3).

5.1.8 In exceptional cases, cryopreservation of a blood stem cell product at the transplant center prior to the beginning of the recipient conditioning therapy may be requested. The medical director of the donor center or his authorized representative must review and document these requests.

5.2 Donor Insurance

5.2.1 The donor center must arrange a procurement of an accident, life and disability insurance contract for the donor.

5.2.2 The donor should obtain a copy of the insurance policy.

5.3 Donor Information

5.3.1 The donor must be informed of at least the items in Appendix C.1

5.3.2 Before the physical examination at the collection center, the donor must have been given information on the procedures of work-up and collection by an appropriately
5.3.3 The donor information session about the blood stem cell donation and its risks and side effects must be performed and documented by the collection center physician.

5.3.4 The donor information session about the risks and side effects of anesthesia for bone marrow collections must be performed and documented by an anesthesiologist or a physician of the department of anesthesia.

5.4 **Donor Medical Evaluation**

5.4.1 The donor medical evaluation must cover at least the items in Appendix C.2.

5.4.2 The donor medical evaluation must be performed at a collection center designated by the donor center.

5.4.3 A physician who must not be member of the transplant team or the team directly in care of the recipient determines the donor eligibility for blood stem cell donation.

5.4.4 The donor eligibility for anesthesia for bone marrow collections must be determined by an anesthesiologist or a physician of the department of anesthesia.

5.4.5 The donor clearance for blood stem cell donation must be performed by a qualified physician from the collection/apheresis center [7]. Verification of the corresponding data by a second person is recommended. After being signed by the physician, the donor clearance is transmitted to the partners involved (WU_009).

5.5 **Donor Informed Consent**

5.5.1 By signing the consent form the donor confirms to be informed of the preparations for and the procedures of collection and the associated risks including the consequences for the recipient if he withdraws his consent to donate after the beginning of the recipient conditioning therapy. The donor confirms in writing that he has understood the information provided and that all his questions have been fully answered.

5.5.2 If the medical evaluation reveals that a central venous line cannot be excluded, a sonographic evaluation is recommended. If a central venous line still cannot be excluded, the donor should only be cleared for bone marrow donation or a different donor should be searched for. In documented exceptions, an apheresis with a central venous line may be planned at the time of medical evaluation if the donor gives his written consent and also consents to cryopreservation of the preparation if the transplant center wishes.

If an insufficient venous situation for a peripheral donation becomes apparent only just at the day of apheresis, a central venous line may be placed under clinical conditions as a documented, justified exception. A central venous line should only be placed for one-day aphereses. As site of insertion, the femoral vein should be preferred. The donor’s written informed consent is necessary.
5.5.3 On the day of the medical evaluation for peripheral blood stem cell apheresis, it must be documented if the donor generally consents to a bone marrow collection if the mobilization or collection does not proceed as planned. If the donor declines a bone marrow collection in the emergency mentioned above, the donor’s written consent for cryopreservation of the peripheral blood stem cell product must be obtained prior to the beginning of the patient conditioning. Additionally, these circumstances must be communicated to the transplant center immediately for approval of the proceedings.

5.5.4 If it is planned to cryopreserve the blood stem cell product, the donor must be informed of the possibility that the product may not be used and may be discarded. Without the donor’s written consent, the product may not be cryopreserved.

5.5.5 The donor’s written consent indicates that aliquots of the preparation may be cryopreserved at the transplant center for a subsequent infusion at a later date if more blood stem cells were collected than needed for the recipient. If the donor does not agree, the transplant center must be informed. The donor consents to the disposal of the product if it is no longer needed for the recipient.

5.5.6 If a transplant center wishes to use blood samples, product parts or data collected as a part of the donation for scientific purposes in an anonymous way, the specifications in chapter 3.3.5 apply. After being informed accordingly, the donor can give his or her written informed consent.

5.6 Procedures

5.6.1 The transplant center is informed in writing in a timely manner of the receipt of the donor request as well as the planned schedule (see data in WU_041).

5.6.2 If stem cells or cell products are requested from an unrelated donor of a foreign registry, the transplant center can ask the ZKRD to request licensure documents and GMP certification of the respective foreign institutions.

5.6.3 The transplant center must be informed as early as possible if the requested cell dose is not feasible based on the experience at the collection center. At the time of donor clearance at the latest, the donor center must initiate the verification of the prescription (ZKRD Forms WU_007, WU_008 or WU_021, respectively – Appendix [9]).

5.6.4 The donor center must inform the transplant center if they are unable to collect the requested volume of the pre-collection donor blood samples (maximum 50 ml) or the donor peripheral blood samples on the day of collection.

5.6.5 After the receipt of the donor clearance for blood stem cell donation (ZKRD Form WU_009) including the collection date as confirmed by the donor center, the transplant center must confirm in writing the collection date, the start date of the recipient conditioning therapy and the transplant date.

5.6.6 Health issues arising during the medical examination which prohibit donor clearance or permit donor clearance by exception only must be communicated in written form to the transplant center (WU_043 or WU_038 as applicable).
5.6.7 The recipient conditioning therapy must not be initiated until donor clearance for blood stem cell donation including the results of the donor infectious disease testing have been reported in writing to the transplant center (WU_009).

5.6.8 Donor G-CSF injections must not begin until the transplant center has confirmed the collection date.

5.6.9 If the collection or transplantation is cancelled, the transplant center and the donor center respectively must ensure in writing that the cancellation request has arrived at the appropriate center, even if a consultation by phone preceded.

5.6.10 At the latest at the time of donor clearance for blood stem cell donation, the donor center must inform the donor of an emergency telephone number.

5.6.11 The organizations involved in the coordination of work-up, blood stem cell collection and transplant must exchange emergency telephone numbers.

5.6.12 The ZKRD should be copied with the data and communication of work-up and blood stem cell collection if the work-up is not coordinated by the ZKRD.

5.6.13 The decision regarding the number of aphereses is the responsibility of the collection physician. If the recommended minimum dose\(^7\)\(^2\) is reached or, if a higher dose is requested and the cell dose collected is less than 10% below the requested dose, the transplant centre should not be consulted and the collection should be concluded\(^8\).

5.6.14 Parts of the preparation can be cryopreserved for later therapeutic use for the same patient. One donor’s cell product is solely destined for the therapy of a specific patient. A whole or partly cryopreservation of the cell product can only be performed with the donor’s written consent. It may only be used as a whole or in parts for research purposes in ethically approved studies with the donor’s written consent. In case the purpose is no longer given, the preparation has to be discarded. This applies to cord blood preparations analogously pursuant to the “NetCord-FACT International Standards for Cord Blood”\(^26\). The donor center must be informed in detail of the processing of the product.

5.6.15 On the day of collection, in addition to the guideline-conform infectious markers\(^7\), the following laboratory parameters are to be performed by the collection unit at a minimum:

- before every PBSC apheresis after G-CSF stimulation: blood count (automated), sodium, potassium, calcium
- before every bone marrow collection or non-stimulated apheresis: blood count

For estimation of the apheresis time, before every first PBSC apheresis after G-CSF stimulation, it is recommended to evaluate the amount of CD34 positive cells in the peripheral blood. Additional blood examinations fall to the physician’s responsibility and the individual donor situation.

\(^7\)status 2017-05-10: 4 x 10\(^6\) CD34 positive cells/kg recipient weight
\(^8\)The reverse is NOT applicable - of course the collection physician must always decide about continuing or concluding the collection in terms of the donor, independent from the requested cell number.
Information pertaining to post-donation donor testing is included in chapter 8.3.

5.6.16 The donor center must inform the transplant center if the results of infectious disease marker testing on the day of collection differ from those determined during medical evaluation.
6 Multiple Donations/Multiple Transplantations

6.1 Multiple Donations

6.1.1 These standards do not apply to cord blood donations. These standards apply to second and subsequent blood stem cell donations (marrow, peripheral blood stem cells) or other blood product donations (donor lymphocytes, whole blood) of a specific donor for a recipient.

6.1.2 After the first donation the donor is reserved for two years for the initial recipient in order to be available for a subsequent donation. During this time the donor is not available for another patient.

6.1.3 After the first donation the donor is asked whether he is available for a subsequent donation for the same recipient if needed. The answer is documented.

6.1.4 Because of the clinical situation, minimum time intervals between donations cannot be defined.

6.1.5 The results of the medical evaluation (section 5.4) in the normal range are a basic requirement for a subsequent donation. The donor has to be reserved for the patient he donated to for at least two years. In the case of the patient's death the donor is to be barred for a year after donation.

6.1.6 A donor who has already donated must not be asked to donate for a second recipient unless no equally compatible donor is available. In such a case, a review by the ZKRD is mandatory.

6.1.7 A donor may generally donate twice, either for one patient or for two different patients. After a donor has donated twice, it is recommended not to make them available for further donations except lymphocyte donations. A further stem cell donation shall only be permitted in cases of urgent medical need, and even then more than two of the same type of donation (bone marrow or PBSC) are not permitted. The ZKRD must review these cases (see 6.1.6).

6.2 Multiple Transplantations

6.2.1 The transplant center must outline in writing the clinical justification for a further blood stem cell donation for a patient who already received an allogeneic transplant. The medical director of the donor center or the authorized representative must review
the request. This regulation is valid regardless of whether the previous transplantation was carried out with blood stem cells from the same (WU_017) or a different donor (informal justification).

6.2.2 The written request must include:

- Proposed time frame for transplantation
- Recipient’s preparative therapy plan if applicable
- Data from previous transplant and the current clinical condition of the recipient
- Request forms for bone marrow or peripheral blood stem cells: ZKRD forms WU_003 or WU_004, WU_017
- Request forms for donor lymphocytes: ZKRD forms WU_001 and WU_005

6.2.3 For non-standard indications or therapies whose efficacy is being assessed in clinical studies, the transplant center must provide a copy of the clinical study protocol and its approval by the responsible ethical committee.

6.3 Procedures for further Requests

6.3.1 Peripheral Blood Stem Cells or Bone Marrow

Procedures (donor information, insurance, informed consent, medical evaluation and collection) are the same as for a first donation (5.2 – 5.6).

6.3.2 Lymphocytes

General procedures (donor information, insurance, informed consent, medical evaluation and collection) are the same as for a stem cell donation (5.2 – 5.6). Those standards only relevant for the collection of peripheral blood stem cells or bone marrow do not apply.

All blood tests listed in Appendix C.2.2 must be performed/repeated. The donor’s general health and suitability for donation should be appropriately evaluated up front. On the day of the leukapheresis at the latest, the donor is physically examined and cleared for donation.

For donors who have previously donated peripheral blood stem cells within the last 12 months, the donor center arranges the examination according to C.2.2 as well as donor insurance 5.2 and also arranges that the donor receives the informed consent form for the lymphocyte donation. When the test results are available, donor eligibility can be evaluated after an interview of the donor by the physician (health history since last donation, remarks on the collection, etc.). Unusual findings can necessitate instrumental diagnostic procedures. The physical examination is done on the day of the leukapheresis.

A donor who previously donated bone marrow or whose first donation is longer than 12 months ago, must be scheduled for an evaluation at the collection center. The procedure is analogous to stem cell collections (5.2 – 5.6), although instrumental diagnostics may not be waived if no abnormal findings are detected.
6.3.3 Whole Blood
For whole blood, the following criteria are applicable: Item 2.5 of the “Guidelines for the Preparation of Blood and Blood Components and the Use of Blood Components (Hemotherapy)” [7].
7 Transport

7.1 General

7.1.1 Either the transplant center (clinical institution) or the collection center (manufacturer) is responsible for product transport. If not documented otherwise in writing, the transplant center is generally responsible for the transport. Couriers must be commissioned in writing. The contracting institution must ensure that the transport is carried out according to the relevant standards, guidelines and WMDA recommendations by an appropriately instructed courier.

7.1.2 The product must be transported in a shatterproof and temperature insulating container that is labelled with the warning as described under 7.2. The courier must supply the transport container.

Bone marrow, peripheral blood stem cells and donor lymphocytes must be hand carried during the whole transport by an authorized courier whose details have been conveyed to the donor center, collection center and transplant center.

Upon request by the transplant center, cord blood and whole blood can be shipped unaccompanied.

The transport temperature must be monitored and documented.

Cryopreserved cord blood units must be transported in a liquid nitrogen shipper (“dry shipper”) that is normally provided by the cord blood bank. The cord blood bank coordinator is responsible for packaging the cryopreserved product in the dry shipper for transport.

Unappropriate transport conditions and deviations must be documented.

7.1.3 The institution responsible for the transport (transplant or collection center) specifies the transport conditions. The product temperature must be electronically logged and documented for all products [2].

7.1.4 The product must be transported without delay ensuring an expedient and safe delivery.

When a car is used for transportation, two couriers should be provided.

7.1.5 In the event of courier travel by air flight, the product must be transported as carry-on luggage.

Locked dry shippers may be transported in the cargo hold of aircraft. The courier shall monitor the loading of the dry shipper.

7.1.6 The collection center must check the identity of the courier and the product.
7.1.7 If there are justified doubts about a proper transport when the product is being picked up, the head of the collection center must immediately inform the institution which contracted the courier in order to take measures to guarantee a proper transport.

7.1.8 The courier details are to be determined and notified to all parties concerned in time before the onset of the transport: within Germany 3 working days, internationally 5 working days prior to collection.

7.1.9 In cooperation with the transplant center, when importing products from (non-EU) third countries, the ZKRD declares the product at customs and provides the necessary customs documentation based on the courier details. The responsibility for the declaration of German products being exported into third countries lies with the economic owner at the time of export. For exports into third countries, the donor center is responsible for handing over the customs documentation to the courier; for imports from third countries, the transplant center or the commercial courier company is responsible.

7.2 Product Labeling

The product must be labeled according to current laws, guidelines and regulations [2], [7], [8], [29].

Due to the small size of cryopreserved cord blood product bags there might not be enough space to list all data on the product label. Data, which does not have to be listed on the product label, will be provided on a separate document.

The label of the container must contain the following warnings:

- MEDIZINISCHER TRANSPORT: Vorsichtig behandeln
- NICHT BESTRAHLEN!
- Menschliche Zellen zur Transplantation
- Von Hitzequellen fernhalten, nicht einfrieren
- Unverzüglich weitergeben!
- MEDICAL SPECIMEN: Handle with care
- DO NOT X-RAY!
- Living human cells for transplantation
- Do not place near heat, do not freeze
- Immediate delivery required!
7.3 Accompanying Documentation

7.3.1 Accompanying Documentation

The documents accompanying the product must meet the requirements of the Paul-Ehrlich-Institut (www.pei.de: pei-mindestanforderungen-behältnisbeschriftung-begleitschein-stammzellen) and the respective approvals according to §21a AMG [8].

The accompanying documentation must fulfill the following minimum requirements of the WMDA:

- product name
- cell count and, if applicable, processing
- product code
- name and recipient number
- donor identifier
- donor ABO/Rh group
- date and time of collection (not for cord blood units)
- name and address of the transplant center and contact details

Additionally the address of the donor center must be included.

7.3.2 Documents for Airport Security

For courier travel by air flight, the courier must carry documentation for security that comprise the following:

- Name of courier
- Identity card number/passport number
- Flight itinerary, especially departure/arrival airports, departure and arrival dates and times and flight number
- Product specification
- Warning that the transplant may not be X-rayed and that every transport delay should be avoided.

7.3.3 For courier travel by air flight, the airport security authorities, the airlines and if international transport is involved the Federal Border Guard of the respective airports must be informed of the product transport.
7.4 **Courier**

7.4.1 **Courier Requirements**

The institution which provides the courier must ensure proper product transport and compliance with the following requirements:

- He must know and understand the significance of the product.
- He must have been approved by the donor center, collection center or transplant center, and they must have trained him.
- He must not be related to the donor or recipient.
- He must be an experienced traveler and know how to deal with typical incidents during transport of stem cells or travel disruptions.
- He must not have other commitments or interests until he has delivered the product.
- For international transport, he must have an internationally valid credit card with an adequate available credit limit.
- For international transport, he must have adequate command of English.
- A back-up flight should be booked.

Furthermore the applicable laws, guidelines and regulations of the country must be followed as well as the standards and recommendations of the WMDA.

7.4.2 **Courier Responsibilities**

- When accepting the product, he must check the number and type of requested product bags and samples. He must check the labeling and the accompanying documents for information as detailed in section 7.2 and 7.3.1.
- He must place the product bags properly in the transport container (this does not apply to dry shippers).
- He must inform the aircraft staff about the medical transport at flight booking, at check-in, at the gate and in the aircraft.
- During export into third countries or import from third countries, the courier must generally show the respective documentation at the customs. Hence the transport may not be significantly delayed.
- He must never leave the product unattended (this does not apply to dry shippers).
- In addition to the documents as listed in section 7.3.1 and 7.3.2, he must carry the following documents during product transport:
  - Product Prescription Form
  - Emergency contact numbers of transplant center and donor center
• He must promptly inform the transplant center of possible delays.
• He must hand over the product to a staff member of the transplant center.
• He must record the delivery and report it to the donor center.
• He must always maintain recipient and donor confidentiality.
8 Post Donation Donor Follow-up

8.1 General

8.1.1 Directly following the donation, the respective collection center physician is responsible for the evaluation of the donor’s well-being. The donor center must be informed about the progress of the donation.

8.1.2 The collection center physician is responsible to assess if and for how long the donor is unable to work and issues a medical certificate of disability if necessary. The donor center must pay for any loss of earnings this incurs.

8.1.3 The donor center is responsible for the donor follow-up after the donor’s discharge from the collection center by the collection center physician in charge.

8.1.4 The donor center and collection center, respectively must keep records of all corresponding donor contacts, his statements relating to the donation and all initiated examinations and therapies.

8.1.5 Serious events and adverse effects during and after a donation as well as during mobilisation must be reported by the donor center to the ZKRD according to the WMDA SEAR program. Annual reporting is required even if there were no events.

8.1.6 Serious events and adverse effects at collection, processing, transport or at/post transfusion of the cells which affect the safety and quality of the cells and therefore the safety of the recipient must be reported to the ZKRD according to the WMDA SPEAR program. Annual reporting is required even if the donor center did not report any events.

8.1.7 There are no risks for the donor (newborn baby) associated with a properly performed donation of cord blood. Therefore, cord blood banks are not required to perform donor follow-up.

8.2 Donor Contacts

8.2.1 The donor center must contact the donor by telephone or in person within one week of the donation to evaluate his physical and emotional well-being. Content-related recommendations can be found in WMDA forms\(^9\). It must be documented if the donor center is unable to reach the donor.

\(^9\)status 2017-05-10: www.worldmarrow.org forms DF1 and DF2
8.2.2 If the donor has any unusual complaints, a medical evaluation must be performed. The responsible collection center physician must be informed about it.

8.2.3 6 months, 1, 2, 5 and 10 years after donation, the donor must be contacted by sending a questionnaire (see appendix B).

8.3 Post Donation Donor Testing

8.3.1 As a minimum, a blood count is to be performed after every apheresis or bone marrow collection. Additional blood examinations fall into the physician’s responsibility and depend on the individual donor situation depending on the blood volume processed or the volume of the collection, respectively.

8.3.2 30 days post-donation, the donor center has to arrange for at least the following tests:

- after aphereses: differential blood count, GOT, GPT, uric acid
- after bone marrow collections: differential blood count, ferritin

8.3.3 The medical assessment of relevant pathological findings must be initiated by the donor center.

8.3.4 Findings that may affect the recipient must be reported to the transplant center.
9 Post Transplant Recipient Follow-up

9.1 Information About the Recipient’s Condition Post Transplant

9.1.1 If the preparation is not infused, the collection center, the donor center and the cord blood bank, respectively, as well as the ZKRD must be informed about the disposition of the preparation. Alternatively only the ZKRD may be informed for forwarding to the respective partners.

9.1.2 The recipient must be informed and his consent must be obtained prior to submitting and using any medical follow-up data. Medical data may not be communicated to the donor, rather only general information (e.g. alive, good general condition, patient is able to work again).

According to the drug licensing procedures of the Paul-Ehrlich-Institut, the cord blood banks must collect recipient follow-up data.

9.1.3 Upon request, the transplant center must inform the ZKRD or the donor center of the recipient’s condition at 3 months, 1 year, 2 years and 5 years post transplant (e.g. ZKRD forms F0_002 and F0_003 – Appendix B).

9.2 Donor Recipient Contact

9.2.1 Donor and recipient may share anonymous correspondence post transplant. Any correspondence must be screened by the ZKRD and the donor center respectively to ensure all personally-identifying information is removed before it is forwarded.

9.2.2 Direct contact between donor and recipient is not allowed until after two years after the first transplant date at the earliest. Before any direct contact is allowed the donor center and the transplant center must inform both the donor and the recipient or his legal guardian of the benefits and risks of direct contact, and they must obtain their signed consent authorizing the release of personal information. (ZKRD Form EV_001 and EV_002 – Appendix B). After a subsequent donation of the same donor on behalf of the same recipient, direct contact is allowed one year after retransplant at the earliest. It is recommended to organize at least one written contact between donor and recipient before anonymity is cleared. The date of retransplantation does not shorten the initial period of two years.

9.2.3 Direct contact between the core family of a deceased recipient/donor and the donor/recipient is allowed without a waiting period if both parties have signed an
informed consent form. If third parties want to reveal the anonymity after the death of a patient/donor, the core family of the patient/donor have to agree.
10 Data Protection, Anonymity and Record Retention

10.1 Data Protection

10.1.1 All institutions involved must have a data protection officer.

10.1.2 The personnel must be informed about the regulations of data protection and must commit themselves in writing to observe the data protection regulations. This also includes medical information with respect to legal requirements involving physician’s confidentiality. Only a physician may inform a donor about abnormal findings.

10.1.3 Data security must be ensured. The spacious condition in particular must ensure that only authorized staff has access to donor and patients records.

10.1.4 The protection of an individual against unlimited data collection, recording, use and transfer of his personal data must be guaranteed according to the Federal Data Protection Law [13] and the German Social Security Code X (protection of social data) [24].

Furthermore, the corresponding federal state data protection laws, state archive laws and health care laws are also applicable.

10.2 Anonymity

In the course of all processing steps and manufacturing processes the anonymity of donors and patients must be strictly maintained and protected. Important measures are that:

- only the necessary personal data of the donor and the patient may be given to the entitled institutions (e.g. donor center, collection center) for the purpose of undertaking the stem cell donation,

- donor-related information that is communicated externally must not contain names but only pseudonymous codes,

- after a collection or transplantation and only upon request, the donor and patient may receive data on gender and approximate origin/age of the partner in a way that the anonymity will be sustained (e.g. "grown-up European patient").

The transplant center is responsible for ensuring that all necessary measures are taken to prevent donor data (e.g. donor ID, date of birth) from becoming accessible to
patients (e.g. by using a sleeve to cover product labelling). For donor and recipient
contact, see also section 9.2.

10.3 Record Retention

10.3.1 Records

The following records must be retained:

- Donor records: Consent forms, documentation of information sessions and
  medical measures, health history questionnaires, all records documenting HLA
  typing and examination results.

- Patient records: Search requests, diagnostic findings, medical reports, consent
  forms and documents pertaining to search initiation, search results and requests
  and results of further testing.

10.3.2 Description of Record Retention

Records and all electronic data are to be kept secured from unauthorized access.
Details are regulated by the Federal Data Protection Law.

10.3.3 Retention Periods

The requirements of record retention must be in compliance with the regulations for
record retention of medical services according to the respective Medical Association’s
professional code of conduct or other legal instructions.

Due to possible controversial cases/questions of liability, patient records should be
retained until the end of the civil law limitation period of 30 years after the conclusion
of treatment. This period starts with the end of the year in which the last entry is
made. This is also valid for records of donors who have donated blood stem cells or
have been pretreated for this purpose.

10.3.4 Disposal of Records

After expiration of the retention period, records must be disposed of or destroyed
in an appropriate way either by the center itself or by a qualified external disposal
company.
References

https://www.wmda.info/


http://www.bundesaerztekammer.de/... 2014; Jg. 111; Heft 38, A 1538).


[5] Querschnitts-Leitlinien (BÄK) zur Therapie mit Blutkomponenten und Plasmaderivaten
http://www.bundesaerztekammer.de/...

[6] Leitlinien zur allogen Stammzelltransplantation der DAG-KBT
https://www.onkopedia.com/de/onkopedia/guidelines

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[13] Bundesdatenschutzgesetz (BDSG)
Art. 1 G v. 25.2.2015 I 162.


[15] Spende von Knochenmark und peripheren hämatopoetischen Stammzellen freiwilliger nicht verwandter Spender
http://www.immungenetik.de/...

[16] Deutscher Konsensus zur immungenetischen Spenderauswahl für die allogene Stammzelltransplantation
http://www.dag-kbt.de/content/public/KonsensusSpenderauswahl2013.pdf


[22] EU Guidelines to Good Manufacturing Practice Medicinal Products for Human and Veterinary Use

[23] Sozialgesetzbuch, Fünftes Buch, Gesetzliche Krankenversicherung (SGB V)
[24] Sozialgesetzbuch, Zehntes Buch, Sozialverwaltungsverfahren und Sozialdatenschutz (SGB X)


[25] International Standards for Hematopoietic Cellular Therapy Product Collection, Processing, and Administration

http://www.jacie.org

[26] NetCord-FACT International Standards for Cord Blood Collection, Banking, and Release for Administration

http://www.factwebsite.org/Standards/

[27] WMDA Donor Medical Suitability Recommendations


[29] World Marrow Donor Association Recommendation: World Marrow Donor Association (WMDA) Guidelines for couriers and the transportation of haematopoietic progenitor cells (HPC - BM, apheresis and therapeutic cells - T Cells)

https://www.wmda.info/professionals/tools?id=74
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A  Appendix: Abbreviations

ALAT  Alanine Aminotransferase
AMG   Arzneimittelgesetz (German Drug Law)
AMWHV Arzneimittel- und Wirkstoffherstellungsverordnung
Anti-HBc Hepatitis B Core Antibody
AP    Alkalische Phosphatase (alcaline phosphatase)
ASAT  Aspartate Aminotransferase
ASHI  American Society for Histocompatibility and Immunogenetics
BÄK   Bundesärztekammer (German Medical Association)
CMV   Cytomegalovirus
CRP   C-Reactive Protein
CT    Confirmatory Typing
DAG-KBT Deutsche Arbeitsgemeinschaft für Knochenmark- und Blutstammzelltransplantation (German Working Party for Marrow and Blood Stem Cell Transplantation)
DGI   Deutsche Gesellschaft für Immungenetik (German Society for Immunogenetics)
DNA   Desoxyribonucleic Acid
EBMT  European Group of Blood and Marrow Transplantation
EBV   Epstein-Barr Virus
ECG   Electrocardiogram
EFI   European Federation of Immunogenetics
FACT  Foundation for the Accreditation of Cellular Therapy
Gamma GT Gamma-Glutamyl-Transferase
G-CSF  Granulocyte Colony Stimulating Factor
HBsAg Hepatitis B Surface Antigen
HCG   Human Chorionic Gonadotrophin
HCV   Hepatitis C Virus
HIV   Human Immunodeficiency Virus
HLA   Human Leukocyte Antigen
HTLV  Human T-Lymphotropic Virus
IATA-DGR International Air Transport Association - Dangerous Goods Regulations
IgG   Immunoglobulin-G
IgM   Immunoglobulin-M
JACIE Joint Accreditation Committee ISCT EBMT
LDH   Lactate Dehydrogenase
NAT   Nucleic Acid Test/Nucleic Acid Amplification Test Technology
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<td>PBSC</td>
<td>Peripheral Blood Stem Cells</td>
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<td>Polymerase Chain Reaction</td>
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<td>PTT</td>
<td>Partial Thromboplastin Time</td>
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<td>SEAR</td>
<td>Serious Events and Adverse Effects Registry</td>
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<td>Sozialgesetzbuch (Social Security Code)</td>
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Appendix: ZKRD Forms and Questionnaires

All current versions of forms and questionnaires are provided on the ZKRD homepage. For English versions please see:

http://www.zkrd.de/en
→ "Partner Login"
→ "Forms"

Forms for Work-up, Cord Blood and Follow-up (Patient)

The donor health history questionnaire, consent form at CT stage and the donor follow-up questionnaire are in German and, therefore, not provided on the website for international partners.
C Appendix: Preparing Blood Stem Cell Donations: Donor Information and Medical Evaluation

C.1 Donor Information and Counselling

The donor must be informed about the details of the donation by an adequately trained person using terms that are easily understood by the donor. Additionally, the counselling about the donation and related medical intervention is done by the collection center’s physician.Translating may only be done by a professionally or linguistically competent person who is not related to the donor. During the medical evaluation, at the latest, the donor must be informed and educated about the following:

C.1.1 Information About the Donor Request and Related Procedures

- Product preference of the transplant center
- Expenditure of time
- Anonymity
- Non-remuneration of donation
- Extent to which donor expenses will be compensated by the donor center
- Type and extent of insurance coverage
- Information on safeguards to protect the donor
- Possibility of consulting a donor advocate if needed
- Possibility of second or subsequent blood stem cell or blood product requests for the same recipient (e.g. in the event of relapse or non-engraftment or if the treatment protocol requires a subsequent donation)

C.1.2 Donor Medical Counselling

C.1.2.1 Request and Procedure

- Donor exclusion criteria for blood stem cell donations
• Possible benefit for the recipient
• Information if the planned transplantation is developmental and if its efficacy is assessed in clinical studies
• Donation methods: bone marrow and peripheral blood stem cell collection
• Examinations before and after donation and the donor’s right to have the results explained as well as the physician’s general duty to inform the donor in case of suspicious findings
• Preparatory pre-collection procedures and the procedure of the blood stem cell collection
• Required blood sample collections (pre-collection samples and blood samples on the collection day)
• Instructions for the time of G-CSF mobilization and availability of a physician on duty including contact information
• Requirement of bone marrow donation if the G-CSF mobilization is unsuccessful or must be interrupted
• Requirement of signed donor consents (section 5.5)
• Right to withdraw at any time, however the donor must understand that if he/she withdraws after the beginning of the recipient’s conditioning therapy, the recipient is in danger of death.

C.1.2.2 Risks

• Risks and side effects of pre-donation examinations, anesthesia, marrow donation, administration of G-CSF and peripheral blood stem cell donation by apheresis and other blood product donations
• Marrow donation: Possible need for allogeneic blood transfusion in emergencies
• Peripheral blood stem cell donation: explicit reference to G-CSF’s side effect profile
• Possible use of a central venous line for apheresis and associated risks if blood stem cells cannot be collected using peripheral veins
• Information regarding the risk of transmission of infectious, genetic or malignant diseases to the recipient by blood stem cell transplantation
C.2 Donor Medical Evaluation (Work-up)

C.2.1 Medical Examination and Education

- Medical education by the physician
- Health history
- Physical examination
- Resting ECG
- Abdomen sonography, in particular a spleen sonography if peripheral blood stem cell donation is performed
- Chest X-Ray as needed
- Pulmonary function test as needed
- For peripheral blood stem cell donations: Assessment of peripheral venous access

C.2.2 Blood Tests

During donor medical examination, the testing below must be performed. The infectious disease testing must be performed on a blood sample that has been drawn within 30 days before donation. It may need to be repeated (see chapter C.2.4).

- differential blood count, CRP
- Coagulation test (Quick’s test, partial thromboplastin time)
- Sodium, potassium, calcium, ferritin, creatinine, uric acid, urea, ALAT, ASAT, lactic dehydrogenase (LDH), alkaline phosphatase, gamma-glutamyl transferase, total bilirubin, recommended before bone marrow collection: choline esterase
- Total protein, protein electrophoresis
- TSH
- Blood sugar
- Infectious disease testing (additional testing must be performed if mandated by the most current guidelines [2]): Syphilis test, HBsAg, HBc Ab, HBV (NAT), HCV Ab, HCV (NAT), HIV-1 and -2 Ab, CMV IgG and IgM, HTLV-1 and -2 Ab, EBV IgG and IgM, recommendation: toxoplasmosis IgG and IgM
- Blood group testing (AB0 group and rhesus type) and irregular antibodies
- For female donors: Pregnancy testing (Beta-HCG testing to exclude pregnancy)
C.2.3 Procedures

- In case of statements in the medical history or findings that may increase the risk for the donor but do not necessarily exclude him from donation: The donor must be counseled regarding the statements and findings and the associated additional risks. The counseling must be documented in writing. The donor has the right to decline donation.

- In case of statements in the medical history or findings that may increase the risk for the recipient: The transplant center must be informed of the statements and findings in writing (WU_038) and must determine whether the statements or findings increase the risk to the recipient. Statements or findings that increase the recipient risk must be reported to the recipient and he must be counseled regarding the increased risk. The counseling must be documented in writing. The transplant center must communicate in writing if the donor is acceptable.

- The examining collection center physician must notify the donor center in writing of the results of the medical evaluation and donor eligibility for collection.

- The donor center must report the donor clearance for collection and the results of the donor infectious disease testing on the appropriate form (ZKRD Form WU_009) to the ZKRD, the transplant center or the international registry if the examining collection center physician determines that the donor is eligible for donation and the donor has signed the consent to donate form.

- The donor must be informed about abnormal findings and examinations resulting from them.

- Counseling of female donors of childbearing age regarding safe methods of contraception must be documented in writing. Repeated exclusion of pregnancy is recommended two days before the first G-CSF injection or bone marrow collection, respectively.

C.2.4 Repeat Examinations

Infectious disease testing must be repeated if results were from testing more than 30 days prior to the scheduled collection.

If more than eight weeks have elapsed since the donor medical evaluation, the following examinations must be repeated (this applies also in the event of a subsequent donation for the initial recipient):

- Between 8 and 12 weeks since the most recent complete donor medical evaluation: Interview with the donor to determine if there are any changes to the donor’s condition or health history. Repeat infectious disease testing. Female donors: Repeat pregnancy testing.

- Between 12 weeks and 6 months since the most recent complete donor medical evaluation: In addition to the above-listed items: Repeat all blood testing according to section C.2.2.
• The donor medical evaluation must be repeated in its entirety if more than 6 months have elapsed since the most recent complete evaluation.
Appendix: List of Differences between Versions 9 and 10

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|                        |          |       | more detailed WMDA requirements |       |
| 1.1.1.9,               | added    |       | &quot;cooperative transplant centers&quot;, qualification only specified in 1.6.1 |       |
| 1.2.1.11,              |          |       |                        |       |
| 1.3.1.8                |          |       |                        |       |
| 1.1.2.4                | added    |       |                        |       |
| 1.2.1.9                | added    |       | exception for pre-existing small donor centers |       |
| 1.2.2.2,               | modified |       | wording adapted (consistent for all partners) |       |
| 1.3.2.3                |          |       |                        |       |
| 1.2.3.4                | modified |       | reworded |       |
| 1.3.3.3                | deleted  |       | in consultation with the transplant center |       |
|                        | added    |       | approval of the ethics committee |       |
| 1.4.1.11               | modified |       | wording adopted from standard for donor centers |       |
| 1.4.2.3                | added    |       | new standard |       |
| 1.4.3.5                | added    |       | &quot;by a physician&quot; |       |
| 1.5.1                  | modified |       | reworded |       |
| 1.5.2,                 | added    |       | new standard |       |
| 1.6.5                  |          |       |                        |       |
| 1.6.1                  | modified |       | transitional arrangement removed |       |
| 2.1.10                 | modified |       | &quot;in pseudonymized form&quot; |       |
| 2.2.2                  | added    |       | new recommendation |       |
| 2.2.3                  | modified |       | tropical diseases, illnesses of the blood or immune system, psychological disorders |       |
| 2.2.4                  | added    |       | &quot;without being distracted by aspects of labor&quot; |       |
| 2.4.2                  | added    |       | DRB1 |       |
| 2.4.3                  | modified |       | contact data check only every five years |       |
| 3.3.3                  | modified |       | evaluation must be performed by a physician, testing on an attached segment |       |
| 3.3.6                  | modified |       | second sentence reworded |       |
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