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Autologous cord blood use: Clinical and scientific aspects

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1. INTRODUCTION

The clinical use of cord blood (CB) from HLA-matched related and unrelated donors in patients suffering from diseases that can be treated with a haematopoietic stem cell transplant (HSCT) is well documented (Rebulla, 2010; Navarrete & Contreras, 2009). There are currently over 148 unrelated cord blood banks (CBB) worldwide that aim at making these products more easily available (<http://www.worldmarrow.org/>, 13 Dec 2010). Also the banking of cord blood units from siblings of patients affected by diseases treatable by haematopoietic stem cell (HSC) transplantation (related CB banking) is already in place in many countries. The practice of allogeneic CB banking as well as its clinical use are well documented and will not be discussed in this advisory report.

In contrast, there is still little scientific foundation for the evidence in support of autologous CB banking and of its clinical use in particular. The aim of this document is to provide scientific and clinical data on the therapeutic relevance and potential use of autologous CB.

At present, there are two main types of CB banking programmes, i.e. allogeneic and autologous banking. For allogeneic banking, an additional distinction needs to be made between the storage of unrelated (altruistic) donations and related storage (when there is a pre-existing medical condition in a sibling of the donor). 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 carried out mostly by human body material institutions that are for-profit (HBMI-FP).

In order to examine the issue of autologous CB banking, the following questions were addressed:

1. What is the scientific evidence in support of autologous CB banking?
2. What is the current or potential clinical application of autologous CB?
3. What are the quality, ethical and regulatory issues surrounding autologous CB banking and transplantation?

In order to answer these questions, 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, which was subsequently submitted to the permanent working group "cells, tissues and organs of human and animal origin" for approval.

2. CONCLUSIONS

The SHC formulates the following answers to the questions above.

1. There is no evidence that CB is an exclusive source of any of the cell populations identified so far, or of any cell population that is obtainable/inducible by culture. Also, every future therapy that the autologous CBB refer to in their claims could also be possible with cells obtained from other sources such as bone marrow (BM) and blood, and at a lower cost (Francese & Fiorina, 2010; Harris, 2009).

Thus, there is no medical or scientific evidence to support autologous CB banking.

2. There are better alternatives to autologous CB in haematology. Moreover, the use of autologous CB could sometimes be harmful to the patient, except in the rare circumstances described in section 3. It should be reminded that family banking in the context of an existing disease already has a place in allogeneic transplantation, e.g. for the treatment of haemoglobinopathies (Locatelli et al., 2003) and in most countries this activity is financed by public funds.

In regenerative medicine, there is no published evidence at all to date in support of using autologous CB.

Furthermore, the data currently available to the SHC in support of autologous CB banking are generally based on weak scientific and clinical grounds. This practice goes against the recommendations issued by the Belgian Advisory Committee on Bioethics (BACB, 2007) as well as several scientific societies. Also the medical literature has provided extensive arguments against this practice (ASBMT, 2008; AAP, 2007; SOGC, 2005).

3. Considering the lack of evidence-based^a scientific data, the weakness of clinical arguments in support of autologous CB banking and its low cost-effectiveness, there is insufficient information to support the public funding of autologous CB banking. Yet if autologous banking becomes a reality, the authorities will have to ensure that this procedure complies with adequate quality standards, including accreditation requirements and the observance of ethical principles.

In addition to addressing the questions above, a series of additional considerations that arose during the discussions were also taken into account to back up the SHC advisory report. They include ethical and financial aspects, as well as information and quality issues.

The information provided to families that are considering CB storage should be clear, accurate and honest. The contracts between the families and the HBMI-FPs should cover foreseeable problems that could affect the products stored and take into account national and international regulations.

This document has been written on the basis of the most recent literature. However, with the field of stem cell research evolving at a rapid pace, it will have to be reviewed periodically and updated in the light of new findings.

^a Evidence-based : based on scientifically objectifiable and reproducible results.

3. FURTHER DETAILS AND ARGUMENTATION

List of abbreviations

AAP	American Academy of Pediatrics
ASBMT	American Society for Blood and Marrow Transplantation
BACB	Belgian Advisory Committee on Bioethics
BM	Bone marrow
CB	Cord blood
CBB	Cord blood bank
CBT	Cord blood transplantation
CBU	Cord blood unit
CFU	Colony forming units
CML	Chronic myeloid leukaemia
EPC	Endothelial progenitor cells
GVL	Graft-versus-Leukaemia
HBMI-FP	Human body material institutions that are for-profit
HLA	Human leukocyte antigen
HSC	Haematopoietic stem cell
HSCT	Haematopoietic stem cell transplant
HTLV	Human T-cell Lymphotropic virus
iPS cell	Induced pluripotent stem cell
MSC	Mesenchymal stem cells
NC	Nucleated cCells
PBSC	Peripheral blood stem cells
SAA	Severe aplastic anemia
SC	Stem cells
SHC	Superior Health Council
SOGC	Society of Obstetricians and Gynaecologists of Canada
TNC	Total nuclear cell count
USSC	Unrestricted somatic stem cells

3.1. Methodology

This advisory report is based on a review of the 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. Definition/Explanation of the various CBB programmes

3.2.1. Unrelated allogeneic banking

Unrelated allogeneic CB banking denotes the collection, processing and storage of altruistically donated CB, in order to create an inventory that can be searched for suitable CB for patients in need of an allogeneic transplantation. This type of CB banking is usually funded by public/government organisations and is carried out and managed by CBBs or registries with a commitment to international donor exchange.

3.2.2. Related allogeneic banking

Related or directed allogeneic CB banking denotes the collection, processing and storage of CB from the sibling of a patient with a disease that can potentially be treated with a CB transplant. This requires coordination between the physician who treats the patient, the obstetrical team that carries out the collection and the CBB in charge of the processing, storage and release of the CBU if required.

3.2.3. Autologous banking

Autologous CB banking denotes the collection, processing and storage of CB for potential autologous use. This is usually performed in HBMI-FPs for a significant fee. The same kind of contract could cover family banking for potential use in a family with no pre-existing condition in its members.

3.3. Scientific data CB: Cell content of CB

The table below provides a list of cell populations that are found in (or that can be produced from) human CB:

Table 1: Generation of cell populations and available sources

Cell type	Exclusively found in CB	Present in thawed CB	Other sources	Comments / references
Lymphoid precursors	No	Yes	Blood, BM	Kim & Broxmeyer, 2010
Hematopoietic cells	No	Yes	Blood, BM	Broxmeyer et al., 2009
Mesenchymal stem cells (MSC)	No	NO ^{*1}	Blood, BM, cord, adipose tissue	CB is not an optimal source Friedman et al., 2007
Unrestricted Somatic Stem Cells (USSC) ^{*3}	Yes	No	No	Kögler et al., 2005 Reimann et al., 2009
Induced Pluripotent Stem cells (iPS)	No	Yes	BM, blood and skin	Broxmeyer, 2009 Broxmeyer et al., 2011
Endothelial progenitor cells (EPC)	No	YES ^{*2}	BM, peripheral blood, adipose tissue	Lin et al., 2010; Nishimura et al., 2005 Lu et al., 2008

^{*1} MSC in frozen and thawed Wharton's jelly (cord) as well as in cord blood (Friedman R et al., 2007; Manca et al., 2008; Girdlestone et al., 2009)

^{*2} It is still unsure whether EPC in cryopreserved cord blood are quantitatively and qualitatively equivalent to EPC in fresh CB (Lu et al. 2008)

^{*3} There is no scientific evidence so far that CB contains unique SC populations that are not present in adult tissues, such as BM (from which much larger numbers can potentially be collected). It is only USSC that are found exclusively in CB. However, they are no longer available in thawed CB.

Based on the studies mentioned above, we can also say the following:

- CB cells are likely to be different from cells obtained from other sources, but they do not offer any advantage in terms of their pluripotency or differentiation potential. In virtually all cases, BM and peripheral blood will be just as suitable as cell sources, at a lower cost and probably with comparable or even greater effectiveness.

- In particular, autologous bone marrow will be the best choice for regenerative medicine therapies when cell populations have to be cultured on demand in any patient.

- Very often, CB is claimed to contain cells of a certain type based on the presence of markers that allow for these cells to be identified, but in the light of current scientific evidence, it is premature to state that they will be able to carry out the expected functions (Kögler et al., 2009; Gale et al., 1997).

- In addition, it is not necessarily the case that *in vitro* findings can be transposed into *in vivo* therapeutic applications.

- There is nothing unique about CB. Many of the cells that can be found in CB and have a therapeutic potential can also be obtained from other tissues (blood, BM) (Broxmeyer et al., 2009;

Kim & Broxmeyer, 2010; Broxmeyer, 2010, Friedman et al., 2007; Lin et al., 2010; Nishuma et al., 2005; Lu et al., 2008).

- Although CB cells differ from cells obtained from adult BM or blood in the sense that they are immunologically "naive", these cells are still mature cells that do not have the pluripotent differentiation potential of embryonic cells.

- *In-vitro* and *in vivo*, the use of CB was shown to be advantageous as a result of its haematological and immunological properties, as well as the proliferative potential of its haematopoietic stem cells.

- Moreover, it is possible that CB cells may be reprogrammed into iPS cells more effectively. Yet, whether or not the iPS can be put to clinical use remains unproven and there are other sources available. Whenever a cell type of interest is identified, it is usually obtained from fresh CB. Even though these cells have been identified in cryopreserved CB (Broxmeyer et al., 2011), they may not show the same biological properties or clinical relevance (See table 1).

3.4. Potential clinical applications of autologous cord blood

There are two broad purposes for which the collection of autologous cord blood units (CBU) is currently being promoted, i.e. haematopoietic stem cell transplantation and tissue regeneration.

3.4.1. Haematology.

a) General considerations

HSCT is a proven therapy for select patients with life-threatening malignancies and auto-immune diseases. Both autologous and allogeneic HSCT can be performed, mostly depending on the disease and age of the patient.

- For malignant disorders, allogeneic HSCT is generally preferable to autologous HSCT because the donor's immune cells can eliminate the patient's residual malignant cells as a result of the graft-versus-leukaemia (GVL) effect (Jenq & Brink, 2010). There is no such effect after autologous HSCT, rendering it less effective to treat leukaemias and other haematopoietic malignancies.
- Studies have demonstrated the presence of preleukaemic and leukaemic cells in the CB of children who later develop leukaemia (Maia et al., 2004; Kim-Rouille et al., 1999; Gale et al., 1997; Buldini et al., 2010). Because these preleukaemic cells could cause the leukaemia to recur, the use of autologous CB to treat childhood leukaemia is contraindicated. The presence of leukaemic cells has been established in some diseases linked to leukaemia, but it is highly likely that more abnormal cells will be found in CB in the future.
- Because hematopoietic stem cells (HSC) in CB carry the same genetic defects as the patients themselves, autologous CB transplantation (CBT) cannot be used to treat any genetic diseases amenable to allogeneic HSCT, such as haemoglobinopathies, immune deficiencies or storage disorders, except when combined with gene therapy.
- For adults, the first choice for autologous transplantation are peripheral blood stem cells (PBSC) (large cell doses). CB should not be the first choice due to insufficient cell doses, which have been linked to slower recovery (Hartmann et al., 1997). Using CB after high dose chemotherapy entails a risk of prolonged aplasia and transplant related complications.
- When autologous HSCT is the preferred option for a given patient, physicians favour collecting and transplanting PBSC over using CB stem cells. Indeed, haematopoietic reconstitution is much faster with PBSC, thus reducing the duration of hospitalisation, the risk of infection and the overall cost of treatment. In

some circumstances (Rosenthal et al., 2011), physicians are talked into making use of autologous CB. Yet in this case, there should be sufficient precautions taken with regard to the current standard of care.

Between 1999 and 2010, there were 7 cases reported in the medical literature in which autologous CB was used in traditional HSCT indications. In some of these cases, the indication for autologous transplantation was questionable and the use of CB rather than PBSC probably not the best option. Though these cases may be mentioned here as examples, discussing them in further detail goes beyond the scope of this advisory report.

It is worth pointing out that in the same period (1999-2010), there were over 10,000 unrelated allogeneic transplantations (from an inventory of 114,546 CBU) reported in standard indications (EuroCord).

More generally, the only possible indications for autologous CB are limited to cases where (1) not only can there be no autologous HSC collected, but (2) there is also suitable good quality autologous CB available and finally (3) there is no suitable sibling or alternative donor. However these situations are exceptional (Ballen et al., 2008; Rosenthal, 2011).

b) (Pre-) clinical data

Allogeneic CB is often used for haematopoietic and immunological reconstitution as well as for the correction of metabolic genetic disorders. It has also been shown to have an antitumor effect (Welte et al., 2010; Brown et al., 2008).

In the autologous setting, there are better alternatives to the use of autologous CB, i.e. SC obtained from adult donors, or allogeneic CB. There has been molecular evidence found of leukaemia in the CB of children who developed this very disease during the early years of life, which is a strong argument against the use of autologous CB in this context (Gale et al., 1997; Ballen et al., 2008; Kim-Rouille et al., 1999; Buldini et al., 2010).

Most transplant centres (both with or without a CBB) store allogeneic CB in the context of a treatment plan (directed donation) when there is a medical indication for doing so. This is funded by social security in e.g. Belgium, France, and the UK.

3.4.2. Tissue regeneration.

a) General considerations

Stem cells (SC) could be used in the future for tissue repair in degenerative or ischemic diseases of the heart (myocardial infarction...), liver, muscle, brain (Alzheimer, Parkinson...), endocrine system (diabetes...), and other organs (Sullivan, 2008). Research investigates the potential of embryonic SC, fetal SC and adult SC for that purpose (Harris, 2009; Arien-Zakay et al., 2010)

- Basic research has demonstrated the existence of pluripotent SC in CB that can differentiate in a number of ectodermal, mesodermal and endodermal tissues. However, these cells are present in very low numbers and cannot be retrieved from all CBUs, especially not from those that have been cryopreserved. It is not known whether current freezing methods used by CBB would preserve them during long-term storage (See table 1).
- Clinical protocols for tissue regeneration use essentially autologous BM or mobilized peripheral blood cells, with some preliminary but promising success. No clinical protocol has shown there to be any benefit in using autologous CB (Uzan, 2005; Uzan, 2004).
- Most of the diseases (Alzheimer's or Parkinson's disease,...) which could be a potential indication for regenerative medicine occur in patients over the age of 50. At the moment, it is impossible to predict the evolution of the treatment of these

diseases in the future. CBUs that are collected today may become obsolete because other therapies will have become available.

- In addition, it is likely that more stringent quality standards will replace the current standards, which would result in old CBUs being unacceptable for clinical use, especially in properly registered protocols.

b) (Pre-) clinical data

There have been very few studies published to date concerning the clinical use of autologous CB. Most are preliminary safety trials or anecdotal case reports (see Table 2).

Table 2: Overview of the recent or ongoing clinical studies and results available

Study	Phase	Conclusion	Reference
Cerebral palsy	I/II	Safety, no benefit	Patoine, 2009
	Later phases ongoing		
Diabetes		Little transient effect, action due to immunosuppressive effect?	Haller et al., 2008 Haller et al., 2009

See <http://clinicaltrials.gov/>

In the case of regenerative medicine, the level of evidence in support of the use of autologous CB (in the sense required by an “evidence-based” approach) is also too weak for the future applications that are put forward to promote the storage of autologous CB. At present, these claims are purely speculative. In the field of cerebral palsy, studies have demonstrated the safety of autologous CB infusion, with no conclusions so far about its clinical significance (benefit) (Patoine, 2009).

As regards diabetes (Haller et al., 2008 and Haller et al., 2009), there have been no data published that indicate that autologous CB offers any advantage.

As far as adult diseases, such as coronary disease, are concerned, the use of CB, which contains a large number of endothelial cell precursors, is not advisable. The reason is that the volume available will inevitably be limited. An additional problem is the uncertainty over the quality of CB that has been kept in a frozen state for a long time (Haller et al., 2008 et Haller et al., 2009 ; Patoine, 2009; Broxmeyer et al., 2011).

3.4.3. Conditions for the use of autologous CB

The SHC draws attention to the fact that, in order to use a CBU collected in the context of directed family banking or autologous CB banking programmes, the 4 following conditions need to be fulfilled (haematology):

1. The disease that is being treated is not genetic
2. There is no HLA-identical donor available
3. There is no unrelated CB available
4. The available CB meets all the quality, safety and clinical requirements (e.g. cell dose) and is free from any of the potential genetic disorders present in the family.

As there are currently no specific clinical indications for the use of autologous CB, the use of such a product in a therapeutic application should be restricted to a duly approved and registered clinical research protocol in haematology as well as in innovative therapies. In this context, compliance with stringent quality standards is a basic requirement.

3.4.4. Conclusion

In haematology, there are better options than autologous CB. Moreover, the use of autologous CB could sometimes be harmful to the patient, except in the rare circumstances described above. It should be reminded that family banking in the context of an existing disease already has a place in allogeneic transplantation, e.g. for the treatment of haemoglobinopathies (Locatelli et al., 2003).

There is no evidence that CB is an exclusive source of any of the cell populations identified so far, or of any cell population that is obtainable/inducible by culture. In regenerative medicine, there is no published evidence at all to date in support of using autologous CB.

3.5. Further considerations

3.5.1. Ethics

Based on the current state of medical care, altruistic donation for possible use in another person is of greater ethical value than keeping it stored for oneself with an extremely low probability of need.

Moreover, even if private autologous CB banking were a scientifically based option, only a minority of families are able to afford it, which in turn means that such a practice promotes inequalities in the access to treatment.

The information provided to families who are considering CB storage should be clear, accurate and evidence-based. It should also remain honest with its targeted audience. The lack of current evidence for the usefulness of autologous CB banking and the existence of better alternatives should be clearly stated. Great emotional pressure is placed on the families and the feeling of guilt can be enormous, especially if the stored product turns out to be unsuitable for medical use (Sullivan, 2008; Kingdom of Belgium, 2008).

Based on the current clinical data, the vast majority of units stored for autologous purposes are unlikely to be used, whereas they could have benefited other patients (unrelated to the families) immediately for a clear medical indication. In fact, the extension of autologous banking to uses that are aimed at other family members is only possible if the rules of donor selection, HLA matching and cell dose are carefully observed. International registries can offer a better alternative (See § 3.4).

3.5.2. Quality

If a family wishes to proceed with autologous CB storage, it should receive assurance that this will be done in a secure manner and that all operations will be carried out properly.

The quality standards that apply to autologous CB banking should be identical to those required for allogeneic banking (collection, processing, storage, distribution, delivery). However, the criteria may be different, e.g. as regards the acceptance of autologous CBU.

If it should turn out to be true that autologous CB has properties that may be put to clinical use in the future, then there must be sufficient guarantees to ensure that it is stored safely and that its biological (and therapeutic) properties are preserved (notions of *purity*, *safety* and *potency*) (Sun J et al., 2010) (see also 3.4.2).

These quality issues concern the following aspects:

- Safety
 - Sterility
 - Infectious disease markers as required by current regulations
 - Monitoring of the storage conditions
- Biological quality
 - Cell characterisation (TNC (total nuclear cell count), CD 34, viability)
 - Function (CFUs)
 - HLA typing, except for autologous use
- Traceability (Product identification)
- Inventory management (identification, storage physically different from that of other products)
- Storage conditions
 - Cryopreservation methods
 - Media used

- Bags
- Pre-release identity testing : product identity verification (finger-printing)
- Equipment used

These quality criteria must also be met by the autologous CBU upon delivery. If at the end of the process, the properties put forward are not available, the parents should be informed.

Public CBB discard two thirds of the units collected because of low cell count. As for the remaining third of the units, with the threshold for autologous transplantation set at 2×10^7 NC/kg, 99 % are suitable for children with a body weight of 20 Kg, but this figure drops to 39 % when the body weight reaches 60 Kg. Therefore many autologous CBUs would not be usable because they contain too few nucleated cells (NC).

The experts suggest that the required standards be those mentioned in the applicable European directives: collection under specific conditions, staff training, packaging, guaranteed and verified sterility, tested for lack of infection (via markers), infrastructure, storage under specific conditions, proper documentation, product assurance for the cryopreserved CB,...

3.5.3. Financial issues

In addition, the cost of collecting autologous CB from all neonates and using it for just a very few far exceeds that of collecting and transplanting PBSC when a patient needs them. Indeed:

- Belgium has a population of 10 million and there are approximately 120,000 births per year.
- The cost of storing a single CBU for 10 years is around 3,000 € (1,500 € initial fee + 150 € per year).

It follows that the cost of banking CBUs from all Belgian newborns over 20 years amounts to approximately 7.380.000.000 € ($(210 \times 120.000 \times 150 \text{ €})^b + 20 \times 120.000 \times 1500 \text{ €}$). In addition:

- The risk of needing an autologous HPCT before the age of 20 is less than 0.005 % (i.e. below 100/year for Belgium). Hence, if all autologous HPCT were to be carried out with CB, the cost per autologous CBT would be 61.500.000 € (7.380.000.000 €/120), as opposed to 5,000 € for PBSC.
- In a more realistic context where CB is used only when no PBSC can be collected and the number of NC is adequate for transplantation, the cost would even be 20-40 times this figure. The annual frequency with which CB would thus be resorted to would amount to < 2-5/10 million inhabitants.

If a HBMI-FP were to put an end to its activities, this would raise the issue of the fate of the units disposed of.

The authorities should make recommendations on the future of the stored units with regard to financial and logistical issues, as well as to the level of compliance with quality requirements.

In such an event, public banks would not be able to take over an inventory that was built according to a set of regulations and quality standards that is too different from those applicable to allogeneic banking.

This would cause significant distress to the families that have invested money/hope in these HBMI-FPs.

^b Total over 20 years: $(1 + 2 + 3 + \dots + 20) \times 120.000 \times 150 \text{ EUR}$
 $= 210 \times 120.000 \times 150 \text{ EUR}$
 $= 3.780.000.000 \text{ EUR}$

3.5.4. Information and informed consent

The SHC insists that there should be a clear contract between the family and the HBMI-FP which states the rights and obligations of each party. This contract should specify e.g. the ownership of the CB and its fate in the event of the contract being terminated. It should also regulate what happens should the CB be damaged or the HBMI-FP go out of business or be delocalised (e.g. to a country with different laws and regulations) and provide guarantees as regards the quality of the product before and after storage. Any cross-border transfer of CBU must abide by the provisions of the EU directives and can only take place between licensed institutions. This is the only way to ensure that the transfer will be adequately controlled

If the information provided to the parents refers to any clinical application, there must be evidence provided in support of the fact that the stored product does indeed have the required biological properties. This is already the case for CB that is stored for allogeneic purposes. The information provided to potential customers should distinguish between scientific facts and speculative statements.

The informed consent form should mention the probability for the CBU to be used. Indeed, there is no strong evidence that a CBU would be suitable for clinical use, and, more importantly, the amount of collected cells may not be sufficient. The issues that have to be addressed in the information provided are: probability of clinical need, latent disease, quality and viability, and GVL effect (better outcome for allogeneic transplantation) (Kaimal et al., 2009).

3.5.5. Conclusion

The information provided to families that are considering CB storage should be clear, accurate and honest. The contracts between the families and the HBMI-FPs should cover foreseeable problems that could affect the products stored and take into account national and international regulations.

Considering the lack of evidence-based scientific data and the weakness of clinical arguments in support of autologous CB banking and its low cost-effectiveness, the SHC would advise against social security reimbursing this procedure. If autologous banking becomes a reality in Belgium, the authorities will have to ensure that this procedure complies with adequate quality standards, including accreditation requirements and the compliance with ethical principles, as described above.

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5. 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 took part in drawing up the advisory report:

ANGENON Elyane*	Nursing, transplant coordination	ULB
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	
DEVOS Timothy	Haematology	KUL
FERRANT Augustin*	Clinical haematology	UCL
KÖGLER Gesine	Paediatric oncology, haematology	Universitätsklinikum Düsseldorf - Germany
LATINNE Dominique*	Haematological biology	UCL
FAUCHER Catherine	Haematology	Agence de la biomédecine ; Institut Paouli Calmettes, Marseille - France
NAVARRETE Cristina	Immunology, transplantation	NHS Cord blood bank, British bone marrow registry, NHSBT, England
NOENS Lucien	Haematology	UZ Gent
SELLESLAG Dominik	Internal medicine, haematology	AZ Brugge
STRAETMANS Nicole	Haematology, cell therapy	Hôpital de Jolimont
VAN RIET Ivan	Medicine, cell therapy	UZ Brussel
ZACHEE Pierre	Haematology	ZNA Antwerpen

The working group was chaired by Elyane ANGENON and 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
GUNS Johan*	Medical-social sciences	UZ Brussel
PIRNAY Jean-Paul*	Medical sciences	LabMCT HCB-KA
THONON Fabienne	Reproductive medicine, embryology	CHR de la Citadelle de Liège
VAN DEN ABBEEL Etienne	Reproductive medicine, embryology	UZ Gent
VAN GEYT 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 FAMHP Organs
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The working group was chaired by Hilde BEELE; the scientific secretary was Muriel BALTES.