REVISION HISTORY						
Rev	**Version (Date)**	**Description of change**	**Author**	**Effective date**	**Reviewed by**	**Signature**
0	Jan 2017	Change of standards and ISO 15189 format	AK	20/03/2017	PC	
1	Dec 2020	New WMDA standards	AK	01/01/2021	PC	

1. Principle

This policy provides basic information to international registries or transplant centres on how to access CYBMDR donors.
The document addresses international registries and transplant centres involved in hematopoietic stem cell transplantation and gives references regarding certain aspects of the search process and the access to our donors in general.
It is not intended to replace other SOPs specific documentation.
CYBMDR's organizational and regulatory information, available on the WMDA website outline the information laid out in this policy.

2. CYBMDR and Related Institutions

CYBMDR was founded in 1996 with the support of the Ministry of Health as the national hub for unrelated donor searches. It currently cooperates with one cord blood bank and one collection centre.
On an international level, it cooperates with registries worldwide and also maintains direct contact with TCs outside of Cyprus, particularly when for the latter no national registry support has been established for performing international donor searches and acquiring foreign stem cell products.
In particular:
 promotes the utilization of computer links based on the EMDIS technology to enable automated processing of requests and exchange of messages and
 creates and maintains forms, as required by WMDA standards to be used for the workup process and the communication with TCs.
It is WMDA accredited since 2008. All cooperative partners must adhere to the WMDA Standards as well as to the National Competent Authority regulations under the Tissues and Cells Law, and all pertinent related national and international laws and regulations.

3. Contact Details

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4. Obtaining Donors through CYBMDR

4.1 Patient-Related Information

4.1.1 Preliminary Search

Preliminary searches can routinely be initiated from international partners who:
 by registries that are operating according to WMDA standards on behalf of cooperating TCs in their country or

 by TCs from countries without an established registry or which have a compelling reason to ask for direct cooperation.
New registries wishing to cooperate with CYBMDR need to contact us before sending an initial search request, since modalities regarding qualification (according to WMDA standards), contact persons, data transmission, and billing need to be clarified and implemented before requests can be processed.

TCs seeking a direct cooperation with the CYBMDR should have an accreditation for allogeneic transplants from JACIE or a comparable organization. If such accreditation is not available, TCs may establish their eligibility by providing specific details which may be subject to approval by the CYBMDR Medical Director and Medical Scientific and Advisory Committee. Alternatively, the WMDA Transplant Center Evaluation Form may be submitted.

Searches in CYBMDR are typically initiated
 using the EMDIS network or,

 using the WMDA preliminary search form or,

 a registry equivalent.
In addition to patient name and HLA data (recommended in high resolution), birthdate, diagnosis and patient gender are required before a search is initiated. It is recommended to provide information about the intended transplant center when initiating a search in order to prevent delays later during the search or workup process.

Technical information/EMDIS
Incoming patient update [PAT_UPD]
 We require either serological or molecular data for at least HLA-A, -B and -DR(B1).
 Search requests for patients older than 85 years will not be accepted.
 Combination of diagnosis and disease phase is checked for plausibility (see Table 1); disease phase is blanked and a WARNING is sent back if the combination is invalid.
 The following default “matching preferences” are applied if no matching preferences are provided along with the PAT_UPD:
P_MATCH_AB = 0:XX:40:2020XXXXXX/
P_MATCH_DR = 0:XX:60:2020XX20XX/
P_MATCH_CB = 0:XX:62:2222XX22XX/ i.e. we routinely exclude antigen mismatches for HLA-A, -B and -DR(B1) but no allelic mismatches for donors but accept up to two antigen mismatches for cord blood units.
 Antigen mismatch searches of AB-only typed donors will not be performed; the default AB matching preferences will be applied instead.
Table 1: Valid combinations of [P_DIAG] and disease phase [P_DIS_PHA] EMDIS-Data Dictionary

diagnosis	phase	diagnosis	phase	diagnosis	phase
ALL	AD	HIS	NA	NHL	Cn
ALL	Cn	HL	Cn	NHL	PF
ALL	PF	HL	PF	NHL	Pn
ALL	Pn	HL	Pn	NHL	Rn
ALL	PI	HL	Rn	OL	Cn
ALL	Rn	IEA	NA	OL	Pn
AML	AD	IIS	NA	OL	RD
AML	Cn	IMD	NA	OL	SD
AML	PF	IPA	NA	OM	None
AML	Pn	MDS	AD	OND	NA
AML	PI	MDS	Cn	PCD	AD
AML	Rn	MDS	PF	PCD	Cn
CML	AP	MDS	Pn	PCD	PF
CML	BC	MDS	PI	PCD	Pn
CML	Nn	MDS	Rn	SAA	NA

* see https://share.wmda.info/display/EMDISPUB/Main+documentation

4.1.2 Search Activation

Searches performed electronically via EMDIS must be set to status “active” before further requests can be accepted. For patients activated within EMDIS, search is carried out every night automatically and a new search report is generated.

All non-EMDIS searches are automatically activated when the first request is made on behalf of a patient. New search reports are provided upon request.

EMDIS Technical information
Incoming patient status change [PAT_STAT]
A search coordinator is notified if the patient age is above 69 years or diagnosis is one of OM (Other Malignancy) or OL (Other Leukaemia) upon activation of the patient.

Prometheus database is checked for duplicate patient records at activation.

If inquiries occur, CYBMDR will contact the requesting center via email.

4.1.3 Cancellation/Discontinuation of Searches

There is no need to cancel a preliminary search which was never activated.
For activated searches, CYBMDR expects a formal cancellation of the donor search.
This is usually performed when a suitable donor has been identified and/or the patient proceeds to transplant, when the patient is no longer interested in or eligible for a transplant or when the requesting centre loses contact with the patient.
It is suggested that a search can be cancelled after three months of no activity for a patient.
The cancellation of a search can be informal but must be in writing.

Technical information/EMDIS
Incoming patient status change [PAT_STAT]
No special information

4.2 Donor-Related Information

Technical information/EMDIS
 Subsequently, the word “donors” always relates to “adult” donors, whereas adult are considered individuals who have reached the age of 18 at the time of a specific request and are no more than the age of 60.
Manually Requested Donors / Mismatched Donors
 In addition, CYBMDR also provides specific donors to EMDIS upon request (e.g. a particular mismatched donor).
 Requests on such mismatched donors are accepted, however, a WARNING will be issued.
All incoming Requests [*_REQ]
 The “reference code” (REF_CODE) must be unique within the sending hub for all types of requests.
 If a requested donor was not reported for that patient or does not match anymore according to matching criteria a WARNING is sent.
All incoming results [*_RES]
 Multiple identical results are rejected.
 Multiple different results are treated as updates/corrections.

4.2.1 Search Reports

CYBMDR provides search reports in a uniform layout released from Prometheus program. The criteria for selection and sorting may be tailored to the specific needs of each patient. For primary selection of donors to be considered (search step 1) the patient's and donor's serological and molecular assignments regarding HLA loci A, B, C, DRB1 and DQB1 are taken into account

The order in which donors will be presented (search step 2) is based on:

a) the probability of (mis-)matching calculated on the basis of five locus haplotype frequencies regarding HLA-A~C~B~DRB1~DQB1, and

b) the donor's age

The search reports also contain information about HLA-DPB1 can be filtered according to various secondary search criteria (e.g. donor- CMV status, donor-Sex, etc.) in order to allow maximal customization to each specific patient's needs. Three separate search reports can be requested:

- potentially suitable donors typed for HLA-A and -B only
- potentially suitable donors typed for HLA-A, -B and -DRB1
- potentially suitable cord blood units

The final layout of the search reports depends largely on a substantial number of user-controlled parameters (filter criteria).

For non-EMDIS searches the number of donors shown on search reports and other parameters are set to "default", i.e. no antigen mismatches for HLA-A, -B and -DRB1 (HLA-C, DQB1 and DPB1 are not considered). If there are less than ten donors who fulfil these criteria, a one antigen mismatch search for HLA-A, -B or -DRB1 is automatically activated thereafter.

All parameters used to compile a search report can be changed by using EMDIS matching preferences for EMDIS patients or by sending a specific request to our search coordinators.

Cord Blood Unit (CBU) search reports, by default, allow up to two mismatches for HLA-A, -B (antigen level) and -DRB1 (allele level) and are available upon request.

Technical information/EMDIS

Outgoing search report [DONOR_CB]

- The donor pool information (DON_POOL) for national donors is set to ZKRD's ION (6939).
- The donor attribute (DON_ATTR) contains for each donor the three- character-abbreviation of the German donor centers (e.g. AKB, ULM, MBG, etc.).

Incoming search report [DONOR_CB]

- Donors/CBUs without a pool information (DON_POOL) are rejected.
- Changes or deletions of an existing GRID are rejected.
- Donors/CBUs with an unknown combination of sending EMDIS node (HUB_-SND/REG_SND) and donor pool are rejected.
- WARNING if search is cancelled (STP) or suspended (SUS) more than seven days.
- A donor (DON_TYPE = "D") must be at least 17 years old. For donors with age below 17 years a WARNING is issued.
- WARNING for donors who are older than 60 years and for Cord Blood Units that are collected before 1990.
- WARNING for donors whose CMV status is reported as negative but the CMV date is missing.

WARNING if donor weight is less than 40 kg or more than 199 kg.

- WARNING if donor height is less than 100 cm or more than 250 cm.
- All errors are downgraded to WARNINGs if donor is to be deleted.

4.2.2 HLA-Typing

HLA tests requested will be performed by molecular methods in high resolution. If any typing is requested on a donor who has not yet been typed for HLA-DRB1, at least a high resolution HLA-DRB1 typing must be requested as part of the typing request.
The results of **high resolution** testing provide at least the first two fields of the current WHO nomenclature for the HLA alleles separated by a colon. Ambiguities are allowed if they contain only variations outside exons 2 and 3 for HLA class I alleles and only variations outside exon 2 for HLA class II alleles.

Technical information/EMDIS
Incoming typing requests [TYP_REQ]
 Requests for invalid typing resolutions will be upgraded to high resolution.
 Requests for typing are not permitted if the requested HLA-information is already available.
 Multiple overlapping requests at the same time are not allowed.
Incoming typing Results [TYP_RES]
 Partial results are rejected.

4.2.3 Test for Infectious Disease Markers and Blood Group

All VT samples requests are also screened for idms. The screening for infectious disease markers (IDM) at the verification typing stage (VT) routinely comprises of HBsAg, Anti-HBs, Anti-HBc IgG+IgM, Anti-HCV, HCV, HIV 1-2+p24, CMV IgG+IgM, EBV IgG+IgM, VDRL syphilis, and HTLVI+II and includes the testing of the AB0 blood group and Rhesus factor.
If only a subset of the IDM screening tests is requested, the complete screening will be performed and invoiced. The fee for the idms is separate from the VT procurement fee.

Technical information/EMDIS
Incoming IDM requests [IDM_REQ]
 Only tests as described in 4.2.3 are allowed.
 If other tests are selected the complete request is rejected.
 If only a subset of the IDM screening tests is requested, the request will be automatically upgraded to the complete set of allowed tests ([1100101011100] and a WARNING is issued.

4.2.4 CT Sample Procurement

The patient must be registered in CYBMDR with verified high resolution data for HLA-A, -B, -C, -DRB1 and -DQB1 at the time of CT request. The total quantity of blood requested for confirmatory typing must not exceed 50 ml per donor.
We cannot guarantee that blood samples will be provided exactly as requested. This may apply to the number and volume of tubes and, in some cases, to variations concerning the anticoagulant. Such deviations will occur but communicated due to the unavailability of certain types of tubes. The procurement of a blood sample always includes IDM screening (see 4.2.3).
Whenever possible, an advance notice is sent at least two days prior to sample arrival via email or EMDIS. The sample arrival date is entered and released via EMDIS or via email for non-EMDIS centers.
VT sample procurement for CBUs varies and depends on numerous factors. Material can be from a frozen DNA sample or an attached segment. The sample can be shipped to the requesting laboratory or tested at CYBMDR HLA EFI accredited lab.
All samples must be tested for HLA-A, -B, -C, -DRB1 and -DQB1 at high resolution. We expect to receive all test results obtained from samples provided (donor or CBU) as soon as possible, which should be within four weeks of sample arrival. Reservation of the donor or unit is for 3 months; upon receipt of the VT result via EMDIS or email, the donor/CBU will be released or extension of reservation be requested. Every 3 months reminders regarding outstanding CT

results are sent to the respective registry/TC by EMDIS message/e-mail. We should be informed about samples delivered with substantial delay or damage.
If all or a part of the blood samples provided are to be used or stored for research purposes, refer to WI5.5. Please provide details of the study along with the request. The registry does not approve requests for studies on blood samples from donors who have been called for tissue typing and/or Confirmatory Typing.

Technical information/EMDIS
Incoming sample requests [SMP_REQ]
 The total quantity of blood samples requested must not exceed 50 ml per request.
 Values for number of tubes must be between 1 and 9.
 The earliest date of sample reception must not be earlier than seven days prior to the date of request processing.
 The earliest date of sample reception must not be later than 30 days from the request processing date.
 The interval between earliest and latest date of sample reception must not be more than 35 days.
 The requested donor must have a valid HLA-DRB1 type.
 The field INST_SMP_SENT must contain a laboratory address registered at ZKRD (via EMDIS NEW_ADD message).
Incoming sample arrival information [SMP_ARR]
 The sample arrival date must not be later than 30 days from the message processing date.
Incoming sample result [SMP_RES]
 The result must either contain at least one HLA value or the donor “release” with an explanation selected in the corresponding remark field.
 If a SMP_RES cannot be sent a NO_RES is expected.
 If a SMP_REQ is cancelled after the CT-sample has arrived, a NO_RES has to be sent to close the request. Without the NO_RES the request will continue to be shown on the list of open requests (EMDIS message RES_REM).

4.2.5 Health and availability check

Under certain conditions a health and availability check (HAC) can be requested **instead** of a VT sample procurement. To protect the interests of donors, HAC should be the preferred option for donors who have previously (repeatedly) been requested for VT.
Prerequisites for this request are:
 DNA-based high resolution typing results for at least HLA-A, -B, -C, -DRB1 and -DQB1 must be available for the donor, and therefore, in the vast majority of cases it will be a 10/10 or 9/10 match.
 The donor has already had at least one previous confirmatory test (high resolution), in which the initial typing was verified for the loci HLA-A, -B, and -DRB1 at a minimum.
 If donor HLA typing has not been verified by previous confirmatory testing, there must be documented urgency for the transplantation, e.g. based on the specific diagnosis and the desired time frame for transplantation. Urgency is justified if transplantation must take place within 6 weeks after the search has been initiated.
 The health and availability check process will be the routine information taken from a donor at VT level. The same health history questionnaire used for the determination of donor medical suitability for VT sample procurement is also used for the health and availability check.
 The indication of the donor’s general availability and health status (number of transfusions, number of pregnancies, donor weight and height, and if anything relevant to transplantation) are updated in Prometheus and forwarded to the requesting center via EMDIS or email.

The donor remains reserved for 3 months as in the VT request case. The reservation may be extended at the request of the transplant center in justified cases. If there is no further response from the transplant, the donor is released.
 If the donor is subsequently requested to donate, the required verification typing must be performed during the workup process by means of pre-collection blood samples. The VT result must be provided before the donor starts with G-CSF application or before patient conditioning is initiated.

Technical information/EMDIS
 The health and availability check is currently not supported by EMDIS.
 Generally, a HAC can be requested by email.

4.2.6 Cancellation and Expiration of Requests

A request may be cancelled at any time. If processing cannot be stopped with any reasonable effort, an invoice will still be issued and must be paid. This is typically assumed if a typing or IDM result can be delivered within 14 days after cancellation. Search cancellation automatically cancels all pending requests except workup.

Technical information/EMDIS
Incoming request cancellation [REQ_CAN]
 No specific notes.

4.2.7 Reservation of a Donor

Donors requested for typing are reserved for the time of the request's validity. After the transmission of the test result the donor is released.
Donors requested for VT are reserved for 3 months. After that time, the donor will be released automatically unless an extension reservation request is received.
The maximum reservation period is six months. Requests for extension of this period shall include a justification.

5. Workup

5.1 Requirements

Workup requests shall be submitted using the most current version of the WMDA forms or any other WMDA compliant forms. Upon request the registries and TCs may ask CYBMDR to forward to them the WMDA forms for completion.

The requesting registry/TC must have submitted confirmatory typing results at least for the loci HLA-A, -B, -C, -DRB1 and -DQB1 demonstrating at least a 9/10 match at high resolution level. An inferior compatibility than 9/10 at high resolution will be subject to review.

In the case of a very urgent workup, VT and workup may be requested concurrently but a high resolution VT result must be submitted before donor clearance can be issued. Such requests must be clearly identified as "parallel CT and workup". If such a VT request is submitted via EMDIS, it has to be designated as "parallel CT and workup" request in the remark field.

Requests on behalf of patients older than 70 years and/or with non-standard diagnoses are subject to review by the medical director and Medical Scientific Advisory Committee of CYBMDR.
If patient registration and donor testing requests have been processed automatically via EMDIS, patient eligibility may not have been subject to review until the workup stage.

Product dosage limit on request (Number of donor cells allowed based on recipient weight):
PBSC: 5 x 10, 6/kg of recipient
BM: 20ml/kg
If the request exceeds the limit, approval of the Medical Director is needed.

Donor IDM results must be performed within 30 days of collection date to be valid and allow the collection to proceed.

Technical information/EMDIS
Incoming workup requests [WOR_REQ]
 A WOR_REQ message via EMDIS is not sufficient to start a workup and is therefore rejected. (A workup must be requested by other means of communication.)

5.2 Subsequent donation requests

Refer to POL_07_Second and subsequent donations.
This is communicated to registries or Transplant centres upon request and is posted on WMDA share in the registry profile.

6. International Transport

CYBMDR only exports hematopoietic stem cell products. There are no Transplant centres in Cyprus. The responsibility of the transport is under the requesting registry or TC. WMDA forms or any other WMDA compliant forms related to transport shall be accepted. Note that additional paperwork is required for exporting products to countries outside of the EU. Refer to WI5.4 for more information.

7. Follow-up

Donor follow-up after stem cell donation is the responsibility CYBMDR.
Patient follow-up is the responsibility of the Transplant centres and has to be performed according to national and any applicable international standards. We expect to receive upon request information about the recipient's condition three months and one year post transplant for international patients.

8. Donor-Recipient Contact

Anonymous patient-donor contact is permitted 100 days after the transplantation. Personal contact is not allowed. Anonymous Donor and Recipient exchange of a letter or card will be allowed one year post transplant. The Donor and Recipient may exchange correspondence that do not disclose Donor-Identifying Information or Patient-Identifying Information. This correspondence will always be via the registry to ensure the anonymity is not compromised.

9. Schedule of Fees

The current Schedule of Fees will be provided upon request. It is also shared on the registry's profile documents in WMDA share.

10. Policy availability

The policy is available to the registry or TC upon request and is visible via WMDA share.

11. Documents

1. WMDA standards,
2. WMDA recommendations