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 of 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 19891 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. With this article, the authors attempt to address the latter point.

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

**Significance statement**

This brief report aims 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. This report also identifies areas of improvement in the way cord blood banks operate to facilitate a more straightforward access to the therapy.
TABLE 1  General data and accreditations

| General data | % 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 | % 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.

aOf the remaining 12%, nine CBBs reported having FACT and/or AABB accreditation and three CBBs reported having other licenses/accreditations/certifications.

contribute. A copy of the complete survey can be found in the Supporting Information.

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. 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 CBUs 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 at that
TABLE 2  CBU collection to processing and current testing on cryopreserved CBU

| CBU collection | % 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 transporta | | Part C: CB Donor Management and Collection. C7.5 | Critical |
| Active | 10% | | |
| Passive | 56% | | |
| Temperature probea | | 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 (x10E7) | 60% | Part D: CB Processing D3.2.4; D3.2.4.1 | Informative |
| Performed % viability CD45 positive cells | 36% | Part C: CB Donor Management and Collection. C5; C7.7 | Informative |
| Performed % viability CD34 positive cells | 40% | Part C: CB Donor Management and Collection. C5; C7.7 | Informative |
| Collection report | 100% | Part C: CB Donor Management and Collection. C4 | 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, SEPA, Optipress, Macropress (and/or) | 75% | | |
| Manual processing only | 24% | | |
| No processing | 1% | | |
| Current cryopreservation methoda,b | | Part D: CB Processing D5: Cryopreservation | Critical |

(Continues)
## TABLE 2 (Continued)

### Processing and CBU storage

| Key indicators                                      | % of CBBs | Related FACT standard                           | Critical or informative |
|-----------------------------------------------------|-----------|-------------------------------------------------|------------------------|
| Conventional controlled rate freezers               | 76%       | D5: Cryopreservation                             | Informative            |
| Bioarchive only                                      | 21%       | D5.3                                            |                        |
| Packaging when a unit is stored                      |           |                                                 |                        |
| Metal canister only                                  | 32%       |                                                 |                        |
| Overwrap only                                        | 1%        |                                                 |                        |
| Both                                                 | 67%       |                                                 |                        |
| At least two segments stored with the unit           | 95%       | D4: Samples                                     | Critical               |
|                                                     |           | D4.1.1                                          |                        |

### Current testing on cryopreserved CBU

| Key indicators                                      | % of CBBs | Related FACT standard                           | Critical or informative |
|-----------------------------------------------------|-----------|-------------------------------------------------|------------------------|
| Standard on maternal sample                         | 100%      | D10: Maternal Testing                            | Critical               |
| HIV 1/2 antibodies and/or HIV 1 and 2 + 0 antibodies:| 100%      | D10.1: Appendix IV; Testing Requirements        |                        |
| HIV NAT                                              | 84%       |                                                 |                        |
| Standard on maternal sample                         | 100%      | D10: Maternal Testing                            | Critical               |
| Hepatitis B surface antigen                          | 100%      | D10.1: Appendix IV; Testing Requirements        |                        |
| Hepatitis B core antibody                            | 88%       |                                                 |                        |
| HBV NAT                                              | 83%       |                                                 |                        |
| Standard on maternal sample                         | 100%      | D10: Maternal Testing                            | Critical               |
| Hepatitis C antibody                                 | 100%      | D10.1: Appendix IV; Testing Requirements        |                        |
| HCV NAT                                              | 84%       |                                                 |                        |
| Standard HTLV 1/2 antibodies on maternal sample      | 88%       | D10: Maternal Testing                            | Critical               |
| Standard CMV on maternal sample                     | 96%       | D10: Maternal Testing                            | Informative            |
| Standard syphilis on maternal sample                 | 100%      | D10: Maternal Testing                            | Critical               |
| At least extra storage of plasma and material for DNA extraction of both CBU and mother | 71% | D4: Samples                                     | Critical               |
|                                                     |           | D4.1; D4.3                                      |                        |
| HLA-A HR typing at time of listing                   | 54%       | D9: CBU Testing                                  | Critical               |
|                                                     |           | D.9.3.3; Appendix IV; Testing Requirements      |                        |
| HLA-B HR typing at time of listing                   | 54%       | D9: CBU Testing                                  | Critical               |
|                                                     |           | D.9.3.3; Appendix IV; Testing Requirements      |                        |
| HLA-DRB1 HR typing at time of listing                | 79%       | D9: CBU Testing                                  | Critical               |
|                                                     |           | D.9.3.3; Appendix IV; Testing Requirements      |                        |
| HLA-C at least LR typing at time of listing          | 100%      | D9: CBU Testing                                  | Critical               |
|                                                     |           | D.9.3.3; Appendix IV; Testing Requirements      |                        |
| ≥100 TNC (×10E7) threshold for accepting a CBU for public use (postprocessing) | 42% (9% UNK or NA) | D9: CBU Testing                                  | Critical               |
|                                                     |           | Appendix V                                       |                        |
| ≥1.25 CD34 (×10E6) single platform threshold for accepting a CBU for public use (postprocessing) | 48% (44% UNK or NA) | D9: CBU Testing                                  | Critical               |
|                                                     |           | Appendix V                                       |                        |
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 2017/2018 because they are most on demand.

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., the Cord Blood Association, and Rocha, 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. 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. Currently 95% of the responding CBBs have at least two attached segments stored with the CBU.

Additionally, in the Cord Blood Association paper 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 CBUs report to perform these tests. Anti-CMV Total/IgG/IgM is also required to be standard performed and 96% of CBUs report to perform these. Anti-HTLV 1/2 is recommended to be standards performed and 88% of CBUs 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 >100x10^6 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 CBB 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 2017/2018 as the CBB field is fast moving, these data should

### TABLE 2  (Continued)

| Key indicators | % of CBBs | Related FACT standard | Critical or informative |
|----------------|-----------|-----------------------|------------------------|
| ≥125 CD34 (x10E6) double platform threshold for accepting a CBU for public use (postprocessing) | 16% (83% UNK or NA) | Appendix V | Critical or informative |
| ≥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.

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

*Multiple answers were possible, therefore 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

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

| Storage of CBUs at the CBB | % of CBBs | % of CBUs in worldwide inventory | Related FACT standard | Critical or informative |
|---------------------------|-----------|---------------------------------|-----------------------|------------------------|
| Storage container⁴        |           |                                 |                       |                        |
| Bioarchive conventional   | 30%       | 33%                             |                       | Informative            |
| 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 | % 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/cancellation policies | % 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 CFUs⁵ | 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 fee⁶                    |           |                                 |                       |                        |
| Never                              | 52%       | NA                             |                       | Informative            |
| Only if release testing has begun  | 32%       |                                 |                       |                        |

| Adverse event reporting | % 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.

⁴Multiple answers were possible, therefore percentage does not add up to 100%.

⁵Not all answer categories are shown, therefore the percentage does not add up to 100%.
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 straight-forward 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 support 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.

How to cite this article: Jöris M, Paulson K, Foley L, et al. Worldwide survey on key indicators for public cord blood banking technologies: By the World Marrow Donor Association Cord Blood Working Group. Stem Cells Transl Med. 2021;10:222–229. https://doi.org/10.1002/sctm.20-0246