1. INTRODUCTION

Following the publication of the Superior Health Council (SHC) advisory report on the autologous use of cord blood (CB) (SHC 8677, 2011), the Minister of public Health has requested the SHC to take another look at CB, this time at CB for allogeneic use. More specifically, the Minister wishes to obtain additional information on its current standard use and translational indications, as well as the need for CB in Belgium. Finally, she would like to know whether or not it is appropriate to organise campaigns to raise awareness about CB donation among the general population and/or specific target groups.

In order to respond to the Minister’s requests, an ad hoc working group was set up which included experts from the fields of haematology, immunology, cell biology, CB banking and cellular therapy. This sub-working group drew up this advisory report. It was then submitted to international experts (peer review) and ultimately to the standing working group “Cells, tissues and organs of human and animal origin” for approval.

2. CONCLUSION

Since their establishment in the 1990s, umbilical cord blood (UCB) banks for allogeneic use have played an increasingly prominent role in haematopoietic stem cell (HSC) transplantation. There is currently a worldwide inventory of about 540,885 immediately available units (BMDW, 22 August 2012). In the meantime CB has become a source of HSCs equivalent to other types of grafts in children or an acceptable alternative source of HSCs in adults. This has been confirmed by the increasing use of these types of graft during the last 15 years. In addition to unrelated donor transplantations, it is also possible, for some indications, to carry out related-donor transplantations, provided that good-quality grafts can be harvested and stored.

Since the establishment of the first UCB banks, banking and transplantation practices have evolved, international standards have been set up and the legal frameworks improved. This has resulted in a better overall quality of available grafts. On the other hand, transplant centre requirements for graft selection have evolved in the same way at the international level.

- Current standard use and translational indications

One of most active and extensive fields of clinical research is haematopoietic stem cell transplantation. This research mainly focuses on improving post-transplant immune and haematopoietic reconstitution by using two grafts at the same time, by resorting to cells from
another donor or by applying in-vitro expansion methods or any other means of improving engraftment (cytokines, intra-bone injection, etc.).

In pre-clinical research in the field of regenerative medicine, CB could potentially be used as a source of non-haematopoietic stem cells.

- **Need for CB in Belgium**

In Belgium, 90 % of unrelated transplantations are carried out with a foreign graft/donor. For patients from certain ethnic groups, the likelihood of finding a compatible donor/graft remains low. Indeed, most donors and available grafts are of Caucasian origin. As a result, recruiting new units should focus more intensely on populations that are underrepresented in the inventories so that they too might have access to compatible grafts.

The medium and long-term development strategies for allogeneic CB banks should be considered within an international framework, and should take into account the evolution of quality requirements. The main lines of these strategies should be:

- Only high-quality units with high cellular content should be stored;
- All banks should have policies in place to check whether CBUs stored prior to the introduction of quality standards comply with current standards (i.e. cell counts, viability and clonogenic activity, infectious disease markers, sterility, packaging and labelling);
- The immunogenetic diversity of the stored units should be broadened;
- More maternity units should be accredited as collection sites.

- **Need for campaigns**

The SHC recommends that campaigns to raise the awareness of the general public and minority groups should be launched once more maternity units have been accredited as collection sites.

Keywords

<table>
<thead>
<tr>
<th>Keywords</th>
<th>Mesh terms*</th>
<th>Sleutelwoorden</th>
<th>Mots clés</th>
<th>Stichwörter</th>
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<tr>
<td>Cord blood</td>
<td>Fetal blood</td>
<td>navelstrengbloed</td>
<td>Sang de cordon</td>
<td>Nabelschnurblut</td>
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<td>Allogeneic</td>
<td>Homologous transplantation</td>
<td>allogen</td>
<td>Allogénique</td>
<td>Allogen</td>
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<td>Stem cells</td>
<td>Stamcellen</td>
<td>Cellules souches</td>
<td>Stammzelln</td>
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<td>Human and histocompatibility</td>
<td>HLA</td>
<td>HLA</td>
<td>HLA</td>
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<td>Tissue establishments</td>
<td>Tissue banks</td>
<td>weefselbanken</td>
<td>Banques de tissus</td>
<td>Gewebebanken</td>
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<td>quality</td>
<td></td>
<td>Kwaliteit</td>
<td>Qualité</td>
<td>Qualität</td>
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<td>Hematological malignancies</td>
<td>Hematologic neoplasms</td>
<td>kwaadaardige hemopathieën</td>
<td>Hémopathies malignes</td>
<td>Maligne hämatologische Erkrankungen</td>
</tr>
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<td>Hematologic diseases</td>
<td>Niet-kwaadaardige hemopathieën</td>
<td>Hémopathies non malignes</td>
<td>Nicht-maligne hämatologische Erkrankungen</td>
</tr>
<tr>
<td>Solid tumours</td>
<td>Neoplasms</td>
<td>solide tumoren</td>
<td>Tumeurs solides</td>
<td>Neoplasmen</td>
</tr>
<tr>
<td>Translational research</td>
<td>Translational medical research</td>
<td>translationeel onderzoek</td>
<td>Recherche translationnelle</td>
<td>Translationale Forschung</td>
</tr>
<tr>
<td>Transplantation</td>
<td>Transplantation</td>
<td>Transplantatie</td>
<td>Transplantation</td>
<td>Transplantation</td>
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</table>

* MeSH (Medical Subject Headings) is the NLM controlled vocabulary thesaurus used for indexing articles for PubMed.
3. FURTHER DETAILS AND ARGUMENTATION

List of abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tbody>
<tr>
<td>AABB</td>
<td>American Association of Blood Banks</td>
</tr>
<tr>
<td>BM</td>
<td>Bone marrow</td>
</tr>
<tr>
<td>Bw</td>
<td>body weight</td>
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<tr>
<td>CB</td>
<td>Cord blood</td>
</tr>
<tr>
<td>CBSCs</td>
<td>Cord blood stem cells</td>
</tr>
<tr>
<td>CBU</td>
<td>Cord blood units</td>
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<tr>
<td>CMV</td>
<td>Cytomegalovirus</td>
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<tr>
<td>EBMT</td>
<td>European Group for Blood and Marrow Transplantation</td>
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<tr>
<td>EBV</td>
<td>Epstein-Barr virus</td>
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<tr>
<td>GVHD</td>
<td>Graft-versus-host disease</td>
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<tr>
<td>HBMI-FP</td>
<td>Human body material institutions that are for-profit</td>
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<tr>
<td>HLA</td>
<td>Human leukocyte antigen</td>
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<tr>
<td>HSC</td>
<td>Haematopoietic stem cell</td>
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<tr>
<td>iPS</td>
<td>Induced pluripotent stem cells</td>
</tr>
<tr>
<td>MSC</td>
<td>Mesenchymal stem cells</td>
</tr>
<tr>
<td>MUD</td>
<td>Matched unrelated donor</td>
</tr>
<tr>
<td>PNH</td>
<td>Paroxysmal nocturnal haemoglobinuria</td>
</tr>
<tr>
<td>PTH</td>
<td>Parathyroid hormone</td>
</tr>
<tr>
<td>RD</td>
<td>Royal Decree</td>
</tr>
<tr>
<td>SC</td>
<td>Stem cells</td>
</tr>
<tr>
<td>SHC</td>
<td>Superior Health Council</td>
</tr>
<tr>
<td>TNC</td>
<td>Total nuclear cell count</td>
</tr>
<tr>
<td>UCB</td>
<td>Umbilical cord blood</td>
</tr>
<tr>
<td>UCBT</td>
<td>Umbilical cord blood transplantation</td>
</tr>
<tr>
<td>URD</td>
<td>Unrelated donors</td>
</tr>
<tr>
<td>WMDA</td>
<td>World Marrow Donor Association</td>
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</table>
3.1. Methodology

This advisory report is based on a review of the scientific literature and takes into account the current state of knowledge in this field as well as the opinion of experts both in Belgium and abroad.

3.2. Elaboration

3.2.1. Introduction

At present, there are two main types of CB banking programs, i.e. allogeneic and autologous banking. For allogeneic banking, an additional distinction needs to be drawn between the storage of unrelated and related donations (when there is a pre-existing medical condition in a sibling of the donor).

Unrelated allogeneic CB banking includes the collection, processing and storage of altruistically donated CB, in order to create an inventory of stem cells (SCs) that can be searched for suitable CB for patients in need of an unrelated allogeneic transplantation.

Related or directed allogeneic CB banking includes the collection, processing and storage of CB from the sibling of a patient with a disease that can potentially be treated with a CB transplantation. This requires coordination between the physician who treats the patient, the obstetrical team that carries out the collection and the CB bank in charge of the processing, storage and release of the cord blood units (CBU) if required.

In most European countries, these two types of allogeneic banking are carried out by public establishments with public funding. Conversely, autologous or directed family CB banking or storage in the absence of a pre-existing medical indication within the family is mainly carried out by human body material institutions that are for-profit (HBMI-FP). This advisory report will not discuss the issue of autologous banking, which has already been the subject of a previous advisory report of the SHC (SHC 8677, 2011).

Over 500,000 units of allogeneic CB are currently available worldwide. This inventory is heterogeneous in terms of the quality of the units stored. Indeed, some of the units were stored before international quality standards were set up (e.g. FACT-NetCord, American Association of Blood Banks (AABB)) (Querol et al., 2009). Also, only about thirty CB banks (of which 4 Belgian banks) have attained FACT-NetCord accreditation since (www.BMDW.org; www.factwebsite.org, 2010 report World Marrow Donor Association (WMDA)).

3.2.2. Typical features

Overall post-transplant outcomes are similar using unrelated UCB or unrelated adult stem cell transplants and each source of stem cells has its own advantages and limitations (Zhang et al., 2012).

Advantages of UCB over other stem cell sources:

- Faster search process;
- Rapid availability and easy access before recipient conditioning (no potential-donor withdrawal);
- Less stringent requirement for Human Leukocyte Antigen (HLA) matching;
- Comparable likelihood of finding a suitable donor (4/6 HLA match: 70 % worldwide), especially for ethnic minorities;
- Transplantation easy to reschedule;
- Less severe graft-versus-host disease (GVHD);
- Lower risk of contamination with viral pathogens such as Cytomegalovirus (CMV) and Epstein-Barr virus (EBV);
- No risk for the donor (non-invasive procedure – no need to harvest BM or peripheral-blood SCs from a donor);
• Well-defined characteristics of graft at collection/storage, which allows for better unit selection.

Limitations of UCB as opposed to other stem cell sources:
• Limited cell dose;
• Delayed engraftment of neutrophils & platelets;
• Delayed immune reconstitution;
• For patients from certain ethnic minorities, the available inventory does not always provide a suitable match with an appropriate cell dose;
• Requires freezing, storage and thawing;
• Impossible to obtain additional collections from donor (lymphocytes or other grafts).

3.2.3 Indications
3.2.3.1. Paediatrics
The following indications have been recognised by the European Group for Blood and Marrow Transplantation (EBMT) for HSC transplantations, including CB:

- Non-malignant disorders:
  • immune deficiencies;
  • hereditary disorders affecting haematopoiesis;
  • metabolic disorders;
  • aplastic anaemias.

- Malignant disorders:
  • haematological: acute and chronic leukaemias, lymphomas, myelodysplasias;
  • solid tumors: neuroblastomas (Ljungman et al., 2010).

More details on these disorders can be found in Ljungman's work (Ljungman et al., 2010). Yet it should be kept in mind that the indications can change over time.

Within a family context, whenever there is CB available, it will always be used as a first choice if it meets the compatibility and quality criteria. It is therefore important to set up structures that make it possible to identify at-risk families and provide for optimal collection, quality control and storage conditions for potentially suitable CB. The indications and usage of such transplantations are currently on the increase (see section on strategies).

In the search for URD, CB eligibility (situation) is considered to be similar to that for other HSC graft sources.

3.2.3.2. Adults
The EBMT recognises the following indications for HSC transplantations:

- Malignant disorders:
  • haematological conditions;
  • leukaemias;
  • lymphomas;
  • myelodysplasias;
  • myelomas;
  • myelofibrosis.

- Non-malignant disorders:
  • aplastic anaemia;
  • paroxysmal nocturnal haemoglobinuria (PNH) (Ljungman et al., 2010).
More details on these disorders can be found in Ljungman's work (Ljungman et al., 2010). Yet it should be kept in mind that the indications can change over time.

Unrelated allogeneic CB grafts are considered an alternative source of SCs for adults. This type of transplantation is only taken into consideration when no compatible HLA-matched unrelated donor (MUD) can be found. However other graft sources are possible options in this situation, such as haploidentical related or mismatch unrelated donors. Prospective studies are ongoing to address this question (Ballen et al., 2011).

For adult patients, the problem is that most CBUs do not contain enough cells (nucleated cells / kg bw of recipient) for successful engraftment. As a result, double CB transplantations are increasingly being carried out as a means of compensating for this limited cell count.

It follows that CB grafts for family use are still infrequently resorted to for adults for the reasons mentioned above.

### 3.2.4. CBU quality and selection

#### 3.2.4.1. CBU quality

CBUs must comply with applicable quality standards and national regulations (Law of 19 December 2008; Royal Decrees (RD) of 28/09/2009, RD of 7 November 2011), as well as the international FACT-NetCord standards in keeping with the requirement of action 17 of the cancer plan. For units stored before the standards and legislation became applicable, current criteria should hold for operations linked to their release and distribution.

#### 3.2.4.2. Graft selection

Each case is analysed individually.

The strategy explained below applies to the transplantation of a single CBU in paediatric patients. It is more difficult to comply with these criteria for adult patients.

Graft selection is preferably based on compatibility (HLA-typing) and cell content/quantity (Total nuclear cell count (TNC), total CD34+ cell count, and for some authors CFU).

The compatibility requirements could be more stringent for non-malignant disorders (survival and engraftment and risk of GVHD). The HLA differences are partially balanced by high TNCs in the CBU.

However, the ongoing trials seem to indicate that strategies for better donor-recipient matching could make it possible to further improve the outcome of the transplantations (HLA-C, HLA-DQB1).

The strategies can be found in the tables below as well as in the article concerned (Barker, 2011).

#### Table 1. Recommended HLA and cell dose (single UCBT) for malignant diseases (Rocha & Gluckman, 2009)

<table>
<thead>
<tr>
<th>HLA match</th>
<th>Recommended TNC</th>
<th>Recommended CD34+</th>
<th>HLA mismatch (MM*)</th>
</tr>
</thead>
<tbody>
<tr>
<td>6/6</td>
<td>2.5 to 3.0 x 10^7 / kg</td>
<td>1.2 to 1.7 x 10^5 / kg</td>
<td>-</td>
</tr>
<tr>
<td>5/6</td>
<td>2.5 to 3.0 x 10^7 / kg</td>
<td>1.2 to 1.7 x 10^5 / kg</td>
<td>HLA-A or HLA-B MM* are preferable to DRB1 MM*</td>
</tr>
<tr>
<td>4/6</td>
<td>3.5 x 10^7 / kg</td>
<td>1.7 x 10^5 / kg</td>
<td>HLA-A or HLA-B MM* are preferable to DRB1 MM*</td>
</tr>
<tr>
<td>3/6</td>
<td>Not recommended</td>
<td>Not recommended</td>
<td>Not recommended</td>
</tr>
</tbody>
</table>

*MM = Mismatch
Table 2. Recommended HLA and cell dose (single UCBT) for non-malignant diseases
(Rocha & Gluckman, 2009)

<table>
<thead>
<tr>
<th>HLA match</th>
<th>Recommended TNC</th>
<th>Recommended CD34⁺</th>
<th>HLA mismatch</th>
</tr>
</thead>
<tbody>
<tr>
<td>6/6</td>
<td>2.5 to 3.0 x 10⁷ / kg</td>
<td>1.2 to 1.7 x 10⁵ / kg</td>
<td>-</td>
</tr>
<tr>
<td>5/6</td>
<td>2.5 to 3.0 x 10⁷ / kg</td>
<td>1.2 to 1.7 x 10⁵ / kg</td>
<td>Avoid DRB1 MM</td>
</tr>
<tr>
<td>4/6</td>
<td>4.0 to 5.0 x 10⁷ / kg</td>
<td>2.0 to 2.5 x 10⁵ / kg</td>
<td>Avoid DRB1 MM</td>
</tr>
<tr>
<td>3/6</td>
<td>Not recommended</td>
<td>Not recommended</td>
<td>Not recommended</td>
</tr>
</tbody>
</table>

HLA compatibility is more important for patients with non-malignant disorders than for those with malignant diseases (Rocha & Locatelli, 2008).

In general:
1) If the criteria for a single UCBT (UCB transplantation) described above are not met, a double CB transplantation should be considered (these CB units should be at least a 4/6 HLA match with each other as well as with the patient. Minimum TNC: 2 x 10⁷/kg for each CBU) (Avery et al., 2011).
2) These values hold for CBUs prior to or at the time of freezing. After thawing, the maximum acceptable cell loss is 25 %.

The search algorithm for CB units involves the following steps (Barker, 2011):
- looking into donor registry listings: analysing the CB search report to find 4-6/6 HLA-matched CBUs with a TNC ≥ 2.0 x 10⁷/kg;
- reviewing the information and the CB banks of origin for each unit;
- grading the CBUs according to the degree of HLA-A, -B antigen – DRB1 allele matching. Within each of these match grades, units should be ranked from those with the highest to those with the lowest TNC:
  o first choice: 6/6 HLA match, choose units with the largest TNC;
  o second choice: 5/6 HLA match, choose units with the largest TNC;
  o third choice: 4/6 HLA match, choose units with the largest TNC.
- making the final selection and planning the shipment of the CBU.

Other criteria to take into account
If several CB units are available that meet with the criteria above, the following criteria probably need to be taken into consideration as well:
- CMV status of the patient/CMV status of CBU donor mother;
- ABO compatibility;
- CBU from an accredited CBB;
- Allele HLA typing of HLA-A and HLA-B.

3.2.5. Translational research
A significant amount of translational research is currently being carried out to extend the range of application of CB transplantations even further.

The major challenge within the field of HSC transplantations with allogeneic CB is how to overcome the risk of delayed engraftment (associated with a slow and often incomplete immune recovery) and “graft failure”. These problems especially affect adult patients because the graft often contains insufficient SCs. As a result, in-vitro expansion or the simultaneous transplantation of 2 CB grafts from separate donors is resorted to in an attempt to increase the number of SCs for transplantation. On the other hand, strategies are also being evaluated that aim to improve the homing and growth of SCs in BM. Current fields of research, such as in-vitro expansion, the use...
of 2 CBUs, the co-transplantation of mesenchymal stem cells (MSC) and HSCs, intrabone injections, as well as other recent developments are described in detail in appendix I of this advisory report.

If current research and the ongoing clinical trials can show that implementing one of several experimental strategies mentioned in appendix I can result in the CBSCs leading to a rapid and lasting haematological and immunological recovery after transplantation (with no increased risk of relapse), there is a definite possibility that the number of patients eligible for allogeneic CBSC transplantation will grow, which means that the demand that the public CB banks will need to face will also be on the rise.

In addition, there is a broad interest in using CB as a source of non-haematological cells for various therapeutic implementations in regenerative medicine and immunotherapy.

3.2.6. Strategies/quality
3.2.6.1. Unrelated allogeneic banking

For some patients waiting for transplantation, no related or unrelated HLA-compatible donor will become available within the required timeframe (depending on the type and clinical status of the disease). In these cases, an alternative solution must be resorted to, such as selecting a partially mismatched donor, CB transplantation and/or haploidentical transplantation.

The place of CB banks in this context can only be considered within an international perspective (in Belgium, 90 % of unrelated transplantations are carried out with a foreign graft/donor). For patients from certain ethnic groups, the likelihood of finding a compatible donor/graft remains low. Indeed, most donors and available grafts are of Caucasian origin. As a result, recruiting new units should focus more intensely on populations that are underrepresented in the inventories so that they too might have access to compatible grafts.

In the future, the development strategies of CB banks should focus on the following:

Quality: Only high-quality units with high TNCs should be stored.

The figure below gives an overview of the TNCs of CBUs stored in Belgian CBBs.
All banks should have **policies in place to check whether CBU s stored prior to the introduction of quality standards comply with current standards** (i.e. cell counts, viability and clonogenic activity, infectious disease markers, sterility, packaging and labeling).

**Diversity:** As regards the collection of new units, more emphasis should be put on ethnic minorities, e.g. by focusing on collection facilities that are known for their high childbirth rates among the immigrant population and appointing nurses or midwives as intercultural mediators who will attempt to convince these mothers to donate their cord blood and will provide them with guidance once they have decided to do so. However the experience made at the London CBB demonstrates that ethnic minorities’ CBUs may not meet the current threshold criteria for TNC, and that these units may not be used for patients even if stored in the bank (Navarrete & Contreras, 2009).

**More accredited collection facilities should be included (NetCord Standards):** Currently, collection facilities which cooperate with the CB banks are in charge of recruiting donors and collecting the CB. This is voluntary work for which there is no financial compensation, although during the past decade, the need to keep up with regulatory and legal requirements has resulted in an increased workload. The collection facilities need more staff who are specifically dedicated to this task. Such a measure would allow broader access to CB-donation for mothers.

**Awareness raising campaigns targeted at the general public AND minority groups.**

**Financial implications**

Whilst the strategies above have to be considered, there are also some financial implications that should be taken into account:
1. Increased overall workload in maternity units performing CB collection;
2. Need for improved maternity unit staff training and additional staff dedicated to the collection of CB;
3. Increased investment in equipment and consumables;
4. Increased transportation costs;
5. Increased workload at the bank level.

Extending the current donor recruitment pool and increasing the number of collection facilities involved cannot be considered without structural financial support.

**3.2.6.2. Related or directed allogeneic banking**

**Providing information to the medical and paramedical staff**

CB could be collected in any maternity unit for family banking purposes and is likely to occur in maternity units that are not connected to a CB bank. Therefore, staff awareness should be improved through adequate training.

**Providing information to the families**

Families at risk should be properly identified by the physicians concerned. Once this is the case, these families should receive appropriate information and be referred to a maternity unit that has the required collection capacities and co-operates with a CBB that is able to set up the collection and storage of a good-quality graft.

The appropriateness of the indication should be assessed periodically within the bank in consultation with the family and the prescribing physician. If there is no longer any such

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1 i.e. maternity units carrying out CB collection
indication, the unit should be destroyed with the consent of the mother and the prescribing physician.
4. REFERENCES

- AABB - American Association of Blood Banks AABB. Internet: http://www.aatb.org/
- EBMT - European Group for Blood and Marrow Transplantation EBMT. Internet: www.ebmt.org
- Foundation for the accreditation of cellular therapy. Internet: www.factwebsite.org
- Kingdom of Belgium. Royal Decree September 28th, 2009 setting standards of quality and safety for donation, procurement, testing, processing, preservation, storage and
distribution of Human body material (HBD), which the banks of HBD, intermediate structures of HBD and establishments of production have to answer. BM of October 23rd, 2009, p. 69409.
- Kingdom of Belgium. Royal Decree of November 07th 2011 setting conditions which the banks of Human body material and intermediate structures have to answer for the procurement and the storage of cord blood. BM of December 07th, 2011, p. 71996.


5. APPENDIX

Appendix 1: Translational research
6. COMPOSITION OF THE WORKING GROUP

All experts joined the working group *in a private capacity*. The names of the members and experts of the Superior Health Council are indicated with an asterisk*.

The following experts were involved in drawing up the advice:

BAUDOUX Etienne*  Medicine, cell therapy  ULG  
BEGUIN Yves  Haematology  ULG  
BENOIT Yves  Paediatric haemato- oncology  UGent  
BILLIET JOHAN  Haematology  AZ Brugge  
DELFORGE Alain*  Medicine, cell therapy  ULB  
DEVOS Timothy  Haematology  KULeuven  
LATINNE Dominique*  Haematological biology  UCL  
NOENS Lucien  Haematology  UZ Gent  
SELLESLAG Dominik  Internal medicine, haematology  AZ Brugge  
VAN RIET Ivan  Medicine, cell therapy  UZ Brussel  
VANDEKERCKHOVE Bart  Clinical biology, cell therapy  UGent  
VERMYLEN Christiane  Paediatrics  UCL  
ZACHEE Pierre  Haematology  ZNA Antwerpen  

The following experts peer-reviewed the advisory report:

FAUCHER Catherine  Haematology  Agence de la biomédecine ; Paouli Calmettes, Marseille - France  
GLUCKMAN Eliane  Haematology  Eurocord Paris France  
NAVARRETE Cristina  Immunology, transplantation  NHS Cord blood bank, British bone marrow registry, NHSBT, UK  

biologie clinique, thérapie cellulaire  
The working group was chaired by Etienne BAUDOUX, the scientific secretary was Muriel BALTES.

The following experts read and approved the advisory report:

BEELE Hilde*  Medicine, dermatology  UZ Gent  
DE SUTTER Petra*  Reproductive medicine  UZ Gent  
DELLOYE Christian*  Medicine, Orthopaedic surgery  UCL  
GUNS Johan*  Medical-social sciences  UZ Brussel  
HEINEN Ernst  Human histology  ULg  
PIRNAY Jean-Paul*  Medical sciences  LabMCT HCB-KA  
VAN DEN ABBEEL Etienne  Reproductive medicine, embryology  UZ Gent  
VAN GETY Caroline*  Medical-social sciences  UZ Gent  
VANDERKELEN Alain*  Medicine, general surgery  HMRA  
VANSTEENBRUGGE Anne  Reproductive medicine, embryology  CHR Namur  
VERBEKEN Gilbert*  Biology, QA/QC/RA  LabMCT HCB-KA  

The administration was represented by:

BONTEZ Walter  Coordination Blood, Cells, Tissues and Organs  
VANTHUYNE Kimberly  Coordination Blood, Cells, Tissues and Organs  

The working group was chaired by Hilde BEELE, the scientific secretary was Muriel BALTES.
Appendix 1: Translational research

I. Allogeneic CB for haematological SC transplantation

- In-vitro expansion

Many research teams have attempted to expand HSC in vitro using expansion cultures with various combinations of haematopoietic growth factors (including G-CSF, SCF,flt-3 and TPO). Preclinical trials initially indicated that in-vitro expansion was more successful for CBSCs (Cord blood stem cells) than it was for BM HSC (van de Ven et al., 1995). Some clinical trials have shown that such in-vitro expanded CBSCs do not cause any adverse effects in the patients they have been administered to, yet this strategy has not always turned out to lead to the expansion of primitive SCs with the ability to regulate long-term haematopoiesis (Shpall et al., 2002; McNiece et al., 2000). In addition, HSC in-vitro expansion with cytokines has also been found to be liable to cause anomalies in the regulation of the cell cycle as well as to result in a potentially reduced homing ability (Glimm et al., 2000; Ramirez et al., 2001). Pre-clinical research is currently being conducted into HSC expansion following the activation of new signal transfer mechanisms such as Notch-1, Wnt/Bcatenin, the receptor Tyrosine Kinase Tie2, or on the basis of the transcription factors Bmi-1 and the homeobox genes HoxB (Hofmeister et al., 2007). Meanwhile, the first clinical results with in-vitro expanded HSC based on Notch ligand δ1 and cytokines are highly promising and should be tested on a larger scale (Delaney et al., 2010). Finally, it has also been shown that CBSCs can be expanded successfully in-vitro through co-culture with MSCs from URD BM (McNiece et al., 2004; Robinson et al., 2011). Based on this observation, various clinical trials have been launched recently (Robinson et al., 2011).

- Use of 2 CB units

For a few years now, research has sought to determine whether the simultaneous transplantation of 2 HLA-identical CBUs (from two different donors) in the same (adult) patient may reduce the risk of “graft-failure” or slow/incomplete post-transplant haematological recovery. The first clinical studies already indicate that this does result in a more limited risk of graft failure (though there is an increased risk of GVHD) and that there is also a significant decrease in relapse rates in acute leukaemia patients in particular (Barker et al., 2005; Verneris et al., 2005). Overall survival is comparable to that achieved after transplantation of a single unit. As there is no clear answer to date to the question whether the use of a single CBU for transplantation is superior to the use of two, this procedure is currently being further examined in phase II-III trials. It is assumed that both units initially contribute towards speeding up the production of white blood cells, yet it is striking that in the long run, only one of the two CBUs ends up regulating haematopoiesis. There is therefore also research ongoing into what factors determine which of the two CB grafts will remain functional in the end (Stanevsky et al., 2011).

- Co-transplantation of MSCs and HSCs

MSCs form the basis of the stromal microenvironment in which normal haematopoiesis occurs and are able to produce haematopoietic growth factors themselves. As a result, several trials have been initiated to verify whether haematological recovery after CB transplantation can be accelerated by co-infusing MSCs from related (Macmillan et al., 2009) or unrelated donors (Gonzalo-Daganzo et al., 2009). Until now, no significant difference could be shown to exist with the rate of recovery after traditional CB transfusion, but there have been no randomised trials published yet. Research should also be conducted on the impact of various factors such as MSC dose, manner of injecting, type of MSC as well as the effect on relapse.

- Haplo-cord transplantation

The simultaneous transplantation of unrelated umbilical cord blood (UCB) and CD34(+) stem cells from a haploidentical relative seems to result in rapid and reliable neutrophil and platelet engraftment following reduced intensity conditioning. Early haploidentical engraftment is replaced by durable UCB engraftment. This has resulted in the following observed effects: low incidences of acute and chronic GVHD, a low occurrence of delayed opportunistic infections, reduced transfusion requirements and shorter stays in the hospital. To confirm this hypothesis, it will be
necessary to carry out a prospective study that compares double UCB transplantations with haplo-cord transplantation (Liu et al, Blood 2011).

- Intrabone injection

Injecting CBSCs directly into the patient’s bone has the advantage that no SCs are lost in the blood flow, as is the case with intravenous injection. In a recent clinical trial, this strategy turned out to result in a speedier recovery of the platelet production (Frassoni, 2010). However, a second trial yielded conflicting results (Brunstein et al., 2009). More research is therefore required on this subject as well.

- Further recent developments

Osteoblasts constitute an important cell population within the microenvironment in which normal haematopoiesis occurs. The number of osteobasts and HSCs has been found to rise in vivo in a murine model following parathyroid hormone (PTH) therapy (Calvi et al., 2003). The kinetics of haematopoietic recovery during PTH therapy following CB transplantation are currently being investigated in a phase II trial (Ballen et al., 2007).

Finally, tests are also being conducted on a few other molecules that affect CXCR4-SDF-1 interaction and may stimulate CBSC homing to the BM as a result. The extent to which preliminary treatment of CBSCs with complement protein a-3a (through CXCR4 upregulation on the SC) can speed up graft growth is being investigated in pre-clinical models (Ratajczak et al., 2004). In addition, research is also seeking to determine whether CD26/DPP1V (CBSC enzyme that breaks down SDF-1) inhibition can improve CBSC homing and growth after transplantation (Delaney et al., 2010).

If current research and the ongoing clinical trials can show that implementing one of several experimental strategies mentioned above can result in the CBSCs leading to a rapid and lasting haematological and immunological recovery after transplantation (with no increased risk of relapse), there is a definite possibility that the number of patients eligible for allogeneic CBSC transplantation will grow, which means that the demand that the public CB banks will need to face will also be on the rise.

II. Allogeneic CB as a source of non-haematopoietic stem cells

Several recent studies have shown that, apart from HSC, CB not only contains other multipotent SCs that can differentiate into MSCs (differentiate into mesodermal cell types such as adipocytes, cartilage and bone) but also more immature SCs that can differentiate into cell types of the 3 germ layers (endo-, ecto- and mesoderm) (Bieback et al., 2004; Kogler et al., 2004). Based on various in-vitro and in-vivo (preclinical) observations, it is being speculated that these SCs can be used for tissue regeneration to treat various congenital or acquired conditions or acute tissue damage. The advisory report issued by the SHC on the storage of autologous CB provided an overview of the potential therapeutic implementations of multipotent CBSCs in the field of regenerative medicine. It is currently unclear to what extent the use of SCs from allogeneic CB offers any added value compared to multipotent SCs from other tissues (BM, fat tissue, peripheral blood) or derived in the patients themselves (autologous use).

CB also appears to be a source of various immunocompetent cells such as T lymphocytes, regulatory T cells, natural killer cells and dendritic cells (McGuckin et al., 2005). As a result, research is also being conducted into the specific therapeutic potential of these cells and their potential added value compared to immunocompetent cells from peripheral blood or BM. It has recently appeared that induced pluripotent stem cells (iPS) can be successfully derived from CB, even from samples that have been cryopreserved for over 20 years (Broxmeyer et al., 2011). However, extensive further research is required as regards the potential clinical applications of iPS as well as the risks involved.

It is therefore necessary to provide more scientific results and clinical observations in support of the significance of public CB banks for clinical applications other than HSC transplantation.
About the Superior Health Council (SHC)

The Superior Health Council is a federal body that is part of the Federal Public Service Health, Food Chain Safety and Environment. It was founded in 1849 and provides scientific advisory reports on public health issues to the Ministers of Public Health and the Environment, their administration, and a few agencies. These advisory reports are drawn up on request or on the SHC’s own initiative. The SHC takes no decisions on the policies to follow, nor does it implement them. It does, however, aim at giving guidance to political decision-makers on public health matters. It does this on the basis of the most recent scientific knowledge.

Apart from its 25-member internal secretariat, the Council draws upon a vast network of over 500 experts (university professors, members of scientific institutions), 200 of whom are appointed experts of the Council. These experts meet in multidisciplinary working groups in order to write the advisory reports.

As an official body, the Superior Health Council takes the view that it is of key importance to guarantee that the scientific advisory reports it issues are neutral and impartial. In order to do so, it has provided itself with a structure, rules and procedures with which these requirements can be met efficiently at each stage of the coming into being of the advisory reports. The key stages in the latter process are: 1) the preliminary analysis of the request, 2) the appointing of the experts within the working groups, 3) the implementation of the procedures for managing potential conflicts of interest (based on the declaration of interest, the analysis of possible conflicts of interest, and a referring committee) and 4) the final endorsement of the advisory reports by the Board (ultimate decision-making body). This coherent set of procedures aims at allowing the SHC to issue advisory reports based on the highest level of scientific expertise available whilst maintaining all possible impartiality.

The advisory reports drawn up by the working groups are submitted to the Board. Once they have been endorsed, they are sent to those who requested them as well as to the Minister of Public Health and are subsequently published on the SHC website (www.css-hgr.be), except as regards confidential advisory reports. Some of them are also communicated to the press and to target groups among healthcare professionals.

The SHC is also an active partner in developing the EuSANH network (European Science Advisory Network for Health), which aims at drawing up advisory reports at the European level.

In order to receive notification about the activities and publications of the SHC, you can send an e-mail to info.hgr-css@health.belgium.be.