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STEM CELLS TRANSLATIONAL MEDICINE

Worldwide survey on key indicators for public cord blood banking technologies: By the World Marrow Donor Association Cord Blood Working Group

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Abstract

The Cord Blood Working Group of the World Marrow Donor Association created a survey for cord blood banks (CBBs) aimed to identify and understand the main technical procedures currently used by public CBBs worldwide regarding cord blood units (CBUs) available for unrelated hematopoietic stem cell transplantation. These technical procedures include CBU collection, (pre-) processing, packaging, testing, storage and transport. The survey was an online survey created with SurveyGizmo and was completed individually by each CBB at the end of 2017. The information is valuable to transplant centers, CBBs as well as the global industry of public cord blood banking. In general, we can conclude from this survey that the majority of CBBs are up to standard in terms of CBB technologies. Areas of improvement include accreditation, increase standardization in testing and setting of total nucleated cells thresholds for acceptance a CBU for public use. Furthermore, there is a need for a consensus in the way CBBs operate in term of reservation and release to facilitate a more straightforward access to the therapy.

KEYWORDS

cord blood banks, cord blood units, public cord blood banks, unrelated hematopoietic stem cell transplantation

1 | INTRODUCTION

Since the first cord blood unit (CBU) transplantation in 1989[1] over 50 000 CBUs have been shipped worldwide for unrelated hematopoietic stem cell transplantation (HSCT).[2] In 2018, 21% of the CBU shipments for HSCT were transported between countries.[2] However, not all cord blood banks (CBBs) operate in a similar way. In recent years, besides the usual CBU parameters of interest, transplant centers (TCs) are increasingly looking for technical details of procedures. In this way, the TC can make the best informed decision in choosing the right CBU for their patient, especially when choosing a CBU from another country.

The Cord Blood Working Group (CBWG) of the World Marrow Donor Association (WMDA) created a survey to gather information specifically from cord blood banks with this in mind. With this survey, the authors aimed to identify and understand the main technical procedures currently used by public CBBs worldwide regarding CBUs available for unrelated HSCT. These technical procedures include CBU collection, (pre-) processing, packaging, testing, storage, and transport.

The information gathered with this survey serves multiple purposes:

1. The information is valuable to TCs—as they are increasingly interested in characteristics of the CBBs themselves, in addition to information about a specific CBU.
2. The information is valuable to the CBBs—as information they can use to compare practices and perhaps improve processes at their individual centers.
3. The information is valuable as a description of the global industry of public cord blood (CB) banking.

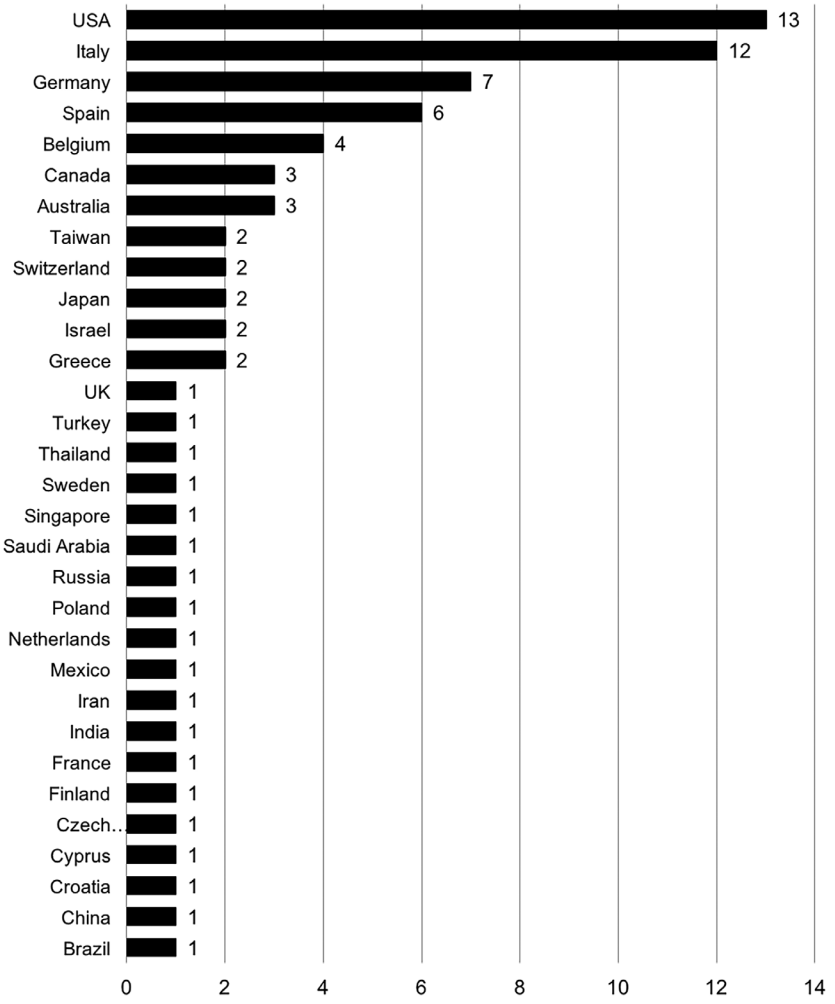
The first two points are addressed with an overview of the results of each responding CBB individually and is publicly available on the WMDA's online collaborative tool.[3] With this article, the authors attempt to address the latter point.

Significance statement

In this brief report, we aim to identify and understand the main technical procedures currently used by public cord blood banks worldwide. The data were provided to World Marrow Donor Association by surveying cord blood banks directly and represent a true global effort to serve the cord blood banking community. In this brief report, we identify areas of improvement in the way cord blood banks operate to facilitate a more straightforward access to the therapy.

2 | MATERIALS AND METHODS

The survey, entitled "Cord Blood Bank Technology Survey," was an online survey and was completed individually by each CBB at the end of 2017. SurveyGizmo was used as the online tool to create the survey. Donor registries were asked to forward the survey to their network CBBs and monitor to be sure they were completed. Only public CBBs with CBUs available for unrelated HSCT were invited to complete the survey. This original project was strongly supported by NetCord (part of WMDA since 2017), as it is in line with its commitment to provide high quality CB products to the transplant community. Therefore, NetCord members were encouraged to actively contribute. A copy of the complete survey can be found in the Supporting Information.



GRAPH 1 Number of cord blood banks participating per country

TABLE 1 General data and accreditations

General data				
Key indicators	**% of CBBs**	**% of CBUs in worldwide inventory**	**Related FACT standard**	**Critical or informative**
Currently listing CBUs in WMDA search and match service	94%	93%	Part B: CBB Operational Standards B1.3; B1.4; B3.1; B3.3; B5.3; B11.7; B11.8 Part E: CB Listing, Search, Selections, Reservation, Release and Distribution E1.1; E1.2	Critical
Current processing method is plasma and RBC reduced (automatic or manual)	93%	NA	Part D: CB Processing D3.2.8	Critical
Inventory of CBUs stored for unrelated patients with TNC >150 (×10E7)	NA	17%	Appendix V: Specification Requirements for CBU Stored for Clinical Use	Informative
Accreditations, licenses, certifications of the CBB				
Key indicators	**% of CBBs**	**% of CBUs in worldwide inventory**	**Related FACT standard**	**Critical or informative**
FACT accredited	50%	69% (CBUs banked in a FACT accredited CBB)	Part B: CBB Operational Standards. B1.2.1 Part D: CB Processing. D1.1	Critical
AABB accredited	19%	27% (CBUs banked in an AABB accredited CBB)	Part B: CBB Operational Standards. B1.2.1 Part D: CB Processing. D1.1	Critical
Licensed by competent authority	88%[a]	NA	Part B: CBB Operational Standards B1.2.1; B5.7 Part D: CB Processing. D1.1	Critical
On-site inspection by national donor registry	36%	NA	Accreditation section, page 2	Critical

Abbreviations: CB, cord blood; CBB(s), cord blood bank(s); CBU(s), cord blood unit(s); FACT, Foundation for the Accreditation of Cellular Therapy; NA, not applicable; RBC, red blood cell reduced, TNC, total nucleated cells; WMDA, World Marrow Donor Association.
[a]Of the remaining 12%, nine CBBs reported having FACT and/or AABB accreditation and three CBBs reported having other licenses/accreditations/certifications.

3 | RESULTS

Provided are the most important findings from the survey presented as key indicators with the percentage of CBBs and percentage of total CBUs in current inventory (as of 2017) complying with those indicators. The key indicators are considered critical or informative depending on the importance to TCs. If applicable, the related FACT (Foundation for the Accreditation of Cellular Therapy) standards are referenced. The sixth edition of the FACT standards were used for cross reference, since this was the version operational at the time the survey was conducted.[4] The authors choose to only include the references to the FACT standards over other accrediting agencies like AABB because they are the most extensive standards in the field. The presented key indicators should not be considered as optimal standards, like those developed by accrediting agencies. They rather give a valuable description of the global industry of public CB banking.

One hundred and thirty-one CBBs in 41 different countries were approached for participation and 77 CBBs in 31 countries completed the survey (Graph 1). Therefore, the response rate of this survey is 59%.

Eighty-eight percent of the responding CBBs are affiliated with a national donor registry. The majority of the participating CBBs started collecting CBUs before 2006 (77%). Inventory size of the CBBs varies widely, with a median (range) inventory of 4224 (33-60 563) CBUs. The total number of CBUs in inventory of all responding CBBs was 590 877, which was 78% of the total worldwide inventory[2] at that time. Only 17% of the total inventory comprise of CBUs with total nucleated cells (TNC) over 150x10E7. These numbers are similar

TABLE 2 CBU collection to processing and current testing on cryopreserved CBU

CBU collection			
Key indicators	**% of CBBs**	**Related FACT standard**	**Critical or informative**
Current CBU collection		Part C: CB Donor Management and Collection. C6.2	Informative
In utero:	53%		
Ex utero:	13%		
CBB uses both methods:	34%		

Conditioning and transport from collection center to CBB			
Key indicators	**% of CBBs**	**Related FACT standard**	**Critical or informative**
Use of secondary bag (to contain any leakage)	82%	Part C: CB Donor Management and Collection. C7.3	Critical
Refrigerated transport[a]		Part C: CB Donor Management and Collection. C7.5	Critical
Active:	10%		
Passive:	56%		
Temperature probe[a]		Part C: CB Donor Management and Collection. C7.5	Critical
Electronic:	70%		
Nonelectronic:	10%		
Qualified transport	78%	Part C: CB Donor Management and Collection. C7.5	Critical
Define a validated temperature	96%	Part C: CB Donor Management and Collection. C7.5	Critical

Preprocessing evaluation—current threshold for accepting a CBU for public use			
Key indicators	**% of CBBs**	**Related FACT standard**	**Critical or informative**
TNC >125 (×10E7)	60%		Informative
Performed % viability CD45 positive cells	36%	Part D: CB Processing D.3.2.4; D3.2.4.1	Informative
Performed % viability CD34 positive cells	40%		Informative
Collection report	100%	Part C: CB Donor Management and Collection. C5; C7.7	Critical
Informed consent	100%	Part C: CB Donor Management and Collection. C4	Critical
Temperature + integrity of the bag	97%	Part D: CB Processing D5; D5.3; D6; D6.5	Critical
Medical history	96%	Part C: CB Donor Management and Collection. C5	Critical
Maternal IDM results	70%	Part D: CB Processing D10 Appendix IV: Testing Requirements	Critical
ISHAGE guidelines for CD34 enumeration method	91%		Informative
External proficiency testing QC of FACS lab	86%	Part D: CB Processing D9: CBU Testing D9.2.7	Critical
Perform postprocessing/prefreeze CD34 cell count	93%	Appendix IV: Testing Requirements	Critical
<48 hours from collecting to processing	97%	Part D: CB Processing D3; D3.2.6	Critical

Processing and CBU storage			
Key indicators	**% of CBBs**	**Related FACT standard**	**Critical or informative**
Current automatic prefreeze processing method		Part D: CB Processing D3.2	Critical
AXP, SEPAX, Optipress, Macropress (and/or):	75%		
Manual processing only:	24%		
No processing:	1%		
Current cryopreservation method[a,b]		Part D: CB Processing D5: Cryopreservation	Critical

TABLE 2 (Continued)

Processing and CBU storage			
Key indicators	**% of CBBs**	**Related FACT standard**	**Critical or informative**
Conventional controlled rate freezers:	76%		
Bioarchive only:	21%		
Packaging when a unit is stored		D5: Cryopreservation D5.3	Informative
Metal canister only:	32%		
Overwrap only:	1%		
Both:	67%		
At least two segments stored with the unit	95%	D4: Samples D4.1.1	Critical
Current testing on cryopreserved CBU			
Key indicators	**% of CBBs**	**Related FACT standard**	**Critical or informative**
Standard on maternal sample		D10: Maternal Testing D10.1; Appendix IV; Testing Requirements	Critical
HIV 1/2 antibodies and/or HIV 1 and 2 + 0 antibodies:	100%		
HIV NAT:	84%		
Standard on maternal sample		D10: Maternal Testing D10.1; Appendix IV; Testing Requirements	Critical
Hepatitis B surface antigen:	100%		
Hepatitis B core antibody:	88%		
HBV NAT:	83%		
Standard on maternal sample		D10: Maternal Testing D10.1; Appendix IV; Testing Requirements	Critical
Hepatitis C antibody:	100%		
HCV NAT:	84%		
Standard HTLV 1/2 antibodies on maternal sample	88%	D10: Maternal Testing D10.1; Appendix IV; Testing Requirements	Critical
Standard CMV on maternal sample	96%	D10: Maternal Testing D10.1; D10.2; D10.3; Appendix IV; Testing Requirements	Informative
Standard syphilis on maternal sample	100%	D10: Maternal Testing D10.1; D10.3.2; Appendix IV; Testing Requirements	Critical
At least extra storage of plasma and material for DNA extraction of both CBU and mother	71%	D4: Samples D4.1; D4.3	Critical
HLA-A HR typing at time of listing	54%	D9: CBU Testing D.9.3.3; Appendix IV; Testing Requirements	Critical
HLA-B HR typing at time of listing	54%	D9: CBU Testing D.9.3.3; Appendix IV; Testing Requirements	Critical
HLA-DRB1 HR typing at time of listing	79%	D9: CBU Testing D.9.3.3; Appendix IV; Testing Requirements	Critical
HLA-C at least LR typing at time of listing	100%	D9: CBU Testing D.9.3.3; Appendix IV; Testing Requirements	Critical
≥100 TNC (×10E7) threshold for accepting a CBU for public use (postprocessing)	42% (9% UNK or NA)	D9: CBU Testing Appendix V	Critical
≥1.25 CD34 (×10E6) single platform threshold for accepting a CBU for public use (postprocessing)	48% (44% UNK or NA)	D9: CBU Testing Appendix V	Critical
		D9: CBU Testing	Critical

(Continues)

TABLE 2 (Continued)

Current testing on cryopreserved CBU			
Key indicators	**% of CBBs**	**Related FACT standard**	**Critical or informative**
≥1.25 CD34 (×10E6) double platform threshold for accepting a CBU for public use (postprocessing)	16% (83% UNK or NA)	Appendix V	
≥85% viability threshold for accepting a CBU for public use (postprocessing)	55% (23% UNK or NA)	D9: CBU Testing Appendix V	Critical

Abbreviations: CB, cord blood; CBB(s), cord blood bank(s); CBU(s), cord blood unit(s); CMV, cytomegalovirus; DNA, deoxyribonucleic acid; FACS, fluorescence-activated cell sorting; FACT, Foundation for the Accreditation of Cellular Therapy; HIV, human immunodeficiency viruses; HLA, human leucocyte antigen; HR, high resolution; HTLV, human T-cell lymphotropic virus; IDM, infectious disease marker; ISHAGE, International Society for Hematotherapy and Graft Engineering; LR, low resolution; NA, not applicable; NAT, nucleic acid testing; QC, quality control; TNC, total nucleated cells; UNK, unknown.

[a]Not all answer categories are shown, therefore the percentage does not add up to 100%.

[b]Multiple answers were possible, therefore percentage does not add up to 100%.

compared with the TNC of CBU inventory available in the international database of WMDA search and match service.[2]

The most important findings are summarized in Tables 1-3.

4 | DISCUSSION

Although 88% of the participating CBBs report to be licensed by a competent authority, only 50% report to have FACT accreditation and 19% have AABB accreditation. As discussed in three recent papers by Dehn et al,[5] the Cord Blood Accociation,[6] and Rocha,[7] selection of CBUs from CBBs that take part in long standing voluntary accreditation programs has now been included in recommended CB selection policies as a criterion to evaluate CBUs. Based on the results of our survey, this appears to be an area where CBBs can make an effort to improve.

Another recommended CB selection policy is to use RBC depleted units.[5] With 97% of the responding CBBs reporting they are currently depleting units of RBC (either automatic or manually) it looks like this is now standard practice around the world. Having an attached segment for HLA confirmatory typing is also essential.[5,6] Currently 95% of the responding CBBs have at least two attached segments stored with the CBU.

Additionally, in the Cord Blood Association paper[6] requirements for infectious disease marker (IDM) testing are given. All tests should be done on the maternal blood sample. Anti-HIV 1/2, Hepatitis C antibody, Syphilis and Hepatitis B surface antigen are required to be standard performed and 100% of CBBs report to perform these tests. Anti-CMV Total/IgG/IgM is also required to be standard performed and 96% of CBBs report to perform these. Anti-HTLV 1/2 is recommended to be standards performed and 88% of CBBs report to perform this test.

Standards for CB donation do not require the need for a second testing in main transmissible diseases and in this situation it becomes critical to perform testing using NAT technologies. As shown in this survey, there is a substantial number of CBBs that performed NAT testing but still 16%-17% of the CBBs answering the questionnaire are not routinely doing this analysis.

It is substandard that only 62% of the CBBs can ship a CBU in 1 week. This does not fulfill the concept that a CBU is an off-the-shelf therapy. To improve the shipping speed, it would require international harmonization between CBBs. Furthermore, there is not a good consensus in when/how to do the release testing on an attached segment. This also generates a non-standardized result between CBBs. This is a field where the CBBs need to work together to facilitate access to the therapy.

Only 42% of CBBs answered they use a threshold of TNC >100x10E7 for accepting a CBU for public use. The standards only have instructions on how much TNC a CBU must contain at the end of the process and only mention a CBB must have a policy in place to verify it. From the survey results, it cannot be identified why a CBB would bank CBU with low TNC counts knowing these are less likely to be requested. In recent years it has become harder to sustain a successful CBB and CBBs perhaps should consider only bank larger units because they are most on demand.

The questions about testing thresholds for accepting a CBU for public use (postprocessing) were answered in a wide range with many CBBs answering not applicable or leaving the answer blank. Therefore, this part of the questionnaire is inconclusive and difficult to interpret. This could either be due to the fact that the questions were unclear and difficult to fill out, or the fact that there is no consensus in the CBB field on thresholds for these tests. Moreover, the FACT standards are not specific about the time point in the CBB process pre-evaluation of the CBU should take place. However, the information gained from these questions about practices of pre-evaluation is still relevant for CBBs to know about. It matters to the CBBs in terms of benchmarking, self-evaluation and how a CBB defines which units are "bankable."

A response rate of 59% is considered high for these types of surveys, which indicates the commitment of the CBB community to make this information available to TCs and other CBBs. One thing to keep in mind is that these results were current at the end of 2017/beginning of 2018. As the CBB field is fast moving, these data should

TABLE 3 Storage, HLA typing, reservation policies and adverse event reporting

Storage of CBUs at the CBB				
Key indicators	**% of CBBs**	**% of CBUs in worldwide inventory**	**Related FACT standard**	**Critical or informative**
Storage container[a]				Informative
Bioarchive conventional:	30%	33%		
Vapor phase conventional:	56%	58%		
Liquid phase:	52%	57%		
Double walled liquid nitrogen:	16%	16%		
At least any storage monitoring	100%	100%	D6.5: Conditions for Storage	Critical

Verification/extended HLA typing of the CBU				
Key indicators	**% of CBBs**	**% of CBUs in worldwide inventory**	**Related FACT standard**	**Critical or informative**
Verification/extended HLA typing currently performed at			B5. CBB operations B5.6	Critical
EFI lab:	51%	37%		
ASHI lab:	36%	50%		
No accredited lab:	13%	13%		
Extended HLA typing results available within 7 days	63%	70%		Informative

Reservation/cancelation policies				
Key indicators	**% of CBBs**	**% of CBUs in worldwide inventory**	**Related FACT standard**	**Critical or informative**
Time to shipment less than 1 week after order placed	62%	NA		Informative
Post-thaw testing of CD34, TNC cell counts, % viability of CD34, CD45, and CFUs[b]		NA	Appendix IV: Thawed segment or thawed representative sample prior to release to the Clinical Program	Informative
At unit reservation or CT:	50%			
When CBU shipment requested:	22%			
Cancelation fee[b]				
Never:	52%	NA		Informative
Only if release testing has begun:	32%			

Adverse event reporting				
Key indicators	**% of CBBs**	**% of CBUs in worldwide inventory**	**Related FACT standard**	**Critical or informative**
Adverse event reporting to competent authority	74%	NA	B2: Quality Management B2.1; B5.10 Part C: CB Donor Management and Collections C5.1; C6.9 E7: Clinical Outcome Data E7.1	Critical

Abbreviations: ASHI, American Society for Histocompatibility and Immunogenetics; CB, cord blood; CBB(s), cord blood bank(s); CBU(s), cord blood unit(s); CFUs, colony forming units; CT, confirmatory typing; EFI, European Federation for Immunogenetics; FACT, Foundation for the Accreditation of Cellular Therapy; HLA, human leucocyte antigen; NA, not applicable; TNC, total nucleated cells.
[a]Multiple answers were possible, therefore percentage does not add up to 100%.
[b]Not all answer categories are shown, therefore the percentage does not add up to 100%.

be closely monitored. Future directions of collecting this kind of data needs to be aligned with the Netcord-FACT standards seventh edition. WMDA will collect a summarized version of this survey in 2020, where CBBs can directly submit their data to the WMDA Share website.[3]

5 | CONCLUSION

In general, we can conclude from this survey that the majority of public CBBs are up to standard in terms of CBB technologies. Areas of improvement could include accreditation, increase standardization in

testing and setting of TNC thresholds for acceptance a CBU for public use. Furthermore, there is a need for a consensus in the way CBBs operate in term of reservation and release to facilitate a more straightforward access to the therapy.

ACKNOWLEDGMENTS

The authors would like to thank all participating CBBs. A list of participants can be found in the Supporting Information.

CONFLICT OF INTEREST

The authors declared no potential conflicts of interest.

AUTHOR CONTRIBUTIONS

M.J., K.P.: conception and design, collection and/or assembly of data, data analysis and interpretation, manuscript writing, final approval of manuscript; L.F.: manuscript writing, final approval of manuscript; M.D., S.Q.: conception and design, final approval of manuscript; S.G.: conception and design, data analysis and interpretation, final approval of manuscript; E.B.: conception and design, data analysis and interpretation, manuscript writing, final approval of manuscript.

DATA AVAILABILITY STATEMENT

The data that supports the findings of this study are available in the supplementary material of this article.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

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