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ARTICLE

Audits of collection and apheresis centers: guidelines by the World Marrow Donor Association Working Group Quality and Regulation

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Abstract

According to the Standards of the World Marrow Donor Association (WMDA), unrelated stem cell donor registries and donor centers are responsible for compliance of their collection and apheresis centers with these Standards. To ensure high stem cell product quality and high standards for safety and satisfaction of voluntary unrelated stem cell donors, we here present guidelines for audits of collection and apheresis centers that can be used by new and established donor registries, as well as by collection centers in preparation of audits. We define the general requirements and recommendations for collaboration with the collection and apheresis centers and define critical procedures for the collection of the stem cell product, such as information session, medical assessment, product collection, quality controls, product handover for transportation, and donor follow-up. The specific guidelines are accompanied by detailed checklists and forms that can be found in Supplementary Information and may be used during an initial or follow-up on-site or paper-based audit.

Foreword

This document was prepared by the World Marrow Donor Association (WMDA) Working Group Quality and Regulation (WGQR) and contains the guidelines for audits of collection centers (CC) and apheresis centers (AC). The Working Group Quality and Regulatory consist of 84 active members from 24 countries, representing the largest stem cell donor registries worldwide, as well as small and medium-sized registries. The work of this subcommittee has been presented more than seven times during WMDA meetings in closed session for all WGQR members and open meetings where all WMDA experts can attend and give feedback. The voluntary subcommittee members are working closely together with the collection centers in their countries and have performed audits or are preparing the audits of their collection centers based on their country's requirements and Service Level Agreements with their collaborating CCs. The first draft version of the document was reviewed by the members of the WMDA Accreditation Committee, then by the WGQR. The WGQR approved the manuscript in November 2016 and the WMDA board approved it in March 2017 before submission for publication.

The guidelines have been developed for hematopoietic progenitor cell (HPC) donor registries (DR) and donor centers (DC) relying on independent CC/ACs that collect HPC from unrelated donors (UD). The goal of these guidelines is to support DRs and DCs in verifying and auditing the cooperating CC/ACs regarding their compliance with WMDA Standards. DRs and DCs are responsible, indirectly or directly, for processing and quality of HPC collections and donor management based on their agreements with CC/ACs, and the respective audits if applicable.

NOTE: Definitions used throughout this document are as given in the WMDA Standards as of 1 January 2017 [1].

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These standards accept the terms hematopoietic progenitor cell (HPC) and hematopoietic stem cell (HSC) equally. Throughout this document the abbreviation HPC will be used. However, the checklist includes the specific WMDA Standards and there the abbreviation HSC will be used as written in the Standards. Throughout this document, no further distinction will be made between a donor registry and a donor center; rather the term "registry" will refer to the organization conducting the audits. Also, if not otherwise specified, the term collection center (CC) refers to the medical facility, where HPC collection from donors is performed. This collection might include marrow aspiration and/or apheresis.

WMDA Standard 1.08 states:

"If a registry relies on an independent collection center for the collection of donor HSC or other donor cellular products, for donor medical evaluation or for the follow-up of donors, the registry must ensure that the collection center complies with WMDA Standards in these areas. The nature of these affiliations and the duties and responsibilities of each entity must be documented in a written agreement".

The here presented guidelines outline the different responsibilities a CC may have and give general recommendations to be followed by the CC, as well as specific requirements during the work-up and follow-up process. Registries need to be aware that these are guidelines and may not cover all aspects necessary to comply with applicable local and national laws and regulations. It is the responsibility of the DR to determine and follow any additional governmental regulations and guidelines that apply in their relevant community. In general, DRs are responsible for audits of CCs to ensure their compliance with WMDA Standards. However, the responsibility for audits of CCs can be delegated to the DCs, especially in countries where DCs contract the CCs instead of the DR. In these cases, the DR has to ensure that the responsibilities are clearly defined in national standards and/or agreements with the DCs.

The guidelines described here do not take precedence over the aforementioned established systems, but instead try to embed these in the framework of HPC collection from UDs and ensures that the current WMDA Standards, as well as the WMDA recommendations will be followed by the CCs. FACT-JACIE Accreditation, Advancing Transfusion and Cellular Therapies Worldwide (AABB) Accreditation, GMP and/or ISO certificates may apply for additional procedures and quality systems at a CC. Also, national and/or local laws and regulations, other Standards, accreditations, or certification systems may have their separate requirements, which are not included in these guidelines.

The present guidelines are based on the current WMDA Standards. This means that the authors interpreted the current standards and deduced specific process steps and requirements for CCs. Also, the current FACT-JACIE standards were used as a basis for specific process requirements, as they are accepted as a common praxis worldwide within the stem cell transplantation community. However, WMDA registries collaborate with both, FACT-JACIE accredited and non-accredited CCs, as there is no requirement for accreditation by WMDA in most countries. To avoid double work for the auditors using the present checklist and additionally the FACT-JACIE checklist, the authors decided to use the relevant FACT-JACIE standards directly instead of referencing them in our paper. In this way, the auditors auditing a CC that is not FACT-JACIE accredited will have all information in one place instead of using several checklists. However, as we already mentioned above, the DRs are responsible for checking their national requirements that apply to the CCs and they are also responsible for adapting the checklists to these specific requirements. This article sets the basis that should apply in most countries worldwide and helps the DRs to ensure that the WMDA Standards are followed in their CCs.

Throughout the document, the most important requirements ('baseline requirements') that are defined according to the current WMDA Standards and best practices are highlighted in bold. In accordance with these guidelines, these baseline requirements must be fulfilled by all CCs performing HPC collection on UD.

In this document a distinction is made between CCs licensed or accredited by national authorities or international institutions that are recognized as acceptable accreditation authorities in their country or community, and those CCs, which are non-accredited. Collection centers licensed or accredited by national authorities or internationally recognized institutions only need to be audited for those requirements that apply to WMDA Standards and which are not already covered by the respective license or accreditation. Otherwise, a copy of the accreditation or license is sufficient to confirm the compliance with the Standards.

It is, however, recommended to conduct a full audit including an on-site inspection of any CC that is to be newly contracted by a DR. During the application period, all national and WMDA requirements must be taken into account. Once the candidate CC is accepted and if the CC maintains a license or accreditation by national authorities or internationally recognized institutions, they will thereafter be audited only for those recommendations/requirements (including WMDA Standards) not covered by the respective license or accreditation.

A few words left about the structure of the present paper: in the first section we give some general advice with respect to audits of CCs. This section is followed by the recommendations and requirements step by step along the processes that are expected to be performed at the CCs collecting HPC from UDs.

The checklist referred to in these guidelines and provided in Supplementary Information offers a comprehensive approach to critical areas in the management of UDs. The checklist is split into sections with specific subjects, which are then listed in further detail. Each specific item in the checklist is categorized as either a recommendation or requirement. When noted as a recommendation, it means that those points are encouraged to be adopted as a best practice by the CCs. The topics categorized as a requirement are part of the WMDA and/or other established Standards and must be fulfilled by all CCs. Also, assessment tools have been provided to enable registries' auditors with easy and convenient solutions to verify the procedures at CCs. However, some of the requirements and recommendations cannot be assessed during audits as they are general in their nature and therefore need to be taken into account. These guidelines and related checklists have been established to assist registries in their daily work. Each DR should establish its own auditing group, including staff, which must be trained in audit procedures, WMDA Standards, Standard Operating Procedures regarding UD management, and local and national laws and requirements. If the responsibility is delegated to a DC, this applies to the DC.

As standards and requirements evolve in the future, the reader is encouraged to make proposals for changes and additions. Feedback can be addressed to the Working Group Quality and Regulation via the WMDA Office.

Format and timing of audits

Improving the safety of volunteer UDs during donation [2], as well as maintaining high standards for HPC product quality is what the WMDA strives for. From the medical evaluation and examination, through sample collection, product collection and UD follow-up, the essential procedures rely on high-quality standards at CCs.

To ensure the safety of the volunteer UD, the DR is responsible for compliance with WMDA Standards at all times before, during, and after HPC donation. As the actual HPC collection will be performed at the CC, the DR is also responsible for ensuring their compliance with the WMDA Standards as a minimum Standard. In some countries it might be the responsibility of the DR to ensure compliance with other country-specific requirements. Regular audits provide the means of monitoring compliance. The DR should embed these audits within their own quality system.

The following formats and frequencies of audits are recommended:

Before a new CC is contracted, it is recommended to conduct an on-site evaluation at the CC facility. Additionally, a paper-based audit is required to ensure compliance with the WMDA Standards and to ensure that the national requirements are fulfilled and necessary accreditations and licenses are available. In some countries it might be appropriate to perform only a paper-based audit before contracting the CC. In these cases, the accreditation status of the CC at the relevant authorities (see also the foreword) can be accepted. The CC staff must have proven experience in HPC collection prior to working with UDs.

For already contracted, experienced CCs, an annual paper-based audit should be performed by the DR, checking at least the following items:

- Change of address or other important contact information for donor physical exams, HPC collection and product pick-up for transportation.
- Relevant staff changes (e.g., Medical Director, CEO, physicians, or coordinators. Some additional country-specific positions could be required by DRs).
- Changes in accreditation, registration, or license status.
- Donor issues which may include the number of serious adverse events and serious adverse reactions occurring and reported to the DR.
- Changes in suppliers, laboratories or other cooperating facilities, if required by the DR.

It is recommended that once every 4 years the DR performs a full on-site audit based on these guidelines and the provided checklists.

For FACT-JACIE [3] or equivalent accredited facilities or those possessing a national equivalent, the reduced audit format may be applied, covering requirements that are not already mandatory for FACT-JACIE or equivalent accreditation.

In addition to a paper-based audit, the DR may choose to perform an on-site inspection of the CC at reasonable intervals or whenever suspicion arises that essential quality requirements are not being fulfilled.

Whenever a CC fails to fulfill baseline requirements, further HPC collections at the specific center must be suspended for UD collections for donor safety reasons until these requirements are again fully met.

Below, some frequently detected non-conformities that can be found at CCs are described exemplarily for special attention:

- Poor understanding of the processes with central venous catheters (when is a central venous catheter to be used for UD collections);
- Sample collections prior to signing the consent form by the donor (for physical examination samples as well as for research samples);
- No or poor communication in case of:

  Collecting less samples than requested by the transplant center (TC);
  Other product dilution/additives than requested by TC

without prior clarification with the TC;
Necessary additional medical clarification on the donor side that might lead to a postponement in the planning;
Donor follow-up for additional clarification;

- Direct communication between the CC and TC without involving/informing the responsible registry;
- Confidentiality breaches (donor data/patient data);
- Poor understanding of UD needs, especially in the case of complaints (medical, as well as personal).

These are just the most frequent examples. We strongly suggest auditors to look closer into these issues and in case of non-conformities find better solutions with the CCs.

As no WMDA Standard exist at this time that defines how the harvest quality needs to be assessed and which indicators must be in place and constantly monitored at CCs, these sections are missing in the present guidelines. However, the WMDA is addressing these issues in a newly started project with the objective to define Key Performance Indicators for CCs. As soon as they will be available, the present guidelines will be adjusted accordingly.

General requirements

Keep in mind that UDs are not patients requiring medical assistance. They come to the CCs to donate for a person who they do not even know. This is a very special situation for them and they should be treated with respect and the understanding that they are doing something very remarkable. UDs are healthy persons who are acting completely altruistically and are willing to take some small risks in order to help others. Therefore, they need to be treated differently than a patient, and they should be treated with consideration to make them feel special and well cared for during the entire work-up and donation procedure.

UDs are volunteers and can withdraw from the process at any time. No undue pressure should ever be applied.

The day of the collection is a very special day for the UD, as well as for their family and friends, who may accompany them, and they may be very emotional. Therefore, it is recommended that the staff at the CC is prepared and handles them with appropriate sensitivity.

3.1 Collection center

3.1.1 **The collection center (CC) must meet at a minimum the criteria mentioned in WMDA Standards, and national regulations and laws [1, 3] (WMDA 2017: 1.08; FACT-JACIE 2017: CM1.3, C1.3).**

3.1.2 **The CC must be registered, licensed, or accredited by all relevant governmental authorities, and adhere to applicable national and international regulations (WMDA 2017: 8.01; FACT-JACIE 2017: CM1.3, CM1.3.1, C1.3, C1.3.1).**

3.1.3 **Any changes to the accreditation and licensing status must be reported to the DR in a timely fashion (WMDA 2017: 8.01; FACT-JACIE 2017: CM1.3.1, C1.3.1).**

3.1.4 **The CC should have an appropriate insurance coverage for UDs and HPC collections (WMDA 2017: 3.10.1).**

3.1.5 The CC should have a plan to provide crisis response, business continuity and disaster recovery (FACT-JACIE 2017: CM5.1.14, C5.1.19) [4].

3.1.6 **The CC must provide intensive care and emergency coverage for UDs (WMDA 2017: 8.02; FACT-JACIE 2017: C2.7, C2.8) and must have an emergency phone that is available 24 h per day, 7 days per week, all year long for the time between the physical examination, during the donation process, as well as after the donation. Country/DR-specific requirements concerning the after the donation care (e.g., the defined timeframe where the CC is responsible for the UD) must be followed.**

3.1.7 **The CC must have and maintain adequate and appropriate staff (WMDA 2017: 8.03), resources, equipment, supplies, and pharmaceuticals to support its collection and associated management activities. (WMDA 2017: 8.01, 8.03; FACT-JACIE 2017: CM2.6, C2.7).**

3.1.8 **The CC must have a designated site for the management of collection activities, and a secure environment for confidential record storage that meets country-specific and DR requirements (WMDA 2017: 8.02; FACT-JACIE 2017: C11.1.2, C11.1.4, C11.3.1).**

3.1.9 **The CC must have controlled storage areas to prevent mix-ups, contamination, and cross-contamination of products (WMDA 2017: 8.06; FACT-JACIE 2017: CM2.1.1, C2.1.1, CM9.1, C9.1, D9.1).**

3.1.10 **The CC must ensure that a direct communication always takes place between the CC and the responsible DR. Direct communication between the CC and TC is possible in exceptional cases with the approval of the DR (WMDA 2017: 2.08, 8.06; FACT-JACIE 2017: C11.1.4).**

3.1.11 The CC should be as easily accessible as possible for UDs and their families by public or private transportation.

3.1.12 Signs, staff assistance, or instructions should be

provided at the CC to assist the UD in finding their way to the right place within the facility.

3.1.13 The CC should be close to and easy to access from the nearest airport especially for international product transportation.

3.2 Collection center quality and safety procedures

3.2.1 The CC must establish and maintain policies and/or procedures addressing all critical aspects of operations and management (WMDA 2017: 8.06 [1], FACT-JACIE 2017: CM5.1-CM5.1.14, C5.1-C5.1.14).

3.2.2 National and DR-specific requirements concerning the quality and safety procedures must be met (WMDA 2017: 1.08, 8.01; FACT-JACIE 2017: CM1.3.1, C1.3.1).

3.2.3 CC quality and safety procedures must cover, at a minimum, WMDA Standards (WMDA 2017: 1.08).

3.2.4 There must be a system in place ensuring that the WMDA Standards will be followed (WMDA 2017: 1.08). Additionally, WMDA recommendations should be taken into consideration (WMDA 2017: 1.09).

3.2.5 All necessary measures must be taken at CCs to ensure donor safety, high quality of HPC products and appropriate donor management at all times during the work-up and follow-up procedures.

3.2.6 CC must have a quality management system in place (WMDA 2017: 2.11; FACT-JACIE 2017: CM4.1, C4.1.1).

3.2.7 The CC must operate an appropriate IT system (hardware, software, and network) to cover the needs for an appropriate UD management, communication between the CC and DR, as well as the technical needs for a HPC collection (WMDA 2017: 5.03, 8.06; FACT-JACIE 2017: C11.7.2).

3.2.8 Access to UD and patient data information at the CC, as well as the transmission of this information to and from the DR and/or suppliers (labs, courier services, etc.), must be organized in a way that accidental or unauthorized access, destruction or modification is prevented (WMDA 2017: 8.02, 5.03; FACT-JACIE 2017: C4.5.3.4, C11.6.3).

3.2.9 The CC must ensure proper documentation of all process steps and communication with the UD, either electronically or in paper format, to ensure confidentiality and to allow for traceability (WMDA 2017: 2.0) of the UD and product throughout all steps of the donation and post-donation recovery process (WMDA 2017: 8.02; FACT-JACIE 2017: CM8.15, C8.16, C11.1.1).

3.2.10 Records must be maintained for an appropriate period of time, in accordance with WMDA Standards and national laws and regulations. In case the requirements differ, national laws and regulations take precedence (WMDA 2017: 5.07; FACT-JACIE 2017: C4.5.3.6, C4.10.3.3, C11.1.1, C11.3, C11.4, C11.5).

3.2.11 The CC should monitor for UD satisfaction and well-being in an appropriate way according to DR's policies and national requirements and laws (WMDA 2017: 9.01).

3.2.12 The CC should provide an adequate waiting area and a recovery area, where the UD can rest after the donation.

3.3 Collection center staff

3.3.1 CC staff (especially clinical personnel) that works with UDs must be experienced in the field of HPC collections (WMDA 2017: 3.11.1, 3.12, 8.03; FACT-JACIE 2017: CM3.3.1, CM6.1, C3.4.1, C6.1) (e.g., autologous, related donors) and/or transplantations.

3.3.2 The personnel working directly with UDs or their companions must be well trained in handling UDs and understand their special needs (WMDA 2017: 8.03; FACT-JACIE 2017: CM3.3.1, CM6.1, C3.4.1, C6.1).

3.3.3 Medical director

3.3.3.1 There must be a CC medical director or their designee who is a licensed or certified physician with postgraduate training in cell collection and/or transplantation according to national and DR-specific regulations. The CC medical director or their designee may also serve as the CC director, if appropriately credentialed (WMDA 2017: 8.03; FACT-JACIE 2017: CM1.4, CM3.1.1, C3.1.1, C1.4, C3.2.1).

3.3.3.2 The CC medical director or their designee (physician) must be responsible for protecting the safety of the UD and product(s), and for identifying conditions in the UD that may be transmissible by transfusion or transplantation (WMDA 2017: 8.02; FACT-JACIE 2017: CM3.1.2; C3.2.2).

3.3.3.3 The CC medical director or their designee must have at least 2 years' experience in HPC collection procedures or have performed or supervised at least 10 bone marrow (BM) collection procedures within his/her career in case of an BM CC and/or 5 PBSC collections per year (WMDA 2017: 8.03; FACT-JACIE 2017: CM3.1.3, CM3.1.4, C3.2.3, C3.2.4.).

3.3.3.4 The CC medical director must participate in educational activities related to HPC collections on a regular basis ensuring practical and theoretical knowledge in this field (WMDA 2017: 8.03; FACT-JACIE 2017: CM3.1.5, CM3.1.5.1 C3.2.3., C3.2.5.1).

3.3.3.5 The physician responsible for the collection must have experience in the field of stem cell collections (WMDA 2017: 8.03; FACT-JACIE 2017: CM3.3.1, C3.4.1).

3.3.4 Medical and supportive staff

3.3.4.1 The staff must be sufficient in number to meet the needs of the CC's activities for daily and emergency coverage (WMDA 2017: 8.01; FACT-JACIE 2017: CM3.3.2, C3.4.1).

3.3.4.2 The PBSC CC staff must be trained in the administration of mobilizing agents to UDs; experienced in the collection procedure and handling of HPC apheresis products; well trained in the management of apheresis of UDs including those with central venous catheters. If central venous catheters are applied at the center, they need to be used according to WMDA Standards (WMDA 2017: 8.05; FACT-JACIE 2017: C8.11, C3.4.1, C5.1.4, C8.10, C8.10.1).

3.3.4.3 The BM CC staff must be experienced in BM collection procedures and handling of HPC marrow products and well trained in the management of marrow donors (WMDA 2017: 8.03; FACT-JACIE 2017: CM8.9, CM3.3.1).

Processes step by step from information session to product collection

4.1 Information session

4.1.1 The information session with the UD must be performed according to WMDA Standards. National laws and regulations must be followed (WMDA 2017: 3.04; FACT-JACIE 2017: CM6.2.1, CM6.2.4, CM6.2.5, C6.2.1, C6.2.4, 6.2.5).

4.1.2 The responsible physician or their designee must explain the procedure in a language and terms the UD can understand (WMDA 2017: 3.04, 3.05, 3.06, 3.11.1; FACT-JACIE 2017: CM6.2.1, C6.2.1).

4.1.3 The information session must cover the following topics at a minimum (WMDA 2017: 3.10, 3.10.1; FACT-JACIE 2017: CM6.2.1, C6.2.1) [5].

4.1.3.1 The risks and benefits of the procedure (WMDA 2017: 3.03, 3.04; FACT-JACIE 2017: CM6.2.1.1, C6.2.1.1).

4.1.3.2 The use of any medical intervention (e.g., administration of G-CSF), and its known risks and/or side effects (WMDA 2017: 8.05; FACT-JACIE 2017: CM6.2.1.1, C6.2.1.1).

4.1.3.3 Tests and procedures performed on the UD to protect the health of the recipient and to make sure that the UD is able to donate without taking an unnecessary medical risk (WMDA 2017: 3.04, 3.05; FACT-JACIE 2017: CM6.2.1.1, C6.2.1.1).

4.1.3.4 Protection of medical information and confidentiality (WMDA 2017: 3.11.1; FACT-JACIE 2017: CM6.2.1.4, C6.2.1.4) [6].

4.1.3.5 The UD's right to refuse to donate (WMDA 2017: 3.03, 3.06; FACT-JACIE 2017: CM6.2.5, C6.2.5).

4.1.4 Informed consent form

4.1.4.1 According to WMDA Standards, the UD must confirm his/her willingness to donate in writing (WMDA 2017: 3.03; FACT-JACIE 2017: CM6.2.6, C6.2.6).

4.1.4.2 The informed consent form must be written according to the national laws and regulations and must adhere to the WMDA Standards (WMDA 2017: 3.11.1).

4.1.4.3 The informed consent form must be written in a way that the UD is able to understand it before signing it (WMDA 2017: 3.11.1).

4.1.4.4 The responsible physician or their designee must be aware of the fact, that the UD can decline the donation process at any time and training should be provided for handling this situation (WMDA 2017: 3.06; FACT-JACIE 2017: CM6.2.5, C6.2.5).

4.1.4.5 The UD must have the opportunity to ask

questions (WMDA 2017 2.0; FACT-JACIE 2017: CM6.2.4, C6.2.4).

4.1.4.6 The UD must be informed about the (potential) consequences for the recipient, if he/she chooses to refuse to donate. This information may need to be in writing (follow your country requirements). He/she needs to know at which point during the process a refusal will have serious consequences (for example, refusal after the patient's conditioning has started) (WMDA 2017: 3.04, 3.10.1; FACT-JACIE 2017: 6.2.5.1, C6.2.5.1).

4.1.4.7 The informed consent form must be signed by the UD after the information session, but before the medical assessment procedure starts (WMDA 2017: 2.0).

4.1.4.8 Confirmation of signed consent must be provided to the DR (WMDA 2017: 3.14) in writing together with other required information after the medical assessment using WMDA forms F60, F80, or a DR-specific form equivalent to one of the forms mentioned here (WMDA 2017: 3.14, 8.06).

4.1.4.9 The information about a refusal to proceed must be provided to the DR immediately after the UD has refused to donate (WMDA 2017: 8.06).

4.1.5 Collecting pre-collection samples (including confirmatory typing samples if necessary)

4.1.5.1 UD must sign the informed consent form before any pre-collection samples can be collected (WMDA 2017: 3.10, 3.11; FACT-JACIE 2017: CM6.2.9, C6.2.9).

4.1.5.2 The CC must ensure the identity of the UD in an appropriate way before collecting the samples (e.g., photo ID) (WMDA 2017: 3.12; FACT-JACIE 2017: D11.1.1.1).

4.1.5.3 The pre-collection samples may be collected as part of the medical assessment as indicated in the work-up request (WMDA form F40 or equivalent), if reasonable.

4.1.5.4 The samples must be prepared for shipping according to the international safety recommendations, national rules and laws and according to the shipping instructions given on the work-up forms (WMDA 2017: 6.02.1).

4.1.5.5 The samples must be labeled according to national regulations, WMDA Standards and accreditation of the facility (WMDA 2017: 2.0; FACT-JACIE 2017: CM7.2.5, CM7.2.8), if not provided by the DR, and must:

4.1.5.5.1 Ensure traceability of the product (WMDA 2017: 2.0, 5.03, 8.07; FACT-JACIE 20115: D11.1.1.1).

4.1.5.5.2 Include UD's unique identification code (WMDA 2017: 2.0).

4.1.5.5.3 Include identification of the recipient according to the national requirements (WMDA 2017: 2.0).

4.1.5.5.4 Include date and time of sample collection

4.1.5.6 National requirements, as well as the DR's policies concerning the maximum volume of peripheral blood at the time of physical examination from an UD must be followed. In case there is more blood from the UD requested than usual, the responsible CC physician or their designee can decide to decline additional blood collection for donor safety reasons. This decision should be reported to the DR immediately.

4.1.6 Collecting research study samples

4.1.6.1 In case the UD is considered a research subject, he/she must be informed about the research study appropriately according to WMDA Standards and recommendations, as well as national laws and regulations (WMDA 2017: 3.10.1, 3.13; FACT-JACIE 2017: B8.3.2, B8.3.2.1, B8.3.2.2; B8.3.2.3, B8.3.2.4, B8.3.2.5) [7].

4.1.6.2 The UD must sign an informed consent form (WMDA 2017: 3.13) which will be provided by the study center. Some countries may have requirements to have the study reviewed by a local institution (e.g., the ethical review board of the CC or DR) and/or adapt the consent form according to national laws (WMDA 2017: 3.13; FACT-JACIE 2017: B8.3).

4.1.6.3 The UD must have the opportunity to ask questions about the research study before signing the consent form (WMDA 2017: 2.0; FACT-JACIE 2017: B8.3.1).

4.1.6.4 The UD must have the choice to decline participation in the research study. This needs to be clarified with the UD independently from the actual collection process (WMDA 2017: 3.10.1; FACT-JACIE 2017: B8.3.1).

4.1.6.5 The decision of the UD must be documented and the informed consent form must be added to the UD's records (WMDA 2017: 3.14; FACT-JACIE 10.3).

4.1.6.6 The DR must be informed about the UD's decision (WMDA 2017: 3.13).

4.1.6.7 For research documentation, the records must be maintained in accordance with applicable research protocol requirements (FACT-JACIE 2017: B8.2) [7].

4.1.6.8 The research study samples must be collected, labeled, and prepared for shipping as required in the research study request or in the request from the responsible DR according to their security and safety regulations (WMDA 2017: 8.08).

4.1.6.9 If the research samples require more blood to be collected from the UD than permitted by national standards or policies, the responsible CC physician or their designee can decline additional blood collection for donor safety reasons. This decision should be reported to the DR immediately.

4.2 Medical assessment

4.2.1 Scheduling

4.2.1.1 The CC must ensure the proper planning and coordination of appointments during the whole work-up procedure (FACT-JACIE 2017: CM3.3.2, C3.4.1).

4.2.1.2 Any issues which may have a possible impact on the collection schedule must be reported to the DR immediately.

4.2.2 Arrival and registration

4.2.2.1 There should be a person available for welcoming the UDs and their companions in an appropriate way. This person must be prepared for potential questions and concerns of the UDs and their companions (WMDA 2017: 8.03; FACT-JACIE 2017: CM3.3.1).

4.2.2.2 There must be a standard operating procedure in place to ensure a proper UD identification process (WMDA 2017: 3.12, 8.02; FACT-JACIE 2017: C6.5, C6.5.1).

4.2.2.3 The identification of the UD must be ensured in an appropriate way (e.g., photo ID) (WMDA 2017: 3.12, 8.02; FACT-JACIE 2017: C6.5, C6.5.1).

4.2.2.4 The anonymity of the UD and recipient must be ensured throughout the donation process. Only entitled personnel must have access to this data (WMDA 2017: 3.07; FACT-JACIE 2017: CM5.1.1, C5.1.1, CM6.2.1.4, C6.2.1.4, C11.1.4, C11.7.2).

4.2.2.5 Information regarding the procedure (including the information about the waiting time, necessary steps, necessary documentation, testing, etc.) must be explained to the UD in an appropriate way (WMDA 2017: 3.04; FACT-JACIE 2017: C6.2.1, C6.2.1.1, C6.2.1.2, C6.2.1.3, C6.2.1.4).

4.2.2.6 Clean and hygienic restrooms should be available close to the waiting room.

4.2.2.7 There should be information material (e.g., information flyers, books, electronic devices) available for the UDs and their companions that they can use to educate themselves during the waiting time about the collection procedure (WMDA 2017: 3.04).

4.2.2.8 The UD should be provided with information about availability of food and drinks for the UD (and their companions), as well as access to television or the internet for their entertainment during the apheresis procedure.

4.2.3 Unrelated donor health and eligibility

4.2.3.1 The medical assessment of the UD must be performed according to the national standards. WMDA Standards should also be applied at a minimum (WMDA 2017: 8.01; FACT-JACIE 2017: CM1.3.1, C1.3.1).

4.2.3.2 The risks of donation must be evaluated and documented (WMDA 2017: 3.23; FACT-JACIE 2017: CM6.3.2, CM6.3.3, C6.3.2), including:

4.2.3.2.1 Possible need for central venous catheter (WMDA 2017: 8.05.2, 8.05.3; FACT-JACIE 2017: C6.3.2.1).

4.2.3.2.2 Mobilization therapy for collection of HPC and apheresis (WMDA 2017: 8.05, 8.05.1 FACT-JACIE 2017: C6.3.2.2).

4.2.3.2.3 Anesthesia and HPC BM collection (WMDA 2017: 3.04, 3.05; FACT-JACIE 2017: B6.3.2.3).

4.2.3.2.4 Pregnancy assessment for all female UDs according to national standards and regulations and WMDA Standards (WMDA 2017: 3.22.3.2; FACT-JACIE 2017: B6.3.4).

4.2.3.3 Infectious disease markers (IDMs) must be tested within 30 days prior to the HPC collection or according to the applicable law and national requirement, as well as to WMDA Standards (WMDA 2017: 3.22. 3.24,

3.24.1, 3.25; FACT-JACIE 2017: B6.4.9.1, CM6.4.2, C6.4.2).

4.2.3.4 If country-specific IDMs are required (by applicable law and/or regulations) the UD must be tested for evidence of clinically relevant infections accordingly (WMDA 2017: 3.24.1).

4.2.3.5 IDM testing must be carried out in a manner to ensure the safety and accuracy of the data (WMDA 2017: 3.17.1, FACT-JACIE 2017: CM6.3.5, C6.3.5).

4.2.3.6 The IDM testing must be carried out by laboratories that meet national requirements and standards (as well as international lab standards if applicable), and using diagnostic tests approved by the government or prevailing authority in the relevant community for performing these services (WMDA 2017: 3.17; FACT-JACIE 2017: CM6.4.2, C6.4.2).

4.2.3.7 Additional tests must be performed as required to assess the possibility of transmission of other infectious or non-infectious diseases (WMDA 2017: 3.23; FACT-JACIE 2017: B6.4.11).

4.2.3.8 UDs which have recently traveled outside their country should be evaluated for infectious agents prevalent in the areas of travel (WMDA 2017: 3.24.1; FACT-JACIE 2017: B6.4.6, B6.4.6.2, B6.4.11).

4.2.3.9 The UD must be counseled in case of positive disease results (WMDA 2017: 3.26; FACT-JACIE 2017: B6.3.1.1).

4.2.3.10 If required by national regulations, an autologous blood back-up as a supplement for the UD must be collected at a blood collection center that fulfills national and/or regional and/or international standards for such a facility (WMDA 2017: 8.04).

4.2.4 Unrelated donor final clearance (WMDA 2017: 3.25)

4.2.4.1 After having collected all required information about the UDs health, the responsible CC physician or their designee decides if the UD is suitable for the requested collection procedure (WMDA 2017: 2.05, 3.10, 3.10.1; FACT-JACIE 2017: B6.4.13).

4.2.4.2 This decision must be documented on the final clearance form according to the WMDA Standards (F60, F80 or equivalent). Additional forms may be required by certain registries (WMDA 2017: 3.23; FACT-JACIE 2017: B6.4.16).

4.2.4.3 The CC physician or their designee is responsible for filling out and signing the clearance form prior to collection. If not required by national laws or requirements, then the subsequent review by a second person is strongly recommended (WMDA form F60: Donor final clearance pre-stem cell collection; FACT-JACIE 2017: B6.4.13, B6.4.17.1).

4.2.4.4 The donor final clearance must be communicated in writing to the DR before commencement of patient conditioning (WMDA 2017: 3.23; FACT-JACIE 2017: B6.4.13) and before the UD begins mobilization regimen.

4.2.4.5 The donor final clearance and the detailed results of the medical assessment, as well as the signed informed consent form from the UD must be added to the UD's records. (WMDA 2017: 3.14, 3.19; FACT-JACIE 2017: B6.4.17, B6.4.17.1).

4.2.5 Medical ineligibility

4.2.5.1 In case of a medical ineligibility of the UD for the requested collection procedure, the DR standards and national regulations should be followed.

4.2.5.2 Additionally, WMDA donor suitability, as well as DR-specific medical eligibility criteria lists can be consulted for general recommendations [8].

4.2.5.3 The DR must be informed about medical ineligibility of the UD immediately. Additionally, this information must be forwarded to the DR in writing using F60, F80, or equivalent (WMDA 2017: 6.01; FACT-JACIE 2017: B6.4.16).

4.2.5.4 CC physicians or their designee should consider national and international ineligibility criteria when determining the UD's eligibility (as above). Consideration of the UD's situation must be evaluated on a case by case basis (FACT-JACIE 2017: CM6.3, CM6.3.1.1, CM6.3.1.2, CM6.3.1.3, B6.3, B6.3.1.1, B6.3.1.2, B6.3.1.3).

4.2.5.5 When a potential risk for the recipient is identified, there might be a need to declare the UD as ineligible for the recipient according to national requirements and laws. The TC needs to be informed about this fact via the responsible DR according to the applicable data protection laws and requirements using

the WMDA form F20 (or equivalent). Additionally, some country-specific requirements have to be fulfilled (e.g., DUMN, declaration of ineligibility). These documents must be added to the UD's records and provided to the responsible DR. UD's eligibility can only be confirmed once TC has confirmed that the risk has been evaluated and is acceptable for the TC (FACT-JACIE 2017: B6.4.15).

4.2.5.6 Additional information about the health situation of the UD that might be relevant for the TC, but does not have a direct impact on the UD's eligibility, can be added to the WMDA form F60, F80, or equivalent as comments.

4.3 Product collection

4.3.1 In general

4.3.1.1 The collections must be performed according to national requirements and laws as well as WMDA Standards and recommendations. This includes G-CSF injection procedures for HPC Apheresis (WMDA 2017: 8.01, 8.05; FACT-JACIE 2017: CM1.3.1, C1.3.1).

4.3.2 The collection procedure

4.3.2.1 The identification of the UD must be ensured in an appropriate way (e.g. photo ID) (WMDA 2017: 3.12).

4.3.2.2 The requested cell dose should be verified by the responsible physician or his designee at the CC. It is generally accepted that the standard cell-count for CD34+ cells is up to 5×10^6/kg bodyweight of the recipient in case of a PBSC collection [9]. If a higher quantity of cells is requested, an explanation is required. The explanation needs to be provided by the TC by using the WMDA verification form F40. F70 or equivalent needs to be approved by the CC before collecting the cells.

4.3.2.2.1 Reasons for higher cell dose requests need to be carefully evaluated by the responsible physician at the CC. The following reasons can be taken into account:

- T-cell depletion planning
- Positive CD34+ cell selection
- Major ABO incompatibility (only for HPC, Marrow collections)
- Active residual disease in recipient
- Research study protocols

4.3.2.2.2 UD safety always takes priority [2]. If the health situation of the UD allows it, a deviation from the standard cell dose 5×10^6/kg patient bodyweight may be granted if permitted by national regulations. The written statement of the TC physician must be considered.

4.3.2.3 HPC, Apheresis

4.3.2.3.1 Administration of mobilization agents must be performed according to the WMDA Standards and national regulations and guidelines (WMDA 2017: 3.05, 8.05, 8.05.1, 8.03; FACT-JACIE 2017: CM8.9, C8.11).

4.3.2.3.2 There must be written documentation of the assessment of UD suitability for the collection procedure performed by a qualified person immediately prior to each collection procedure (WMDA 2017: 2.05, 3.19, 3.02, 8.03; FACT-JACIE 2017: CM8.7).

4.3.2.3.3 Encourage the practice of single-day collections to achieve the requested number of CD34+ cells while not unnecessarily prolonging the apheresis procedure. In general, collections must be performed within one day whenever possible. In the event that the cell count, according to the work-up request is not adequate for transplantation, a 2nd day collection may be considered.

4.3.2.3.4 If $<2 \times 10^6$ CD34+ [10] cells were collected, the need for further actions must be discussed. It is the responsibility of the CC physician to decide whether or not a 2nd apheresis is feasible and can be performed without affecting the health of the UD (WMDA 2017: 5.05.1).

4.3.2.3.5 A collection of an alternative cell source has to be carefully considered by the CC physician and the DR, taking into consideration the health of the UD, the eligibility of the UD for an alternative collection procedure, and the recipient treatment plan.

4.3.2.4 HPC, Marrow

4.3.2.4.1 The maximum harvested BM volume defined by the local authorities must not be exceeded [11]. The goal is to reach the optimal total nucleated cell (TNC) count in a relatively low volume of product.

4.3.2.4.2 General or regional anesthesia generally must be performed or supervised by a licensed,

specialist-certified anesthesiologist. If this is not required by the national requirements, the DR-specific requirements should be followed (FACT-JACIE 2017: CM8.8).

4.3.2.5 Handling products with low cell counts (e.g. poor mobilization)

4.3.2.5.1 In the event of poor mobilization [12] (for HPC, Apheresis) or low cell count (for HPC, Marrow) [13], the responsible UD DR must be informed immediately about this fact (WMDA 2017: 8.05.1). It must be considered if the already collected cells can be infused, then alternative cell sources or alternative donors should be considered involving the responsible TC physician.

4.3.2.5.2 If facilities are available, the UD may be approached to consider an alternative collection procedure (e.g., BM collection). This can only take place after the information session, medical clearance of the UD for the alternate procedure and signing of an informed consent by the UD (WMDA 2017: 3.04, 3.05).

4.3.3 Medical emergencies

4.3.3.1 Medical emergencies or other issues can arise at any time: between medical assessment and the collection, during the collection or shortly after the collection. In such cases, the CC is responsible for decisions regarding further actions, as well as for the medical care of the UD. All emergencies which may have an impact on the collection or on the recipient must be reported to the DR immediately (WMDA 2017: 8.10.1, 9.04.1; FACT-JACIE 2017: CM5.1.13, C5.1.19).

4.3.3.2 Every effort must be made to help the UD in case of an emergency. Close collaboration with the local medical services may be required (FACT-JACIE 2017: CM5.1.14, C5.1.19, CM2.7, C2.8).

4.3.3.3 If necessary, hospitalization of the UD needs to be considered.

4.3.3.4 To comply with WMDA Standards and any national regulations, serious adverse events and reactions affecting UDs undergoing collection of HPC and occurring either long term or short-term as a consequence of the donation must be documented and investigated (WMDA 2017: 8.09, 8.10, 9.03, 9.04; FACT-JACIE 2017: C4.10.3.1, CM4.10.3.1).

4.3.3.5 Every serious adverse event and serious adverse reaction must be reported to the WMDA using the WMDA's international centralized database via the responsible DR or to the WMDA directly, if a national DR is not in place. The DR's policies for reporting the serious adverse event and serious adverse reaction cases must be followed (WMDA 2017: 9.04).

4.3.4 Product identification

4.3.4.1 Each cellular therapy product must be labeled and coded according to national requirements and laws and applicable international regulations. The WMDA Standards for labeling should be taken into account (WMDA 2017: 8.07; FACT-JACIE 2017: CM7.3.1).

4.3.4.2 Each cellular therapy product collection must be assigned a unique numeric or alphanumeric identifier by which it will be possible to trace the cellular therapy product to the UD and to all records describing the handling and final disposition of the product (WMDA 2017: 2.0, 8.07; FACT-JACIE 2017: CM7.3.1, C7.3.1).

4.3.4.3 The cellular therapy product, as well as samples from the UD and the product, must be labeled with the same UD identifier (WMDA 2017: 2.0, 8.06; FACT-JACIE 2017: CM7.3.1, C7.3.1).

4.3.4.4 If a single-cellular collection product is stored in more than one bag, there should be a system to identify each container (FACT-JACIE 2017: CM7.3.1.2, C7.3.1.2).

4.3.4.5 CCs may designate an additional or supplementary unique numeric or alphanumeric identifier to the cellular therapy product. Supplementary identifiers must not obscure the original identifier. The entity associated with each identifier must be noted in the documentation (WMDA 2017: 2.0, 8.07; FACT-JACIE 2017: CM7.3.1, C7.3.1).

4.3.4.6 Personal data of the UD must not appear on the label (e.g., name, date of birth) (WMDA 2017: 3.07, 8.02; FACT-JACIE 2017: CM7.3.1, C7.3.1).

4.3.4.7 The "Product Information Form" must include the essential data required by using WMDA form C10 or equivalent (WMDA 2017: 8.07; FACT-JACIE 2017: CM7.3.1, C7.3.1).

4.3.5 Label content

4.3.5.1 To ensure that the product has been labeled with the correct label, labeling should be verified by two separate persons and verification of the labeling must be recorded (WMDA 2017: 8.06, 8.07; FACT-JACIE 2017: C8.1, CM7.3.1, C7.3.1).

4.3.6 Process controls

4.3.6.1 Collection of cellular therapy products must be performed according to written procedures (WMDA 2017: 8.06; FACT-JACIE 2017: CM8.1).

4.3.6.2 Equipment for the collection procedure must conform to laws and regulations, where applicable (WMDA 2017: 8.06; FACT-JACIE 2017: CM8.3, C8.3).

4.3.6.3 There must be a system in place to uniquely identify, track and trace all critical equipment, reagents, supplies, and labels used in the collection of cellular therapy products (WMDA 2017: 8.06; FACT-JACIE 2017: D11.2.1-D11.2.1.11).

4.3.6.4 Each supply and/or reagent used to collect HPC products must be visually examined for damage or evidence of contamination, both at receipt and prior to use. There must be a quarantine procedure in place for contaminated supplies and reagents (WMDA 2017: 8.06; FACT-JACIE 2017: CM8.2.2, C8.2.2, D9.4.3.2).

4.3.6.5 Supplies and reagents coming into contact with cellular therapy products during collection must be sterile and of the appropriate grade for the intended use (WMDA 2017: 8.06; FACT-JACIE 2017: CM8.2.3, C8.2.3).

4.3.6.6 Methods for collection must employ procedures validated to result in acceptable cell viability and recovery (WMDA 2017: 8.06; FACT-JACIE 2017: C8.12.2, CM8.12).

4.3.6.7 Collection methods must employ aseptic techniques to ensure that cellular therapy products do not become contaminated during collection (WMDA 2017: 8.06; FACT-JACIE 2017: C8.13, CM8.11).

4.3.6.8 The CC must have a process for assessing the quality of cellular therapy products to ensure their safety, viability, and integrity and to document that the product meets predetermined release specifications (WMDA 2017: 8.02, 8.06, 8.07; FACT-JACIE 2017: CM8.10, C8.12).

4.3.6.9 Results of each assessment must become part of the permanent record of the collected product (WMDA 2017: 8.07; FACT-JACIE 2017: CM8.10, C8.12).

4.3.6.10 Cellular therapy products must be packaged in a sealed sterile transfer pack appropriate for blood or marrow products (WMDA 2017: 8.08; FACT-JACIE 2017: C8.15, C8.13).

4.3.6.11 Records must be made concurrently with each step of collection of each cellular therapy product which allow for all steps to be accurately traced (WMDA 2017: 5.01, 5.03, 5.04; FACT-JACIE 2017: CM8.15, C8.16).

4.3.7 Product quality

4.3.7.1 Testing must be carried out by laboratories that meet standards established by the government or prevailing authority in the relevant community for performing these services (WMDA 2017: 3.17; FACT-JACIE 2015: CM6.3.4, C6.3.5).

4.3.7.2 Testing must be carried out in a manner to guarantee the accuracy of the data (WMDA 2017: 3.17.1; FACT-JACIE 2017: CM6.3.4, C6.3.5).

4.3.7.3 The correlation between the requested and collected cell count in the product needs to be verified by the CC's laboratory and communicated to the DR/TC as soon as possible

- **For HPC, Marrow: TNC, and CD34+ cell counts, if possible.**
- **For HPC, Apheresis: CD34+ cell count.**
- **For T-Cell, Apheresis: CD34+ cell count, additionally mononuclear cell (MNC) count can be provided (WMDA 2017: 8.06, FACT-JACIE 2017: CM8.10, C8.12).**

4.3.7.4 Testing for possible product contamination must be performed according to national regulations (FACT-JACIE 2017: CM4.1, C4.9-C4.9.4).

4.3.7.5 If the collection of HPC requires a 2nd day apheresis, the 2nd day product also needs to be tested (WMDA 2017: 8.06, 3.17).

4.3.7.6 In case of any positive result, the DR must be informed immediately in writing (WMDA 2017: 8.10.1; FACT-JACIE 2017: CM4.1,

C4.9, C4.9.1, C4.9.2, C4.9.3).

4.3.7.7 In addition, if sterility testing is performed at the CC sites, in case of positive results the report must be sent to the DR as soon as available.

4.3.7.8 For HPC, Apheresis product's erythrocyte contamination should be considered.

4.3.7.9 In case of a serious adverse event or reaction, the report must be generated and sent to the respective DR and national authorities and the WMDA S(P)EAR committee, in case there is no DR in place (WMDA 2017: 8.1; FACT-JACIE 2017: CM4.1, B4.10.4.1, B4.10.4.2, C4.10.4.1, C4.10.4.2, C4.10.3.3).

4.3.8 Hematocrit value and plasma volume in products

4.3.8.1 The TC requirements concerning the hematocrit value in the product, as well as the required plasma volume in the product should be taken into account.

4.3.8.2 The product hematocrit results, as well as the plasma volume should be included in the product information.

4.3.8.3 Any planned deviation from the requested dilution, addition of anticoagulants or additives (e.g., due to local requirements) must be communicated to the TC prior to the collection procedure. The planned deviation should be sent to the DR with the clearance paperwork and should include an explanation for the reasons for the planned deviation. The planned deviation from the requested product should be confirmed by the responsible TC physician.

4.3.9 Packaging

4.3.9.1 Packaging of the product must comply with national laws, international regulations and DR standards (WMDA 2017: 8.08; FACT-JACIE 2017: CM8.13, C8.15).

4.3.9.2 The WMDA Standards must be respected and the World Marrow Donor Association (WMDA) Guidelines for couriers and the transportation of hematopoietic progenitor cells (HPC—BM, apheresis and therapeutic cells, T cells) should be taken into account (WMDA 2017: 1.08) [14].

4.3.9.3 The transportation box must be validated for required transportation conditions (WMDA 2017: 8.08; FACT-JACIE 2017 CM10.1, C10.1).

4.3.10 Product storage

4.3.10.1 CC should establish policies for the duration and conditions of storage of products prior to distribution to a processing lab or TC (FACT-JACIE 2017: CM9.2, C9.2).

Product handover

5.1 The staff involved in the handover of the product must be appropriately trained in the handover procedure (WMDA 2017: 8.08).

5.2 The handover procedure should be performed according to WMDA recommendations and national requirements and cover at minimum the following steps:

5.2.1 Ensuring the identity of the courier (WMDA 2017: 8.07, 8.08; FACT-JACIE 2017: D11.2.1.10) [14].

5.2.2 Ensuring the proper preparation for transportation, checking at minimum the following:

5.2.2.1 The transportation paperwork and labeling is correct (WMDA 2017: 8.07).

5.2.2.2 The documentation is signed by two different people, e.g., cross-checking the information together with the courier (WMDA 2017: 8.07) [14].

5.2.2.3 The staff member responsible for international product handover should have adequate command of the English language to communicate with the courier.

5.2.2.4 There is appropriate packaging for HPC for transportation according to national or international requirements and recommendations (WMDA 2017: 8.08).

5.3 The CC should be aware of the transportation constraints of the courier e.g., timing of the apheresis when there are limited flight connections.

5.4 Any incident concerning the handover process (e.g., inadequate transportation equipment) needs to be reported to the responsible DR immediately (WMDA 2017: 8.08).

5.5 The primary cellular therapy product container should be placed in a secondary container that is sealed to prevent leakage, if not otherwise communicated by the TC (WMDA 2017: 8.08).

5.6 There must be a record of the date and time the cellular therapy product was handed over to the courier (WMDA 2017: 8.08; FACT-JACIE 2017: CM10.5, C10.5).

Unrelated donor follow-up (post-donation care)

6.1 In general, the UD DR is responsible for the UD follow-up (WMDA 2017: 9.01, 9.03).

6.2 The UD follow-up, in case this is the responsibility of the CC according to the agreements with the responsible DR, must be performed according to DR standards and any national regulations and laws (WMDA 2017: 9.01, 9.02).

6.3 The CC must provide the UD and DR with post-donation care instructions as required by the responsible DC (WMDA 2017: 9.01).

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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