Global Registration Identifier for Donors (GRID) of Hematopoietic Stem Cells: Road to Automation and Safety

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Keywords

GRID · HSCT · Identifier · Standardization · Safety

Summary

Once a cohort exceeds a certain size, it becomes mandatory to assign an identifier (ID) for each individual to ensure a secure, reliable, and unambiguous assignment. In the field of hematopoietic stem cell transplantation, with a still growing number of voluntary unrelated donors, it was recognized that a system needs to be developed to uniquely identify potential donors on a global scale to facilitate communication and to prevent errors in identification of donors. Efforts in this respect resulted in establishment of the GRID, with a defined structure and allocated rules. To successfully implement such a project, collaboration among all organizations involved in the process of volunteer donor recruitment, facilitation, and provision of hematopoietic stem cell products is necessary. Therefore, rapidly accessible information combined with a high level of communication and exchange of experiences is crucial. Established systems like the ISBT 128 and the Single European Code (SEC), which standardize the terminology, identification, coding, and labeling of tissues and cells of human origin, serve as a basis on how to successfully implement the GRID on a global scale.

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Introduction

At the time of the Persian Gulf War (1990–1991) the need for blood products became essential, and requests from different countries in a variety of sources were made. This massive and rapid use of donated blood revealed major problems in labeling and bar-coding [1]. A report of the US Department of Defense summarized thousands of labeling mistakes and listed key sources of errors: different labeling languages, errors in barcode substitutions, non-standardized donation identification start codes, improper start codes in registration number, duplication of donation numbers, noncompliance with labeling guidelines [2]. To overcome these problems, the International Society of Blood Transfusion (ISBT) created a new coding system called ‘ISBT 128’ using a uniquely defined product identifier and standardized barcode information. The ISBT, the American Association of Blood Banks (AABB), and the American Red Cross established the International Council for Commonality in Blood Bank Automation (ICCBBA) to manage and develop the standard [1–4]. In 2005, a serious problem concerning tissue recovery was discovered, in which an organization recovered donors without their families’ permission or any adequate medical screening, finally resulting in many falsified records. More than 8% of tissues distributed all over the world at any one time were untraceable [5]. After this scandal, the US Center for Disease Control and Prevention (CDC), the Food and Drug Administration (FDA), and the Health Resources and Services Administration (HRSA) convened a workshop including members of blood, organ, and tissue communities as well as government representatives. The main conclusion was to increase safety by developing a communication network for tracking and reporting of distributed organs and tissues with the prerequisite of a unique donor

Table 1. List of critical observations in the process of donor search or donor work-up on the basis of complaints documented in the ZKRD in 2015 and 2016. The complaints are categorized via their observation and resulted in potential uncertainty and/or time delay

Observation	Problem	Could GRID improve or eliminate problem?
Use of two or more IDs on forms and product bags (e.g. local ID for foreign donors)	confusion of the different IDs and inaccurate mapping of the corresponding (donor) registry; no traceability	eliminate by defined GRID-format and checksum
Use of local IDs on shipped samples.	no assignment possible at TC lab	eliminate by defined GRID-format
Different IDs between product bag and notification of donor clearance	incorrect ID through manual entry of notification of donor clearance	improve by checksum
Use of an closely related, but variable (internal) donor ID because of incompatibility of IT system	unknown donor ID, test could not be done	eliminate by defined GRID-format
Use of format-identical patient and donor IDs	i) application of the donor ID in the same field as the patient ID ii) mistake in request of the donor by using the patient ID (e.g. both were 6 digits numerical)	eliminate by defined GRID-format
Omit of the country or donor center prefix of the donor ID.	ambiguity of the donor ID	eliminate by defined GRID-format and checksum
Combined shipment of several blood samples with incorrect labeling of different samples	samples could not be used; re-request of sample and shipment	improve when usage of barcodes
Handwritten ID on test sample	illegible ID; test could not be done	improve when usage of barcodes
Labeling of blood samples for HLA testing with wrong donor ID	samples cannot be used; re-request of samples and shipments	no
Transmission of completely wrong ID or transposed digits.	incorrect mapping; traceability problems	improve by checksum

identifier [6]. At the same time, the new Cellular Therapy Coding and Labeling Advisory Group also came to the conclusion that, because of increasing numbers of exported hematopoietic stem cell (HSC) products, distinct identification codes linking donors and products are mandatory for traceability [7]. In 2010, the World Health Assembly Resolution WHA63.22 called on member states to ‘encourage the implementation of globally consistent coding systems for human cells, tissues, and organs as such in order to facilitate national and international traceability of materials of human origin for transplantation’. ICCBBA is working closely with the World Health Organization (WHO) in order to achieve this objective using the ISBT 128 Information Standard [8]. In 2015 the European Commission finalized the requirements for a Single European Code (SEC) for tissues and cells as a common format representing the information required in the EU [9]. Currently, there is wide recognition of the need to standardize the terminology, coding, and labeling of medical products of human origin in order to improve traceability and transparency [10].

The explicit identification of unrelated donors is an inherent part of the hematopoietic stem cell transplantation (HSCT) field since its beginnings. During the 1990s the first big shift evolved from the use of HSC products within spatially determined institutions to regional distributions within clinical networks and groups [11]. No later than in the 2000s, the second big shift evolved to-

wards international distribution, irrespective of borders [12]. Both shifts extended the varieties of donor identifiers to be dealt with, hence intensifying the requirement of interoperability. With respect to the reported problems of the whole blood field, and to prevent impractical or even inconsistent regulations, it was an important step for the World Marrow Donor Association (WMDA) to become active.

Complexity of a Non-Standardized System

In this article, we will discuss the envisaged implementation of a new global donor identifier (ID) in relation to existing problems, projected changes, and the challenges of a proactive and collaborative project involving many departments and organizations on a national and international level. The most important and most frequently asked question is: ‘Why do we need a globally standardized donor ID although we already have a consistent taxonomy in our country?’ First, we should consider two different aspects of IDs: eye-readable and electronically readable presentations. A person’s cognitive process often fade out unnecessary parts like delimiters (e.g. spaces) between parts of IDs whereas IT systems simply count every single character. Taking that into consideration, the initial assumption of having a unique donor ID within a country is often

Table 2. Exemplary part of a long list of compiled plausibilities to revise ID formats of different countries. Dedicated to each of the centers, that exhibit a self-defined structure of their IDs, is the regular expression (Regex) of plausibility control. (Z defines a number; B defines a character; n/a means not available)

#	Structure	Examples	Regex
1	ZZZZZZZ	1001764, 1036396	^d{7}\$
2	AR-ZZZZZZ	AR-000181, AR-030194	^AR\d{6}\$
3	ATZ...	AT609, AT38668	^AT[1-9]\d*\$
4	AUZZZZ-ZZZZ-Z	AU4023-1671-5, AU2003-1470-6	^AU\d{4}-\d{4}-\d{1}\$
5	SDZ...D	SI6465D, SI1650D	^SI[1-9]\d*D\$
6	Z...	103922, 1698478	^[1-9]\d+\$
7	n/a	n/a	^\$
8	CHBB-Z... or CHSBS-Z... or CHCBS-Z... or CHCGE-Z...	CHZL-3086, CHSBS-205882, CHCBS-213	^CH([A-Z]{2})[SBS CBS CGE]-[1-9]\d*\$
9	MZ... or DZ...	M10032, M05061, D27634	^[MD]\d+\$
10	FRBBBZZZZZ or FRCB...	FRFAN00929, FRCBBE2803422, FRCBBE6415060580-, FRCBBE-2703700679	FR([A-Z]{3}\d{5})[CB[-A-Z0-9]+)\$
11	GR20-D-ZZZZZZZZ	GR20-D-00007059, GR20-D-00189011	^GR20-D\d{8}\$
12	Z... or SHDZZZZZ	288876 or SHD120256	^([1-9]\d+ SHD\d{6})\$
13	INBMSTZBZZZZZZ	INBMST12A003456, INBMST45K648521	^INBMST\d{2}[A-Z]\d{6}\$
14	UDZ... or CBZ...	UD0064988, CB12345	^(CB UD)\d+\$
15	ZZAZ...	98A147, 08A6380	^d{2}A\d+\$
16	KAR ZZZZZZ	KAR 004185, KAR 002804	^KAR \d{6}\$
17	TZZZZZZZZZZZZZZ	T00271508048056, T12345678912345	^T[0-9]{14}\$
18	ZZZZZZP	504539P, 106298P	^[1-9]\d{5}P\$
19	WBZ...D	WB11321D, WB1158D	^WB[1-9]\d*D\$
20	PC Z... or PN Z... or PS Z...	PC 297683, PN 124698, PS 48378	^P[CNS] [1-9]\d*\$
...	...	...	...

not true. In practice, many more problems can result in a time delay for the patient or the risk of choosing the wrong donor (table 1).

Several incidents of donor mix-ups were reported, from recoverable mistakes in handwritten IDs to a completely HLA-mismatched allogeneic unrelated HSCT due to a series of inadvertences and lack of controls (table 1) [13].

Each organization that starts recruiting donors is confronted with the same question: ‘What kind of taxonomy will be implemented for determination of a donor identifier?’ As long as there is no common standard, individual solutions will be used, resulting in a global ‘alphabet soup’. When the first transport of HSCs crosses borders, it requires every country (including all involved organizations) to ensure acceptability of and acquaintance with all existing donor ID formats. This leaves the organizations receiving requests, blood samples or HSC products with two possibilities: either simply accepting all incoming IDs without any kind of plausibility check, or setting up an extensive test system based on as many control procedures as possible. An exemplary part of the list of German National Bone Marrow Donor Registry’s (Zentrales Knochenmarkspender-Register für die Bundesrepublik Deutschland; ZKRD) cooperating registries and, if applicable, their donor ID formats, are shown in table 2.

As shown in table 2, there are plenty of formats using different lengths, numeric or alphanumeric coding, added characters, miscellaneous delimiters, or even multiple variations within some countries. Even after a number of inquiries, it was not possible to define rules applicable for all organizations facilitating HSCT. In addition, keeping this list up to date became more challenging over time. Despite this, and taking into account the hundreds of donor

IDs search or work-up coordinators have to deal with in their daily work, today we are able to detect many, if not substantially all, errors. How is it possible to reduce the error rate towards a minimum, thus improving safety of patients and donors?

Global Standard for Hematopoietic Stem Cell Donors

In 2005, 7,921 HSC products were collected and a total of 10,730,712 donors were registered worldwide. A substantial portion, 39%, of collected HSC products were shipped abroad, i.e. involved two donor ID numbering schemes [14]. With increasing numbers of donors, collections, and international shipments (2016: 17,297 HSC products; 30,973,284 donors; 50% shipped abroad [12]), the WMDA recognized that a standardized donor identification is necessary to fulfill future requirements in the field of HSCT. The GRID was designed to be compatible with both IT-based systems and manual transfers, allowing the transition to safer technological solutions to develop alongside existing manual systems. The purpose is to uniquely identify HSC donors on a global scale, facilitate communication, prevent errors in identification, and provide a standard machine-readable format (e.g. barcode scanner) for electronic processing as well as a standard eye-readable format [15]. Until 2010, a WMDA project group in cooperation with the ICCBBA developed a donor identifier called Global Registration Identifier for Donors (GRID), which was first approved by the WMDA board in 2014 and revised before implementation could start in 2017. The major changes are summarized in table 3.

Table 3. Summary of conceptual and format-related changes of the GRID valid from June, 2017

Old GRID concept	New GRID concept
GRID for HSC donors and CBU	GRID for HSC donors
GRID for life: once assigned, the GRID remains independent of migration behavior	abandonment of old GRID and reassignment of new GRID when donor migrates in the territory of another IO
External check character [0–9, A–Z, *]	integral checksum [00–36]

In HSCT, several options of cell sources are available. Siblings or other relatives do not need a special identifier, since the number of family members is usually manageable, patient and donor know each other, and no difficulties in documentation and product tracing are expected. Consequently, the GRID concept initially included potential donors of unrelated HSCs, and also cord blood products. This, unfortunately, would have mixed the distinct paradigms of a person (donor) and a product (HSCs from umbilical cord blood cryopreserved long time ago). Grafts are products in a pharmaceutical sense, and are legally obliged to bear a donation number [9]. An umbilical cord blood unit is a product including a unique donation number from the beginning. Due to other obligatory systems for tissues and cells of human origin like ISBT 128 and the SEC for the terminology, identification, coding and labeling [16], it was decided to abandon GRID for umbilical cord blood products and to focus on registered unrelated HSC donors.

To achieve optimal traceability, the so-called ‘GRID for life’ concept was initially envisaged, meaning that once a GRID is assigned to a donor, the donor will keep this GRID permanently, independent of temporal and spatial migration behavior. To accomplish such a goal, a huge effort would have had to be taken to enable every single partner to implement the concept. Thus, the concept of ‘GRID for life’ was withdrawn, allowing every issuing organization (IO) to assign a new GRID to an existing but relocated donor.

The fact that an external check character can be easily omitted in manual transfers led to the decision of using an integral checksum, taking into account the current and future situation of some small- and medium-sized registries.

To facilitate accurate manual transcription a standardized layout for the eye-readable presentation of the GRID has been specified using blocks of characters in a 4,4,4,4,3 pattern. Consistency of electronic presentation is achieved by use of the ISBT 128 standard data structure 039 that includes the data identifier ‘&:’ specifically reserved for the GRID [17]. The structure that met all criteria defined above is shown in fig. 1.

The GRID must be of a fixed length of 19 characters, composed of three specified elements (fig. 1, E1–E3). The first four-digit number represents the issuing organization number (ION), which is allocated by ICCBBA in collaboration with the WMDA and provides the necessary part to create uniqueness on a global scale. The last two digits of the GRID (E3) display the checksum as internal part of

Fig. 1. Rules for the GRID structure. **A** Worldwide given format of 19 characters, where the ION is determined as four numerical characters assigned by ICCBBA and the checksum as two numbers between 00 and 36. The remaining 13 characters in the middle serve for integration of the existing or newly-assigned identifier, prefixed by leading zeros. **B** Format as in A, but characters 5–7 are determined as a DCN to ensure national uniqueness.

the GRID for validation of manual data entry, in order to detect the misidentification of HSC donors due to transmission or typing errors. Element 2 provides space for 13 alphanumeric characters for integration of the existing or newly assigned ID prefixed with leading zeros if required. In Germany, IDs for HSC donors are assigned locally by donor centers but listed in the central database of the ZKRD to ensure comprehensive results for donor searches for national and international patients. Therefore, arbitrary three-digit numbers were assigned to all German donor centers (positions 5–7), that are called donor center number (DCN). This additional element is necessary to fulfill the requirement of uniqueness (fig. 1, E1) and limits the length of donor identifiers to 10.

Regarding privacy, the coding elements ensure donor anonymity as the ION is the only part publicly available and traceable. In order to ensure a long-term usage of the GRID, the WMDA and ICCBBA entered into a memorandum of understanding, defining mutual benefits and interests, arrangements, and the annual license fee for the use of ION that will be charged to GRID issuing organizations [18]. The ION definition provides sufficient alternatives for inactivation, reactivation, or the assignment of new issuing organization numbers in the future. In order to guarantee uniqueness, reassignment of previously existing IONs is not allowed [15].

Depiction of Involved Collaborators and Stakeholders

Any successful project requires a clear goal, open and honest communication, a specified timetable including appropriate transition periods, and a collaborative implementation process involving all relevant collaborators and stakeholders. After dismissing the idea of using GRID for umbilical cord blood products, the new goal is to achieve a globally unique ID for donors of hematopoietic stem cells to guarantee a high level of safety. What kinds of entities are involved? At the top level is the WMDA, a global association that strives to facilitate the exchange of high-quality blood stem cells for clinical transplantation, and to promote the interests of donors. There are substantial differences between the roles and operational models of WMDA members to facilitate HSCs for trans-

Fig. 2. ZKRD's role as German hub. Shown in the upper section (square) is the WMDA with its participating registries, which list their donors in the global database Bone Marrow Donor Worldwide and use the European Marrow Donor Information System for data exchange. The lower section shows the ZKRD with its collaborating partners, which are either acting on behalf of patients or donors or both.

plantation in various countries. Figure 2 shows, for example, ZKRD's role in relation to its major stakeholders.

From the recruitment of a donor up to the final infusion of the transplant, the donor ID is the central identifying attribute throughout the entire process, enabling anonymity, or more precisely, pseudonymity and traceability. In this long process, many different organizations are involved, either on the side of the donor or the patient. Donor centers are competent in recruiting and communicating with their donors and incorporate or collaborate with collection centers responsible for collection and preparation of the HSC products. Transplantation centers attend to the patient and, if indicated, initiate the search for an unrelated donor, either directly or via a collaborating search center which requests a match list of potential donors, in Germany supplied by the ZKRD, to identify the best donor possible. Both, patient and donor side cooperate with HLA laboratories to initially type or confirm patients' or donors' HLA data. Finally, when a donor meets all criteria and a product is collected, the transportation of the HSCs to the patient is performed by courier companies or trained volunteers.

Once the GRID is incorporated into the first IT system, it should remain there over the whole supply chain, meaning that all involved partners should be able to handle the GRID without manual transfers or transcriptions into other ID schemes. In Germany there are 26 donor centers, 18 search centers, and 72 transplantation centers cooperating with the ZKRD for unrelated HSCT using many different IT systems [19]. This means that there is a high variability and that many individual adjustments have to be done

Fig. 3. Ten steps towards a successful project in WMDA. Shown are the ten steps towards a successful project in the WMDA (right of the arrow) and several changes made within the GRID project (curved arrows left of the arrow). The user acceptance test was not conducted until publishing the schedule (a, b). After the user response, the task force was reorganized several times (c). Later on the specifications were changed (d), which resulted in another change of the task force (e) and will prompt another schedule modification.

to adopt the new standard in each center. Therefore, the big challenge for a successful implementation in Germany and worldwide is to clearly show future advantages in interdisciplinary interactions with respect to automation and to emphasize an overall increase in safety for patients and donors at any stage of the whole complex process. This challenge is a balancing act between standardized rules and definitions in the consensus of WMDA as well as

Fig. 4. Examples of HSC product labels.

A Potential future Eurocode label of HSC product. Shown within the outer black frame is an exemplary label including all information actually been mandatory in Germany. In the middle left section the required data of the donor are depicted including the GRID complemented by a linear barcode. The multiple subdivisions of the upper part represent adhesive labels for use on accompanying documents or samples. **B** ISBT 128 international standard label incorporating GRID and SEC.

A

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SEC: XX001234A999615987654 A0S112500020150124																																																							

the consideration of all variable requirements from the biggest to the smallest stakeholder. Our approach to solving this problem is first to share all necessary information on a common platform, which is available to all German partners. Second, to provide a ready-to-run system for search purposes and requests as well as a system with the interface to directly incorporate donors into the central database. Finally, the ZKRD shares new developments with the entire community involved in the process so that all partners benefit from the most up-to-date information and overall efforts and costs are reduced. Nonetheless, to reach maximum quality, the most important part is the collaborative work towards the common goal, meaning that every single partner contributes to the success of the project as a whole.

Future Usage of the GRID

What is needed to achieve a successful outcome of implementing the GRID? In figure 3 the ten most important steps under the umbrella of the WMDA are outlined, and setbacks of the GRID project that occurred in the past are shown. The repeated setbacks resulting in inclusion of more and more representatives of registries that had already begun with the implementation of GRID, clearly indicates the utmost importance of collecting project requirements as early as possible and providing all stakeholders with up-to-date planning. A specific schedule defining distinct limits and including well-defined transition periods that are adaptable for every country has to be provided. We think adhering to a top-down approach is of paramount importance, allowing the partners to implement the GRID and populate the database with reassigned and newly assigned GRIDs, not showing them until a globally concerted point of time.

Another important aspect will be how to make available the display of listed GRIDs. For search purposes, in particular the generation of long lists of potential donors, the GRID will be the mandatory ID. For example, it is imperative when requesting extended or verification typing but will not be essential for the physicians to make their final decision. In the global comprehensive database Bone Marrow Donors Worldwide and the data exchange system European Marrow Donor Information System all relevant information, i.e. origin of registered donors or non-HLA criteria, is already implemented as separate attributes. It means in effect that the actually practiced procedure of deriving information from the donor ID will change with the introduction of the GRID, mainly focusing on attributes and building the foundation for future filtering or sorting and real-time updates.

For the work-up process, the goal is to make forms redundant by providing and transferring information, whenever possible, in an integrated systemic way. Therefore, once a GRID has been incorporated into the database, no manual transcription must occur. In case of necessity of a hardcopy or printed document, there should also be a possibility of generating reports at every relevant step. Where manual entry of a GRID into an IT system occurs, it is essential that the receiving IT system performs a checksum calculation to verify the integrity of the number entered.

After the collection of HSCs, the resulting product must be labeled as described in the German Standards for Unrelated Blood Stem Cell Donations according to current laws, guidelines, and regulations [20–23]. Examples of potential future labels for a HSC product newly distributed are shown in figure 4. All potential IDs, including the SEC with its integral parts, the DIS (donation identification sequence) and the PIS (product identification sequence), as well as the GRID, are included as eye-readable numbers and the GRID additionally as a scanner-readable barcode. To differentiate

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between different identifiers on a product label, both the SEC and the GRID have to be preceded with the respective uppercase letters and a colon, i.e. 'SEC:' or 'GRID:' [9, 15]. The other information currently mandatory in the Eurocode Standard or in the ISBT 128 international standard is depicted on the labels (fig. 4A,B). Due to limited space on a label and the growing need to include further information, in the future, new qualities of barcodes, like 2D barcodes and other developments, will be required.

Seen from an operational point of view, we are only one step away from combining all essential information on the product label within a 2D barcode, allowing for the secure and anonymous transfer of information and traceability from the donor to the recipient. Considering the fact that very different regulations are defining individual labeling instructions (legal vs. community-based regulations; national vs. international regulations), this will be the main obstacle to overcome in the future by uniform global standards.

Conclusion

In a changing world with continuous technological progress, rapid migration around the globe and ever increasing processing speeds, accomplishing global standards which can guarantee high levels of safety for patients and donors by preventing errors is be-

coming more and more important. In order to meet the needs for donors in the field of HSCT, the GRID was developed and still has to undergo global implementation, overcoming all obstacles. To quote Henry Ford after his successful production and commercialization of self-propelled vehicles: 'If I had asked people what they wanted, they would have said faster horses'. This enlightening quote exemplifies the importance of a vision for our collaborative pursuit of a promising goal.

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Disclosure Statement

The authors have no conflict of interest to disclose.

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