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Identification and management of the backup donor: recommendations from the World Marrow Donor Association

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INTRODUCTION

Timing of allogeneic hematopoietic cell transplantation (HCT) is a crucial factor that can significantly impact transplant outcome, with delay potentially leading to disease progression or patient condition deterioration [1]. While the availability of unrelated donors is a key performance indicator of the World Marrow Donor Association (WMDA), registries often struggle to meet benchmark thresholds established to ensure that patients have timely access to transplant [2]. At workup (WU), if the donor is unable to proceed due to unanticipated personal or medical reasons, the impact to patient care can be catastrophic; the transplant centre (TC) must urgently identify another suitable candidate for donation whose requisite testing and preparation can significantly extend the timeline to transplant. A single-center study in 2005 reported that 1 in 11 donors requested for WU were unavailable, while in 2024, global organisations indicated that 16% of all WU were cancelled due to donor-related reasons, although unavailability rates varied substantially between participating registries [2, 3]. Despite an initial rebound post-pandemic, donor unavailability at WU has increased steadily since 2021, now exceeding that experienced at the height of the pandemic in 2020, where it peaked at 15.2% [2]. These findings underscore the need for patient registries and TC to define backup donor (BUD) strategies to mitigate patient risk [2]. However, differences in national practices have resulted in variability in the search strategies, policies, and procedures currently used by organisations to ensure that various donor and treatment options are available for patients to minimise the risk of delayed transplant if a primary donor becomes unavailable. Reciprocally, these inconsistencies, combined with insufficient TC communication, can cause confusion for donor registries and donor centers (DC), potentially resulting in misinformed donors, unnecessary WU and/or product collection, and increased resource burden. The WMDA believes it is imperative that both donor and patient registries define policies for the proactive identification and management of BUD to minimise patient risk and to increase transparency and safety for BUD.

Management of BUD at WU is a complex issue in which patient access to timely transplant must be balanced with the impact on prospective donors, DC and collection centre (CC) resources, and potential costs incurred by TC and their respective registries. Lack of standardisation in practice, including the definition of a BUD, has prompted the WMDA to provide the following guidance toward BUD policy and introduce a common language for describing BUD activities and emerging practices in donor management (Table 1). We encourage organisations to define their policy in observation of the recommendations set forward herein.

Importance of backup options as part of the patient search process

Verification typing. Verification (confirmatory) typing (VT) organically creates a BUD opportunity. While confirming donor identity and HLA typing, VT also allows for assessment of infectious disease markers (IDM) to confirm the safety of potential products (Table 2) [4]. In 2024, only 48% of VT requests reported worldwide resulted in shipment of a blood sample for testing, although variability in fulfilment rates between registries was noted [2]. Due to attrition, it is good practice to request more than one donor for VT; considering global donor availability rates, it would be advisable to request two or three donors for each VT sample desired [2]. Donor availability at VT could be an indicator of donor suitability and readiness for WU. A donor requested for VT will also be reserved for the patient per registry policy. Since the VT process is intended to assist in the identification of optimal donors for transplant, a donor's priority as the primary or BUD is often unknown when the VT request is placed.

In a 2021 WMDA survey, it was reported that VT testing is generally completed on samples provided for VT. However, not all TC complete testing, often reporting financial limitations and/or laboratory capacity restrictions. In some cases, samples are screened for non-HLA attributes (e.g., CMV serostatus) with HLA typing subsequently conducted on only a subset of samples from donors with favourable results. In other cases, only the primary donor(s) of interest are HLA typed with samples from other donors retained and tested only if the preferred donor(s) are unable to proceed. VT samples should be tested and the results returned to the donor registry; however, if testing is not possible, this should be communicated to the donor's registry so that the donor can be managed accordingly (Table 2) [4]. If a donor is tested but will not proceed to WU, return of VT results could improve the resolution and/or comprehensiveness of registry HLA data, offering future

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Table 1. Definitions of the World Marrow Donor Association (WMDA).

Term	Definition
Backup donor (BUD)	A donor who will be requested for donation *if the primary donor selected for workup is unable to proceed to donation*.
Best practice	A working method or set of working methods that is officially accepted as being the best to use in a particular business or industry.
Health and Availability Check (HAC)	An alternative to verification typing in which a donor is contacted, offered information and counseling, administered a health history questionnaire, and availability to donate is determined. Verification typing can then be performed at workup on pre-collection blood samples. HAC is offered under specific circumstances (e.g., known HLA match level, transplant urgency) by some organisations.
Primary donor	The donor that has been selected on behalf of a patient in need of HCT. The primary donor proceeds to workup, the final stages of donor testing and medical clearance prior to donation.
Reserved	Status of a donor who is actively being considered on behalf of a patient in need of a transplant and which precludes activation on behalf of other patients. A donor could be reserved by request, following testing, at HAC, pending workup, or while workup is underway. A donor who is reserved for a patient may appear in other patient searches; however, the donor's reserved status should be indicated.
Strongly recommended	Something that should be considered; familiarisation with the topic and, at a minimum, contemplation of timely implementation should be conducted in the interest of patient and donor safety.
Workup (WU)	The final stages of donor testing and medical clearance prior to hematopoietic cell donation. The potential donor will be provided with information and counselling and have their medical eligibility to proceed will be evaluated. Further testing of HLA and/or IDM could also be required.

opportunities for optimal donor selection by patients in need of transplant. In its agreements with national transplant centers, a registry should consider including a requirement that VT results be tested and returned to the donor registry.

It is best practice that the requesting registry notify the donor's registry if VT results will ***not*** be returned to allow the donor's registry to inform their donor and reduce unnecessary requests for VT results that will not be forthcoming (Table 2) [4]. If an organisation routinely fails to conduct HLA typing on VT samples due to screening of non-HLA attributes, it is recommended that the requestor advise the donor's registry of this practice.

Health and availability check (HAC). Improvements in HLA typing methodologies over the past decade have resulted in the implementation of DNA-based prospective donor HLA typing strategies by many registries, allowing for unambiguous determination of compatibility with patients seeking HCT [5]. A suitably matched donor can now often be identified at search onset, eliminating the need for additional donor HLA typing. The health and availability check (HAC) is an emerging type of donor request that can be leveraged to expedite a patient's timeline to transplant by eliminating the need for VT prior to WU.

HAC begins with donor contact, provision of information about the donation process, administration of a health history questionnaire, and determination of the donor's willingness and availability to proceed to donation. TC product preference and timing of collection is also discussed and any donor-related product restrictions are communicated to the requesting organisation. Unlike VT, the donor is not required to submit a blood sample; these tests will instead be performed at WU using pre-collection blood samples, as the WMDA Standards require that VT be performed prior to or concurrent with WU (Table 2) [4]. HAC offers a convenient mechanism for prioritization of donors to be subsequently requested for concurrent VT/WU.

While several organisations have implemented the HAC, there is a lack of standardisation across registries; it is thus strongly recommended that both registries acting on behalf of TC and those acting on behalf of donors define policies for the management of HAC requests. A general overview of the HAC is presented in the WMDA Handbook [6].

Defining a registry's HAC policy. A donor registry should first determine whether it will permit HAC requests of its donors. If so, donor eligibility criteria for HAC must be established.

A registry must further determine the circumstances under which an HAC request may be accepted. The minimal HLA typing requirements for donor and recipient must be defined; HLA typing should be of sufficient quality to allow for unambiguous match level determination per organisational standards. If the donor or patient's typing quality does not meet these criteria, HAC may still be permitted in cases of extreme patient urgency.

In some cases, a donor's high-resolution registry typing might be the result of prior VT. Since the donor's identity and correlation with registry HLA typing have already been confirmed, HAC would offer an alternative to VT that could be used to establish the current health and availability of the donor without the burden of an additional blood draw prior to WU. Similarly, it would be advisable to consider HAC if an extended period has elapsed following VT to reconfirm the donor's availability and health and the TC's continued interest in the donor. A HAC could also be requested if the TC is interested in pursuing a donor as a backup option for their patient.

HAC is conventionally offered as an alternative to VT to avoid duplication of efforts during the search process. A registry should determine whether it will allow a donor who has completed HAC to be requested for VT prior to and independently from WU. The time interval during which a donor requested for HAC will remain reserved for a patient must also be defined. These considerations, among others, should be weighed when establishing a registry's HAC policy.

Although the HAC process is convenient for the donor and can reduce the patient's timeline to transplant, the HAC is not without limitations. While modern HLA test methods boast low rates of error, the possibility of technical or human error in registry typing cannot be completely excluded. Furthermore, the risk of positive IDM results cannot be assessed by HAC. These factors must all be considered in the development of an organisation's HAC policy.

The Backup Donor (BUD)

Regardless of registry search processes and donor testing strategies, it is strongly recommended that at least one BUD or alternate transplant option (e.g., cord blood, related donor) be identified during a patient's search. Reciprocally, a registry should allow its donors to be requested as BUD (Table 2) [4]. To standardise terminology used in search processes, the WMDA defines a primary donor as the donor who is selected on behalf of a patient in need of HCT. The primary donor proceeds to WU, the final stages of donor testing and medical clearance prior to

Table 2. Applicable WMDA Standards (2024) [4].

Standard Number	Standard
WMDA Standard 3.10	Donors must be counselled when selected for further tests and when selected as a donor for a specific patient.
WMDA Standard 3.22	Donor health requirements regarding the suitability of donors must be established.
WMDA Standard 6.02.3	The registry/cord blood bank must have a policy for reserving a donor/cord blood unit when requested for a specific patient.
WMDA Standard 6.02.5	The registry should make their policy for accepting requests for a backup donor for a specific patient at the workup stage readily accessible to the relevant healthcare professionals.
WMDA Standard 6.02.5.1	Registries requesting donors for workup should ensure that a policy is in place describing if and under which circumstances a backup donor can be requested in addition to the primary donor.
WMDA Standard 6.04.1	All specimens requested by the transplant centre for verification HLA typing of the donor or cord blood unit should be tested accordingly and results provided to the donor registry in a timely manner. If not tested, the transplant centre should inform the donor registry as to the status of that donor/unit request.
WMDA Standard 6.05	The HLA typing of the adult donor (or cord blood unit) and the potential recipient should be at high resolution and include sufficient loci to allow the evaluation of the pair matching appropriate for the clinical application. This HLA typing should be available prior to requesting a specific donor for workup and at the latest must be available before the donor begins mobilisation or proceeds to collection, or the patient begins with the preparative regimen, whichever is earliest. Cord blood unit typing results must be available prior to shipment for a specific patient.

donation. A BUD is the donor that will be requested for donation *if the primary donor selected for WU is unable to proceed to donation*. The main objective in securing a BUD is to ensure that the transplant will not be significantly delayed if the primary donor is unable to donate. The degree of HLA match between BUD and the recipient must thus be unambiguous and acceptable for transplant, and the donor must be prepared for the possibility of donation.

Identification of a BUD does not necessarily mean that this donor will be requested for WU, nor should the BUD's workup process commence, unless the primary donor is unable to proceed to donation; the BUD should only be requested for workup under exceptional circumstances. Exceptional circumstances could include factors arising from the medical status of the patient or the results of their search, for example, but not limited to, the urgency of transplant and/or difficulties identifying matching donors. It might be advisable to consult with and request the Medical Director's approval for exceptional cases. Donor readiness scores and feedback from donor contact during the search (i.e., availability problems at VT, potential donor medical issues) should also be considered in the assessment of exceptional circumstances. For example, if there are strong indications that a primary donor in workup will be unable to proceed to donation, initiation of WU of the BUD could be warranted. A registry should define its policy surrounding which circumstances are considered exceptional.

For the TC/patient registry, securing a BUD who is prepared and willing to donate ensures that the impact on patient care will be minimised should the primary donor become unavailable during WU. However, BUD preparation primarily includes the provision of information and the determination of donor willingness to proceed within the discussed timeframe. As aforementioned, BUD management should not include a complete physical examination and obtaining consent for donation, nor should it include other workup-related preparative activities, such as scheduling collection, pre-collect sample acquisition, or determination of peripheral access. The physical and emotional impact that donation-related activities exert must be minimised until it is clear that a donation request is imminent.

A donor registry should identify the number of BUD that may be permitted per patient to ensure that the cost and workload required to administer these activities do not become prohibitive and that donors are not subjected to unnecessary testing or otherwise inconvenienced if the likelihood of proceeding to donation is small. Donor and collection centre capacity must also be considered since over-selection of BUD and their subsequent management could pose excessive and/or unnecessary burdens on healthcare systems. Further, registries must be cognisant that donors who are reserved, whether as BUD or pursuant to other search-related activities, are unavailable for other patients who might benefit from their altruism. Additionally, case-specific factors, such as the urgency of the patient's transplant and the difficulty of the patient search, could also impact the number of BUD requests that are prudent for a specific patient.

Characteristics of the backup donor

A BUD **must**:

- Be known to be of acceptable HLA match with the intended recipient;
- Have demonstrated suitability through VT (preferred) or HAC (minimum);
- Be reserved for the patient (i.e., at VT, HAC or held for WU); and
- Understand explicitly that they will be asked to donate if the primary donor is unable to proceed.

HLA match. Unambiguous match level between donor and recipient must be known and be determined to be suitable for transplant (Table 2) [4]. While HLA match criteria vary by region, donor selection must be conducted in alignment with national and local protocols. Examples of widely accepted histocompatibility and donor selection guidelines have been published by the Center for International Blood and Marrow Transplant Research (CIBMTR) and by the European Society for Blood and Marrow Transplant (EBMT) [7–9].

Donor suitability. Ideally, VT and IDM testing should be conducted on the BUD to confirm donor identity and ensure the safety of the potential donation. Submission of the blood sample required for testing is also indicative of a donor's commitment and is often prognostic of a donor's willingness to proceed to donation. However, simultaneous VT/WU following HAC may be conducted to expedite timelines and reduce the initial burden on donors and DCs.

Donor reservation. The BUD must be reserved for the patient until it has been determined that either the BUD donor will proceed to WU, becoming the primary donor, or that the BUD will not be asked to donate. A donor selected for a specific patient must be placed on a "reserved" status (Table 2) [4]. Donors requested for VT and for whom VT results have been reported are

generally reserved for the patient as part of the VT procedure; this is similarly true of donors who have performed a HAC. Extension of the donor reservation following these requests is also possible. If the BUD proceeds to WU as the new primary donor, the donor will continue to be reserved for the patient throughout the WU process until donation or WU cancellation. Donor reservation policies are determined by the donor registry.

Donor communication. Donors must be counselled when selected for further tests and when selected as a donor for a specific patient (Table 2) [4]. It is essential that registry or DC staff contact the BUD and explicitly indicate that they have been selected as the backup for donation. Where possible, the preferred product (marrow or peripheral blood) and transplant timeline must be communicated to the BUD. If a sample has not been provided for VT and IDM testing, this could also be arranged; however, it is not required that physical examination (i.e., for the purpose of medical clearance) or other WU-related activities be initiated.

The Backup Donor at Workup

When a donor has been chosen as a backup option during WU, it must be communicated to the donor's registry. A BUD's registry must also be informed in a timely manner of any change in the donor's priority (i.e. if the donor is now being considered as the primary donor) and when the BUD may be released.

If, under exceptional circumstances, a TC/registry actively requests that a BUD proceed to WU in parallel to the primary donor's WU, clear and timely communication becomes even more crucial. All institutions involved in managing both the primary and the BUD must be proactively contacted by the TC/registry as updates occur. At critical stages of the WU, such as donor clearance, communication is especially important to ensure that only the primary donor proceeds to G-CSF mobilisation or is admitted for bone marrow collection. Even if the TC accepts clearance documents for more than one donor, it must simultaneously be communicated to the BUD's registry that no further action is required to avoid accidental preparation of the BUD.

Cancellation of a BUD must be communicated clearly and as soon as it becomes evident that a collection will not be needed [10]. At the latest, the TC/registry must notify the BUD's registry when the primary donor has donated and formally cancel the BUD WU. Depending on the timeline, initial cancellation of BUD WU by telephone might be necessary to ensure the immediate cessation of WU-related activities; an immediate telephone cancellation must be followed by a written cancellation and all cancellations should be confirmed by the BUD's registry.

Independent of communication received from the TC or patient's registry, the BUD's registry should re-confirm the status of the primary donor before the BUD begins G-CSF mobilisation or is admitted for bone marrow harvest. Although uncommon, these situations could occur if a BUD's status changes to primary donor or if the collection of the primary donor is uncertain. Under no circumstances should a donor initiate G-CSF or proceed to collection if they are not the primary donor.

Regardless of whether the BUD proceeds to WU or is kept on hold until the primary donor proceeds to collection, all requests for BUD must be formally cancelled by the TC/registry once the BUD is no longer needed.

TCs and their respective registries must be aware that the management of BUD requires additional resources at all institutions involved. Therefore, fees could be incurred by formally requesting a BUD. The amount that may be billed and the timing of invoice issuance vary across DCs and registries and should be presented in the organisation's fee schedule.

Summary

It is strongly recommended that every organisation develop and document its policies surrounding BUD requests and management and these policies should be transparent and readily available to collaborative registries and TC (Table 2) [4]. The recommendations described herein are intended to guide and support this complex undertaking; the WMDA offers additional resources, including the WMDA Handbook and additional information that can be found on the WMDA website and in WMDA Share [6]. A summary of the recommendations of the WMDA are presented in Table 3.

Table 3. Backup donor recommendations of the World Marrow Donor Association (WMDA).

	WMDA Recommendation
1.	All patients should have at least one backup option
2.	Registries should allow their donors to be requested as BUD
3.	Registries, DCs, and TCs have policies surrounding BUD management Consider: • Number of BUD per patient • Exceptional circumstances for BUD to proceed to WU
4.	Registries should define a HAC policy Consider: • Number of HAC per patient, communication, VT prior to WU

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AUTHOR CONTRIBUTIONS

VGS was a member of the project group, supported from development, and drafted the manuscript. SM was a member of the project group, developed associated forms (F10), and provided a critical review of the manuscript. AK was a member of the project group, developed the HAC form, and provided a critical review of the manuscript. SP, GR, PJ, AM, and IE were members of the project group and provided critical reviews of the manuscript. MS coordinated the project group and provided a critical review of the manuscript. IT led the project group and contributed to drafting the manuscript.

COMPETING INTERESTS

Authors are employees of their affiliate organisations and volunteers of the World Marrow Donor Association (WMDA). The views expressed herein do not necessarily reflect those of the authors' organisations but the consensus of the WMDA community as conveyed through the project group comprising the authors. The authors declare no competing financial interests.

ADDITIONAL INFORMATION

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