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Towards a Global Standard for Donation, Collection, Testing, Processing, Storage, and Distribution of Allogeneic HSC and Related Cellular Therapies

Position Paper from the Alliance for Harmonisation of Cellular Therapy Accreditation (ACHTA). ACHTA represents American Association of Blood Banks (AABB), American Society for Blood and Marrow Transplantation (ASBMT), European Federation for Immunogenetics (EFI), European Group for Blood & Marrow Transplantation (EBMT), Foundation for the Accreditation of Cellular Therapy (FACT), International Society of Cellular Therapy (ISCT) (Europe), Joint Accreditation Committee ISCT & EBMT (JACIE), NETCORD, World Marrow Donor Association (WMDA).
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Background

There is an increasing awareness of the need to ensure the quality and safety of tissues and cells for transplantation. At the same time in the field of human haematopoietic stem cell transplantation (HSCT), there is increasing use of cells from unrelated bone marrow, peripheral and cord blood donors and 42% (2007) of all transplants now cross international boundaries. This imposes an added layer of complexity for individual countries, i.e. how to ensure that these imported cells meet the requirements of their regulatory authorities.

The European Union (EU) Directive 2004/23/EC (EU Tissues and Cells Directive; EU TCD) requires Member States to ensure that tissues and cells imported from non-EU countries meet “standards of quality and safety equivalent to the ones laid down in [the] Directive” (Article 9, 2004/23/EC). These cells include haematopoietic progenitor cells

(stem cells) collected from either bone marrow (haematopoietic progenitor cells, marrow; HPC, Marrow), from peripheral blood (haematopoietic progenitor cells apheresis; HPC, Apheresis), or from cord blood (haematopoietic progenitor cells, cord blood; HPC, Cord Blood) and also therapeutic cells collected from blood or marrow such as donor T-cells for infusion (TC-T cells). The EU-TCD requires also that the assessment, safety and follow-up of the donor are ensured.

In the US, the Food and Drug Administration (FDA) requires imported cells to comply with specific requirements for donor eligibility and donor testing (particularly with reference to infectious disease markers (IDM). It also requires collection centres in the country of origin to be registered with the FDA. Some other countries outside the US and the EU have similar requirements imposed through national legislation. However there are many countries where some or all of the necessary regulations and standards are not yet in place.

It is therefore important to develop global harmonisation of standards, so that different countries operate under similar guidance and regulations. There also needs to be a system of ensuring the standards are met.

Both the AABB and FACT-JACIE standards and accreditation systems for HPC, Marrow and HPC, Apheresis collection facilities (CF) and the AABB and Netcord-FACT standards and FACT-Netcord accreditation system for HPC, Cord Blood collection and cord blood banks (CBBs) would ensure that cells provided by accredited centres and CBBs meet the requirements of the EU TCD and the FDA. However, it will be some time before all facilities in the US and Europe can be accredited, and many cellular therapy products will continue to be imported from countries that do not as yet take part in these accreditation systems.

Accreditation of HPC, Marrow and HPC, cord blood registries by WMDA could provide similar confirmation. All cells from unrelated donors are sourced through international bone marrow and cord blood donor registries. These are linked through the Bone Marrow Donors Worldwide (BMDW) online database and some cord blood banks are also linked through the NETCORD registry.

All these donor registries operate using WMDA standards which cover aspects of donor recruitment, assessment, collection, testing, searches and transport. These standards now incorporate the requirements of the EU TCD. However, again it will be some time before all donor registries can be accredited.

There is therefore a need to develop criteria for ensuring quality and safety that can be immediately adopted and implemented. These criteria should be sufficient to meet the requirements of the FDA, the EU TCD and other relevant national legislation (e.g. in European countries outside the EU), but not so detailed as to lead to compliance difficulties for registries and associated CF/CBBs. It is most important that any regulatory requirements do not inhibit or delay the provision of HPC and related cells across international boundaries.

The above referenced organizations set up the Alliance for Harmonisation of Cellular Therapy Accreditation (AHCTA), with the goal of harmonising accreditation requirements worldwide, and with the initial aim to develop core standards for HPC (and related cells including TC-T cells) which are globally applicable and which are practicable. This goal is in accordance with the aims of the World Health Organisation as set out in the document

Aide Mémoire on Key Safety Requirements for Essential Minimally Processed Human Cells and Tissues for Transplantation [link].

The main issues and approach to be adopted are outlined below.

Issues affecting quality and safety of Tissues and Cells

These include

1. Donor assessment and testing
2. Procurement / collection /processing
3. Storage (in the case of cord blood banks)
4. Donor selection
5. Transport and distribution including reception at the tissue establishment or, in the case of direct distribution, at the clinical facility using the cells
6. Labelling

Donor assessment and testing is organised by the international donor registries and may be performed in donor centres (medical centres which medically assess the donor but do not perform the actual collection and which are not transplant centres), collection facilities (medical facilities which also perform the collection), or transplant centres (centres which also perform transplants).

Collection is carried by Collection Facilities. Collection Facilities may collect cells either from bone marrow or from peripheral blood by apheresis. Cells collected by apheresis include HPC and also in some cases donation of T cells by the same donor for donor lymphocyte infusion or other forms of specific immunotherapy.

There are also cord blood collection facilities, which collect cells for storage by cord blood banks. The AABB and Netcord-FACT standards and accreditation system consider cord blood collection facilities as an integral part of the accreditation of CB banks.

HPC other than cord blood are generally not stored but transported directly to the recipient transplant centre or associated tissue establishment / processing facility. In this case the Collection Facilities are responsible for labelling and transport.

HPC, Cord Blood units are stored and subsequently transported to the recipient transplant centre. Both collection facilities and CBBs are therefore involved in transport and labelling. The donor registries are not directly involved with distribution of the stem cell products. These cellular therapy products go directly from the donor centre (in the case of samples), collection facility or CBB to the recipient centre. However the donor registries must ensure that the transport and labelling of the products conform to specified standards.

1. Donor Assessment and Testing

For participating collection facilities, this is currently organised by Donor Registries and, as above, may be performed in donor centres, collection facilities or transplant centres. However, the donor registry has overall responsibility for ensuring that the donor is fit to donate and that appropriate informed consent has been obtained. The donor registry is also responsible for confirming donor eligibility. (See WMDA recommendations: Haematopoietic stem cell donor registries: World Marrow Donor Association

recommendations for evaluation of donor health - Bone Marrow Transplantation (2008), 1–6)

Donor eligibility is defined according to international standards set by the EU Commission Directive 2006/17/EC, by the FDA and by AHCTA organisations. If additional eligibility testing is required by the recipient country, this may be performed either by the centre assessing the donor, or by the transplant centre in the recipient country, using samples sent from the donor assessment centre.

Testing for infectious disease markers (IDM), HLA typing and ABO/Rh is performed on samples sent to laboratories assigned by the donor registry or donor assessment centre. Transplant centres in the recipient country may also perform their own IDM analyses and repeat ABO/Rh typing and/ or HLA typing on received samples to meet national requirements. The Donor Registry provides documentary evidence to the recipient centre to confirm results (Donor Clearance Report).

The responsibility for ensuring that donors fulfil donor eligibility requirements as per EU Commission Directive 2006/17/EC, FDA regulations and/or those of other national regulatory agencies is therefore that of the donor registry.

2. Collection

Collection facilities for harvesting cells from individual donors are assigned by the donor registry in the relevant county. Different situations apply in different countries as to whether the registry is able to use only facilities that are accredited by FACT-JACIE or another body. WMDA standards require registries to use collection facilities that meet relevant national guidelines where these exist. There are however countries where no such guidelines exist. There is therefore a clear need to produce appropriate standards for collection facilities on a global basis, to cover critical areas such as staff training.

3. Storage (Cord Blood Banks)

Similarly, not all cord blood banks are currently accredited by AABB or Netcord-FACT, and although many such banks will be licensed as tissue establishments by the competent authority in the relevant country, there are countries where regulation is not yet fully established. There is therefore a clear need to produce appropriate standards for cord blood banks on a global basis.

4. and 5. Transport/Labelling

Currently labelling is the responsibility of the collection facility. Transport to the receiving institution is the responsibility of the receiving centre which either will send a courier to the collection facility to collect the product, or arrange collection by a commercial courier. It would be desirable to ensure a standard system of labelling that meets the requirements of AABB, FACT-JACIE and Netcord-FACT (and hence the requirements of the FDA and the EU TCD), and also to ensure that protocols and procedures for labelling and transport meet these requirements also. Towards this end, AHCTA member organisations support the ISBT 128 Standards for the Terminology and Labelling of Cellular Therapy Products. The use of standard terminology will help to ensure a common understanding of product definitions. The labelling standard, supported by the ISBT 128 information system, will ensure unique global identification of cellular therapy products, an international reference table for product descriptions, and label design that is consistent worldwide.

In developing the terminology standard the ISBT 128 Advisory Group recognized that the frequent movement of cellular therapy products between countries (and continents) required a consistent use of terminology between ISBT 128 and other published standards (e.g., Circular of Information, AABB, FACT, JACIE, Netcord). The Advisory Group has attempted to achieve these aims by removing complexity and redundancy from the coding system wherever possible and, by wide consultation, agreeing to terminology acceptable to all for inclusion in future publication of their standards and guidance

Approach to be adopted to develop a Global Standard

1. Donor Assessment and Testing

The donor registries already have a comprehensive procedure for ensuring donor fitness, consent and eligibility. All that is needed is to develop a globally agreed definition of eligibility and required testing. The donor eligibility criteria and requirements for testing listed in the current FDA and EU TCD requirements are almost identical; there are minor differences such as whether HTLV testing is required in all donors or only in those from specific risk groups. It should therefore be possible to produce agreed globally applicable criteria by using appropriate wording.

2. Collection, Storage, Labelling and Transport

The EU requires that collection facilities and CBB in so-called third countries work to appropriate standards. The FDA and Australian Therapeutic Goods Administration (TGA) have similar requirements. These need not be as detailed as those required by AABB, Netcord-FACT and FACT-JACIE but should be consistent with these standards and should fulfil requirements of the FDA and the EU TCD.

These standards should cover the following areas

a. Personnel
b. Facilities and Equipment
c. Procedures for donor assessment, consent and collection.
d. Processing
e. Storage/banking (for CBBs)
f. Labelling
g. Transport and Distribution
h. For CBB, service level agreements with collection facilities
i. Collection of outcome data

There must be a system of ensuring these standards are met. This could be at two levels.

1. Accreditation by an international body e.g. AABB, FACT-JACIE or Netcord-FACT
2. Accreditation by a national body or national competent authority

Where neither of the above is in place, some type of registration of CF or CBBs would be required, as currently operated by the FDA for non-US facilities. This could require submission of documentation to demonstrate compliance with the specified minimum requirements.

Actions required

1. To develop draft proposals for
    a. Globally accepted donor eligibility criteria
    b. Globally accepted minimum safety criteria for collection facilities and cord blood banks
    c. A system of verification of compliance with standards
2. To consult widely on the above, with relevant professional organisations, with regulatory authorities and with others involved in global healthcare issues.

References

- AABB Standards for Cellular Therapy Product Services, 3rd ed. (available for purchase at www.aabb.org or upon request at celltherapy@aabb.org for government officials)
- FACT-JACIE International Standards for Cellular Therapy Product Collection, Processing and Administration, 3rd edition, 2006, www.jacie.org & www.factwebsite.org
- ISBT 128 Standard for Cellular Therapy Coding, www.iccbba.org/cellulartherapy_home.html
- Netcord-FACT International Standards for Cord Blood Collection, Processing, Testing, Banking, Selection and Release, 3rd edition, 2006, www.factwebsite.org
- WMDA standards, version effective December 2007, www.worldmarrow.org

Table 1. Current origin of stem cell products and the potential impact in the event of restrictions on this movement of cells

Data courtesy of the WMDA.

Unrelated BM/PBSC in EU (2007)					
Europe	Import %	Own country	Total Imported products	From EU country	From non EU country
		No. BM/PBSC in 2007	No. BM/PBSC in 2007	No. BM/PBSC in 2007	No. BM/PBSC in 2007
Austria	80	18	72	62	10
Belgium	93	8	111	98	13
Bulgaria	67	1	2	2	0
Croatia	100	0	8	8	0
Cyprus	25	3	1	1	0
Czech Republic	76	32	99	81	18
Denmark	83	9	45	39	6
Finland	68	20	42	41	1
France	77	127	419	339	80
Germany	17	1,230	250	98	152
Greece	94	2	33	29	4
Hungary	95	2	38	32	6
Ireland	91	3	29	22	7
Italy	67	147	294	197	97
Lithuania	58	5	7	7	0
Netherlands	85	22	120	97	23
Norway	80	5	20	12	8
Poland	86	24	142	130	12
Portugal	61	13	20	19	1
Slovakia	100	0	6	6	0
Slovenia	90	1	9	6	3
Spain	87	21	142	89	53
Sweden	89	12	93	68	25
Switzerland	97	2	57	43	14
Turkey	82	5	23	18	5
United Kingdom	43	318	241	145	96
TOTAL		2,030	2,323	1,689	634

Annex I: AHCTA Minimal Standards

1. Consent

Must be taken by a doctor or other appropriately trained healthcare professional and must explain:

- the procedure in straightforward terms that will be readily understood by the donor
- any significant risks to the donor and likely benefits to the recipient
- the nature of laboratory investigations conducted to protect the donor and the recipient of their cells
- the right to anonymity where this is required and to review the results of all tests performed
- alternatives to donation
- the right to withdraw or refuse to donate

There should be no coercion to donate or payment involved other than reasonable reimbursement of expenses.

All donors should be given appropriate information.

Consent should be documented.

2. Age

Unrelated donors are normally aged 18-60 years.

3. Medical History and Examination

(A) Specific enquiries should be made about:

- Vaccination
- Travel
- Blood transfusion
- The risk of transmission of inherited, haematological, immunological, infective or malignant conditions

Specifically the medical history and examination should ascertain the following:

- Whether the donor has active bacterial, viral, fungal or parasitic infection
- Whether the donor has been exposed to risk of infection
- Whether the donor has malignant disease (excluding basal cell or carcinoma of the cervix in-situ)

- Whether the donor has an immunological, haematological or inherited disease
- Whether the donor is at risk of transmission of prion disease
- Whether the donor has connective tissue disease e.g. rheumatoid arthritis, SLE
- Disease of unknown aetiology

(B) Tests should be validated and where appropriate licensed. They should be conducted in accredited laboratories for the following:

(i) Haematology/transfusion – full blood count and coagulation screen, clotting screen, ABO and Rh groups and compatibility testing
(ii) Biochemistry – electrolytes, renal and liver function tests
(iii) Chest X-ray (only for donors over 45 years) and ECG
(iv) Microbiological tests:

- Hepatitis B virus – HBS Ag*, anti HBC*antibody nucleic acid test (NAT)
- Hepatitis C virus – anti-HCV* antibody
- HIV 1+" – anti HIV 1+2* antibodies
- Syphilis*
- CMV – anti-CMV antibody

(* mandatory in the EU and USA)

Other tests which will be performed at the discretion of the donor registry, cord blood bank or transplant centre include anti-HTLV1+2 antibody, HIV NAT, and tests for VZV, HSV, toxoplasmosis and malaria.

(v) Histocompatibility and immunogenetics – HLA typing of the donor at a minimum for HLA-A, B, DR type.

4. Marrow, donor selection and collection facilities

- Appropriate areas for donor counselling and evaluation, the collection procedure, stores and storage of the HPC component.
- There should be a Medical Director who is responsible for all medical aspects of donor assessment, counselling, consent and the collection procedure.
- There should be a director or supervisor responsible for all operational aspects of the facility including care of the donor during the collection procedure. Both these individuals and other staff in the unit should be appropriately qualified and have received the necessary training.

5. Quality

The collection facility should have a quality management plan (QMP) and associated standard operating procedures (SOPs) covering all aspects of the operation of the facility, the conduct of collection procedures including the reporting of adverse events to national and international authorities. The QMP and SOP should address labelling, transport and record keeping.

Labelling should include the following:

- Product name in English according to the ISBT 128 nomenclature
- Date and time of collection
- Hazard warnings e.g. *donor not tested for markers of infectious disease*, *donor has risk factors for infectious disease*, *donor has positive markers for infectious disease*
- Additives and anti-coagulants
- Identification of the intended recipient as a minimum by reference number
- Medical specimen handle with care, do not X-ray