a gift for life

WMDA handbook for blood stem cell donation
Cover pictures

Tessa (received a blood stem cell transplant in 2009) stands for over 300,000 patients worldwide who have received an unrelated blood stem cell transplant in the past 40 years.

Frank (donated his blood stem cells in 2012) stands for over 23 million voluntary donors worldwide who have or are willing to donate a gift for life.
a gift for life

WMDA handbook for blood stem cell donation

WITH AN UNRESTRICTED EDUCATIONAL GRANT FROM HistoGenetics
Dear Readers,

Welcome to the first edition of the WMDA Handbook. Our idea was to create a handbook to help newcomers to existing donor registries and staff members in newly-established registries become familiar with the way donor registries are organised and to understand each step from the initial donor recruitment through to the transplant taking place.

Setting up a registry involves more than recruiting adult volunteer donors. There are many important considerations such as creating robust information technology (IT) infrastructure and finance systems, which are vital to a registry’s success. Factors such as IT should be the first to be considered when creating a new registry. Despite this, the authors decided to organise the chapters of this handbook in a logical order following the process from donor recruitment through to transplant. You can find the crucial chapters on IT and Finance at the end of the book.

Histogenetics is the corporate partner of the WMDA handbook. This partnership has been provided through educational grants and with exemplary respect for the scientific independence of the editors and authors.

We are grateful for comments from our readers, as it is the only way that we can continue to improve the handbook. Please visit the WMDA website at www.worldmarrow.org/handbook and fill in the survey to let us know your feedback on this first edition of our handbook.

We extend our many thanks to all our contributors who worked so hard to meet our deadlines and to Svenja Haenni (Swiss Blood Stem Cells), who had the task of reminding the authors of deadlines to ensure that the book would be ready for distribution at the WMDA 2013 Fall Meeting. Very special mention must be made of Katie Day, responsible for the final editing process, who was so accommodating of late arrivals and so precise in her work.

Please begin reading the handbook and we hope you will find the tips and recommendations given by the authors useful.

— World Marrow Donor Association
Colophon

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Design Sam Gobin, www.samgobin.nl
Print AD Mercurius

Cover pictures Marc de Haan

Chapter opening pictures Chapter 0: Swiss Transfusion SRC/Swiss Blood Stem Cells; Chapter 1: Swiss Transfusion SRC/Swiss Blood Stem Cells; Chapter 2: Anthony Nolan, UK; Chapter 3: Leiden University Medical Center, The Netherlands (picture by Sam Gobin); Chapter 4: Cellex, Germany; Chapter 5: Swiss Transfusion SRC/Swiss Blood Stem Cells; Chapter 6: Anthony Nolan Cord Blood Bank, UK (pictures by Alex Griffiths); Chapter 7: IT server Europdonor Foundation, the Netherlands (picture by Sam Gobin); Chapter 8: Europdonor Foundation, the Netherlands (picture by Sam Gobin)
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‘I was given a second chance at life’

Stephanie Crast, Hagenbuch (received a stem cell transplant in 2012) with her Godchild Valentina.
Preface

Not too long ago, curing leukaemia seemed to be a distant dream. The advent of allogeneic transplantation of haematopoietic stem cells, published in 1982\(^1\) in a paper by John Goldman \textit{et al.}, showed that this new treatment could be an effective therapeutic answer to numerous disorders of the haematopoietic system. In the 1980’s, relatively few bone marrow donors were available from very few donor registries. The need for intensive international collaboration was identified, which led first to the founding of the Cooperative Marrow Donor Program in 1988, by three pioneers of blood stem cell transplantation: Jon J. van Rood of the Netherlands, John Goldman of the United Kingdom and Nobel Prize Winner E. Donnell Thomas of the United States of America.\(^2\)

A few years later, in 1994, the World Marrow Donor Association (WMDA) was founded in Leiden in the Netherlands, to formalise the cooperation of numerous national registries under one international umbrella and to facilitate the exchange of knowledge, ideas and – last but not least – blood stem cells. Currently, more than 22 million adult donors and more than 650,000 cord blood units are registered in 73 donor registries, 145 cord blood banks and 350 donor centres. These organisations are providing blood stem cells to some 1,400 transplant hospitals in 56 different countries. It is expected that the WMDA will continue to grow, as new registries are already emerging in Africa, Asia, Europe and South America.

The mission of the WMDA is to foster international collaboration to facilitate the exchange of high-quality haematopoietic stem cells for clinical transplantation worldwide and to promote the interests of donors.

In pursuit of that mission, the WMDA has systematically developed and published standards, recommendations and guidelines relating to best practices in virtually every aspect of the operation of unrelated donor registries. Adoption of, and adherence to, these standards and recommendations has been actively promoted through the dissemination of the standards and recommendations to the worldwide community of registries. The WMDA has also developed and implemented a process for accrediting registries. Accreditation provides...
additional assurance to the network of organisations involved in blood and marrow transplantation, including regulators, that members of the WMDA are committed to the safe and effective management of volunteer donors, who are willing to help save the life of another person. So far, 20 registries are accredited by the WMDA.

‘Share knowledge and share expertise’ is a key message of the WMDA. In this spirit, 67 authors from 24 countries, spanning 19 time zones, have gathered in numerous teleconferences and face-to-face meetings, to create this handbook and share their knowledge and expertise with the worldwide community.

The development and the publication of this registry handbook is an example of the WMDA’s commitment to advancing the international exchange of blood stem cells. The registry handbook was conceived to provide guidance to those seeking to establish a registry, and to act as an ‘encyclopedia’ for those who already have established their registry. The provision of the handbook – reflecting the collective wisdom of a dedicated group of experts within their organisations, illustrates that the WMDA sees its role as not only promoting good practices amongst established registries, but as a leader in guiding emerging registries.

The establishment, as well as the maintenance, of a registry is a complex and difficult task. This handbook is intended to provide essential information relating to the establishment and the operation of a registry and to direct the reader to additional resources if necessary.

The handbook recognises that each country may have a unique set of circumstances under which a registry would need to operate. It also recognises that, in order to engage internationally, all registries need to follow a basic set of standards and procedures to ensure that the donors they manage are appropriately registered, screened and qualified for donation. Without international cooperation, many patients would go without a donor. It is therefore incumbent on the existing registries to serve the interests of patients in their communities by continuously updating their own knowledge and by actively promoting the development of registries in other countries.

This handbook is the result of the hard work of many individuals who, with the support of their respective organisations, have spent countless hours revising
the text to ensure it will serve as a valued guide for those within the community, as well as for those who wish to join the network of registries serving patients worldwide.

We hope that the valued readers will find this handbook helpful and we look forward to welcoming some of them as members of the growing family of organisations which are committed to helping altruistic donors to connect with the patients who are in dire need of the life-saving cells of those individuals.

Thomas Bart  
*Chair of the Donor Registries Working Group; Chair of the Handbook Project Group*

William Hwang  
*President, World Marrow Donor Association*

Michael Boo  
*President elect, World Marrow Donor Association*
‘When I put myself in the patient’s position, my decision was clear: Yes, I will donate!’

Maico Bentivoglio, Zürich (Bone marrow donor, September 2011)
Contributors

The following people have contributed to the creation of this handbook.

Chapter 1
LEADER
Pam Robinett, USA
 AUTHORS
Janaki Anant, India
Meral Beksc, Turkey
Roman Danielewicz, Poland
Julia Dausend, Germany
Malgorzata Dudkiewicz, Poland
William Hwang, Singapore
Martin Maiers, USA
Mihran Nazaretyan, Armenia
Annette Rasche, Germany
Nira Shriki, Israel
Jerry Stein, Israel
Raghu Rajagopal, India

Chapter 2
LEADER
Sabine Hildebrand, Germany
 AUTHORS
Sandra Bothur, Germany
Irina Evseeva, UK
Mary Halet, USA
Raghu Rajagopal, India
Pam Robinett, USA
Jerry Stein, Israel

Chapter 3
LEADERS
Gabi Rall, Germany
Annette Rasche, Germany
 AUTHORS
Lauren Bosco, Australia
Andrea Mitterschiffthaler, Austria

Chapter 4
LEADER
Michael Punzel, Germany
 AUTHORS
Vladimir Bogolepov, Ukraine
Raewyn Fisher, New Zealand
Claire Harper, Australia
Andrew Liu, Taiwan
Scott Liu, Taiwan
Susanne Morsch, Germany
Tom Wiegand, USA
Heidi Elmoazzen, Canada
Ngaire Elwood, Australia
Eliane Gluckman, France
Susana Gomez, UK
Matt Korhonen, Finland
Judith Maec, Germany
Sergio Querol, Spain
Annalisa Ruggeri, France
Marta Torrabadella, Spain

Chapter 5
LEADERS
Grazia Nicoloso, Switzerland
Irina Evseeva, UK
 AUTHORS
Mats Bengtsson, Sweden
Veronica Borrill, South Africa
Karen Dodson, USA
Jay Feinberg, USA
Francis Gregg, USA
Robert Lown, UK
Maria McWilliams, USA
Laura Moreno, UK
Beth Murphy, USA
Ursula Python, Switzerland
 Rochelle Roest, UK
Ann Shurlock, UK
Heidi Elmoazzen, Canada
Ngaire Elwood, Australia
Eliane Gluckman, France
Susana Gomez, UK
Matt Korhonen, Finland
Judith Maec, Germany
Sergio Querol, Spain
Annalisa Ruggeri, France
Marta Torrabadella, Spain

Chapter 6
LEADER
Jacqueline van Beckhoven, Netherlands
 AUTHORS
Etienne Baudoux, Belgium
Merry Duffy, USA

Chapter 7
LEADERS
Ann Green, UK
David Steiner, Czech Republic
 AUTHORS
Jack Bakker, Netherlands
Hans-Peter Eberhard, Germany

Chapter 8
LEADERS
Bruce Schmaltz, USA
Carine Mijnarends, Netherlands
 AUTHORS
Alan How, UK
Jennifer Philippe, Canada
Carlheinz Müller, Germany
Registry

Testing laboratories

Collection centre

Donor centre

Transplant centre

Research

Cord blood bank
Introduction

This handbook was created by the Donor Registries Working Group of the World Marrow Donor Association (WMDA). It is intended as a guide to establishing a bone marrow donor (stem cell) registry or cord blood bank in countries where no such structure currently exists. It should also assist existing registries and cord blood banks in ensuring that they are working in accordance with WMDA guidelines and best practice.

This handbook is not an exhaustive list of rules and regulations. It provides an overview of the functions carried out by a registry and cord blood bank and offers advice on issues which need to be considered when establishing either of those entities. It also highlights standards which may need to be adhered to; directs the reader to areas of further research and sources of additional information.

Donor-patient transplantation pathway
To understand the role and functions of a registry, it is important to understand the transplant process and the journey the donor (or cord blood unit) and the patient undertake. The timeline in Figure 0.1 shows the different stages of the transplant process for donor, cord blood unit and patient.

Registry models
Donor registries function as a hub between different entities involved in the transplant process. The different entities relate to one another in different ways, depending on the country involved and the roles the registry chooses to take on. For example, a registry can recruit and manage donors and therefore be a registry and a donor centre.
Figure 0.1  The timeline shows the different stages of the donation and transplant process for donor, cord blood unit and patient.
Cord blood unit shipped to transplant centre

Approved to donate

Admitted to hospital
Transplant preparation begins

Final transplant eligibility testing

DONATION

Follow-up

Donor and patient may correspond*

Donor and patient may correspond*

6-12 days
Pre-transplant treatment

30-100 days
Recovery in hospital

>100 days
Discharged but ongoing hospital care

>100 days
At home

*Communication between donors and patients may not be allowed in all countries.
Definitions as set out in WMDA Standards

**Registry** A registry is an organisation responsible for coordination of the search for Haematopoietic Progenitor Cells (HPC) from donors (including cord blood) unrelated to the potential recipient.

**Cord blood bank** A facility responsible for management and the collection, processing, testing, cryopreservation, storage, listing, reservation, release, and distribution of cord blood units.

**Donor centre** An organisation responsible for adult volunteer donor recruitment, consenting, testing, management and the collection of adult volunteer donor personal, genetic and medical data.

**Collection centre** A medical facility where HPC collection from volunteer adult donors takes place. This collection might include marrow aspiration or apheresis. The collection centre, or designee, performs the medical work-up of the adult volunteer donor and provides the final approval of the adult volunteer donor for collection. The collection centre packages the donation for transport to the transplant centre.

**Testing laboratories** These laboratories perform the histocompatibility, blood group, infectious disease, and other testing of the prospective donors and patients. They may be under the direction of a registry, donor centre or transplant centre or may be separate from these entities.

**Transplant centre** A medical facility where a patient (recipient) receives a transplant (graft) with HPC from an unrelated donor or from an umbilical cord blood unit. The transplant centre oversees the immediate medical treatment and provides long-term follow-up of the recipient. The search unit undertakes the search for an unrelated donor for specific patients using criteria defined and documented by the transplant centre. This entity may be contained within a transplant centre or may be separate from the transplant centre. If separate, the search unit may coordinate searches for one or several transplant centres. In the standards, reference to a transplant centre should be interpreted as a transplant centre and/or a search unit as appropriate. Transplant centres/search units seeking an international donor work through the registry in their country.
1 · General organisation of a registry
The potential donor is called and asked to come in for a preliminary examination.

Blood is taken at the regional blood transfusion service: the HLA-typing is verified and the blood checked for infectious disease markers (e.g. HIV, hepatitis B and C).

The donor is contacted and his/her consent obtained for the donation and type of donation.

The transplanting doctor decides on a donor and proposes the desired type of donation (donation of bone marrow or peripheral blood stem cells).

Personal briefing for the donation of blood stem cells.

Medical examination of the donor in the responsible collection centre (Zürich, Basel or Geneva) to verify his/her suitability.

Collection of the blood stem cells.

Provision and transfusion of the collected blood stem cells within 48 to 72 hours.
Summary

You are likely to be reading this publication because you or others have determined there is a need for more people from a certain region, race or ethnicity to be registered as volunteer unrelated haematopoietic stem cell donors. Perhaps a family member or friend needs to find an unrelated donor and you understand that the best match will most likely be found among donors who share the same race or ethnicity as the patient and the largest source of those people reside in a country that has not yet established a registry. Alternatively, you may live in a country which has started to perform unrelated donor transplants and a decision has been made by either private individuals or a government body to establish a registry. This chapter will reference the proposed registry as ‘your registry’ and refer to it as being located in ‘your country’. This chapter sets out an overview of the way registries operate and what you may need to consider before beginning the process of establishing a new registry.

Assessment and planning

The World Marrow Donor Association (WMDA) defines a registry within the WMDA Standards as ‘An organisation responsible for coordination of the search for haematopoietic progenitor cells from donors (including cord blood) unrelated to the potential recipient’. Establishing an unrelated donor and/or cord blood registry is a very large and complex endeavour which requires extensive resources. It also requires commitment, motivation, funding, competence in the field of transplantation immunology and a highly-developed immunogenetics and informatics infrastructure.

Registry versus cord blood bank

A registry may manage adult donors, cord blood units, or both. Chapter 6 addresses cord blood bank development. Most chapters of this handbook focus on development of a registry and the process from recruiting adult volunteer
donors till facilitating haematopoietic progenitor cells from adult volunteer donors for transplant.

There are clinical advantages and disadvantages of both adult donor and cord blood products when compared to one another.\(^5\) Whereas there are some similarities in the operation of both types of registry, both also have their own unique requirements.

**Registry**

A typical registry will have multiple inter-related functions and entities which may be organised into a network. These will include donor recruitment, donor management, donor search, human leukocyte antigen (HLA)-typing laboratories, transplant centres, apheresis and marrow collection centres, stem cell couriers, information technology and administration.

A registry stores the HLA-typing information and relevant personal data of adult volunteer donors. Should the HLA-type of a patient seeking a haematopoietic stem cell transplant match the HLA-type of a registered volunteer donor, the registry also facilitates the collection and transportation of stem cell products from that donor.

**Cord blood bank**

Blood collected from the umbilical cord and placenta after the delivery of a baby is a rich source of stem cells for transplantation. With the increasing use and success of unrelated cord blood units for unrelated stem cell transplantation, countries may consider developing a cord blood registry.

Due to the less stringent HLA-matching requirements of cord blood, cord blood transplants with up to two HLA-antigen mismatches (i.e. a four out of six match) between the cord blood unit and the recipient have shown Graft vs. Host Disease (GvHD) rates and survival outcomes in paediatric and adult patients similar to those seen in six out of six HLA-matched unrelated donor marrow transplants.\(^6,7,8,9,10,11\)

Over 80% of all cord blood banks collaborate with a registry

Cord blood is a stem cell source that is cryopreserved and stored immediately after delivery, so it can be shipped and infused with minimal delay. As the foetus,
to which the cord blood belongs, is well-protected from micro-organisms, the cord blood is a sterile stem cell product containing immune cells which have not been modified by host immunogenic cells and latent viruses. Therefore, patients transplanted with cord blood cells result in a lower incidence of GvHD when compared to stem cells from adult unrelated donors. A disadvantage of using cord blood is the limited number of cells contained within a cord, which restricts its use to paediatric or small adult patients. Novel approaches are currently under investigation with the aim of increasing the number of cells obtained at collection, or which are available at the time of infusion. Such methods include double cord transplants and \textit{ex vivo} expansion.

Currently, the number of volunteer unrelated adult donors is almost 40 times the number of stored cord blood units worldwide. The major limiting factor for cord blood collection and storage is the huge cost arising from cord blood cryo-preservation. Most banks find that only cord blood units with the highest total nucleated cell count are used, which can be only a small percentage of their inventory.

The following sections of this chapter focus primarily on the issues related to the creation of a registry.

\section*{Assessment}

The motivation to start a registry is often a patient in need of an unrelated donor, in the country of his or her ethnic origin. For example, a patient living in Europe whose family roots are in Nepal may determine that the best chance for a matching donor for themselves, or for future Nepalese patients, would be to establish a registry in Nepal. Whereas this approach may indeed yield the best-matched donors for those patients, it is important to assess the feasibility of establishing a registry.

\begin{figure}[h]
\centering
\includegraphics[width=0.5\textwidth]{demographic_breakdown}
\caption{Demographic breakdown of Singapore}
\end{figure}
Investigate the status of unrelated donor transplantation

One factor which influences the feasibility of creating a registry is the status of unrelated donor transplantation in your country. If unrelated stem cell transplants are already being performed in your country, this will be a promising starting point to justify the creation of a registry.

Consider the following: Are there transplant centres in your country which are currently performing stem cell transplants? If not, why not? Is it due to lack of technology, lack of trained physicians or lack of matched donors? Is it due to the cost of establishing a transplant programme? Is it because of a national need to focus medical attention on other, more prevalent diseases, national health problems, or other national priorities?12

If stem cell transplantsations are carried out, you need to determine the number of centres performing such transplants, the capacity of each centre and the type of transplants they perform (for example, autologous vs. allogeneic). Furthermore, if a transplant centre is performing only autologous transplants, it is important to understand the reason behind this. Is it because of a lack of availability of matched unrelated donors or lack of technology or infrastructure? Is it due to costs or country-specific regulatory requirements? Are transplant physicians interested in performing unrelated transplants?

Need for unrelated donors

Once you have assessed the status of the unrelated donor transplantation in your country, the next thing to determine is the need for unrelated donors in your country. Which country or registry is currently providing the donor products for patients in your country? Can your country continue to import these products with acceptable HLA matches and at acceptable cost?

What percentages of patients are unable to find matches among their siblings or family members? Are there large family sizes or consanguineous marriages in your country that minimise the need for unrelated donors? Family size and consanguineous marriages are factors which reduce the need for unrelated donors, whereas genetic heterogeneity which causes hybrids of rare haplotypes increases the need.
Also consider whether haploidentical transplants, where HLA-type is matched on one chromosome but not the other, are preferred over unrelated donor transplants.

Many physicians are successfully using haploidentical graft sources as an alternative to unrelated donor sources due to logistical and financial limitations. These haploidentical donors are usually parents or children of the patient. The advantage of performing haploidentical transplants is that donors are almost always available for the patient. However, post-transplantation, immune reconstitution for the patient may be poorer and relapse rates may be higher.

**Other existing registries**

If there are other registries already established in your country, you should determine if you will be collaborating with them or if each registry has unique goals. In general, the development of a single registry in a country is preferable, as it is generally easier for the transplantation community, funding agencies, potential donors and the general public to recognise a single entity. If, as a new registry, you choose to work independently from an existing registry, it will be important for you to be able to distinguish and communicate to these parties what the reasons are for creating a separate registry.

**Funding and resources**

Obtaining funding and support to develop a registry in your country will be very difficult if the medical ability to perform unrelated transplants in your country has not yet been established. Whereas there is always likely to be some level of need in your country to utilise unrelated donor graft sources, one must consider the other necessary resources and competing priorities. Unless an adequate number of patients reside in your country which could benefit from a registry, it will be very difficult for funders to justify an investment to create a registry that would benefit only patients who live in other countries. Funding and budgets should consider not only start-up costs, but also the costs of maintaining the registry, taking into consideration that it may take years to build a registry of sufficient size to routinely provide products.
Funding is typically the biggest obstacle for establishment or expansion of a registry. Cord blood banking is often the most expensive component, requiring guaranteed cellular storage which is continuously and indefinitely monitored in accredited environments. Establishing a donor registry or cord blood bank is for the benefit of the whole society and healthcare system, therefore government funding sources are identified as the most logical solutions.

Important questions to ask include: has a funding source (or sources) been identified? Will the registry be funded by the government, through private donations, fees for services provided, or a combination of sources? There are many varieties of successful funding models.

Perhaps one way to approach a funding source is to characterise how patients pay for their medical treatment in your country. For example, if most medical care is provided to citizens at no cost, the government may be a promising source of funding. In some countries people tend to expect all health costs to be covered by the government and do not agree that they should have to cover any costs to donate their stem cells. However, in some European countries, this is not the case and funds for complete or partial coverage of typing costs have been supplied by volunteers themselves. Private funding of the registry is also an option, but this requires continual efforts to maintain income, whether you are soliciting major individual or corporate donors, or planning numerous public fundraising events. Private sources may yield other types of support, for example, corporations offering services such as information technologies, HLA-typing, donor recruitment and donor education. The financial and personnel needs of a registry are great and are very difficult for private sources alone to maintain. Fundraising has been very successful in some societies. Ethical concerns, such as confidentiality issues regarding the identity of patients and donors, can easily be damaged during campaigns driven by an individual or the family of the patient.
Personnel must also be budgeted for. The minimum personnel should include a medical director (physician), HLA expert(s), information technology (IT) support, financial professionals, donor recruitment personnel, donor management personnel, quality management personnel, communications and media experts and search coordinators. For a small registry, these positions may not necessarily be full-time jobs. Some of these positions may be subcontracted, provided by consultants, or be provided part-time by a sponsoring university or hospital. Questions to consider include: where will the registry staff be located – within a university, a laboratory or an office building? Will staff be full-time? Will consultants be used? See Chapter 8 for more recommendations on the financial aspects of establishing a registry.

When considering income from services provided as a funding source, you may wish to consider whether revenue from services will be applied directly back to the registry. Do laws in your country allow for the collection of fees which also incorporate indirect costs and slight additional fees to allow for an escrow fund for future expenses? If your registry falls under a ‘parent company’, such as an existing registry or laboratory, how will their policy affect what happens to your revenue? How will the funding be sustained?

Information Technology needs to include a network, computers, landline and mobile telephones, scanners, printers and fax machine(s) for staff. You will need to plan to lease or purchase a computer server to run the donor searches. As the amount of data stored on donors and HLA-typing increases, the hardware and software requirements will also increase, which will impact on the cost requirements. You will also need to determine if you will purchase pre-existing software for your search algorithm or if you will be paying software developers to create and maintain your own HLA-matching algorithm. See Chapter 7 for more information on IT and HLA matching algorithm.

Funding should also be sought to cover the costs of donor education materials such as pamphlets, posters, cards and registry forms (consent forms, data reporting forms and reports).

Budget allowances need to be made for additional costs relating to international standardisation, communication between registries, transportation of fresh or frozen stem cells and international travel.
This is because the low probability of finding a match within one registry necessitates the international use of donor cells. Worldwide, 46% of all products collected in 2012 \(^{14}\) were exported (Figure 1.2). Funding should be made available for staff travel costs, allowing senior staff to perform educational visits to other registries and to attend international meetings, such as the World Marrow Donor Association (WMDA) meetings, which are held twice yearly.

**Vision, mission and goals**

Once it has been determined that the establishment of a registry is realistic, it is recommended that you set out a mission, vision and goals for your registry. Mission statements describe the purpose of the organisation and vision statements describe what the organisation aspires to do. These statements are usually brief, consisting of one to three sentences. Some organisations combine goals and objectives into a mission statement and others use both the vision and mission statements to create goals and objectives.

For example, you may want to determine whether your primary mission is to establish a registry of unrelated donors to provide products within your own country or internationally, or both. You may want to determine if there will be research performed by your registry, if you will provide financial or other support services to patients, or if you will coordinate searches for transplant centres in your country. The number of products which cross international

![Figure 1.2](image) Percentage of stem cell donations provided for national and international patients
borders is increasing each year. The WMDA Annual Report 2012\textsuperscript{14} indicated that 46\% of all donations were provided to a patient residing in a different country than the donor.

**Operational strategy**

It is recommended that you define the operational strategies and policies for the registry. Establishing these will determine how you need to tailor donor education, donor recruitment, donor testing, donation strategies and public awareness campaigns.

**Cultural factors**

You should consider the cultural factors when anticipating how people will respond to appeals to join a registry. Consider the following: Are there religious or cultural beliefs that may negatively affect the recruitment of donors? Once donors agree to be listed in the registry, might there be cultural beliefs among the donors or their families which may negatively affect their commitment once they are found to be a potential match? Are there generational differences within families which may impact on a donor’s final decision to donate? Are there any social conventions which may influence the decision-making capability of women and dependent adults? Would donation be considered so unusual that people may consider it a form of medical research? Would potential donors in your country be willing to donate to strangers in another country or to a patient with a different ethnicity or religion? Does the culture value the opinion of a family physician? These are issues which affect potential donors in many countries. You need to tailor your strategy to address these.

Courtesy of Catholic Hematopoietic Stem Cell Bank, South Korea
For example, if a culture emphasises parental involvement or approval, you should ensure that potential volunteer donors have discussed their decision to be listed on the registry with their family before they have initial HLA testing performed. If a culture places a high value on the opinion of the family’s physician, it will be important for your registry to plan for how you can educate these physicians about your mission and the donation process.

Awareness levels

Stem cell donation and transplantation are procedures which are not well-known in most societies and countries. Rates of transplantation are higher in more prosperous countries where there is better government healthcare support. Although the phrase ‘stem cell’ is a scientific term, it can also be confused with the term ‘embryonic stem cell’ and strong views exist in some cultures surrounding scientific work involving those cells. Many individuals and their families have concerns about the potential harm to the donor which may result from donation. The side-effects and possible adverse effects of prescribed drugs are usually acceptable to an individual if it is part of their own treatment, because there is a personal benefit. However, in the setting of volunteer donation, the donor is considering the risks which may be posed to their health as a result of helping a stranger.

Investment of time and effort by the donor

Another consideration is the time spent by the donor completing the donation process and the potential financial losses which may result if the donor does not receive payment from their employer for any time they are absent from work. This issue can be magnified by the geographical distances between the donor’s location and the donation centre. The testing, work-up and final donation procedures all require the individual to take time out of work, studies and family commitments. Some registries choose to provide compensation to the employer or donor; whereas others do not.
Support for other types of donation

The general level of altruism with respect to other forms of donation is also an influencing factor which may help predict the success of stem cell donor recruitment in your country.

Blood donation is a well-accepted activity in many societies, as the complications and side-effects are considered to be negligible. Explore whether there is awareness and acceptance of volunteer blood donation in your country. Consider whether the organisation that coordinates blood donation is a respected organisation in your country or region. Will this blood donation organisation be affiliated with your efforts to start a registry?

Consider also whether there is awareness and acceptance of apheresis platelet donation in your country. Many registries have found that platelet donors are successfully recruited as stem cell donors, because there are similarities between the method used to donate platelets and peripheral blood stem cells. Even if recruitment efforts start with the recruitment of blood or apheresis platelet donors, it is important to recognise that, while there are similarities, stem cell donation is still a different process.

The factors mentioned above are important to consider, given that the cornerstone of unrelated donor registration is the concept of people being willing to donate to a patient in need, regardless of the recipient’s race, religion or nationality.

Other factors

You should also determine if there are any potential limitations to the operation of your registry due to geography or infrastructure. This may not be an issue in small countries but, in larger countries, it is critical to determine where you will locate your operations. It is important to consider whether your efforts to establish a registry will be planned according to a region’s population density, its population diversity or its distance from the location of your operation. For example, most registries begin official operations by recruiting donors (see Chapter 2). Consider whether you will limit donor recruitment to one major city at first. Is a full spectrum of resources available for the entire search and
donation process? For example, if a donor is called to provide additional samples for testing, who will draw the blood samples? Which laboratory will do the testing? How will the blood sample be delivered or shipped to the laboratory or to an international delivery service? Where will the donor’s physical examination and the process of product collection take place? How will the registry qualify and educate other parties which will be affiliated with it? Is the donation centre conveniently located near to a domestic and international airport?

A new registry may want to restrict the location of its donor recruitment drives to large cities in its early stages of development, in order to reduce the logistical factors which need to be considered and to reduce the number of affiliated organisations involved, until an efficient model is developed.

Once operations and processes are stabilised and predictable, the registry can consider expanding services and size, by adding additional recruitment, testing, donor evaluation and product collection sites.

**Determining the optimum registry size**

The numerous and highly-variable HLA-types of patients requires millions of possibilities for matches, so a pool of millions of volunteer donors and thousands of cord blood units is likely to be necessary in order to facilitate transplants. Even though there are more than 22 million donors and cord blood units listed by registries across multiple continents, there are still some patients who are unable to find a 10 out of 10-matched donor or a 6 out of 6-matched cord blood unit. This tells us that, while determining an optimum registry size is important, it is even more important to ensure the origin of donors will meet the needs of your patients.

Although the major limitation against increasing the size of donor registries is the cost of HLA-typing, it is important to set a target registry size. You should review the current literature for data and methodology before establishing the target size of your registry. This size will, in particular, depend on the diversity
of your population, which may have to be investigated first, in a random pilot study with adequate sample size.

A recent study by the German registry Zentrale Knochenmarkspender-Register für die Bundesrepublik Deutschland (ZKRD),\textsuperscript{16} presented at the International Donor Registry Conference (IDRC) 2012 in Sydney, indicated that male gender, young age, and typing for additional loci, particularly HLA-C and -DRB1 and typing at high resolution all independently substantially increase the chance of a donor being chosen. See Figure 1.3 from the study.

The optimum registry size can be difficult to predict, as it is dependent on the HLA heterogeneity of the donor population and the overall availability of donors. Unfortunately, it is not as simple as recruiting a certain percentage of the overall population as donors. Some countries with a more HLA-homogenous populations, such as Japan,\textsuperscript{17} are able to provide donors for 95% of their patients (at HLA-A, -B and -DR antigen level), even though the size of the registry (400,000 donors) represents only 0.003% of the total population. This contrasts with Turkey, whose population is more HLA-heterogeneous. Donors were found for only 30% of patients seeking a match, from a registry size of 5,000 donors, which was 0.007% of the population.\textsuperscript{18}
You will also want to assess what percentage of your current patients have matched donors from other registries around the world, what the resulting unmet need is and if there is a goal to reduce your country’s dependence on imported products. The WMDA 2012 Annual report\(^{14}\) shows that most countries import more adult stem cell products than they export. The HLA-types of a certain population may differ between the members of that population who live in their native country and the members of the population who have emigrated. For example, the Turkey-Ankara (TRAN) Registry compared the most frequent haplotypes occurring in their registry to the common haplotypes among donors of Turkish origin in the registry files of Germany (Deutsche Knochenmarkspenderdatei, DKMS), USA (National Marrow Donor Program, NMDP) and Switzerland (Swiss Blood Stem Cells). They were not ranked in the same order, suggesting regional and incomplete representation of Turkish haplotypes in other countries.

**HLA laboratories**

Building a registry does not stop when a database of typed donors is established. Once a donor is identified as a potential match for a recipient, there is likely to be a request for additional HLA-typing to be performed, unless your registry performs high-resolution typing on all five or six loci at the time of donor recruitment.

Many established registries began by using HLA laboratories in a university-based setting. However, the speed of increase in registry size may quickly surpass the in-house HLA-typing capacity. This has led to a demand for contracting HLA-typing from external providers. Small registries may also find some advantage in outsourcing HLA-typing services to larger and more developed laboratories, where there is likely to be higher volumes and more reliability, and where reduced costs due to economies of scale could outweigh any cost relating to shipment of samples. The basic principle for the requirements from HLA-typing laboratories is that international accreditation, such as The American Society for Histocompatibility and Immunogenetics (ASHI) or European Federation for Immunogenetics (EFI), is essential for donor-patient HLA data to be transmissible across borders. Donor-patient matching criteria for stem cell
transplantation are generally similar among all transplantation centres. Allele-based donor testing at four loci (HLA-A, -B, -C and -DRB1, with or without -DP and -DQ) is a must at the time of verification typing (also known as confirmatory typing) and is recommended even for initial donor typing. The IT structure of a registry and organic integration of IT with the HLA-typing laboratories are essential elements for up-to-date data transmission. These are more applicable to small registries; as such organic integration becomes almost impossible with registries possessing millions of donors.

Thought should also be given to whether additional donor samples will be stored for future high resolution typing, as this can reduce the amount of time it takes to contact a donor to come back to the laboratory or registry for a high resolution typing request.

**Infectious disease marker (IDM) testing**

WMDA Standards currently require testing for a minimum of human immunodeficiency virus (HIV), Human T-cell lymphotropic virus I and II, Hepatitis B virus, Hepatitis C virus, cytomegalovirus (CMV) and *Treponema pallidum* (Syphilis), as well as other infectious agents as defined by national health authorities and any locally prevalent diseases that are important to consider in transplantation. Donors who have recently travelled outside of their country should also be evaluated for infectious agents prevalent at those locations.

The WMDA requires that infectious disease testing should occur at the time of verification (confirmatory) typing for donors and at the time of cord blood collection for maternal donors. Depending on the incidence of infectious disease in your country, you may wish to perform this testing at the time of initial recruitment, to disqualify potential donors before resources are used to HLA-type the donor.

When your registry is coordinating the request for IDM testing on donors chosen for recipients in your country, you will need to determine if you can accept the IDM results performed by the registry, or if the tests must be done at another laboratory chosen by the transplant centre in your country, or by your registry. Most registries prefer to have the IDM testing performed in both countries. You must ensure that samples from other countries can be received and cleared (by
customs) quickly and efficiently and can be shipped or transported quickly to the respective IDM laboratories in your country.

It will be important for you to work with laboratory professionals to determine if these testing resources, such as staff, machines and reagents, are readily available in your country. They will help you to determine the number and type of blood tubes that should be used, how to label and transport the samples and how quickly the samples must be tested. Restrictions here may dictate where the donor and recipient samples must be shipped to and tested. The laboratories used should be inspected or accredited by a relevant national authority.

Many countries have strict requirements for infectious disease testing for their patients and will probably require fresh donor blood samples from your country to be collected and shipped quickly to their country for testing. You will need to ensure that you have a shipping company that can export and deliver these samples quickly.

Product collection network

Once a donor is selected for work-up, they must be evaluated to make sure they are fit to donate and that the product will be free of infectious diseases. Depending on the size of your country and the location of recruited donors, you will need to establish a network of potential product donation sites (collection centres), both for bone marrow and peripheral blood stem cells. It is imperative that the registry establishes criteria to address the experience level of the collection centre and staff and to monitor the quality of the products collected and the safety of the donors. These product collection centres are the public face of your registry during the most important part of the donor’s experience. You should ensure that these centres are experienced in collection of the product, whether it is bone marrow or peripheral blood stem cells and that they have experienced clinical staff who understand the processes. Also ensure that they have systems in place to ensure donor safety and product quality and that they will report data on their product collections and donor experience to your registry. Service level agreements must be in place between the registry and these centres, including payment schedules. The agreements should clearly detail the responsibilities of the centre and the responsibilities
of the registry. For example, scheduling and performing the physical exam, health history questionnaire and other tests for the donor, obtaining informed consent from the donor, protecting confidentiality of the donor and recipient, scheduling the product collection, labelling the product, testing the product, storing the product, completing data forms, validating the transport coolers and providing the product to the courier. Uniformity and consistency between product collection centres is very important. Physicians within and between these centres must agree on a standardised product collection protocol and must agree to submit data to be reviewed for quality oversight.

If there is a lack of product collection expertise in your country, consider arranging for product collections to occur in a neighbouring country where there are organisations with this experience. This will, however, introduce additional considerations for the donor and your registry.

Organising personnel and establishing a steering committee

During the planning stages, you should establish an organising committee or steering committee comprised of representatives from your national government or Ministry of Health, transplant physician(s), HLA experts, transfusion experts, blood banking experts, IT experts, donor recruitment experts, registry operations personnel and financial analysts. Transplant physicians will be the primary customers for the services your registry provides. HLA and IT experts offer an invaluable but often unrecognised service to patients and physicians, by supporting the functions of the registry. Blood banking organisations may be the best resource to recruit stem cell donors, as committed and dedicated blood bank staff may play a significant role in converting their regular donors, who are already accustomed to apheresis platelet donation or blood tests, to become stem cell donors. As your registry becomes more established and staff become more experienced, the role of the steering committee may change, as may the frequency of their involvement.

Fee schedules

The financial aspect of international stem cell and cord blood transportation involves a large volume of invoicing, handling accounts payable, dealing with
multiple currencies, referencing fee schedules from multiple registries and processing wire transfers. These issues necessitate an accounting department which works closely with the operational staff in your registry. It is critical to publish and review a fee schedule for your registry regularly, to announce changes in your fee schedule with at least 30 days notice (60 days notice is preferred by many registries) and to clarify potential issues with other registries as soon as you begin working with them. Please see section 10 of the WMDA Standards\(^3\) and Chapter 8 for more information.

**Product and sample movement**

For handling products and samples within your country, consider how donor blood, filter paper and buccal swabs or saliva can be transported from recruitment drive sites to testing laboratories in a timely and secure fashion. Recruitment drives should be limited to areas that allow for timely transport of both recruitment samples and samples which may be required from donors in future. Will samples be shipped or be hand-carried to a laboratory? Will donor samples be shipped individually or in large batches? What kind of courier companies are available to transport samples on weekdays and weekends? Are there restrictions on the type of courier company which can be used due to the biological nature of the sample? Are there restrictions on days or time of day that a laboratory can accept samples?

For international business, research should be done to determine if there are governmental, regulatory or logistical limitations on importing or exporting blood samples or stem cell products. Discussions should take place with the appropriate government institutions and national customs officials to assess if there are restrictions, licences and other paperwork that must be in place to allow for expedited shipping (exporting) or processing (importing) of samples and products. Arrangements should also be made with courier companies to organise the fastest service and to allow for delivery to another continent within 48 hours of the sample being taken from the donor. Blood samples that arrive at the laboratory or transplant centre haemolysed,

Courtesy of Leiden University Medical Center, the Netherlands
or otherwise untestable, are costly in terms of search delays and also subject to potential refusal of payment from the registry which requested the service. It may be necessary to limit initial recruitment to areas within your country that are well served by ground or air transport services.

In addition, movement of the collected product to the airport should also be considered. Will the product be transported by a professional courier service or a volunteer courier, and is the route from the product collection centre to the airport convenient, efficient and safe? Will your registry provide the courier, or will you require the requesting registry to provide the courier?

**Research**

Thought should be given to whether the registry will lead or participate in research. Will there be research studies using patients or donors as the research subject? Will donors from your country be asked to participate in a research study conducted by a donor centre or registry in another country? Will the research utilise blood or DNA samples? Will the research involve data collection? Will it be retrospective or prospective? Will your registry mandate submission of data by its network transplant centres to international data registries such as the European Group for Blood and Marrow Transplantation (EBMT), Centre for International Blood and Marrow Research (CIBMTR) or Asia-Pacific Blood and Marrow Transplantation Group (APBMT) or the Eastern Mediterranean Blood and Marrow Transplantation (EMBMT)? Some countries require submission of data (donor-based or recipient-based) to the registry. It is important to ensure that the correct consent documents and processes are in place as early as possible, as well as an Ethical Review Board which is familiar with stem cell transplantation. It is important that transplant centres within your country have the ability to provide the required information in a timely manner.

**Information Technology (IT) support**

Information technology is vital for a registry to be able to store and transmit data, to carry out the matching process and capture post-transplant data accurately and efficiently. IT support is not only essential but also very helpful in organising data, creating task lists, highlighting missing or completed data lists and performing statistical evaluations. IT is an essential element of
a successful registry. Searches cannot be completed without IT involvement. There must be an IT team which has a thorough knowledge of the HLA-typing and matching system. The algorithm used for matching must utilise standardised HLA nomenclature, it must be validated and must consider international communication of data. See Chapter 7 in this handbook for more information on IT support.

Thought should be given to whether the search algorithm will be developed internally or by external contractors? Will daily IT support be available to your registry? Also consider the costs of equipment support and repair.

**Expectations for World Marrow Donor Association (WMDA) affiliation**

As your registry is developing, it is highly-recommended that representatives become familiar with the World Marrow Donor Association (WMDA) and its standards and recommendations.\textsuperscript{3,20} It is also beneficial to attend WMDA meetings to meet other registry representatives and to learn about alternative practices. Your registry should become a member of the WMDA as soon as possible to allow key staff to familiarise themselves with WMDA requirements and recommendations. It is imperative that your registry formulates its policies and procedures to comply with WMDA standards, as well as ensuring that WMDA standards are also followed, transplant centres, product collection centres, donor management centres and laboratories affiliated with your registry. Written agreements must be in place between the registry and any other organisations that participate in registry’s operations. These agreements must stipulate that the organisation in question complies with WMDA Standards. The advantages of WMDA membership include the following benefits.

**Recognition**

The WMDA is a very well-recognised and respected international association that is viewed as the *de facto* society overseeing the international exchange of
haematopoietic stem cell products and promoting the interest of unrelated donors. Membership of the WMDA will help grant legitimacy to a new registry’s transplant programme with local governmental bodies, as well as with international organisations like the World Health Organization (WHO).

**Participation**

The WMDA is the principal association overseeing global standards for unrelated stem cell donations and the international exchange of stem cell products. Being a member will give your registry the ability to participate in the crafting of international policies and decisions pertaining to bone marrow, peripheral blood stem cell and cord blood donations. This is important because many new registries may have needs that are important for the WMDA to take into account when creating policies.

**Accreditation**

WMDA accreditation is a highly prestigious status held by many of the registries, which together hold 75% of the donors listed in the Bone Marrow Donors Worldwide (BMDW) global database. WMDA accreditation status will, in the future, be reflected in donor search reports made via BMDW. WMDA membership will give the registry the ability to apply for accreditation.

**Leadership**

Membership will give the registry and its representatives the potential to be elected as one of the many office-holders in this prestigious organisation. As office-holders, your registry’s personnel could help shape future policies and strategies and participate in an active learning process, while sharing knowledge. More information regarding this can be found on the WMDA website.

The WMDA general members meet twice each year. In the spring of odd-numbered years, meetings are held before or after the European Group for Blood and Marrow Transplantation (EBMT) meetings, in the same city. The WMDA meetings consist of educational talks and WMDA committee meetings. In the spring of even-numbered years, an international donor registry conference is planned and hosted by a different registry around the world, which includes educational talks
and WMDA committee meetings. Each autumn, the WMDA holds a meeting in Minneapolis, USA, in conjunction with the annual network Council Meeting of the USA’s registry, the National Marrow Donor Program (NMDP) / Be The Match.

Legal structure

General

WMDA Standards requires that the registry be designated as a legal entity. When considering legal implications, one of your first steps should be to determine whether there are any laws or regulations that refer to stem cell or organ transplantation in your country. If so, it is recommended to carefully read the paragraphs dealing with organisation of stem cell donor registries. It is important to know if the scope and methods of collecting stem cell, bone marrow or umbilical cord blood donor data are regulated and to verify whether there is an idea of a centralised national registry described in any regulations.

Determine whether there are any restrictions regarding where donors can be recruited. For example, can donors only be recruited in your own country? Also research whether there are restrictions on where testing can occur and whether donor blood or saliva samples can be sent to laboratories in other countries for HLA-typing and infectious disease testing. Also determine where product donations can occur. These questions can be very important for a newly-established registry as it may cause difficulties if testing and product collection services are not available, have limited capacity, or are not economically feasible in your country.

Blood transportation regulations are always crucial because sending blood samples for verification (confirmatory) typing is one of the basic activities of a registry.

Personal data protection rules should be considered during the very early stages of registry organisation. Requirements relating to sensitive personal data storage should be implemented during the design of your registry’s informatics systems. This may include server-room security, network protection, appropriate fire-wall
systems, passwords and codes, as well as general office security planning and writing standard operational procedures regarding data safety. If your registry is considering listing its donors within another registry’s database, or even listing your donors in the Bone Marrow Donors Worldwide (BMDW) database, research should be done to ensure this is allowed within your country.

When considering the legal structure of the registry, keep in mind that there are many different successful models. A registry can function as a part of an HLA laboratory (private or public), part of a medical university, part of a public or private health care facility, part of the country’s blood bank, as a private foundation, or a public not-for-profit organisation. Determining who is legally responsible for signing contracts and agreements, hiring personnel, determining budgets and salaries and purchasing equipment are important decisions that must be made as soon as possible. The registry funding source will affect the legal responsibilities and liabilities of the registry. In some countries, registries are founded and partially or fully financed by the national Government. Other registries may be totally reliant on private donations, supplemented by fees collected for registry services performed. Other registries use a combination of funding sources. All solutions have advantages and disadvantages and differ according to the cultural conventions and economic climate of the country. This means that although one model works well for one country, it may not work for another. Registries may change their funding sources as they grow. For example, a new registry may be able to start its operations with private money, then may be able to obtain government funding once it has demonstrated success. The opposite may also occur, with a registry initially funded by the government then being supplemented by private donations once the programme is recognised to be successful. Cost-sharing of space, personnel and equipment may also be a successful approach for new registries, for example, starting a registry within hospital, HLA laboratory or blood bank.

If the registry is run privately, it can collect funds in many ways, depending on the activity, spirit of enterprise or initiative of the registry leaders. It also has more freedom regarding organisational issues, public relations and salaries for employees but must pay more attention to economics and often has to outsource to recruit professional staff, while registries within healthcare facilities or universities can use the local personnel, scientific contacts and experience to support their operations.
There is no formal recommendation regarding the form of organisation for a registry – it is dependent on the organisers and founders of the registry. See the table below for a comparison of advantages and disadvantages.

| Advantages and disadvantages of organisational structure and financing options |
|---|---|
| **Advantages** | **Disadvantages** |
| **Public Government** | | |
| - Access to public funds and government health care programs. Funding could be guaranteed for several years at a time. | - Funding may be limited. |
| - Public support from professionals and official national authorities. | - Competition with other publicly-sponsored programs for funding and recognition. |
| - Contracting with a government institution could be beneficial for contractors. | - Contracting with a government institution could be slow and inflexible. |
| - Transparency and official legal framework; utilising services or processes from other government departments to procure services. | - Dependency on higher-level institutions can result in less flexibility and delays due to multiple levels of approval required for decisions. This may be a slow process due to the inertia of large public entities. |
| **Private** | | |
| - Independent from government institutions. | - Lack of official support (financial and organisational) from government. |
| - Free market rules for fundraising, freedom to organise donor drives and collect money from different private sources. | - Need to continually devote employee time to renew and find new sources of funding. |
| - Flexibility of organisational framework, salaries and number of employees. | - Lack of access to professional medical staff. |
| - Possibility of fast evolution and adaptation to new situations. |

**Insurance**

The operation of a business that affects the health of both donors and recipients carries many legal risks, so proper preparation and knowledge of the potential legal issues is very important for the registry staff. Regarding donor insurance, WMDA Standard 10.123 indicates that ‘the Registry, or its designee, should offer disability and death benefits to all adult volunteer donors’. Insurance should also cover hospitalisation during the donation, as well as medical follow-up for donors in case there are any complications that occur during the course of testing or donation.
Depending on your country, the insurance may be provided through a national government policy; otherwise additional private insurance may need to be purchased.

The registry should also provide its employees with appropriate liability insurance in case of any external conflict. It is important to define the staff duties and responsibilities regarding each step of the procedure and what to do in case of emergencies. Staff must be aware of their duties and existing standard operating procedures (SOPs). This can be confirmed by having staff acknowledge their understanding by signing SOPs and accepting their responsibilities. It will be important for insurance carriers to understand the scope and location of where the staff are carrying out their duties.

**Confidentiality**

It is essential to train staff regarding maintaining anonymity of the potential donors and recipients during all steps of the matching procedure and to establish clear and precise rules of disclosure in case a patient or donor wishes to be informed about each other’s identities. According to WMDA standard 3.07,3 ‘To ensure confidentiality, the identity of donors must be protected. Approaches to ensure donor confidentiality must be established’.

**Donor consent**

Another very important issue in the context of legal limits and responsibilities is the obligation of obtaining fully-informed consent from the potential donor, at least at the final step of the matching procedure. It is recommended to obtain signed consent also at other stages of the matching and donation process, as stated in WMDA standards definitions.3 According to the WMDA definition, signed valid informed consent is, ‘Signed documentation indicating that an adult volunteer donor or the maternal donor of umbilical cord blood has been provided with information on the procedure and tests performed, the risks and benefits of the procedure, that they have understood the information provided, have had an opportunity to ask questions, have been provided with satisfactory responses and have confirmed that all information provided is true to the best of their knowledge. The consent is valid when it complies with national regulation’. According to the WMDA obligatory standard 3.11,3 ‘signed valid informed consent must be obtained from all adult volunteer donors at the time of workup’ and, according to
WMDA standard 3.09,3 ‘signed valid informed consent must be obtained initially at the time of recruitment’.

Consent forms should be reviewed by legal personnel, as they are created as legal guarantee for the registry and its employees and are legally indispensable for functioning of the registry.

A consent must be also obtained, ‘if donor blood or other biological material or information is stored and/or used for the purpose of an ethically approved research project’, according to WMDA standard 3.13,³ which is crucial in case of any scientific studies involving data collected by the registry. The term *biological information* refers to collected data.

All registries should be monitoring data to ensure the safety of the donor and the quality of the product. Recipient outcome data should also be collected and analysed, with proper consent. Data can be provided to regional or international data registries such as the EBMT or the CIBMTR or other regional data registries to monitor recipient outcomes.

**Personnel requirements**

**Registry director**

The registry must have a designated director with experience in programme administration in a healthcare setting. If the director does not possess personal experience in the field of stem cell transplant, he or she should appoint an expert in this field as an assistant or readily-available consultant. It is essential that, among the management-level staff of the registry, there be physicians with expertise in the field of clinical stem cell transplantation, for example, indications for stem cell transplant, methods of stem cell procurement, donor safety, histocompatibility and the many regulatory issues involved in establishing and maintaining a registry. It is important that the director and their designated assistant be sufficiently conversant in the field of stem cell transplantation so as
to maintain a professional level of communication with collection, transplant and donor centres.

The registry director bears responsibility for ensuring that the registry adheres to standards imposed by national and international accreditation agencies. The director is also responsible for supervising the business management of the registry.

**Physicians**

There are many medical issues associated with the daily routine of a registry, such as donor health, unusual transplant centre requests and complications ensuing during the stem cell procurement process. The registry should have a designated pool of physicians to review these issues on a real-time basis in order to provide an immediate plan of action regarding each case. These physicians should be experts in the field of stem cell transplantation and histocompatibility and should have a broad familiarity with general medicine. The registry physicians should be available during recruitment to answer questions regarding suitability of potential volunteer donors, during the donor screening process and during the stem cell procurement stage to provide advice to registry staff and to collection centre personnel. These consultations can be performed by phone. The minutes of phone consultations for specific donors should be recorded in the donor’s file.

**Medical review panel**

Registries are often confronted with donor and recipient issues that are either complex or vague. In such cases, a panel of physicians with expertise in the areas described in the previous section ‘Physicians’ above should be available for discussion and decision-making. Many registries use a conference call format to expedite the functions of this medical review panel. Decisions of this panel should be recorded in the donor’s file for future reference.
Consultants

The registry should have ready access to designated experts in specific fields, such as histocompatibility, quality control and information technology. These experts may not be official employees of your registry. Their services may be provided on either a voluntary or paid basis, depending on the needs of your registry.

Staff

A well-trained and motivated workforce is the nerve centre of a registry. Staff members need to be trained in their specific area of responsibility and their competence should be evaluated on a regular basis.

The registry should have, at the very least, coordinators for donor recruitment, testing requests, product procurement, donor follow-up and data management. These coordinators should be trained in accordance with WMDA recommendations relating to their specific fields. In addition, the registry should have dedicated quality managers and individuals who are responsible for the maintenance of the registry database. The registry should have a business manager and a designated information technology staff. Small registries can use contractors to perform some of these more technical tasks, for example, a computer software company or an accounting firm. An office manager should coordinate the functions of these staff members.

Staff meetings are an effective tool for maintaining a high level of performance in the registry. These meetings should take place on a regular basis and attendance should be mandatory.

The workforce should be sufficiently large to ensure the proper and efficient functioning of the registry. The registry director should set specific performance goals for the registry, for example, turn-around time for requests, and should ensure that enough people are working in each division to meet these goals. It is vital to make sure that there are enough people performing each specific function so that the smooth operation of the registry does not falter if one person is away on leave.
Staff members should be well-qualified for their specific role in the registry. Their performance should be assessed by the quality manager on a regular basis. Records must be kept to document the training and on-going competence of staff members.

Staff members should be made aware of the sensitive nature of their job. Confidentiality is the foundation on which the enterprise of unrelated donor recruitment rests. Refresher lectures on confidentiality should be included in the quality management plan. Breaches of confidentiality should be dealt with quickly.

A comprehensive and easy-to-read book or on-line resource containing the current version of all the registry’s standard operating procedures (SOPs) should be readily available to all staff members for quick consultations. Even though all staff members have read these SOPs on a regular basis, questions will arise and staff members should feel free to consult the SOPs for reference. In addition, the registry may choose to maintain a library or an online account to assist in daily functions of the registry.

Building and structural requirements

The requirement for building space will depend on which activities will take place at the registry. There are multiple models and no single registry model is appropriate in all situations or locations. The determination of what is the appropriate service model for a particular country, state or province must take into account a number of considerations including the existing transplantation and relevant clinical services infrastructure, transportation routes and venues and the availability of trained and skilled staff.

Some registries are ‘office-space only’ and some incorporate other features, such as a donor recruitment area, a testing area (laboratory) and a donation centre. Some registries are located in a stand-alone building, while others are...
co-located within a hospital. Note that if a registry is co-located within a hospital, it is important for donors not to be treated as patients and for staff to be sensitive to environmental factors, such as sights and smells that could be considered by the donor to be a negative factor, for social or cultural reasons. When co-located, the registry should consider having its own address, signage and entrance, separate from other hospital entries. WMDA standard 2.09 states that ‘the registry must have a fixed physical location’.

**Space**

The facility space should ensure that the staff can work to meet the registry’s mission in an efficient, productive, secure, safe, pleasant and cost-effective manner. The space should also be attractive to all categories of people who will visit, including donors, patients, suppliers and contractors. Registry signage should also be considered. Below are some general categories of functions, which will dictate the type and amount of space necessary:

- Public visitation area for donors and/or patients.
- Reception area with room to display educational materials, awards, photos.
- Confidential areas for donor interviews or meetings.
- Donor medical examination and sample procurement room.
- Donor search coordination and registry administration.
- Security and restricted access to donor/patient information.
- Personal work space to include computer and telephone, filing space, access to faxes, copiers and scanning machines. Consider areas that can be open and shared and the fact that some staff may require private offices.
- Shared space for multiple meeting rooms (with audio visual capacity), lounge area or lunch room, kitchen area, lavatories.
- Laboratory space for HLA, donor, product and/or infectious disease testing.
- Water supply type, gas supply, power supply, laboratory hoods, sinks, liquid nitrogen delivery and electrical needs.
- Sample storage (blood tubes, freezers, filter paper and/or buccal swabs).
- Equipment space and future needs, security, special electrical needs.
- Cord blood storage (liquid nitrogen tanks).
- IT operations.
- Air conditioning, security, networking, internet, cabling access, uninterruptible power source, telephone equipment, shipping delivery area, equipment and supply storage, tools, custodial closet.
Building design, whether owned or leased, must comply with local and national regulations regarding ceiling heights, corridor widths, exits, weight limits.

**Location**

To maintain visibility, the facility’s best positioning would be in well-populated city-centre district, close to municipal social, cultural and administrative centres, business centres and frequently-visited public attractions and recreational areas.

An alternative solution, especially when the registry will be utilising centralised laboratory or product donation services at a local hospital, is to lease or rent space in a large medical or university campus district or in a hospital centre. The site should be located where vehicles can easily access the building and the site should be easily accessible by public transport. Disabled access should be provided in accordance with local regulations.

**Quality management requirements**

Quality management should never be an end in itself but should promote the control of important parameters for a registry. When developing a quality management system, one should start with a few core processes and then expand – for example, one long-term aim might be a DIN EN ISO 9001 certification. There are four main aspects of quality management, detailed as follows.

**Fulfil expectations**

The main point is defining your goals. Therefore you should keep in mind your stakeholders – the patients, the donors and your partners. If you know your goals, look for performance parameters to monitor. These might be the number of donors, donor typing stage or resolution and age structure of your register, the number of searches performed, number of requests dealt with, time until requests are answered, time until payment received, the number of and reasons for non-fulfilled requests, the quality of stem cell products, or participation in data submission to the WMDA.
As a registry, you may represent many independent partners in your country, such as donor centres, transplant centres and laboratories. During interaction with other registries, you are responsible for the associated partners in your country, so you will also need to analyse the performance of these other entities.

Apart from performance parameters and their trends, a common way to measure how well expectations have been fulfilled is to perform regular internal or external audits.

**Job descriptions**

Having qualified staff is vital for ensuring quality. Define and document job functions with requirements and define and document a training programme for new staff, as well as on-going staff training. One job function should be a quality manager who maintains the quality system and the documentation. It may be a part-time job, but it is essential for a quality management system to have one person in charge and keeping an overview.

**Process control**

To achieve a reasonable grade of process control and uniformity, written standard operating procedures (SOPs) and forms are mandatory. An SOP should cover the following topics:

- the process aim (objective).
- interfaces with others and their responsibilities.
- adequate comprehensive working instructions for the sub-process including checkpoints.
- how the process should be documented.

Further information is also given in the Guidance for the WMDA Standards. SOPs and forms should be written by the people doing the work to which they relate. When you start writing a SOP, remain descriptive and do not try to enhance your processes at the same time. If you decide to change your process, make a new version of the SOP or form later. Every document should be reviewed and updated frequently, for example annually.
Designating responsibilities is one of the key points of quality management and consideration should be given to the areas system administration and backup. Maintenance of equipment such as communication devices and servers should be planned, including backup solutions. A deviation and complaint management should be set up, allowing for grading of the issues reported and detailing what measures will be taken to resolve them and prevent them, if possible, in the future.

**Documentation**

The most important function of documentation is to allow the tracking of single cases and avoiding errors. There are different kinds of documents which will describe how your system works and help staff to do single tasks in a standardised manner which ensures quality.

For daily work, the SOPs and forms are the most important documents. When some forms and SOPs are established, you should interconnect your documents. If, for example, a form is used for a certain process, refer to it in the corresponding SOP describing that process. Depending on your total number of SOPs, it might be helpful to have a survey document describing the general procedure from a higher level and giving an overview of all accounting processes. You should also set up a quality management handbook describing and referring to all your processes, including general management policies and quality assessment. A quality management handbook could be structured according to the International Organisation for Standardisation (ISO). The ISO 9001 document sets out requirements which must be fulfilled for an organisation to be considered ISO-certified and explain how each standard is addressed.

Documentation is worthless if it is not properly structured and maintained. It is helpful to name controlled documents in a unique and clear way. The quality manager and quality management system must ensure that only current and authorised controlled documents are available. Records such as filled-in forms or log files must also be controlled. Concerning records, you should consider things which have not been documented as not being complete.
As you are probably planning to act worldwide, consider setting up national rules of operation, explaining how you plan to interact with international partners and what special regulations might have to be observed.

One of the most important pre-requisites for quality is a ‘quality culture’. This means everybody in your registry – managers and staff members – has to be involved with quality aspects. Quality comes from feedback, so everybody should be invited to make suggestions. It is important to remember: there is no 100% perfection in quality management, simply continuous improvement.
2 · Recruitment of volunteer donors
Summary

This chapter deals with the recruitment of new potential adult volunteer donors, including suggestions for increasing both the size and quality of your registry’s donor list. For the purposes of this chapter, a ‘registrant’ or ‘donor’ is defined as a person who has permitted the registry to obtain a DNA sample for HLA-typing and to list this, along with personal details, in order that the registrant may be found to be a match for a patient anywhere in the world. According to WMDA Standards definitions, a donor is ‘a person who is the source of cells or tissue for cellular therapy product. Donors are unrelated to the patient seeking a transplant’.3

Some registries recruit donors themselves, while other registries have an agreement with an organisation that recruits donors and then lists them with the registry. These organisations are known as donor centres or donor recruitment groups. The donor centre (DC) can be a blood bank, a transfusion centre or an organisation, while the donor recruitment group consists of family members and friends of a patient in need of a transplant. Donor recruitment groups usually organise public donor recruitment drives, where registrants fill in consent forms and have DNA samples taken for HLA-typing. The registrants’ information is provided to a registry, which is responsible for listing the donors in the international database and handling communication with transplant centres.

This chapter describes the activities which need to be undertaken at the stage of donor recruitment. These activities can be done either by a registry, a donor centre or donor recruitment group.

Main tasks involved with donor recruitment

A registry, or donor centre, should be responsible not only for recruiting adult volunteer donors, but also for ensuring that all donors have received appropriate counselling and have given the necessary signed, informed consent. The registry or donor centre is also responsible for coordinating the testing of prospective adult volunteer donors.
Registries and donor centres should feel responsible for the care and well-being of the donor and should also be aware of the standards required for managing donor care. The registry or donor centre has an obligation to respect the donor’s rights and to act in accordance with ethical principles.

At the time of registration, donors should be made aware that they need to be willing and physically able to donate either bone marrow or peripheral blood stem cells (PBSC). It has to be clear that becoming a donor is absolutely voluntary. It is vital to get the donor’s written informed consent for typing their blood or saliva sample and also for storing their personal data in the registry or donor centre database.

The donors should be made aware of the matching process and should understand that having their details listed does not mean they will automatically be asked to donate their stem cells or bone marrow. The registry must inform the donors about the registration regulations and also their right to withdraw their agreement at any time.

If a donor is selected to donate, the type of collection process required should be discussed with the donor again during the work-up process, taking into account the needs of the patient. The donor’s decision regarding the process will be respected at all times. If the donor does not agree to undergo the collection procedure requested by the transplant centre, it may be necessary to look for an alternative donor.

The main tasks involved with donor recruitment are to:

- Attract people’s attention to the issue of bone marrow and stem cell donation and show them how they can support the cause.
- Educate new potential donors in a thorough and transparent way.
- Offer simple and transparent methods of donor recruitment.
- Strive for retention and reliability of new donors, which can be evidenced by donors’ interest in supporting the registry or donor centre and by examining donor availability and rates of withdrawal.
Preparation

Preliminary considerations
The table below contains aspects which should be considered before a new registry or donor centre starts recruiting.

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Legal aspects

Age limits for donors
The legal age of consent has to be considered when it comes to recruiting and registering adult volunteer donors and also at the point of stem cell or bone marrow donation. The WMDA standard 3.13 says that ‘prospective unrelated adult”
Volunteer donors selected for Haematopoietic Progenitor Cells (HPC) collection must have passed a minimum age established by national regulations or their 18th birthday if no regulations exist and an upper age-limit for donation must be stipulated after which donors will be removed from the Registry.’

Donor recruitment organisers should consider the fact that donors may need to be dismissed from the worldwide database at a certain point, for age reasons. This has led some organisations to focus on recruiting younger donors, as they will remain in the registry for many years and are also preferred by transplant physicians.

**Data protection**

Each country has its own laws and regulations relating to the protection of personal data. It is a duty of the registry or donor centre to clarify what the law and regulations are in their country and to determine whether it is necessary to apply for authorisation before beginning to collect donor data. All parties who will work with donor data need to sign a contract to ensure confidentiality and protection of personal data. Data protection standards may vary in different countries, therefore a lawyer should be involved to advise you on how to adhere to requirements in your country.

**Consent form**

To create a donor consent form, you will need to clarify the information necessary to ensure the donor meets medical criteria and can be contacted if they are a match for a patient. This will help you to decide on the information that you need to collect at the time of registration. When creating the form, you should also bear in mind that signing to consent to registration does not automatically imply that the registrant is giving consent for donation. Forms should be kept clear, easy to understand and as brief as possible and the use of jargon should be avoided. Laying out information in a tabular form is easier to read than displaying information in large sections of text.

The following is a list of recommended information elements to collect from a donor at the time of registration:

- Full name.
- Date of birth.
- Gender.
Current postal address.
- Permanent postal address (important if recruiting college students).
- Telephone number.
- Mobile telephone number.
- Email address.
- Contact information for an alternate contact, such as a friend, parent or relative who does not live with the donor. This is important when recruiting in a country where the residents move frequently and can change their address without being required to notify a regional or national registration organisation.
- National identification number (where possible).
- Height.
- Weight.
- Ethnicity – gathering this data from donors may help to give an indication of the HLA diversity of your registry. In some countries, it is not deemed appropriate to ask for ethnicity on forms.
- Signature and date – this documents the donor’s consent to having their sample tested and their details listed in the donor registry.

WMDA standards 3.09 and 3.15 say, ‘signed, valid, informed consent must be obtained initially at the time of recruitment’, and, ‘information on donor age and gender must be collected at the time of recruitment’.

Labelling
It is also important that you are able to link the donor’s personal data with the corresponding sample sent for HLA-typing. This can be done by labelling both the data and the sample with the same unique donor identification number (donor ID). This can be achieved by using identical barcode stickers on the consent forms and corresponding blood tubes, buccal swabs or saliva samples. Using the same barcode on the consent form and samples minimizes any potential for mixing up samples and forms. It is best practice to affix the labels at the time that the donor completes the consent form and provides the samples.

Tissue typing and transportation of samples to laboratories
Before collecting any samples, it is necessary to obtain legal advice to determine whether you need authorisation for collecting samples at different locations, whether this is regional or nationwide.
Depending on how you decide to recruit donors, you will need to consider how you will transport the required materials – either by car, by courier system or by post. The method you choose will also depend on the infrastructure, the transport circumstances and costs involved. If you have to send all the samples you collect to a laboratory which is located in another city or even abroad, you must check the legal requirements relating to the transportation of biological samples.

You will also need to search for companies who may deliver the sample collection kits, whether they are buccal swabs, saliva kits or blood tubes.

Medical aspects

Medical criteria for donor exclusions
The WMDA standards 3.22 and 3.22.1\textsuperscript{3} state that ‘donor health requirements affecting the suitability of adult volunteer donors must be established’ and ‘an initial health screening should be performed at the time of recruitment’. Generally, a donor should be in good health. There are always criteria set out in national medical guidelines, which must also be considered.

A document should be compiled to define and clarify all medical criteria that would exclude an individual from joining the registry. The criteria must be based upon safety considerations for the donor undergoing a collection procedure, as well as considering the safety of the patient who would receive the transplanted cells. The guidance provided by the World Marrow Donor Association (WMDA) aims to provide minimum standards by which potential donors should be assessed.\textsuperscript{22}

Study of genetic background in your country
Ethnic heritage is an important factor, as patients are more likely to match with a donor who is of a similar ethnic background. Increasing the diversity of the donors listed in the international databases will increase the likelihood of creating life-saving matches between donor and patient, not only in your country but worldwide. Recruitment strategies should be built upon the patient’s need within your country.
Method for sample collection
There are different methods of sample collection, such as saliva kits, buccal swabs or blood. It has to be decided which method a registry or donor centre will offer to prospective donors. A balance should be struck between making registration as simple as possible, while ensuring that the new potential donors are aware of what they are committing to by registering. Collecting buccal swabs or saliva samples may simplify the registration procedure, but new registrants must be made aware that, if they are chosen to donate, they will have to cope with needles and a potential overnight stay in hospital. The practicalities of taking samples from donors by buccal swab or saliva testing helps to increase donor numbers. However, the fear of having blood samples taken via needles can be a reason for a donor who registered through buccal swab or saliva to withdraw their consent at a later stage of the donation process.

For this reason, some registries and donor centres choose to register donors by taking blood samples, as they believe it avoids the registration of potential donors who have a needle phobia.

The costs of procuring oral specimen collection kits vary. It is advisable to check with several suppliers before signing a contract. If you have decided to take blood samples, you should check whether there are any collection restrictions in place. For example, in your country are only doctors allowed to take blood samples? Will they require payment or collect samples voluntarily? In some countries, it is possible to have nurses, medical students or volunteers from blood donation centres collecting blood samples at recruitment drives, without cost to the registry or donor centre.
The method of sample collection chosen can also affect what happens at the donor typing stage. Buccal swabs and saliva samples are easier to obtain and less costly to collect, but there is some debate as to whether the DNA content is as good as that obtained from blood samples.

**Finding a laboratory and defining which tests need to be done before you list your donor in an international database**

A donor needs to be tested before they can be listed in an international database and be available for a patient in need of a transplant. Testing is done by laboratories. A registry or donor centre may collaborate with different laboratories.

A laboratory is needed for the following testing:
- Histocompatibility testing of donors (HLA-typing).
- Blood group (ABO/Rh) (WMDA Standards, 3.21).\(^3\)
- Infectious disease marker (IDM) testing (WMDA Standards 3.24).\(^3\)
- Other testing required of the prospective donors.

Depending on your country’s system, you may either work together with public laboratories or find a private institution which will be able to handle the estimated number of new potential donors. The arrangement should allow the samples to be typed as quickly as possible. A price should be set for each method of testing and should be considered when formulating your budget, as costs may vary depending on the number of samples being tested and also on the experience and reputation of the laboratory.

The WMDA standard 3.17\(^3\) specifies that ‘testing must be carried out by laboratories that meet standards established by the government or prevailing in the relevant community for performing these services’. WMDA standard 3.17.1\(^3\) state that ‘testing must be carried out in a manner to ensure the accuracy of the data’. A minimum of typing to loci HLA-A, -B, -DRB1 should be defined prior to listing newly-recruited adult volunteer donors in the registry. WMDA standard 3.20\(^3\) also states that, if not all the newly-recruited donors are DR-typed, the registry should have a reasonable policy and strategy for selective DR-typing of some donors.

There is evidence that donors who are typed for loci HLA-A, -B, -C and -DR, using DNA-based methods, are often selected more quickly as potential matches. Therefore it is important to consult with an immunogenetics expert to define a
strategy for the typing of samples from newly-recruited donors. The quality of the HLA-typing should be taken into account.

Two international societies have set up an accreditation program for HLA-typing laboratories: European Federation for Immunogenetics (EFI) and the American Society for Histocompatibility and Immunogenetics (ASHI). To ensure good quality of HLA-typing, you may want to consider having samples typed in an ASHI or EFI-accredited HLA laboratory.

Administrative aspects

Finding donor recruiters

Donor recruiters may be employees of donor registries or donor centres, or they may be volunteers. You must consider the tasks involved, knowledge required, availability and flexibility needed before deciding whether you prefer to hire staff for donor recruitment or to work with volunteers, or do both. You should define the tasks they will undertake and any qualifications needed. You should also define the person responsible for training and monitoring them. You need to decide whether volunteers may be made responsible for organising a donor recruitment event. You should be aware that working with volunteers might be more difficult, as they do not usually have any specific experience in this field and will need adequate training in order to represent your registry or donor centre properly.

Donor recruiters need training

Donor recruitment methods vary from country to country, because some registries or donor centres focus their efforts on converting routine blood donors to become stem cell or bone marrow donors, while others reach out to the wider public. However, in general, a donor recruiter is someone who takes care of the following tasks:

- Counselling potential donors.
- Checking eligibility of potential donors.
- Collection and storage of donor consent documentation and donor identification data.
- Maintaining authenticity, integrity and confidentiality of donor data.
- Collection and storage of samples for HLA-typing.
More information can be found in WMDA standard 3.023 and in the publication ‘Qualifications and training of adult stem cell donor recruiters’. In addition, a standard operating procedure (SOP) for staff training should be designed and followed. If special licences or permits are required for recruitment activity by local law, these documents should be obtained and filed by the registry or donor centre.

Motivation, information and education

In most countries, the general public often knows very little about the possibility of registering as a potential stem cell donor. So you need to consider this level of awareness when establishing how you will begin recruiting donors. Working the concepts of altruism, solidarity and social engagement into your awareness-raising activity can help you to reach the people you would like to recruit.

People may show great interest in helping the cause, once they feel well-informed. One of the first steps in recruitment is defining the methods you will use to raise awareness and motivate people to register. It is always helpful to contact people who are already involved in this area, such as transplant physicians, patient organisations and self-help groups. They may assist in helping you find appropriate and clear wording for your information material, which should be provided to potential donors. The consideration of cultural and educational conventions in your country can help you to find the right way to raise both awareness and inform potential donors in the most transparent way.

Possible information tools and channels include:
• Printed materials, such as flyers or brochures.
• Website.
• Films.
• Radio or TV appearances.
• Social media, such as Facebook, Twitter and blogs.
• Press coverage.
Possible content of information material includes:

- Who you are.
- Your mission.
- Your goals.
- Some facts and figures.
- Overview of different kind of blood disorders and treatments.
- Step by step guide to becoming a donor.
  - Registration and HLA-typing
  - Further blood tests (verification typing)
  - Donation – explanation of the two different methods of collection, including risks and probability of donation.
- Patient-related information material and press coverage.

Public relations and media support

Personal stories usually create higher emotional involvement and therefore lead to more effective media coverage. This can be a good way for registries to raise awareness among potential donors. Establishing personal contacts and long-term relationships with media outlets will help you to reach as many potential donors as possible.

Olympic champion short track speed skating YANG Yang joined the CMDP. The NBA basketball super star YAO Ming is one of CMDP’s blood stem cell donors. Courtesy of China Marrow Donor Program

Many donor registries and centres have used prominent media spokespeople to promote their message and attract potential adult volunteer donors to recruitment events. Sportspeople, celebrities, fashion models and politicians can all be approached to serve as high-profile advocates for your recruitment efforts.
Some organisations have found that the best spokespeople are the actually photogenic and articulate patients who are in need of a donor. Pairing such a candidate together with respected community leader in your media coverage can be an effective way to attract attention to your donor drives. Testimonials from transplant physicians, transplant recipients and donors who have already donated can also be useful. You can also organise a press conference or invite a selected group of journalists to explain your work, your aims and the need for public relations support.

The more activities that are organised by your registry or donor centre, the higher your chances are of receiving media coverage and raising awareness. Social media and online publishing outlets can also be very helpful in promoting your work in donor recruitment. Facebook, Twitter and other platforms can be used to inform and motivate potential donors. It is advisable to manage all media activities by your registry and not by the patients or their family.

Information events

One way to spread the word about your organisation is to arrange information events at community locations, such as universities, town halls, hospitals or sports clubs. Appearances by transplant physicians, patients, transplant recipients and donors who have already donated allows the audience to hear real stories, ask questions and receive authentic answers from people who have experienced the transplant process. You might wish to compile a general presentation which gives an overview of your work, your tasks and objectives and clear information about the donor registration process and the processes involved in donation.
Education

People should be informed by the registry or donor centre about the importance of their commitment and the obligations which they are signing up to by registering as donors. Basic information regarding peripheral blood stem cell and bone marrow collection should be supplied. The safety of the procedures should be stressed, but basic information about the risks of the procedures should be given. Potential donors should be aware that a thorough medical screening will be performed if they are asked to donate and that they will always have a representative from their registry or donor centre as a contact person. If possible create your own video, including all important information but also photos of public drives, donor and patient interviews. Marketing, communication, and graphic design students from universities might be interested in assisting you with creating this piece of work.

Donor retention and reliability

To strengthen donor commitment, confidence and willingness to donate and to ensure the greatest rate of donor availability, it is necessary to keep in touch with donors. The World Marrow Donor Association has set out some guidelines in its paper, ‘Key Performance Indicators for Registries’, published in March 2013. You should consider:

- Issuing a donor certificate or card and welcome letter or e-mail when donors register.
- Providing on-going information for the donor about your organisation’s work, such as through an annual donor mailing.
- Engaging in on-going media work.

Many registries or donor centres give each newly-registered donor some form of certification to confirm they have been registered and to remind them of what they have committed to. Whether you distribute a certificate or a donor card, the document should contain the contact address of the registry or donor centre and may also show the donor identification number. This means donors will know who to contact about any changes in their contact information or availability.
Returned mail or incorrect email addresses are often a sign that the donor has moved without informing the registry or donor centre. Efforts should be made to get the new address and staff should be assigned to contact donors whose mail or emails are returned. It is more efficient to maintain up-to-date donor records than to search for new donors, so updating contact information is an important tool in maintaining a high-quality database of donors.

In order to keep the donors in your database well-informed and motivated, it is recommended to consider engagement tools. One method is to initiate an annual mailing to all donors you have registered. It is a chance to advertise the annual accomplishments of the registry or donor centre, to encourage philanthropy and to prompt donors to notify you of changes in their status. You could also include stories written by donors or initiative groups who have organised events, as people are often very interested in reading about the outcome of these efforts. You could include information on the number of donors who registered at events, the number who have already donated for a patient and possibly details of a subsequent donor-recipient meeting. It is important to note that not all countries allow the exchange of donor and recipient information or addresses, therefore meetings may not be possible in some cases.

**Methods of donor recruitment**

The methods you choose for reaching and registering adult volunteer donors must adhere to the laws of your country and also take account of the population’s habits. Recruitment drives are events held over one day, or several days, during which members of the public are invited to register as bone marrow or stem cell donors. Drives can be on-going – for example, the presence of a donor registration booth at a local train station – or they may be episodic, such as a large public event held on a specific date.

Consider the challenges you may face if a donor drive request comes from a different city or town, which is far from where your office is located. Think about the travelling time involved, the infrastructure and what will happen if a donor
recruited at the event is selected as a possible match and is required for further testing. Is it feasible for them to have samples taken and for you to receive those samples in a timely fashion? How far away is their nearest collection centre?

Consider whether there is any opportunity to cooperate with blood donation centres. If there is a cooperative agreement with blood donation centres, ensure that blood donors receive detailed information about registering as stem cell donors and be sure to stress the difference between a blood donation and a stem cell donation. It is important to check what processes are used by the blood donation centre before any cooperative event and, if necessary, inform your laboratory of the details. It is advisable to allow time to plan the specific goals of the drive and to resolve any complicated logistics.

Initiative groups may help and support in organising a donor drive, working together with a trained donor recruiter from your organisation. They also can help secure volunteers for the day of the drive, who may assist donors in completing the consent forms and they may help to find phlebotomists for taking blood samples, if required.

If you are taking blood samples, you should check first whether regulations allow nurses to assist, or if you need doctors for supervision. The number of volunteers required at an event may vary, depending on the duration of the drive and the estimated number of new potential adult volunteer donors expected to attend. You should calculate the time involved in completing the consent form, sample collection and a brief counselling session for each new donor. This estimate will help to determine
the number of volunteers needed to register the estimated number of new potential adult volunteer donors within the time available.

Turning donors away because your recruitment sites are too busy, because you have run out of sample kits, or due to poor organisation will damage your chances of running successful drives in the future. Long queues at registration sites may also cause registrants to leave without completing the registration process.

If your target population features healthy, young and highly-motivated donors, a permanent booth at the Armed Forces enlistment stations can be an excellent recruitment channel. Also members of immigrant communities can often be encouraged to register and can contribute to the ethnic diversity of the donor pool in your country.

Public drives

In some countries the best method of donor recruitment is to organise a public drive. A patient-related drive can be the most successful way to engage people with the idea of registering as donors. When organising a patient-related public drive, it is vital to make clear that this particular patient represents all patients who are searching for their matching donor. It also has to be pointed out that there is only a small chance of finding the matching donor for this particular patient at this particular drive. However, patients and their relatives who are willing to publish their story and support a specific drive or a campaign often feel hope and encouragement, especially when they can see a positive response and outcome from an event.

Before publishing a patient’s story you must check the legal regulations in your country and also ensure the patient’s agreement. A short, signed document is often sufficient. You may ask the patient for a picture, perhaps including their family, pets or a local celebrity and ask for details of their personal story, hobbies and any messages they would like to share with the public. If the patient agrees, you could also get in touch with their physician to explain what you are doing and invite them to the drive to get to know your organisation and to see how donors get registered.
Initiative groups

The number of donor drive requests you receive could become problematic if you do not have enough people supporting your work. It is advisable to look for supporters who live near to where a donor drive is due to take place. Often the patient’s family will have friends in the local community who would like to help in any way they can. Plan an initial meeting with this group and develop a plan to guide them and organise everything which will be required up until the day of the event.

If possible, divide tasks so that each person is responsible for one. If the patient is not well or is staying in hospital, a close friend could be the point of contact for you, providing updates. Activities the initiative group may engage in include: media coverage, fundraising, securing a drive location, finding volunteers and organising refreshments for those attending the recruitment drive.

Recruitment sites

Pick your recruitment sites carefully. Keep in mind relevant aspects such as the amount of space that you will need, access for your staff and potential
registrants, security, electricity supply and communications facilities, privacy for counselling potential registrants, ambient noise levels and lighting. Ensure that the recruitment site is easy to find and access, so that everyone who would like to register can easily attend. Most municipalities or shopping centres will not charge for the space that you use, but you may require permits to use some public spaces. If a permit is required, make sure that it is obtained well in advance. You can also choose to hold your drive over one or more sites on the same date, depending on the estimated number of donors you are expecting and to make it easier for people to attend.

It is advisable to consider the number of volunteers, medical practitioners and the amount of coordination work required before holding events at different locations on the same day. Make sure that there is enough furniture and also that there are appropriate facilities to deal with any health emergency which may arise.

**Staffing**

The registry or donor centre should determine the level of training that is required of recruitment event staff and volunteers, if they are being involved. A decision should also be made about the number of people needed to staff each recruitment event site.

Staff should be very familiar with the forms that new potential adult volunteer donors must complete, and should be able to answer any questions regarding this form. The staff should be fluent in the languages spoken by the potential registrants attending the event. It is also very important to ensure that all new potential donors are very well-informed about the registration and donation process and the health criteria. This information can be conveyed either in writing, in a video format or by electronic media. If electronic media are used for this purpose, it is probably also worthwhile to have a printed hand-out for distribution at recruitment site.
Table 2.1 Some key considerations for donor recruitment.

<table>
<thead>
<tr>
<th>Patient</th>
<th>Public relations</th>
<th>Fundraising</th>
<th>Day of Drive</th>
</tr>
</thead>
<tbody>
<tr>
<td>If patient-related drive please make sure</td>
<td>Contact press and media, raise awareness</td>
<td>Initiative groups are very creative! Ask them to...</td>
<td>Together with ‘your’ initiative group Organise...</td>
</tr>
<tr>
<td>Patient agrees to go public (signed consent)</td>
<td></td>
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<tr>
<td>Patient needs a transplant.</td>
<td></td>
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<tr>
<td>Unrelated donor search has been already initiated.</td>
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<tr>
<td>Inform patient’s physician about donor drive and invite him/her to drive</td>
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<tr>
<td></td>
<td>Organise a sponsored walk</td>
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<tr>
<td></td>
<td>Contact companies for financial support</td>
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<td></td>
<td>Organise a concert, a ball, an event in favour of the drive/your registry/donor centre</td>
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<td></td>
<td>Ask donors to donate for their registration</td>
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<tr>
<td></td>
<td>A location (good infrastructure)</td>
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<tr>
<td></td>
<td>Furniture</td>
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<td></td>
<td>Volunteers</td>
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<td></td>
<td>Drinks and food for volunteers</td>
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<td></td>
<td>Information material</td>
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<td></td>
<td>Registration kits</td>
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<tr>
<td></td>
<td>Courier for transport</td>
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</tr>
<tr>
<td></td>
<td>Laboratory for HLA typing</td>
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</tbody>
</table>

Donor registration by mail

There may be some countries where people are not used to driving long distances, or where there is no flexible public transportation system. This can complicate or hinder public drives. The internet offers an opportunity to both inform the community and give them an easy way to register as donors. Check with information technology experts whether a registration form can be installed on your website homepage and determine how to send the required registration materials to the donors who have applied. You can use social media to encourage people to visit your website and also leave their address, in order for you to send necessary material to their homes where they can read the information brochure, fill in the consent form and give a saliva sample or buccal swab. Information has to be provided about where to return the completed sample and consent form.
Donor recruitment drives

Drives can also be carried out privately at a company, university, the Armed Forces and other institutions. These institutions provide a good platform for reaching a manageable group of new potential adult volunteer donors, especially younger donors.

Companies
Companies are interested in engaging with social projects, as a way of demonstrating social responsibility. One very effective approach is to organise a donor drive within the company, reaching many interested employees. The first step to organising a successful donor drive is to raise awareness among company management, the human resources department and employees at all levels regarding the importance of hosting a donor drive. A participation rate of 20% represents a huge success.

In companies with 500 employees or less, close relationships between staff increases the probability of higher participation rates. This is also the case when people in the company know someone personally who is affected by the need for a transplant, or if an employee has already been registered as a potential stem cell donor.

When planning a donor drive, it is absolutely essential to provide employees with detailed information and an explanation of the donation process. The registry or donor centre provides the material, which should be forwarded to the employees before the event. It is advisable for one contact person from the company to be involved in the planning and implementation of the drive. This includes the selection of the location, setting up the room and looking for volunteers. Information sessions, internal email alerts and advertising on the company intranet are also suggested. These tools offer all employees the opportunity to get involved and to ask questions to dispel any doubts.

School or university projects
Drives at universities and schools offer the opportunity to inform, educate and motivate young people to register as potential stem cell donors. These drives can be organised together with students, with the university management and with teachers or directors. These events often take place in context of a health
week or a project week, which gives students the chance to engage with the subject intensively. This might influence the retention rate and commitment of donors. Registries and donor centres have a wide range of opportunities to cooperate with schools and universities. Besides organising a donor drive, you also can hold information sessions, invite a stem cell donor to tell their story, or encourage fundraising through school concerts, events, sponsored walks or cake sales. You may also advertise for a competition between schools or universities, involve the media and look for a local celebrity to support the project.

**Armed Forces**

You could ask the blood donation or health sectors of the Armed Forces if they will cooperate with your registry or donor centre. You may participate in their blood donation days to inform and register new young donors. You should ensure that all registrants are aware of the difference between blood donation and registering as a stem cell donor. Specific information material, lectures beforehand and posters act as tools to achieve this awareness.

**Wrap-up phase and follow-up**

After running a donor drive, many steps will be needed to complete the donor recruitment process. The same applies for donors who have chosen to register via mail.

**Transportation of samples and consent forms**

After the drive is finished, all materials have to be sealed in boxes and brought back to the registry or donor centre office. The most important items are the donor consent forms and blood or saliva samples. They should never be left unattended and their transportation has to be organised in advance of each drive.
Either your staff or a courier service will take care of the transportation and will deliver consent forms and samples to your office, or deliver the samples to the laboratory straight away.

Donors registering by mail should send their registration set back via the postal service or a courier. Depending on the number of newly-registered donors who have applied, you may engage voluntary or paid assistants to key in the data, or find a data entry company who will do this. To archive all consent forms, scan them and import the file into your data management system. Then store the physical forms in a lockable storage room. National data protection directives have to be adhered to, so ensure that your staff and the data entry personnel have already signed a confidentiality clause before handling any data.25

Controlling the import of typing results

The laboratory will take a certain amount of time to type the donor samples, depending on the level of resolution you have asked for. The turn-around time you agreed on should be tracked by you. Donor details and HLA-typing should be checked for completeness. If details are missing, try to add all necessary information by contacting the donor or the laboratory.

Donor listing

If all information criteria are fulfilled, the donor can be registered in the international database and be made available for a patient seeking for an unrelated donor. The listing of donors is performed by registries. You may have to establish a secure way of transferring the donor identification number and the HLA-typing information to another registry.
Donor availability

If a donor is identified as a match for a patient, they should be contacted as soon as possible. Keeping donors’ data up-to-date is one key factor in your registry’s success. Some countries have local registration offices which can help to find the donor if they have moved. Donors can be identified by their social security number or other methods, depending on the country they live in. It also can be helpful to ask the donor when they register to give a preference for the way they would like to be contacted, or to have contact details of a second person, such as a relative.

A donor may be in the registry for many years before they are identified as a potential match. Therefore, regular contact is necessary to keep the donor committed to the idea of donation. Mailings or email communication can also encourage the donor to be an ambassador for your mission and inspire them to encourage other volunteers.

Raising of further funds to cover HLA typing costs

Depending on the costs involved in paying for each HLA-typing result at the laboratory, you may need to seek funds. Keep in contact with volunteer groups, staff from company drives and other supporters, as they may have ideas for further fundraising activities. If they are committed to the work you do, a long-lasting partnership can be developed. Companies, or community organisations such as Rotary or Lions Clubs and the Inner Wheel society are only few examples of groups you can cooperate with to initiate campaigns for raising money.
On-going media work and contacts

Providing results of drives, news about successful transplants received by patients, and donor interviews are all very important media tools to show that donor drives increase the number of life-saving matches facilitated by your registry. Potential donors are interested in reading these stories. More potential donors could be attracted by creating awareness in this way.

You should research whether it is allowed in your country to facilitate meetings between donors and recipients, as these occasions are not only special for those involved but also of great interest to the public and the media. Ensure that all media contacts are saved in your data system, with detailed information such as previous dates of contacts, methods of support and updates. A good media contact may provide you with the opportunity to initiate an awareness campaign including donor recruitment.

Further examples of how to raise awareness among potential donors. Courtesy of Datri Blood Stem Cell Registry, India
3 · Donor search request
Summary

This chapter details issues which a new registry should consider in relation to facilitating search requests which may be received from national transplant centres or other registries. The chapter sets out what you will need to consider in terms of infrastructure, search personnel and outlines the processes and requirements involved in preliminary search requests, donor typing and subsequent donations.

General issues

A new developing registry has to ensure that the facilitation of search requests, first and subsequent donations is performed within the legal requirements of the country where the registry is located. If the donor or the patient is from abroad, then international standards will need to be maintained.

- It is strongly recommended to determine who you will accept search requests from. It might be easier to start with national requests only.
- Guidelines should be set regarding the patient’s diagnosis, constitution, age and minimal HLA-typing of the patient.
- Rules and procedures for the identification of potential matched donors, testing of potential matches and final donor selection should be defined. It is reasonable to set up these rules and guidelines in accordance to the WMDA Standards as a first step to becoming a WMDA accredited registry.
- Computer-based systems are ideal when establishing a registry and are helpful for running an organised operation. More information can be found in chapter 7, 'Information Technology and data management'.

To facilitate search requests, the registry has to have systems for communicating with other organisations which are involved in the transplant process, such as transplant centres and other registries. In addition to traditional communication methods, such as phone, email and fax, it is useful for a registry to utilise the European Marrow Donor Information System (EMDIS).

The first step is to list your donors on the Bone Marrow Donors Worldwide (BMDW) database. For further details see www.bmdw.org. EMDIS connects the
databases of international donor registries, allowing a smooth data flow between all participants. This leads to a faster, more reliable and more transparent donor search process and offers an easy way to present your donors to the international transplant community. For further details, see www.emdis.net.

Covering the financial costs of the search and work-up processes is an important factor which should be considered before any search requests are made or accepted.

**Figure 3.1** Screenshot matching result following a search carried out via BMDW

## Infrastructure

To run a registry, it is necessary to build up a network of internal and external service providers. These may include, but are not limited to donor centres, recruitment groups, search units, transplant centres, laboratories performing HLA-typing and infectious disease marker testing, international registries and medical associations involved in the fields of haematology and transplantation, as well as travel agents, airlines and shipping companies for sending donor samples to domestic and overseas transplant centres. Business relations with the network partners should be outlined in contracts or agreements.
The infrastructure and cultural differences in different regions have to be considered, as well as legal requirements and country-specific terms and conditions. For example, you may want to consider whether an efficient mail system exists in the country. Is it allowed to export and import blood samples? Are permissions needed to import and export blood samples or DNA of donors and recipients? What is the best way to send blood samples or DNA nationally and internationally? Is collection of bone marrow or peripheral blood stem cells from an unrelated donor allowed in the country? What are the requirements for importing and exporting bone marrow and peripheral blood stem cells?

Organising personnel

It is recommended that the registry has a medical director, an HLA-expert and a specialist in search strategies. These roles can all be fulfilled by one person but preferably if they are carried out by more than one individual.

It is also recommended that a registry has staff who are well-qualified to deal with search requests. It is also recommended that a registry should have different but equally well-educated staff to manage the donors during the search and work-up process. It is advisable to have an IT specialist on the registry’s staff, in order to operate your registry using a computer-based model.

Preliminary search request and formal search process

Providing donors and requesting donors for a patient requiring a transplant are processes which can be carried out by one institution. But a registry fulfilling both functions must take care to adhere to the different responsibilities involved with each role. It must also be kept in mind that the search for an unrelated donor is an anonymous process, as is the donation itself. Therefore, the donor and patient have to remain anonymous to each other.
The following points should be considered:

- The search must be submitted by the patient’s physician or an authorised representative of a transplant centre. Search requests submitted directly by patients or patients’ families cannot be accepted.
- Searches can be submitted as a preliminary search request to check whether transplantation of allogeneic haematopoietic stem cells is appropriate as a therapeutic option for the patient. Registries should offer this preliminary search for free.
- WMDA offers forms for all steps of the search process.²⁸

If your registry is acting as a donor centre, you will need to provide information on potential matching donors from your database, following a search request.

If your registry is acting as a search unit, attention should be paid to the following points:

- When you receive a search request, the first step should be to search your national donor database for a suitable match.
- If there are no matching donors in your country, then a search should be made on BMDW. For more details on BMDW, refer to Chapter 7, ‘Information Technology’.
- If you identify a match on BMDW, send out preliminary search requests to every registry who listed a matching donor in order to get a search report with

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**Figure 3.2** Flow diagram showing the steps involved in the search process.
donor identification numbers and additional donor details. Establishing an EMDIS connection will reduce the manual effort involved in requesting search lists from registries.

- After reviewing the search results, create a list of all potential donors and provide this list to the patient’s physicians for further consideration.
- If the number of potential donors is limited, due to the patient having an unusual HLA-type, a HLA expert can be asked for their assistance and recommendations.26
- Additional HLA-typing of donors may be the necessary next step in identifying a match.
- See also the publication for suggested procedures for international donor searches.27

Additional typing or verification (confirmatory) typing should only be initiated if the patient is approved for transplant with an unrelated donor.

The following points should be adhered to:
- The transplant physician will review the search results to determine what kind of additional testing will be requested and of which potential donors.
- A search shall be considered formal or active when a transplant physician submits a request to the registry for any additional testing of reported potential matches.

Request for further DNA based donor typing

If donors are not typed on all loci or are not typed in high resolution, further donor typing of the missing loci or to a higher resolution may be requested.
- The number of donors requested simultaneously for further typing will be determined by the transplant physician, based on the number of potential matches available. This may be limited by funding. Further DNA typing can be requested for several loci or a single locus. All DNA-based typing should be done in an EFI or ASHI or equivalent accredited laboratory determined by the registry or donor centre.
- The goal should be to find the best matching donor and consider another well-matched donor for back-up.
Example request forms are available on the ‘forms’ page of the WMDA website, www.worldmarrow.org.\textsuperscript{28}

If the registry operates as a donor centre it is recommended that DNA from the donor’s initial typing is stored in the laboratory. These DNA samples can be used for further testing to avoid multiple blood collections. However, donors should be contacted again to ensure their availability and to make them aware of the additional typing being carried out. It should be explained that this increases the likelihood of them being requested for further testing and donation.

- The health status of the donor should be checked at this time using a health history questionnaire.
- Further typing should not be performed if the donor is not going to be available for a donation. If the donor is not available, the status of this donor should be reported to the transplant centre immediately.
- The registry or donor centre handling requests should make every effort to process them in a timely manner.\textsuperscript{24}

Verification typing

Samples for verification typing (also known as confirmatory typing or CT) may be requested from a donor who has been identified as a potential match for a patient. Blood samples from donors with known mismatches may only be requested if all participants of the search and work-up process are aware of them and agree to proceed with a mismatched donor for transplantation.

The following points should be observed:

- The verification typing should be performed in a laboratory selected by the transplant centre.
- To request blood sample shipment, WMDA form 540 DRWG Blood Sample Request for Verification Typing may be used.\textsuperscript{28}

On receiving a blood sample request, attention should be paid to the following:

- Fresh blood samples must be used for verification typing. This means arrangements must be made for drawing and shipping the blood samples. The expected delivery date should be announced to the requesting registry.
- In addition to the verification typing, the registry or respective donor centre should perform infectious disease marker (IDM) testing, in accordance with
the WMDA Standards (3.243) relating to donor characterisation, and report the results to the requesting registry.

- If a registry does not provide IDMs and blood group testing, the requesting transplant centre must be informed immediately, so they may perform the IDMs and blood group testing in their own laboratory from the requested samples.

- An information session should be performed with each donor before the blood samples are drawn. This session should give the donor the opportunity to ask questions. The registry should determine upfront if the information session provided for the donor at verification typing and donation stages can be performed over the phone or if it needs to be held face to face. This may depend on the legal requirements of the country. The information session should include information for the donor about the likelihood of being a match for the patient. The peripheral blood stem cell (PBSC) and bone marrow donation processes should be explained in full, including the risks of donation, the required time commitment of the donor, possible reimbursement of the donor’s expenses and a reminder that donation is an altruistic process and, therefore, the donor will not be paid for it.

- A health history screening, using a health history questionnaire, must be done on each donor who is providing a sample for verification typing.

- Relevant health information which could influence the donor selection should be reported to the requesting registry or transplant centres.

- The completed health history questionnaire should be available before blood collection is carried out and should be reviewed by a trained person with a medical background.

- The registry or transplant centre which made the request should be told immediately if donors are found to be temporarily unavailable, deferred due to medical reasons, not responding to contact or no longer interested in donating.

- Donors who are temporarily unavailable should be blocked for the entire time that they are not available.

- Donors who are not able to, or who are unwilling to, donate should be removed from the registry in which they are listed immediately.

- Any additional information provided by the donor at verification typing stage which may influence the transplant centre’s decision should be forwarded to the transplant centre or registry which made the request.
Information may include:
- Preference of donation method (PBSC or bone marrow).
- Restriction to donate only one product for medical or personal reasons.
- Restrictions on availability.
- Evidence of communicable diseases or autoimmune disorders and any other notable pre-existing conditions.

The registry or donor centre should make every effort to process requests in a timely manner.\textsuperscript{[24]} In the event that the sample cannot be shipped within the recommended time frame, the receiving transplant centre should be informed about the reason for the delay.

The transplant centre or registry due to receive the sample may cancel the request, before a sample is drawn, if the blood samples are not expected to arrive within a certain time frame. After receiving the donor’s blood samples, the transplant centre’s HLA-typing laboratory will perform the testing.

Once this has been done, the transplant physician or an HLA expert should review the results. The result of the verification typing performed by the transplant centre’s HLA laboratory should be reported to the donor centre which provided the sample.

Within 30 days after completion of typing, the transplant centre should indicate whether the donor should be released or continue to be reserved for the patient. The registry must decide whether or not they will add the typing results from the transplant centre’s tests to the donor’s records on their own database.

Any discrepancies between HLA-typing results must be resolved by the registry or donor centre. If a discrepancy cannot be determined to be due to a clerical or technical error, a sample should be sent to a third party reference laboratory.

**First donation request: work-up request**

When a donor is identified as the best match for a patient, the transplant centre may request this donor for donation. This request should be made in writing...
and should include the HLA-typing of the patient and donor and a prescription of the desired product. It should be signed by an authorised person.

It should be noted that single donation may involve more than one procedure. For example, a peripheral blood stem cell apheresis may fail and the donor could be asked to undergo a second session.

If a donor’s stem cells fail to mobilise into the peripheral blood and insufficient cells are collected after two PBSC apheresis collections a bone marrow collection may be necessary. Whether the number of cells collected is sufficient is determined by a process called \( \text{CD}34^+ \) analysis. If the result is less than \( 2 \times 10^6 \) \( \text{CD}34^+ \) cells per kg of the patient’s body weight, then the number of cells is deemed insufficient.

A bone marrow collection following a failed PBSC apheresis must only occur after \( \text{CD}34^+ \) analysis at the transplant centre indicates that the bone marrow collection is needed and after a review of the donor’s fitness to donate. For further details see Chapter 4.

**Subsequent donation requests**

Sometimes a transplant centre will make a second request for a donation of haematopoietic progenitor cells (either from peripheral blood or bone marrow), therapeutic cells and whole blood for a patient who has previously received HPC from the same donor.\textsuperscript{29}

Again it should be noted that a single donation may involve more than one procedure as explained in the previous section ‘First donation request: Work-up request’ of this chapter.

**Request and approval procedure for subsequent donations**

Registries must have a policy setting out the acceptable frequency, number and method of subsequent donation requests made of its donors.
The following points should be considered:

- Requests for a subsequent donation should be received from the requesting centre on request forms which clearly describe the previous transplant history, patient’s clinical condition and clinical justification for the request.
- This documentation should also be accompanied by a formal work-up request and should clearly state the product required and the requested collection date. Examples and templates for these request forms can be found on the ‘forms’ section of the WMDA website, www.worldmarrow.org.28
- All requests for a second or subsequent donation should be examined by a subsequent donation committee. This committee should be comprised of a group of physicians with the medical knowledge and ethical oversight to decide whether or not the request is reasonable, ethical and feasible for the requested donor.
- On receipt of the request from the transplant centre, the national registry, with support from the donor and collection centres, must circulate the details by fax or email to the members of the subsequent donation committee.
- Approval by the subsequent donation committee is required before the donor can be approached about a subsequent donation.
- Decisions should be made on such requests within two working days of the request, if possible.
If the request is approved, the registry or the donor centre is responsible for approaching the donor to ask them to undergo a subsequent donation procedure.

In addition to the above guidelines, the following should be considered when dealing with subsequent donations:

- A clear division between donor and transplant centres must be maintained, especially if the donor and patient are living in the same geographic area.
- All requests for subsequent donations must be made through the donor’s national registry.
- The possibility of a subsequent donation must have been discussed at the original donor work-up stage.
- A full disclosure of the procedure and risks must be made, as with any donation.
- The donor must be given ample time to make their decision and be given the opportunity to ask questions, to which all answers must be freely given.
- No pressure must be placed on the donor to agree to subsequent donations. The donor must feel free to decline.
- The physician responsible for the collection must be satisfied that the donor has a good understanding of the procedure and the risks involved.
- The number of donations made by a donor should be limited to two of either bone marrow or peripheral blood stem cell apheresis, or a combination of both.

**Suggested time intervals between first and second donation**

The suggested minimum time intervals between the first and second donation represent the time between product collection dates, not between product request dates. Each registry should establish time intervals that they feel are reasonable and appropriate for their donors. The suggested minimum time intervals between first and second donation should always be 4 weeks, with the exception of whole blood donation as second donation after PBSC apheresis (HPCA), which may follow after two weeks.

**Suggested time intervals between second and third donation**

The suggested minimum time intervals between second and third product collection dates are given in Table 3.1, below.
Table 3.1 The suggested minimum time intervals between second and third product collection dates

<table>
<thead>
<tr>
<th></th>
<th>Second donation</th>
<th>Third donation</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Bone Marrow (HPC M)</td>
<td>PBSC apheresis (HPC A)</td>
</tr>
<tr>
<td>Second donation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bone Marrow (HPC M)</td>
<td>Not allowed</td>
<td>Not allowed</td>
</tr>
<tr>
<td>PBSC apheresis (HPC A)</td>
<td>Not allowed</td>
<td>Not allowed</td>
</tr>
<tr>
<td>TC Apheresis</td>
<td>4 weeks</td>
<td>4 weeks</td>
</tr>
<tr>
<td>Whole Blood</td>
<td>4 weeks</td>
<td>2 weeks</td>
</tr>
</tbody>
</table>

* In general, a second donation of HPC(A) must not be undertaken if the donor was a non-mobiliser at the time of first donation

Subsequent donation - donor laboratory requirements

Prior to the approval of a subsequent donation, there are requirements relating to the requested product which must be met by the donor medical assessment. If the donor’s medical shows that the donor will not meet these requirements, the subsequent donation cannot proceed. These requirements are described in Table 3.2.

Table 3.2 Donor laboratory requirements prior to second or third donation.

<table>
<thead>
<tr>
<th>Donation type</th>
<th>Bone Marrow (HPC M)</th>
<th>PBSC apheresis (HPC A)</th>
<th>TC Apheresis</th>
<th>Whole Blood</th>
</tr>
</thead>
<tbody>
<tr>
<td>Laboratory test value</td>
<td>Normal</td>
<td>Normal</td>
<td>Normal</td>
<td>N/A</td>
</tr>
<tr>
<td>White blood cell count</td>
<td>&gt;1×10^9/L</td>
<td>&gt;1×10^9/L</td>
<td>&gt;1×10^9/L</td>
<td>&gt;1×10^9/L</td>
</tr>
<tr>
<td>Absolute lymphocyte count</td>
<td>&gt;1×100 g/L</td>
<td>&gt;1×100 g/L</td>
<td>&gt;1×100 g/L</td>
<td>&gt;1×120 g/L</td>
</tr>
<tr>
<td>Haemoglobin level</td>
<td>Normal</td>
<td>Normal</td>
<td>Normal</td>
<td>N/A</td>
</tr>
<tr>
<td>Platelet count</td>
<td>Normal</td>
<td>Normal</td>
<td>Normal</td>
<td>N/A</td>
</tr>
</tbody>
</table>
4 · Collection and transportation
Summary

This part of the handbook describes the procedures which should be followed during donor work-up prior to the donation of haematopoietic progenitor cells (HPC), via either peripheral blood stem cell apheresis or bone marrow collection, to be received by patients requiring a transplant. A registry should consider insuring donors with compulsory accident insurance, including disability and life assurance. Please see Chapter 1 for more information on insurance.

Donor work-up

Work-up occurs when a search has identified a donor, or donors, as a potentially suitable match for a patient.

Description of work-up procedure

A work-up is the process a selected donor goes through to make sure that they are medically fit and suitable to donate. The work-up should include:

- A counselling session.
- A physical examination.
- The collection of blood samples for testing and screening.
- The marrow or peripheral blood stem cell collection itself (including GCSF-administration).

The counselling session and coordination of the work-up can be provided either by the registry or donor centre. A work-up coordinator, or their authorised representative, must be trained in the complete process. However, the collection centre or the third party haematologist involved are ultimately responsible for providing comprehensive information to the donor, disclosing any risks to the donor and for conducting the physical assessment.
Forms

To request work-up of a donor, the following forms, or their international equivalent, must be completed by the HLA-typing laboratory associated with the transplant centre. Examples can be found at www.worldmarrow.org.28

- Final patient HLA-typing verification (confirmation) of donor typing.
- Prescription for haematopoietic progenitor cell (HPC) collection. This form must be completed by the patient’s physician at the transplant centre.
- Formal request and prescription forms for haematopoietic progenitor cell (HPC) collection.
- After completion, the documentation should be forwarded by the transplant centre to the local registry for action, or be sent on to the international registry providing the selected donor.

Responsibility of the registry in the donor’s country

In this section we will refer to the responsibilities of the donor centre (DC), apheresis centre (AC) and bone marrow collection centre (BM).

Confirm acceptable donor selection criteria

The registry is responsible for ensuring that the criteria to allow the donor to undergo a collection process have been met. The registry must:

- Confirm HLA-verification (confirmatory) typing has been carried out, in accordance with relevant national and World Marrow Donor Association (WMDA) Standards.3
- Confirm the transplant centre’s product preference is consistent with registry policy.
- Confirm whether research protocol and consent forms have been completed and are appropriate.
- Evaluate any cryo-preservation request and obtain donor consent for this process.
- Evaluate whether any subsequent donation requests meet the relevant national and WMDA standards.
Review documentation for completeness and accuracy

The following documentation needs to be reviewed by the registry to ensure it has been completed and is accurate:

- Formal request for human stem cell collection.
- Review for completeness and accuracy, requested dates and billing information.
- Prescription for human bone marrow collection.
- Review for completeness and accuracy.
- Prescription for stimulated peripheral blood stem cell collection.
- Review for completeness and accuracy.
- Formal request for human peripheral blood lymphocyte collection.
- Review for completeness and accuracy.
- Determine whether this request meets the relevant registry standards.
- Determine that there are no contra-indications for this request.
- Prescription for human peripheral blood lymphocyte collection.
- Review for completeness and accuracy.
- Final compatibility test results.
- Review for completeness and accuracy.
- Confirm all required typing has been performed for specified antigens and at proper resolution.
- Previous transplant history and formal request for subsequent stem cell collection.
- If applicable, review for completeness and accuracy.

Interface between the national registry in the donor’s country and the apheresis or collection centre

The registry should ensure that the following information is provided during work-up:

- Standard documentation forms.
- Formal request for work-up provided by the transplant centre.
- Prescription forms and indication of product choices (peripheral blood stem cells, bone marrow or donor lymphocytes) provided by the transplant centre.
- Verification of prescription forms.
- Declaration of Urgent Medical Need (DUMN) forms must be provided or signed by transplant centre if donor meets certain exclusion criteria according to national regulations.
Donor clearance forms to be sent to transplant centre by the clearance deadline.
• Courier information and customs forms.

Practical arrangements which should be made between the registry in the donor’s country and the apheresis or collection centre include:
• Travel, hospitality and appointment arrangements.
• Reimbursement for donors, collection centre and donor centre.
• Coordination of donor communication between donor centre, collection centre or apheresis centre after the donor’s medical examination and until collection takes place.

Donor information and counselling

The registry or donor centre must confirm:
• The donor’s willingness to donate.
• Agreement on dates for the donor to receive an information session and a medical examination.
• Arrangements for product collection.

The registry or donor centre must contact the donor as soon as possible after receiving a request from a transplant centre for a donor work-up. Any difficulties in contacting the donor or other problems with the request must be communicated to the registry and the transplant centre as soon as possible.

Once a donor has provisionally agreed to donate, a work-up schedule or collection plan should be sent to the transplant centre. This document should include, but is not limited to, the following pieces of information:
• Scheduled date for physical examination.
• Expected donor clearance date.
• Confirmation of any requests for pre-collection samples.
• Start date for donor conditioning with GCSF.
• Confirmed apheresis or bone marrow collection date.

It is also helpful to provide the collection centre location to the transplant centre at this time, along with any courier instructions to allow the transplant centre to begin organising any necessary flights and accommodation.
Donors must be informed about what will be involved in the collection process, whether that is apheresis or bone marrow. They should also be counselled about what is involved in the administration of GCSF, which may be given to stimulate stem cell production and mobilisation. Due to the technically detailed nature of this information, it must be accompanied by careful explanation by the donor centre coordinator or their authorised representative, the collection centre staff or the third party physician involved.

Donors should be given the opportunity to have an advocate or third party present at the pre-collection physical examination and information session and also to accompany them on the day of collection.

Donor physical examination before haematopoietic progenitor cell donation

Prior to donation, the donor should be provided with a health questionnaire. This must be signed by the donor in the presence of the collection centre representative or third party physician or their authorised representative and then reviewed and signed off by the authorised representative of the transplant centre. The donor’s peripheral veins must be assessed. The possibility of inadequate venous access on the day of collection, despite the donor being cleared for apheresis donation, must also be discussed with the donor. The registry should have a policy in place for the use of central lines; in case the peripheral vein assessment determines that it is necessary to use a central venous catheter, sometimes known as a central line.

The work-up and physical assessment of the donor should include:

- Full infectious disease marker (IDM) testing, as requested by the transplant centre, which must be performed within 30 days of the transplant date.
- The IDM test results, blood type and supplementary donor information must be documented and signed off by the collection centre or third party physician once the laboratory results and the health questionnaire have been reviewed. The final signed documents should be sent to the transplant centre for review.
The results of IDM testing performed at work-up stage should be reported no later than five working days after testing.

Positive results for any of these infectious disease markers may not necessarily exclude a donor from donating. However, the transplant centre, donor centre medical manager, search coordinator, third party haematologist and the patient’s national registry must be made aware of any positive results so that a decision can be made as to whether to proceed with the transplant.

It is advisable to use a unique form for reporting any abnormal donor results discovered during workup.

A collection centre or third party physician must perform a physical examination on the donor.

A medical assessment form should be completed at this time. The results of the examination must also be reported on a formal donor clearance form, clearly indicating whether or not the donor is in good health, fit to donate and signed off by the third party haematologist.

When assessing for apheresis:

- Particular care should be taken over the peripheral venous assessment as central venous access is generally discouraged.
- The person who is due to undertake the collection procedure should ideally perform the assessment at the time of work-up.
- Failure to obtain good venous access may result in a need to abort the procedure and change the selected product to bone marrow collection, subject to donor counselling, medical and anaesthetic assessment and agreement by all parties.
- If the donor is in doubt about the procedure or unsuitable for an apheresis donation, they should be informed that bone marrow collection may be requested.
- If the donor chooses not to donate via apheresis but prefers to donate bone marrow, the transplant centre must be informed.
After the donor has received full information and the physical examination has been completed, the donor should be asked to sign the consent form if they agree to the donation.

If pre-collection samples have been requested, they can be drawn at the time of work-up. Each registry should determine what volume of blood samples they will allow at this stage and clearly communicate this limit to the transplant centre.

**Postponement**

In the event of postponement, all involved parties must be informed immediately. The registry should have guidelines in place detailing which parts of the work-up and medical examination should be repeated, bearing in mind the applicable laws of their country and the applicable laws of the country of the recipient. Infectious disease marker testing must always be performed and reported back to the transplant centre within 30 days of the scheduled transplant date.

**Suggested time frames for interval assessment**

- Between eight and 12 weeks: a telephone follow-up with the donor is suggested.
- Between 12 weeks and six months: a telephone follow-up or in-person interview is suggested.
- Longer than six months: A complete physical assessment must be repeated. This must be recorded on a formal donor clearance form.
- A pregnancy assessment must be performed on all women of child-bearing age. Assessment can mean a serological assay or an ‘over the counter’ test.
- Depending on the timing of the work-up and patient conditioning, and the administration of GCSF, the pregnancy assessment may take place on one or two occasions.
- Chest X-rays for female donors, who are thought to be pregnant, must be avoided.
- The pregnancy assessment should be performed at work-up, within 30 days of the transplant date.

Postponement may lead to extra work.
If bone marrow collection is being considered:
• The donor must be asked if there is a likelihood of pregnancy.
• If there is any possibility of pregnancy, the woman must be offered a pregnancy test using a serological assay.
• If they decline to have the test, this must be documented by the donor centre coordinator or authorised representative or the third party haematologist and signed by the donor on the medical assessment form.
• Assessment should also be repeated within the week prior to commencement of the patient’s conditioning regime.

If apheresis is being considered:
• Pregnancy assessment should be repeated within the week prior to commencement of GCSF injections.

Donor centre responsibilities

Some of the following requirements may be carried out either by the donor centre or by the registry, depending on national guidelines.

Donor consent

The registry or donor centre must confirm:
• The donor’s willingness to donate.
• Agreement on dates for the donor to receive an information session and a medical examination.
• Arrangements for product collection.

Information session

The registry or donor centre must contact the donor as soon as possible after receipt of the request for work-up. Any difficulties must be communicated to the registry and the transplant centre as soon as possible. Donors should be given the opportunity to have an advocate or third person present at the information session.
A trained donor centre representative, or a case manager, should counsel the selected donors about the donation process and have them sign the informed consent paperwork. The delivery of the information session and the content included must meet WMDA standards and national laws and regulations.31

When talking to the selected donors, counsellors should give them a comfortable environment and adequate time. Prior to making the final decision, a selected donor may ask a friend or relative to accompany them to the session or on the day of collection. Donors should be encouraged to ask questions.

The information session must cover:

- Confidentiality and anonymity for donor and patient.
- Patient’s need for transplant and chance of success.
- Requirements of further blood samples for:
  - Infectious disease marker testing.
  - Blood chemistry.
  - Research purposes.
- Explanation of the physical examination.
- Alternative collection methods.
- Collection procedures and associated risks.
- Whether the donation involves a clinical trial for the patient.
- Autologous unit (if required).
- Time commitment required from the donor.
- Right to withdraw and consequences of withdrawal, after patient conditioning has begun.
- Possibility of request for second donation or blood products.
- Provision for expenses.
- Insurance cover.
- Location of collection centre.
- Signed informed consent to donate.
- Signed informed consent to provide blood samples for research purposes.
- Signed informed consent for product cryo-preservation, if permitted by the registry.
Confidentiality and anonymity for donor and patient
For the respect of donor privacy, neither the recipient or their family, nor the transplant centre, may make direct contact with the donor or their family. All contact must be coordinated by the donor centre or registry. The identities of both the donor and the patient must remain confidential during the work-up and collection processes and only appropriate personnel must have access to this information. Under no circumstances shall personal information of either the donor or the recipient be disclosed.

Patient’s need for transplant and chance of success
The donor should be told that their HLA-typing and that of the patient have been found to match. Information should be given about the probability of the transplant being successful and what this will mean in terms of a cure for the patient.

Requirements of further blood samples
When considering infectious disease markers testing WMDA Standards,3 state that markers to test include, at a minimum: human immunodeficiency virus (HIV), Human T-cell lymphotropic virus I and II, Hepatitis B virus, Hepatitis C virus, cytomegalovirus (CMV), Treponema pallidum (Syphilis) and other infectious agents as defined by national health authorities. The selected donors should receive biochemical and serological examination blood tests. Some centres may include urine examination and stool tests.

Physical examination
At this stage, the donor should be informed about the purpose of the work-up procedure. Donors can receive copies of their physical examination results. Donor should be told that they may be required to undergo further consultations or subsequent tests if physical examination results show any abnormal issues. The collection centre which performed the donor physical examination may report to the local authority if any positive indication is shown of infectious diseases specified by relevant government laws and regulations, such as AIDS.

Alternative collection methods
Explanations should be given to the donor about the collection process of bone marrow and peripheral blood stem cells (PBSC), including the advantages and
disadvantages of each method. Staff must obtain informed consent for the collection. Additional consent forms may also be required in the situations below:

- Bone marrow donation: Autologous Blood Donation Informed Consent – if requested by the donor’s haematologist
- PBSC donation: Donor Central Venous Catheter Insertion Informed Consent – if the use of central lines is permitted by the registry.
- Bone marrow collection consent form – if the donor’s stem cells fail to mobilise for a PBSC collection.

**Procedures and risks of collection**

The donor should receive information about the process of donation, the recovery time and the short-term effects, including that a small number of cases will need a longer than usual recovery time. The risks of collection include: anaesthesia, blood transfusion, infection and damage to the bone, nerves and tissue at the site of injection.

**If the donation involves a clinical trial for the patient**

The donor should be informed if the donation is part of a clinical trial being performed for a patient. Explain the objectives and potential scope of research prior to collecting any samples from donors and obtain signed authorisation from them.19

**Autologous unit (if required)**

Autologous donor blood may need to be collected before performing a bone marrow collection. The autologous donor blood must be collected at a blood collection centre that fulfils national, regional and international criteria. The number of blood units required is dictated by the difference in bodyweight between donor and recipient and must meet the national laws and regulations. The time intervals between autologous blood drawing and bone marrow collection must comply with the national laws and regulations.

**Time commitment**

Donors must be informed of the time commitment required for the information session, medical examination, collection and the recovery time involved post-donation. If the proposed collection date does not suit the donor, the registry will need to negotiate a date suitable to both the transplant centre and...
The donor. Inform the donor that the schedule of donation may change due to the health conditions of the recipient and remind the donor to notify the donor centre or registry if there is any change in their contact information and any unexpected time conflict which arises.

**Right to withdraw and consequences after patient conditioning begins**
The donor should be told that they have the right to withdraw from the donation at this stage. But the donor also needs to comprehend that the recipient’s life is at risk if the transplant is not performed once the patient has begun their conditioning treatment.

**Possibility of request for second donation or blood products**
Based on the condition of recipient after the transplant treatment, the transplant centre may ask the donor to give subsequent donations. Therefore, work-up staff should enquire about the donor’s willingness to give a subsequent donation. When making the inquiry, staff should emphasise that only the medical director of the registry and the donor centre can contact the donor to make such a request. Donors have the right to decline at the time that a second donation is requested.

**Provision for expenses**
The registry must assume responsibility for all donor expenses related to work-up, collection and follow-up testing. Donors will not receive monetary rewards for the donation.

**Insurance coverage**
The registry should offer disability and death benefits to all volunteer donors. Donors should verify that the coverage of such insurance will not harm the existing rights and benefits of their existing insurance policies.

**Location of collection centre**
Donors must be informed of the physical address of the collection centre and times of all appointments.

**Signed informed consent to donate**
Fully-informed and legally-valid written consent must be obtained at the time of work-up. The consent documents must include information on the collection,
confidentiality, receipt of medical information and the right to withdraw. The consent form must include the signature of a medical specialist or health professional involved in donor counselling.

**Signed informed consent to provide blood samples for research purposes**
Prior to collecting blood samples for storage or for the purpose of an ethically-approved research project, staff should explain to donors the objectives and scope of research and must obtain signed consent.

**Signed informed consent for cryo-preservation**
If cryo-preservation is permitted by the registry, signed informed consent must be obtained from the donor beforehand.

**Coordination of donor communication**

This should take into account the following:

- Date and place of information session.
- Date and place of medical assessment.
- Donor medical clearance – counselling in case of positive identification of health risk.
- Date and place of collection.
- Transport and accommodation.
- Reimbursement of expenses.

**Date and place of information session**
Donor centre staff should set the schedule with the donor and reserve a place for the information session. A comfortable environment and adequate time allotted for communication will help the donor to feel relaxed. The donor must be told they may have someone accompany them to the session.

**Date and place of medical assessment**
The donor centre should set the schedule with the donor and make arrangements for the medical assessment. The directions to the medical centre should be clearly detailed to the donor and transportation for the donor may need to be arranged.
The donor should be informed in writing of:
- Date and of medical assessment.
- The period of fasting required (known as limosis duration) before blood draw.
- Time for the donor’s arrival at the medical centre.
- Transport reservation details.
- Address and contact information of the medical centre.
- Duration of medical assessment.
- Emergency contact details for medical centre and donor centre.

**Donor medical clearance and counselling**

When donor health problems are found, the donor should be informed. If there is doubt about the eligibility for donation, consultation or re-examination by the relevant specialists should be arranged. Infectious disease markers must be tested within 30 days of the collection date. All expenses of the donor medical assessment, as well as extended medical examinations related to the donation, will be covered by donor centre, unless medical examinations are requested which are not related to donation.

**Date and place of collection**

The date of collection must be set and confirmed with sufficient notice. The directions to the collection centre should be clearly detailed to the donor. The schedule for donor autologous blood collection and GCSF administration need to be planned and communicated clearly to the donor and any other organisations which are involved. The donor should be informed in writing of date of collection.

Information should include:
- Time for arriving at the collection centre.
- Transportation and accommodation reservation details.
- Average duration of collection.
- Address and contact information of the collection centre.
- Emergency contact details for the collection centre and donor centre.
Using a bone marrow aspiration needle, the bone marrow is punctured parallel on both sides of the posterior iliac crest and the bone marrow (mixed with blood stem cells) is repeatedly extracted. The procedure is done several times from both sides of the iliac crest until the required amount of cell material is obtained. During the whole process the donor is under general anaesthesia. (Courtesy of Cellex, Germany)
Transport and accommodation

The donor centre or registry should arrange the transportation and accommodation for the donor and their companion, with sufficient notice. Providing reservation details with clear explanations will put the donor and the companion at ease. Transportation and accommodation details and emergency contacts should also be sent to the medical organisations involved and the collection centre if necessary.

Reimbursement of expenses

It should be made clear to the donor that they will not receive financial compensation for the donation itself, nor will they receive a monetary reward. However, they should be informed that they will not need to pay for any part of the process and that the registry is responsible for all reasonable expenses incurred by the donor.\(^{32}\)

Collection centre responsibilities

Collection centres must be appropriately licensed, registered and accredited to adhere to laws and regulations in their country. National laws and regulations may require registration or certification with the government or accreditation from professional organisations for the activities performed within the collection facility. The collection centre must ensure the identity, safety and privacy of the donor. International standards and recommendations are outlined in FACT-JACIE International Standards for Cellular Therapy Product Collection, Processing, and Administration, 5\(^{th}\) Edition.\(^{33}\)

Verification of prescription

The collection centre should communicate any concerns regarding the prescription submitted to them, for example, a discrepancy between the amount of cells requested and the donor’s weight.
Ensure confidentiality

The entire staff of the collection centre must ensure patient and donor confidentiality. Any patient identity information provided by the transplant centre or registry must be kept confidential from the donor. Personal information relating to the donor must not be sent to the transplant centre.

Donor medical pre-collection evaluation

The collection centre should arrange for assessment of the donor’s medical suitability to donate. Investigations should include obtaining proof of identity for the donor (such as a national identity card or passport) and other relevant documentation.

Questionnaire and interview

The health questionnaire and interview conducted with the donor should cover:

- Health history.
- Travel history.
- Risk status for infectious diseases.

Full physical examination

This examination should include:

- Abdominal ultrasound.
- Echo-cardiogram (ECG).
- Further investigation according to risk assessment (such as spirometry, ergometry and chest X-ray).
- Anaesthetic risk.
- Vein assessment.

Laboratory tests

Laboratory tests conducted at work-up should include:

- Full blood count
- Blood group, antibody screening, Rh-factor.
- Coagulation screening.
• Biochemical screening: liver enzymes and function, kidney function, electrolytes, blood sugar, basic thyroid function, protein and electrophoresis, iron storage and lactic acid dehydrogenase (LDH).
• Pregnancy test for all female donors.

**Infectious disease markers**

Testing for infectious disease markers should include:
• *Treponema pallidum* (Syphilis).
• Hepatitis B virus (HbsAg and core antigen).
• Hepatitis C virus (NAT and serology).
• HIV (NAT and serology).
• CMV status.
• HTLV I/II serology.
• EBV serology.
• Toxoplasmosis.

Other infectious disease markers which may be screened, according to national law or if indicated because of the donor’s travel history, may include: Varicella zoster virus (VZV), Herpes simplex virus (HSV), Parvovirus-B19, West Nile virus (WNV), Chagas disease and malaria.

Identify any concerns about obtaining requested cell count and alert search centre

The donor clearance report should be forwarded to the search centre within seven days of completion of the work-up procedure. Donor clearance and suitability must include eligibility and safety of donor and patient, like, for example, any information regarding communicable diseases and other risks for the patient.

**Collection or apheresis centre responsibilities**

The responsibilities of the collection or apheresis centre include:
• Arranging appointments.
• Performing collection procedures according to standard operating procedures (SOPs) and national approval guidelines with appropriate anticoagulant.
• All product analyses, which must include cell concentrations and requested progenitor counts, viability and sterility testing as well as infectious disease markers. All analyses must be performed in nationally certified laboratories.
• Preparing product reports, detailing cell count, number of bags and anticoagulant used.
• Labelling the product preferably according to ISBT128 standards.\textsuperscript{34}
• Producing adverse events reports, where required.
• Providing discharge instructions for donors.
• Ensuring appropriate storage of product and cooling elements.
• Storing back-up product samples at 4°C for at least 72 hours and re-evaluating the product in case of queries from the transplant centre.

**Peripheral blood stem cell apheresis**

- **ACDA** (Anticoagulant)
- **Collecting bag**
- **Extract** about 60–100 ml/min
- **Return** whole blood
- **Centrifuge** about 2000 rotations/min
- **Amount collected** about 1 ml/min
- **Total amount** about 200 ml
- **Whole blood**
- **Blood plasma**
- **Red blood cells**
- **White blood cells, stem cells, blood plasma**

(Courtesy of Cellex, Germany)
Transferring responsibilities of the product to the courier

When handing over the product to the courier, the collection centre should:
• Check courier identification and courier information paperwork.
• Ensure the appropriate transport conditions and equipment is provided by courier.
• Ensure the documentation and label includes information on:
  – Identity of the product.
  – Number of cells collected.
  – Donor’s unique identification code.
  – Donor ABO group.
  – Identification of the patient.
  – Date and time of collection.
  – Any processing details.
  – Contact name and contact information of the transplant centre.

Storage and processing of the product

The collection centre should be able to facilitate storage, cryo-preservation and any processing of the product, either if it is requested or in case of emergency.

Courier responsibilities

The courier has sole responsibility for the safe and timely transport of HPC from the collection centre to the transplant centre. Selection and assignment of courier responsibility is a collaborative process between the registry, transplant centre and collection facility. In the courier manual of the WMDA,35 you can read more details about the responsibilities and guidelines for transport of HPC products.
Summary

The donation of haematopoietic progenitor cells (HPC) is an altruistic and generous act, whereby an individual (whether related or unrelated to the patient) undergoes the risk and inconvenience of a medical procedure in order to help save the life of a patient in need. Whereas HPC donation is generally agreed to be very safe, there remains a real and documented profile of adverse reactions, some of which may be serious.

As the number of allogeneic HPC transplantations performed globally each year continues to increase, the need for internationally standardised, continuous and rigorous donor follow-up has become paramount, not only from a legal but also a moral point of view. Data on the incidence of short and long-term donor adverse reactions is crucial to ensure maximum donor safety and availability. It also forms the core of a global surveillance system that may identify rare, but serious, complications associated with HPC donation.

Legislation and guidance

In May 2010, the World Health Organization (WHO) published their Guiding Principles on Human Cell, Tissue and Organ Transplantation (endorsed by the 63rd World Health Assembly). From this, Guiding Principle 10 states: ‘The long-term outcomes of cell, tissue and organ donation and transplantation should be assessed for the living donor as well as the recipient in order to document benefit and harm’.

The WMDA Standards detail the required follow-up of unrelated HPC donors and stipulates both short-term and long-term follow-up. Additionally, donor registries must report serious adverse reactions and serious adverse events to the WMDA through the S(P)EAR committee (see ‘Reporting of serious adverse events and reactions’). The fifth version of FACT-JACIE standards also refers to the WHO principles in section B6 ‘Donor Selection, Evaluation, and Management’. FACT-JACIE standards are drawn up jointly by two organisations: the Foundation for the Accreditation of Cellular Therapy and the Joint Accreditation Committee of the International Society for Cellular Therapy (ISCT) and the European Group for Blood and Marrow Transplantation (EMBT).
Data collection

Introduction

Registries are encouraged to collect data internally on donor complications, both during and following donation, and to ensure that high standards of clinical governance are maintained in everyday practice. This includes regular auditing of donor adverse reactions, including serious adverse reactions, as well as key performance indicators that may have a bearing on donor safety, such as the use of central lines for venous access and the incidence of two-day collections.

In 2012, the Worldwide Network for Blood and Marrow Transplantation (WBMT) published ‘Allogeneic haematopoietic stem cell donation: standardised assessment of donor outcome data. A WBMT consensus document’. The WBMT identified two key components of donor follow-up that needed to be urgently addressed:

- Prospective data collection should include all serious adverse events and serious adverse reactions occurring during the donation procedure from all types of donors in the same way, that is, both for unrelated and related donors.
- Prospective data collection on potential long-term complications should focus on a minimal data set, that is, incidence and type of malignancies and autoimmune disorders only, and include all donors as above.

The paper proposed a ‘minimum-standard’ data set for prospective donor outcome follow-up, collected by international data registries. As well as ensuring that minimum standards of donor follow-up are adhered to, this data set is also intended to provide consistency between the various international follow-up organisations, such as CIBMTR in North America and ProMISe in Europe.

For users of the EBMT ProMISe database, a donor follow-up manual (Donor Outcome Data Manual), including forms, are available from the EBMT website www.ebmt.org. On the WMDA website in the forms section you can find templates for donor follow up forms.
Minimum frequency of donor follow-up

The WBMT consensus document stipulates donor follow-up, as a minimum, at:
• 30 days after collection.
• One year, five years and 10 years (although annual or biannual long-term follow-up is recommended).

If the donor cannot be reached after at least two attempts, they can be considered as ‘lost’ and no further follow-up is required.

Minimum dataset for short-term follow-up (up to 30 days)

The minimum data set to be collected on day 30 is detailed in the WBMT publication. Data collected at the day 30 point includes donor demographic data, details of the HPC source and donation procedure and any serious adverse event (SAE) or serious adverse reaction (SAR) occurring as a complication of the donation procedure. The donation procedure is defined as starting with the first injection of a mobilising agent, the start of anaesthesia or the start of apheresis collection, in case of non-stimulated leukapheresis.

Minimum dataset for long-term follow-up (one, five and 10 years)

The minimum data set for long-term follow up is detailed in the WMBT publication. Essentially this describes donor survival and incidence of autoimmune disease or malignancy. ICD-10 codes should accompany reports of late donor adverse events.

Reporting of serious adverse events and reactions

Numerous clinical procedures rely, for their success, on the application to patients of haematopoietic progenitor cells from unrelated donors. Since the first
successful bone marrow transplant in 1956, thousands of patients with lethal diseases such as severe leukemia, aplastic anemia, and inherited immune deficiencies have been successfully treated with haematopoietic stem cells (HSC) that can reconstitute the marrow of the recipients, restoring a healthy blood system. The World Health Organization has developed a database, the Notify library. The database focuses on the rare occasions when unforeseen complications or errors result in negative outcomes. Although such incidents are unusual, they present opportunities for the field to learn and improve, so that these services can be made safer and more effective for future donors and patients.

The literature review summarises the various reactions that bone marrow donors might experience. Reactions included constitutional symptoms such as nausea, fatigue (most common) and site-related localised pain and injury to bone and soft tissue. The more common reactions in peripheral blood stem cell donors are related to mobilisation agents or to the apheresis procedure (catheter-related pain).

**Definitions (according to WMDA)**

**SAR – Serious Adverse Reaction** An unintended response, including a communicable disease, in the donor or in the recipient associated with the procurement or human application of tissues and cells that is fatal, life-threatening, disabling, incapacitating or which results in, or prolongs, hospitalisation or morbidity.

**SAE – Serious Adverse Event** Any untoward occurrence associated with the procurement, testing, processing, storage and distribution of tissues and cells that might lead to the transmission of a communicable disease, to death or life-threatening, disabling or incapacitating conditions for patients, or which might result in, or prolong, hospitalisation or morbidity.

**SEAR – Serious Events and Adverse Reactions** A centralised international database recording adverse reactions occurring during procurement of HPC that have or may have resulted in harm to an unrelated donor and the outcome of any investigation to determine the cause of the event.
**SPEAR – Serious Product Events and Adverse Reactions** A centralised international database recording adverse reactions that impact the quality of a donated cellular product that have or may have resulted in harm to the recipient and the outcome of any investigation to determine the cause of the event.

**Reporting SAEs and SARs**

Registries must be aware of any national legislation regarding the reporting of SAEs or SARs to competent authorities, as such reporting is often mandatory by law. Additionally, reporting of SAE and SAR is required as part of the WBMT-recommended minimum dataset and any such incidents should also be reported to the relevant donor follow-up registry, such as ProMISe or CIBMTR.

However, the WMDA also runs a global surveillance reporting system, called S(P)EAR. Although reporting to such a system is voluntary, it is expected of all registries seeking WMDA accreditation. SAE and SARs reported to the WMDA are reviewed by the chair of the Clinical Working Group within seven days and the S(P)EAR committee meets quarterly to discuss such events and reactions. A summary of reported S(P)EARs is issued on an annual basis. The S(P)EAR committee has produced a guide to SAE and SAR reporting. Reporting SAEs or SARs may also be done electronically through the WMDA website.

**Extended data set for donor follow-up**

**The need for extended donor follow-up**

Whilst the minimum data set is designed to alert and inform the community regarding serious adverse events and reactions, a more detailed donor follow-up schedule is recommended. This has many purposes. Firstly, periodic donor contact and provision of appropriate support will help ensure a positive donor experience. Secondly, regular data collection that is standardised between donors will allow registries to document the adverse reaction profiles
of their donors and audit key performance indicators from affiliated collection centres. Thirdly, analysis of the data will allow checks to be made regarding the relevance of the donor eligibility criteria.

**Recording adverse reactions**

Ideally, adverse reaction data should be documented prospectively from the start of the donation process, either from the first dose of GCSF or when anaesthesia commences. The EBMT has established a Donor Outcome Committee in 2012. The goal of the committee is to organise educational courses on how donor follow up data can be recorded.

**Frequency of extended donor follow-up**

The same frequency of extended donor follow-up should be applied for the frequency used when gathering information for the minimum data set.

**Donor follow-up process**

The registry is responsible for overseeing donor follow-up, but the task can be delegated to and performed by either the donor centre or the collection centre.

**Donor visit – day of donation**

The registry or donor centre can send a trained volunteer or staff member to visit the donor in person during a peripheral blood stem cell (PBSC) or lymphocyte donation, or following a bone marrow collection. This is an opportunity to assess any adverse reactions associated with the donation process and answer any questions the donor may have. Some registries may provide the donor with a thank-you gesture at this point.

This visit is also an opportunity to explain the post-donation follow-up process which the registry has implemented and to remind the donor of certain registry policies that may be relevant, such as subsequent donation, communication between patient and donor and

Be honest to a donor about the safety and risks of the procedure
updates on patient status. Providing a booklet containing all the information discussed at the visit is recommended. The donor must be also assured that all their data will be treated confidentially. You can read more on systems for handling donor data in Chapter 7 of this handbook.

During this visit, if not already done at medical check-up, the donor should sign an informed consent which allows the registry to forward their data to an international donor follow-up registry, such as SEAR, EBMT, CIBMTR, etc.

**Follow-up phone-call**

The donor should be contacted shortly after donation, usually within two to seven days. This can be done with a telephone call. As well as reiterating the information given during the donor visit, a short interview should be carried out to establish if there have been any new adverse reactions, or if previously reported adverse events have resolved, or if they have persisted. Donors with persistent adverse reactions should be contacted by telephone again a few days
later and weekly follow-up sessions should continue until the adverse reaction has resolved. If necessary, additional medical investigations and management of any serious adverse reactions should be organised, if possible in the collection centre. The investigations should be managed by trained medical staff and reported to the relevant authorities as necessary. As a rule, bone marrow donors have a longer recovery period than PBSC donors and therefore more likely require additional follow-up calls.

**Questionnaire**

At day 30, one year, five years and 10 years, a questionnaire should be sent to the donor by post or by secure electronic media. This can be done annually or every two years. The primary aim of this follow-up is to ensure that any adverse reactions remain fully resolved and that no new adverse reactions have occurred.

The questionnaire at day 30 is also an opportunity to ask the donor about the level of service and care received from the registry, donor centre and/or any other appropriate parties.

**Staffing**

The size of the registry, and the number of HPC collections facilitated by the registry, will determine the staffing levels required for post-donation follow-up and donor welfare. Where larger teams exist, different staff may have varying levels of responsibility and so the level of training and skills required for these roles may also vary. It is essential for any staff member involved in donor follow-up and welfare to have the support of a physician with training in HPC transplantation.

As a guideline, the following criteria are recommended for staff working within the field of donor follow-up and welfare:

- A qualified social worker, medically-trained person or someone with equivalent experience and skills.
- Good counselling and administrative skills.
Training and knowledge in the following areas is considered essential for staff working within this field:

- Different methods of donation.
- Visiting donors at the time of collection.
- Expected adverse reactions associated with donation.
- Rare, but serious, adverse reactions associated with donation.
- Indications for allogeneic transplantation.
- Indications for subsequent donations and rates of subsequent donation requests within the registry.
- Process of referring adverse reactions to trained medical staff, and reporting of SAE and SARs.
- Patient and donor confidentiality and data protection, with particular reference to donor and recipient correspondence and contact.

The following should be considered essential as part of on-going training:

- Annual review of standard operating procedures (SOPs).
- Ad hoc review of SOPs in response to any change of policy by the registry or external regulatory body.
- Regular review of SAE and SARs with medical committee and quality team.

Recommended on-going training:

- Information Technology and administration skills refresher courses, as and when necessary.
- Counselling and communication skills refresher, as and when necessary.
- Attendance at relevant conferences and meetings, such as WMDA or EBMT, within the registry’s country and where budget allows.

**Liabilities and insurance issues**

**Insurance**

It is imperative when starting a new registry that the donor is adequately insured against each adverse event that can occur during and after a donation. Not only do the registry and donor need to be insured, but the place and person performing the procedure must be fully insured against any claim for damages.
due to malpractice or accidents. It is important that all parties involved know the parameters of the insurance, including the time, length and amount.

**Transparency**

It is important to be sensitive to the donor, as he or she is a healthy person engaging in a process which carries potential risks. It is important to be honest about the safety of the procedure, but also to ensure that the donor is aware of the risks involved with the donation process.

**New registries**

Registries should pay particular attention to ensuring that their affiliated collection centres and donor centres have comprehensive professional liability insurance. Insurance companies will require a registry to demonstrate adequate standards, procedures and accreditations for the registry and the organisations affiliated with it.

**Communication between patient and donor**

**Considerations**

Each country or registry will have unique policies and legislation governing anonymity, communication and the exchange of gifts between donors and recipients and, as such, there is no standard practice between registries. The only consistent policy worldwide is that contact between donors and patients is not permitted prior to transplant.

As participating members of the WMDA, registries need to be aware of the policies and laws governing contact between donors and patients in their country. Some countries will never allow any form of communication. It is therefore important to manage the expectations of both parties involved by detailing the correct post-donation communication information in any materials and also to explain the registry’s policy when speaking to the donor.
Protecting the confidentiality of the patient and the donor through all stages of the transplantation process is paramount. The WMDA standard 6.07 states that ‘donor and patient identity must remain confidential during the search process so that only appropriate Registry personnel have access to these data’.

Even post-transplant, this rule will apply until it is time for the necessary steps to be taken to disclose patient and donor information, if this is allowed in the registry’s country. Each registry must have well-defined policies on preserving donor and recipient confidentiality, post-transplant exchange of gifts and letters, and conditions under which donors and recipients might communicate.

The National Marrow Donor Program (NMDP) has created a document which can be shared between registries and provides guidance on how to facilitate anonymous exchanges between donor and recipient.

There are three different options for donor-recipient contact post-transplant. They are detailed in the sections below.

**Direct contact between donor and recipient allowed**

Direct contact between a donor and recipient can occur after a certain time post-transplant. Some countries have a waiting period of one year and others have a period of two years or longer.

In countries where local laws or regulations do not prohibit direct contact, it should only be allowed when both recipient and donor have agreed to such contact via written consent and have been appropriately counselled as to the potential consequences of such contact. A program of donor and recipient advocacy must be in place to monitor and support the donor and recipient during and after direct contact, if needed.

Recipients who appear likely to require subsequent donations from the donor, at the time of deciding whether to allow contact, should not be permitted to contact the donor until the potential need has abated. Proper counselling of the donor and recipient must include education about exchanging information and the potential impact of direct meetings. The policies of the transplant
centre regarding contact must be communicated to the donor centre and vice versa. Consent for the release of personal information should be exchanged between centres before the interested parties are allowed to communicate directly. If language is a barrier, the registry or transplant centre should evaluate how much involvement they would like to have as translators.

**Only anonymous correspondence allowed**

Another approach is to allow anonymous correspondence between donor and recipient, but never allow direct contact.

Anonymous exchange of letters and small gifts (if allowed) must be carefully screened by the registry. It is the registry or transplant centre’s responsibility to:

- Screen all correspondence or gifts that the donor or recipient wishes to give to the other party, prior to allowing the exchange process.
- Delete any reference that might allow the donor or recipient to identify one another, such as location, names, and identifying landmarks.
- Inform the donor or recipient that the regulations of some transplantation centres, and cooperative registries, may never allow donors and recipients to have direct contact, regardless of the registry’s own policy. The registry should train its couriers not to pass on gifts or cards from the collection centre to the transplant centre. These items should be screened by the registry before being passed on.

*Courtesy of Armenian Bone Marrow Donor Registry*
All forms of communication prohibited

The final option for post-transplantation communication is prohibition of all forms of communication between the donor and recipient. In this case, registries should inform the donor that the regulations of some transplant centres, and cooperative registries, may never allow donor and recipient to exchange anonymous correspondence or gifts, or direct communication ever, regardless of the registry’s own policy.

Cord blood donation

The international standards for cord blood banks (Netcord-FACT) require that personal information related to the infant donor and the infant donor’s family shall remain confidential and is only available for review for individuals designated by the cord blood bank. The identity of cord blood donors always remains confidential. Therefore, contact between cord blood donors and cord blood recipients is not permitted at any time.

How to request communication post-donation or post-transplant

Each registry should have a well-defined policy and procedures in place to request and follow-up on donor-recipient communication taking place post-transplantation. According to NetCord-FACT standard E7 accredited cord blood banks are expected to make reasonable attempts to obtain transplant outcome data relating to the safety, purity and potency of the cord blood unit involved.

Consent to release personal information

It is desirable that consent to release personal information, or to begin direct contact, is obtained. This consent should be recorded by the registry. The donor and recipient’s decision to release their information is a personal one. Whereas some donors and recipients will want to release their information, others will make the decision to remain anonymous. It is the responsibility of the registry or donor centre to counsel the donor and explain that there is no guarantee the recipient will wish to be in contact with them and that no assumptions should
be made as to why the exchange of personal information between the donor and recipient cannot take place. Once both parties have signed consent for their information to be shared, the information can be disclosed in order for the donor and recipient to begin direct contact.

**Contact requests when the recipient has died**

In the event that a close family member of the recipient wishes to initiate direct contact with the donor after the recipient has passed away, the registry should review their policies and decide whether to initiate direct contact in a similar way as if the patient were still alive, presuming the donor is willing and local legislation permits direct contact. Consent should be obtained for this specific type of communication.

**Recipient follow-up**

**Aim of the recipient follow-up**

Recipient follow-up should be mandatory and be part of a registry’s quality management system. It applies to every recipient for whom the registry organises a donation. This is stipulated in the WMDA standard 9.063 which states ‘WMDA Qualified/Accredited Registries should require their own country’s Transplant Centres to submit data to a regional or international patient outcome databases in order to collect clinical outcome data of the transplanted patients’. Such follow-up is also very relevant to cord blood banks, if the cord blood bank is NetCord-Fact accredited.

Following transplantation, the registry should enquire about the recipient’s state of health in order to ensure:

- Quality control of the donation procedure
  - Collection: sufficient quantity of cells in the product, absence of bacteria in the product
  - Processing: quality and viability of the cells.
  - Clinical: absence of any transmissible disease which could be passed on by the donor.
• The therapeutic use of the product:
  – Ensuring that the cell product collected from the donor is intended solely for the purpose of immediate therapeutic treatment for the mentioned recipient and to establish if the product has been either totally or partially cryo-preserved.
• Standardised questionnaires should be used to assess the above points.

Time-frame of the recipient follow-up

The recipient follow-up should take place in the first three to six months, with one or two questionnaires, for example, taking place after 24 hours or seven days and at three or six months. Examples may be found on the WMDA website.28 Depending on national regulations or registry policy, additional patient follow-up can be requested later on, for example, one or two years after the transplantation.

Communication of the recipient follow-up data

The registry should forward the results of the recipient follow-up to the responsible collection centre or cord blood bank after deleting all data which could lead to identification, such as recipient name. This information will allow the collection centre or cord blood bank to carry out quality control.

If this information is also used to inform the donor about the recipient’s health post-transplantation, it is necessary to respect the policies of your country which govern communication between patient and donor.
6 · Cord blood banking
Summary

This chapter covers public cord blood donation – from the consent process to the maternal donor follow-up. See the table below for a general overview of a cord blood banking organisation. This chapter includes information on the processing, storage and testing of cord blood units to ensure a safe, effective and potent product available for patients in need of a stem cell transplant. The clinical use of cord blood is discussed including search and selection principles, release criteria, transportation, thawing, infusion and recipient follow-up. Furthermore, cord blood transplantation outcomes and the sustainability of cord blood banking is reviewed. There is no question that cord blood should be available to all patients in need of haematopoietic stem cell transplantation and should be regularly offered when there is a clear indication.

Introduction

The first successful umbilical cord blood transplantation was performed in 1988 – the patient was a five-year-old boy with Fanconi’s anaemia. Since that time, umbilical cord transplantation has become recognised as an effective form of therapy for an increasing number of both malignant and non-malignant disorders and an established method of haematopoietic reconstitution.

Umbilical cord blood transplantation has expanded the pool of available donor possibilities for patients needing a stem cell transplant. According to the World Marrow Donor Association (WMDA) 2012 Annual Report, more than 33,930 unrelated cord blood units have been shipped for transplantation between 1999 and 2012. Currently, more than 560,000 units are registered in the Bone Marrow Donors Worldwide database. There are several advantages to the use of cord blood units (CBUs) as a source of stem cells for unrelated transplantation. Cord blood units are a ready to use cellular product and, clinically, result in a low incidence of Graft vs. Host Disease (GvHD) and increased match tolerance, which increases the donor pool availability.

Cord blood units increase the donor pool availability
However, the number of stem cells in a cord blood unit is relatively low for use in adult patients, which can delay engraftment and, in principle, there is no possibility to use a donor lymphocyte infusion after transplantation. The delay in myeloid recovery that is observed following cord blood transplantation remains a critical barrier to successful outcomes.

Many novel approaches are currently under investigation, with the aim of enhancing engraftment in cord blood recipients. These approaches range from increasing the number of cells obtained at collection to increasing the number of stem cells available at the time of infusion, through double cord transplant or \textit{ex vivo} expansion. Other areas of research include enhancing the homing capacity of the cells that are available. As an example, therapy has been extended to older patients using reduced toxicity conditioning and the double graft approach.

![Figure 6.1 Number of cord blood units shipped for adults and children in 1993-2012](image)

**What is a cord blood bank?**

A cord blood bank (CBB) is a multi-disciplinary structure that is responsible for the recruitment and subsequent management of maternal donors as well as the collection, processing, testing, cryo-preservation, storage, listing, reservation, release, and distribution of cord blood units. Public cord blood banks aim to store cord blood for allogeneic transplantation purposes. These banks are typically not-for-profit entities where units are cryo-preserved and stored at no
cost to the donor and family. They may be independent stand-alone banks, but are often affiliated with a registry that offers CBUs from multiple banks using a defined search algorithm and sophisticated matching programmes.

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In addition to public banks, a large number of private banks have also been established. These cord banks aim to store cord blood for autologous or family use. Newly-explored models of public-private partnership, the so-called hybrid banks, are currently being proposed, driven by the need to improve the financial viability and sustainability of cord blood banks.

**Challenges of cord blood banking**

Typically, cord blood is not only searched by Human Leukocyte Antigen (HLA) matching – cell dose and quality are important selection factors as they are critical issues affecting clinical outcome of transplants. The high cost of providing good quality CBUs is a challenge cord blood banks must face. As the standards for what is considered to be an acceptable quality of cord blood have risen, the percentage of units deemed viable for banking has decreased. This high rate of cord blood units being discarded has added to the overall cost per unit. Total inventory numbers have to be balanced with a need to maximise the ethnic representation and diversity of the cord blood bank. The rapid growth in the global inventory has resulted in a proportional decrease in the number of units released by each cord blood bank – making public banking activities economically challenging.

**Regulatory framework**

The regulatory framework of cord blood collection has evolved considerably over the past 25 years. What began as an effort to
broaden the available transplant options has developed into an expensive industry with robust regulation.

Cord blood has become the first Food and Drug Administration (FDA) licensed tissue product in the United States. Prior to this, concerns about safety and efficacy led the industry to develop voluntary standards, mainly set out by the NetCord-FACT (Foundation for the Accreditation of Cellular Therapy) and AABB (www.aabb.org) accreditation programmes.

The WMDA, as part of its registry accreditation standards, has provided a specific status for cord blood banks that are accredited by NetCord-FACT or AABB and wish to apply for WMDA accreditation.

This is particularly important, as there is significant and increasingly more exchange of cord blood across national boundaries. From these WMDA regulations, standards have been established for safety, quality, identity, purity and potency from a given point in history, but questions still remain regarding units banked before implementation of these international regulations. At present, some form of regulatory guidance is in place in virtually every country with a cord blood bank. Accreditation and regulation has instilled confidence in clinicians, allowing them to select a cord blood unit from a wide range of banks in many different countries.

**Cord blood donation**

**Models**

There are two main models of cord blood banking: private or ‘family’ banks and the public model. In some cases a ‘hybrid’ model that combines public and private characteristics may also exist.

**Public cord blood banks**

Public cord blood banks are dedicated to the collection and storage of donated cord blood for allogeneic use for patients who require a stem cell transplant and do not find an HLA-matched donor within their own family. In public cord
blood banking, the mother and family relinquish all rights to the cord blood unit once it is donated and it becomes available to any patient who may need it. The cells collected are genetically identical to the baby (called the infant donor for the purpose of this handbook), however, it is the mother (maternal donor) who signs the informed consent on behalf of the infant and is the source for the mandatory Infectious Disease Marker testing (IDM). There is typically no charge to donate to a public bank. Units in public cord blood banks often have stringent quality criteria governing cell counts, volumes, absence of bacteria or fungal contamination. Sometimes units that do not meet these criteria may be used for research purposes if the cord blood bank has a research programme and proper consents are in place. HLA-typing of the cord blood unit is performed after processing the unit. This is a critical part of cord blood unit selection for transplant physicians. In public banking, the cord blood unit information is uploaded to a registry so that the unit can be listed with match programmes such as Bone Marrow Donors Worldwide (BMDW) and can be seen by transplant physicians. However, any information which may lead to identification of the donor is kept completely confidential.

Private cord blood banks
Private cord blood banks or ‘family’ banks are for-profit companies that facilitate the collection and storage of umbilical cord blood for possible future use by the child from whom it was collected, or by a member of the child’s immediate family.

With private banks, the family has the right to use the cord blood unit for their own anticipated need or for future use. The cord blood unit is perceived as ‘biological insurance’. These units are considered to be property of the infant, under the guardianship of the parents until the infant reaches age of consent.

There is a cost associated with private banking. Initial collection and shipping fees are typically between USD 1500–2000 and annual storage fees typically range from USD 90–200. Often private banks do not have the same stringent quality criteria as public cord blood banks. These banks usually inform the family of any quality concerns they may have and then may dispose of the unit based on the wishes of the family. Unlike public banks, where the units are HLA-typed
immediately, private cord blood banks only HLA-type the units if there is a potential need for transplantation. Information about privately stored cord blood units is not uploaded to search registries or match programmes.

**Hybrid cord blood bank models**
There are several cord blood banks that offer a hybrid approach to cord blood banking, collecting units both for private storage and for public banking. This model allows the advantages of private banking to those who wish to use their service but also means the cord blood bank can collect cord blood units which can be listed by national and international registries. The WMDA Cord Blood Working Group edited a statement on hybrid cord blood banks, which provides more information.46

For the purpose of this handbook, we will focus on the collection activities in public cord blood banking.

**Collection sites**
The cord blood collection site is the place where the infant donor is delivered and the cord blood unit is collected. A cord blood bank may be linked to single or multiple collection sites. In addition, the NetCord-FACT Cord Blood Standards44 qualify them as fixed or non-fixed sites, depending on the quality agreements in place:

**Fixed cord blood collection site**
A fixed collection site has a written agreement between the collection site and the cord blood bank, for the collection of cord blood units. The agreement describes the interaction between the cord blood collection site and the cord blood bank for all aspects of the collection process including, at a minimum: personnel training, record keeping, collection, storage and transportation or shipping of a cord blood unit.

**Non-fixed cord blood collection site**
A non-fixed collection site has no on-going documented agreement with a specific site, but there is documentation showing that a licensed health care professional has agreed to perform the collection and training that covers each aspect of the collection process.
Recruitment

Donor recruitment practices vary among cord blood banks and among hospitals. Donor recruitment often begins during the antenatal period, facilitated through the pregnant woman’s physician or health care provider, but may occur as late as at labour stage and admission into the delivery unit of the hospital. Cord blood banks often provide information booklets or brochures to inform the mothers-to-be about cord blood banking. The material usually provides information on topics such as: what is cord blood, the importance of cord blood, how cord blood is collected, the risks and benefits and the next steps required for the mother to donate the baby’s cord blood. It is during this period that the expectant mothers are encouraged to gather information and ask questions about cord blood banking by phone or via a website. When designing a cord blood programme, you should consider the diversity you wish to have in your inventory. This will depend on the ethnic background of the patients and thus will influence your decision about which maternity units you will collaborate with.

Informed consent

Performing infectious disease marker testing of the mother’s blood, as well as testing of the cord blood unit and, ultimately, the donation of cord blood, all requires informed consent from one or both parents. It is commonly obtained only from the mother. Cord blood banks differ in how and when they obtain consent. It is ethically important to obtain informed consent for all cord blood donations. There are different steps in order to obtain a full informed consent:

Pre-consent

It is preferable to obtain consent in the antenatal period of the mother’s pregnancy. This gives her the opportunity to obtain information about cord blood banking, to ask
questions and make an informed decision regarding donation. Consent for the collection of cord blood may be obtained during this period by the mother’s health care provider or clinic staff or by cord blood bank staff.

**Full consent**

For mothers to give their full informed consent, they must be provided with information regarding all the procedures for collection, processing, testing, storage and use of the umbilical cord blood they are donating. It is important that they are informed that their personal and medical information will be kept confidential. Mothers also should be counselled about how abnormal test results will be handled and disclosed to them and the importance of them contacting the cord blood bank in the event that their child develops a serious illness.

Informed consent is difficult to obtain during labour and some accrediting and regulatory bodies may not recognise consent obtained during active labour. Mothers should not be approached during labour, as they are distracted by physical and emotional stress. It is preferable to obtain informed consent either before labour and delivery, or after cord blood collection after adequate disclosure of information. Informed consent should be obtained and documented while the mother is able to concentrate on the information and is not distracted by aspects of labour.

**Collection**

A successful cord blood collection will have a high volume, a high total nucleated cell (TNC) count, no contamination and the proper documentation. These factors are necessary to produce a unit that can be used for transplantation. A cord blood banking programme’s continued viability depends on the ability to
maximise the proportion of units collected which are suitable for banking and transplantation.

A cord blood collection typically involves the following steps:
• The umbilical cord is clamped as far from the placenta as possible.
• A section of the cord is prepared with alcohol or another disinfectant.
• The umbilical cord vein is punctured and the cord blood is collected in a collection bag.
• The collection bag is filled via gravity until the cord looks ‘white’ and the placenta and umbilical cord are drained of cord blood.
• The collection bag is labelled appropriately (see p. 156 for details).

There are two main techniques to collect cord blood from the umbilical vein: before the placenta is delivered (in utero) or after the placenta is delivered (ex utero). Both collection techniques have their own unique advantages and disadvantages, but both techniques require that the individuals performing the collections are adequately trained. With either technique, the collection is done in a collection bag that contains a citrate base anti-coagulant.

**In utero collections**

During an in utero cord blood collection, the collection is performed in the delivery room after the baby has been delivered, but before the placenta has been delivered.

After the baby has been assessed and the umbilical cord has been clamped and cut, the cord blood is collected by venepuncture after disinfection of the insertion site. The umbilical cord is cleansed by wiping a large area around the insertion site to clean off excess blood and then the area is scrubbed for 30 seconds with a topical antiseptic.

The cord blood unit is collected by gravity, a process that takes about two to four minutes, during which time the collection bag should be gently rocked to mix the blood with the anticoagulant in the bag. The collection is complete when blood stops entering the bag. The total time required for an in utero collection by a health care provider is less than 10 minutes. The unit is then sent to the cord blood bank for processing and storage.
One benefit of *in utero* collection is lower collection costs, because the collection is performed by physicians and midwives rather than motivated cord blood bank personnel and could result in higher volume of blood and cells being collected.

**Ex utero collections**

During an *ex utero* cord blood collection, the collection is performed by motivated, trained staff in a separate clean collection room as soon as the placenta has been delivered. This method has the benefit of not interfering with the birthing process.

In the delivery room, immediately after the delivery, the physician, nurse, or midwife clamps and cuts the cord, before passing the placenta and cord in a basin to the collection staff. The placenta is usually placed on a stand or frame, allowing cord blood to be collected by gravity. The umbilical cord is disinfected.

In utero CB collection. Courtesy of Programa Concordia Banc Sang i Teixits, Spain
with an aseptic solution and the needle from the collection bag is inserted into the vein. The collection of the cord blood unit can take five to 20 minutes and should not stop until the cord is ‘white’ or before the flow stops.

Some of the benefits of ex utero collections include: less clotting, less bacterial contamination and fewer labelling errors due to dedicated and trained collection staff, but it may also result in a lower volume being collected. The need to have dedicated collection staff in the hospitals adds increased expenses to a cord blood bank.

**Donor eligibility**

Maternal and infant donor eligibility is based upon results of screening and testing in accordance with regulations. To assess donor eligibility, a donor’s medical history interview is carried out, which includes assessment for high-risk behaviour and identifying risk factors for transmissible and genetic disease. The mother will be asked to provide a personal and family medical history. Written criteria should be available for maternal and infant donor evaluation and management. Maternal and infant donor evaluation results need to be documented and reviewed by trained cord blood bank personnel. Cord blood banks should use procedures for infant donor and mother evaluation to assess the risk of infectious and genetic disease transmission from cord blood units.

**Medical record review**

Maternal and infant donor evaluation results must be documented. Medical records can identify and provide a link between the mother and infant donor. Records should be kept indefinitely in a confidential way. A history of the mother’s communicable disease risk behaviours should be obtained and documented. Infant donor screening should also be documented by review of the history of the current pregnancy and delivery, including infant donor’s birth data, gender, gestational age and results of clinical examinations for diseases potentially transmissible through transplantation of a cord blood unit.

Family medical history for transmissible genetic and malignant diseases should be assessed. Donors originating from areas with a high incidence of certain genetic diseases should, if the risk is identified during medical examination, be screened for the disease and should be deferred, if test results are positive.
Cord blood units that were collected from families who are potential carriers of genetic diseases must be screened prior to listing and use and, if test results are positive, should be discarded.
Maternal questionnaire
Medical and travel history should be obtained from the maternal donor and documented while she is able to concentrate on the information and is not distracted by aspects of labour. Medical and travel history must be obtained in a language the mother understands. Family or friends should not serve as interpreters or translators. Confidentiality must be preserved.

The medical history questionnaire for cord blood donation should cover maternal and family history and the expectant parents’ ethnic background. If responses generate cause for concern, the collection should be rejected or cancelled. The mother’s travel history should be obtained and documented and her eligibility to donate should be determined according to national regulations.

Screening for human transmissible spongiform encephalopathy, including Creutzfeldt-Jakob disease, should be documented. If the history for communicable disease risk was obtained prior to the maternal donor’s presentation for delivery, the medical history should be updated to include information up to the time of delivery.

In case of a surrogate mother who gives birth to an infant donor who is not genetically hers, a communicable disease risk history of the surrogate mother should be obtained. A medical and genetic history of the infant donor’s family – parents, grandparents, siblings, and parents’ siblings including egg, sperm, or embryo donors – should be obtained from the mother and documented. The questionnaire needs to include questions to obtain, at a minimum: genetic history, malignant disease and inherited disorders that may be transmissible to the recipient.

The collection of cord blood from families with a genetic disease should be avoided and, if such units have been collected in the past, they should be screened prior to release. The WMDA Cord Blood Working Group recently published a paper listing the more frequent diseases which should be taken into account when determining donor eligibility.47

Maternal testing
A maternal blood sample should be obtained within seven days before or after collection of the cord blood unit and should be tested for evidence of infection
of HIV 1, HIV 2, Hepatitis B virus, Hepatitis C virus, HTLV I, HTLV II, Treponema pallidum (Syphilis) and any additional markers according to local regulations. Assays used for testing must be validated for use in volunteer blood or tissue donations. In some countries, there is a requirement for a second testing for infectious disease six months after donation. This is not mandatory in all countries, if determination using nucleic acid tests (NAT) is performed at the time of the infant’s delivery.

Genetic prenatal testing, if performed, could indicate risk of chromosomal abnormalities, such as Down’s syndrome, or genetic disease transmission and any such results should be appropriately disclosed to the maternal donor.

**Donor follow-up**

Cord blood donation is a special case of tissue donation involving two people. The ‘donor’ is the biological mother with regard to infectious disease screening, testing and consent and cord blood is collected from the umbilical vein of the child, after cord clamping. Donor follow-up, as well as donor adverse events, should be documented for both mother and child.

The cord blood bank should have a policy for follow-up of donors and for management of adverse events associated with donation. The cord blood bank retains the right to follow-up with the mother or relevant healthcare provider at a future date.

**Child health questionnaire**

There is a higher risk of transmission of genetic diseases by cord blood units than from donations of stem cells from peripheral blood or bone marrow, as disease might not easily be recognised at birth or even some time later. It is possible that some genetic diseases are missed, as they may not manifest themselves until six months after birth or later. Theoretically, all congenital diseases originating from bone marrow-derived cells are transmissible.

The CBB should request information on the health status of the new-born infant from its family, even if some time after donation but prior to listing the
cord blood unit. This second health questionnaire should ideally be performed within six months after donation.

**Counselling**
Mechanisms should be in place to inform the family in the event of a positive test result for any infectious disease marker (other than cytomegalovirus) an abnormal haemoglobinopathy screening or any other abnormal test result. An attempt should be made to notify the mother and the Vigilance and Surveillance staff responsible in the collection centre. The cord blood bank should have policies for handling specific cases. Failure to make contact with the mother for purposes of notification should not interfere with the decision to discard the cord blood unit. The nature of the genetic abnormality or the infectious disease discovered should determine the level of urgency in contacting the maternal donor.

**Donor feedback if child develops abnormalities**
The mother shall be provided with information to contact the cord blood bank if the infant donor develops a serious disease later in life.

**Serious adverse reactions (SEARs) in cord blood donors**
According to current knowledge, donation of cord blood does not carry a risk for the maternal donor. However, some questions remain about the safety of cord blood donation.

**Non-frozen transportation**
Collection units can be located far away from the cord blood bank and an appropriate and validated procedure for transportation between these two facilities is needed. Standard procedures should be in place.

**Conservation: time and temperature**
After collection, an appropriate conservation method needs to be in place to preserve the viability and potency of cord blood cells, as well as to protect the health and safety of the collection unit personnel. A validated method, which assesses maximum time for this transportation, must be in place, to ensure that cord blood units will not lose their viability and potency and that they arrive at the cord blood bank in acceptable condition.
Cord blood units must be transported at the appropriate temperature which will safeguard the integrity and quality of the cells. An evaluation should be made of the most appropriate procedure to follow in order to ensure the necessary transport conditions. Transport boxes or containers must be used and evaluations must be performed in standard and worst-case scenarios to make sure all possible conditions are considered.

Transportation from the collection site to the cord blood bank
Cord blood units must be transported with a validated and trained courier, following standard procedures written by the cord blood bank.

The cord blood collection bag must be identified with the following labels and paperwork:
- Unique cord blood unit number.
- Product name.
- Collection site name.
- Date and time of collection.
- Name and volume/concentration of anticoagulants.
- Recommended storage temperature.
- Biohazard sign and other warning labels, following appropriate regulations of your country.

This collection bag should be placed in a sealed secondary container which prevents any leakage. This secondary container must be placed in an outer container, which is proven to maintain recommended temperatures during transportation. A procedure is needed to document that the recommended temperature has been maintained or a continuous electronic monitor can be used. The outer container will be labelled with the product name and should protect the unit against any leakage, pressure changes, shocks or other incidents which could affect the unit’s integrity.

All transportation records should facilitate the unit to be tracked from the collection site to the cord blood bank and should record any deviation. To comply with NetCord-FACT Cord Blood Standards, a list with cord blood units and other reference samples, such as maternal blood and tissue, should accompany transportation.
Transportation records should identify: the personnel at the collection site who are responsible for transportation, the date and time of transportation, the identity of the trained courier and the date and time of delivery of the unit at the cord blood bank. Upon receipt of the units at the cord blood bank, the integrity of the units and their containers must be checked and any deviation will be recorded.

Cord blood processing and storage

Banking structure and resources

A cord blood bank must have appropriate facilities and personnel for the receipt, processing, testing and storage of cord blood and maternal blood. All processes should be performed in compliance with the regulations of the country where the cord blood bank is located. Wherever aspects of processing, testing or storage are performed by an external party, there must be a written agreement in place between the cord blood bank and the external party providing the service.

Processing laboratory

The laboratory needs to be secure and must have adequate space to perform all activities in a safe and sanitary manner. There must be a well-documented process for cleaning and sanitation. Relevant environmental conditions, such as temperature and humidity, need to be defined and monitored.

Cryogenic storage requirements

Cord blood units must be stored in either liquid or vapour-phase liquid nitrogen at –150°C or colder. In order to maintain long-term stability, all refrigerators, freezers and cryo-storage tanks used for storage of cord blood units, associated reference samples and maternal samples, must have a system to continuously monitor and record the temperature. In addition, there must be an alarm system in place 24 hours a day for staff to be notified immediately.
and with adequate time to respond, if a problem occurs with rising temperatures or liquid nitrogen levels. Finally, the processing laboratory needs to have access to additional storage devices of appropriate temperature in the event that a primary storage device fails.

**Testing laboratories required**

The cord blood processing laboratory needs to have testing control procedures in place to support the processing and characterisation of cord blood units. This is vital to ensure the integrity and quality of the units, in terms of how well the unit will engraft post-transplantation, but also to ensure the safety of the recipient with respect to transmission of disease and microbial contamination. Where a specific test is not performed by the processing laboratory, the cord blood bank needs to have agreements in place with external parties who perform these tests on behalf of the cord blood bank.

Testing should be undertaken in accordance with regulations of the country where the cord blood bank is located. Testing control procedures need to ensure the use of established and validated assays, standards and test procedures for the evaluation of the cord blood unit, with appropriate identification, linkage and handling of all reference samples.

**Collection: cellular thresholds**

The decision as to whether a collected unit will be acceptable for processing and banking will be made based on the acceptance criteria specified by the cord blood bank. The acceptance criteria will include parameters such as cord blood volume, total nucleated cell (TNC) count, factors identified by maternal and family history, transport conditions and cell viability. Acceptance criteria adopted by each bank should be based on rationale and justified, usually on quality and safety of the end product. However, many banks have further refined their acceptance criteria based on economics and the desire to build an international inventory of units with very high TNC or a certain percentage of units from ethnic minorities. Cord blood units of high TNC are highly-desirable for adult transplantation, since there is a positive correlation between number of TNC infused per kilogramme of the recipient’s weight and successful transplant outcome. Many
banks are now committed to processing and storing only those units with high TNC, which is defined as being greater than $120 \times 10^7$, based on the greater likelihood of these units being used and balanced against the cost of processing and storing units with lower TNC, which have a low likelihood of being requested for transplantation.
Reception
The collected cord blood unit should be received at the processing laboratory in a validated, secure, temperature-monitored transport container. On receipt of a shipment, a series of checks need to be performed on the collected unit, associated samples and documentation to verify the contents and determine if the cord blood bank’s specific acceptance criteria are met.

Triage
Initial triage of a collected cord blood unit and determination of its viability to continue on to processing will be based upon parameters such as volume, TNC content, correct documentation and labelling, signed maternal donor consent, appropriate transport temperature, absence of large or multiple clots and acceptable transit time from collection centre to processing laboratory. For NetCord-FACT accredited banks, the unrelated cord blood unit must arrive at the processing laboratory in time to allow initiation of cryo-preservation within 48 hours of collection.

Collection to processing
Once a unit meets the initial acceptance criteria, as described above, it will continue on to be processed. The processing of cord blood units is an expensive and time-consuming exercise and the establishment of appropriate initial acceptance criteria by a cord blood bank will ensure that only those units of the highest quality are processed.

Volume reduction
Volume reduction of cord blood is considered essential to the provision of a high-quality product and cost-effective banking. The final product volume and cellular characteristics are dependent on the product collected, as well as the processing methodology.

Rationale
Despite some loss of cells, volume reduction has additional practical and clinical benefits; the process eliminated red blood cells (RBC) and plasma components as waste products, which can be used for immediate or future testing, thereby minimising the loss of the actual stem cell product for testing purposes. Reducing the volume of the final product increases the stem cell yield per ml
available for transplantation. It allows for storage efficiency in terms of space and cost and, most importantly, reduces the risk of ABO incompatibility and Dimethyl Sulfoxide (DMSO) toxicity to the potential recipient.

**Methods**
Early attempts at volume reduction resulted in unacceptably high loss of haematopoietic progenitor cells (HPC). Over the years, a variety of techniques have been explored, including density gradients, RBC lysis and differential sedimentation. However, most methods were unsuitable for large-scale banking as they were manual, labour intensive and employed open systems.

Over the past decade, there have been three main methods used in large-scale banking which produced results that could be standardised. These include the manual hydroxyethyl starch (HES) method, the semi-automated bottom and top method – BAT process and the newer fully-automated and programmable closed systems – Sepax (Biosafe SA, Eysins, Switzerland) and AXP™ AutoXpress™ (ThermoGenesis Corporation, Rancho Cordova, CA, USA) and more recently the SynGenX – 1000 system (SynGen, CA, USA), which were designed specifically for the cord blood banking market. More recently, other processing platforms have entered the market, such a Prepacyte-CB.

Additional platforms being assessed by those in the field include novel filtration methods and double extraction techniques.

**Expected results**
Several groups have performed or reviewed in-depth comparative analyses of the various cord blood processing platforms being used by banks around the world.

These studies have evaluated TNC and CD34+ recovery, as well as RBC reduction and colony forming unit (CFU) assays to evaluate engraftment potential. Each system has its advantages and disadvantages, with no system at this stage being clearly superior to another.

Whichever platform is employed by the cord blood bank for processing, it is essential that the equipment and reagents used do not adversely affect the
viability of the cord blood units and that the process does not allow the introduction of potentially-damaging agents or the transmission of communicable disease.

Acceptable end points for processing should be defined by the cord blood bank, based on documented rationale and validation. Examples of desirable end-points are:

- A minimum threshold for post-processing TNC recovery. Based on the literature, ideally this would be 70% or greater.
- A target range for RBC depletion.
- A target limit for final volume after processing.
- A target limit for viability.

**Cryo-preservation**

The selection of a suitable protocol for cryo-preservation of cord blood for use in transplantation is critical to optimise the recovery of functionally-viable stem – and progenitor cells, most of which are the $\text{cd}34^+$ cells. Most stem – and progenitor cells present the $\text{cd}34$ marker on their membrane. These marked cells are called $\text{cd}34^+$ cells. Some potential sources of cell damage include: the type and concentration of cryo-protectant, the cell concentration and the cooling and warming rates.

Standard operating procedures (SOPs) relating to cryo-preservation should specify that the following information is recorded for each unit:

- TNC concentration within a defined range.
- The cryo-protectant, its final concentration and the duration of cell exposure prior to freezing.
- Method of freezing and end-point temperature of cooling.
- Cooling rate within a defined range.
- Freezing curve parameter within a defined range.
- Storage temperature.

Cord blood units must be stored in freezing bags designed and approved for cryo-preservation of human cells and must be placed into metal canisters to
offer protection during freezing, storage, transportation and shipping. It is important that, after filling, each freezing bag is visually examined for possible leakage and breakage of seals.

**Cryo-protectant**

Dimethyl Sulphoxide (DMSO), a plasma membrane-permeating molecule, has been used for over 30 years as the cryo-protectant for freezing HPC, almost exclusively in a final concentration of 10%, although there are some reports to indicate that a 5% concentration is also appropriate.

In general, a concentration of 10% DMSO is considered optimal for cord blood. Dextran-40 is a neutral polysaccharide of high molecular weight that does not easily permeate white blood cells and maintains a favourable osmotic environment. When used in conjunction with DMSO, Dextran-40 enhances the cryo-protective effect by allowing stabilisation of the cell membrane.

Whereas alternatives have been proposed, it is generally considered that a combination of 10% DMSO and 10% Dextran-40 results in the best recovery rates for TNC, CD34+ and colony-forming units (CFU) and is therefore the ideal cryo-protectant.

Prolonged exposure of cells to DMSO can result in damage to cells. It is therefore essential that the time period from addition of cryo-protectant to initiation of freezing is minimised and the time allowed is validated by the cord blood bank.

**Controlled rate freezers**

Ideally, cord blood units should be cryo-preserved using a controlled rate freezer with a validated freezing program. Most, but not all, banks use cooling rates of 1–5°C per minute in order to allow the cells to slowly dehydrate as the ice phase progresses and the extra-cellular concentration of the solution increases. If controlled rate freezing is not performed, an equivalent procedure, such as ‘dump freezing’, may be used, but it must be validated to maintain equivalent recovery and viability of nucleated cells.
Inventory management

The storage of cord blood units and associated reference samples must be in a secure storage device, in a secure location. The storage device and area must be locked when the area is not occupied by cord blood bank staff.

There must be an inventory management system to ensure that each unit and its associated reference samples, maternal samples and records can be located in a timely manner. This inventory management system should be designed in such a way as to prevent mix-ups, contamination of the units during storage and the improper release of quarantined units.

The inventory management system must be designed to address the duration of the storage for cryo-preserved units. The cord blood bank, or the facility storing the units, needs to validate the duration and conditions of storage, and pay particular attention to the effects of long-term storage on unit viability, function and stability.

Quarantine

There must be procedures defined and maintained to minimise the risk of microbial cross-contamination of units.

Each cord blood bank needs to have a procedure to define when a unit can be released from quarantine. Each unit must remain in quarantine storage until the cord blood bank director or their delegate has approved the release of the unit from quarantine status, based upon satisfactory testing and screening results and as required by the relevant regulatory authorities. Quarantine status may be temporal, physical or a notification in the batch record of the cord blood unit.

Supplies, reagents and equipment

The inventory management system must include a system to document receipt, inspection, verification, acceptance and storage of all critical supplies and reagents used for cord blood processing.

It is important that refrigerators and freezers used for storage of cord blood units and all associated reference samples, as well as reagents used in cord
blood unit collection, processing or cryo-preservation, should not be used for any other purpose, in order to minimise the risk of cross-contamination.

**Transient warming events**
Units must be stored at $-150^\circ\text{C}$ or colder. Significant warming events may occur when the unit temperature rises above $-123^\circ\text{C}$. Each cord blood bank needs to assess the potential risk within their processes for transient warming events to occur, such as when a unit is outside of its proper storage temperature for extended periods of time. Examples of these opportunities include: transfer of units from the controlled rate freezer to the cryo-storage tank, removal of segments of the unit for confirmatory testing and storage of units in vapour vessels that may exhibit unstable temperatures when opened. Each of the relevant scenarios pertinent to a cord blood bank’s operations should be validated to show that, at the end of processing and all accumulated transfers, the viability of the cord blood unit has not been compromised.

Storage tanks were kept intact during the 2011 earthquake in Japan, because tanks were connected to each other by hard belts (green) and casters (blue) under the tanks absorbed the shaking shock. Courtesy of Miyagi Cord Blood Bank
Any warming events that may occur after the process of storage must be mini-
mised in order to prevent the occurrence of transient warming events.

**Testing and product conformity**

A cord blood bank must be able to confirm testing and product conformity in
order to be able to release a unit for transplantation. All tests performed must
use established and validated relevant assays and, if required, comply with di-
rectives from local regulatory authorities.

**Safety (virology, sterility, haemoglobinopathy)**

In order to provide a safe product for release, it is essential that cord blood
is screened for those infectious diseases which can be transmitted via blood.
Maternal blood, obtained seven days before or after collection of the unit, is
used as a surrogate test for infectious disease markers (IDM) and is strongly re-

dlective of the infectious status of the cord blood units, due to the shared circula-
during gestation. Testing the unit for IDM provides an additional degree of

safety. At a minimum, prior to release for administration, the maternal donor
of each unit must be tested for evidence of infection of communicable disease,
using licensed donor screening tests according to national regulations.

Below a list of viruses to test for, as required by NetCord-FACT standards:

- Human immunodeficiency virus, type 1 (HIV 1).
- Human immunodeficiency virus, type 2 (HIV 2).
- Hepatitis B virus.
- Hepatitis C virus.
- Human T cell lymphotropic virus, type 1 (HTLV I).
- Human T cell lymphotropic virus, type 2 (HTLV II).
- *Treponema pallidum* (Syphilis).
- Any additional agents required by national regulations.

Cord blood units for unrelated use must be shown to be free of microbial con-
tamination. Microbial testing must be performed using a system validated for
the growth of aerobic and anaerobic bacteria and fungi.

Prior to release for administration, each unit must have undergone haemog-

globinopathy screening. Abnormal red blood cell diseases can be carried by
populations previously considered unable to be affected by them and, therefore, haemoglobinopathy testing must be performed regardless of the family’s ethnic background or history.

**Identity (HLA, maternal HLA, blood group)**

An error in cord blood unit identity could be catastrophic to a transplant recipient and it is therefore imperative that all identity checks are performed on a unit prior to release for transplantation.

Human leukocyte antigen (HLA) typing must be performed on a reference sample from each unit. HLA-A, -B and -DRB1 loci must be determined using DNA-based methods and the result must be included when listing a cord blood unit in the search registries. Many transplant centres also use HLA-C and -DQB1 matching in their unit selection algorithm and, therefore, the cord blood bank may also wish to determine and report HLA-C and -DQB1 typing. At a minimum, DNA high-resolution molecular typing must be performed for Class II-DRB1 typing, prior to a unit being released. It is recommended that HLA-typing is performed in an accredited laboratory.

Prior to release of a unit, it is imperative that HLA-identity of the unit to be shipped is confirmed as matching that of the unit requested for transplant. This is known as verification (formerly confirmatory) HLA-typing. Ideally, verification typing will be performed on a sample taken from a contiguous segment of the unit. However, this is often not possible in older units, which were banked prior to the requirement for contiguous segments being taken. Therefore, processes must be in place to ensure linkage between the reference sample used for HLA-typing and the cord blood unit. The use of a contiguous segment to verify unit identity through HLA-typing is considered critical to patient safety.

HLA-typing on maternal blood may also be performed prior to release of a unit. Haplotype matching between maternal donor and infant donor confirms linkage between the two and serves as a secondary confirmation of identity. Furthermore, many transplant centres now consider non-inherited maternal allele (NIMA)\textsuperscript{52,53} matching as part of their analysis of transplantation outcome,
which is not possible if maternal HLA-typing is not performed. ABO blood group and Rh type must be reported prior to listing a unit as available for search.

**Cellular content (NC, nRBC, cd34, others)**

The purity or cellular content of a cord blood unit is often an important factor in selection of a unit for transplantation. It is now well-established that a minimum of $2.5-3 \times 10^7$ TNC per kilogramme of the recipient’s weight is required to ensure the best chance of engraftment and favourable outcome post-transplantation. Since the number of TNC infused per kilogramme of weight depends on the size of the recipient, it is highly desirable that the cord blood units contain a high number of TNC (ideally greater than $120 \times 10^7$).

The total nucleated red blood cell count (nRBC) must be reported. This is to determine the contribution of nRBC to the nucleated cell population, which enables the transplant centre to make an informed selection of cord blood unit.

cd34 is a surface glycoprotein which is present on stem and progenitor cells and the number of cd34+ cells in a unit provides an indication of the number of stem and progenitor cells available for transplant. The total number of cd34+ cells must be reported.

In order to screen for any haematological abnormalities the infant donor may have, a cell blood count (CBC) with differential should be performed, with parameters for neutrophils, lymphocytes, monocytes and platelets being clearly defined.

**Potency (CFU and viability)**

Potency testing to determine the growth potential and viability of progenitor cells in a unit should be performed post-processing but prior to cryo-preservation, in addition to being performed on a thawed sample prior to the unit’s release for transplant. Potency assays should be performed both post-processing – prior to cryo-preservation – and post-thaw, as the cryo-preservation and thawing process inevitably leads to some loss of viability of cells.

Viability and potency can be assessed measuring viable cd34+ cells in the unit, using flow cytometry and by performing a colony forming unit (CFU) assay to enumerate clonogenic progenitor cell growth and differentiation in semi-solid
media. Studies have shown that the post-thaw viability or potency of cells is a more accurate indicator of how a cord blood unit will perform post-transplantation than the post-processing cell viability and potency results.

Clinical use of cord blood

Release for listing

Cord blood units are made ready for listing after a comprehensive review has been performed of details or characteristics for each unit, including maternal donor selection and maternal and infant donor evaluation for specific medical requirements, as well as testing to ensure the product meets requirements, at a minimum, testing for the following information: gender and race of the infant donor, TNC, HLA-typing, testing done on the mother and on the cord blood unit, collection date, processing method, sample inventory and the type of bags used for cryo-preservation of the unit. The WMDA form CB21 cord blood unit report shows a summary of these requirements. It is the cord blood bank’s responsibility to ensure that the information provided to the transplant centre is correct and complete.

The information of a cord blood unit (CBU) which is presented on form CB21 can be requested by the TC. If this CBU is produced in a period when the CBB was already accredited (i.e. by NetCord-FACT) this information must be available or can at least be provided after the formal request for issuing. Otherwise if this is a CBU, produced before the CBB was accredited or even before the release of International Standards, the so called ‘grandfather CBU’, the CBB must indicate if it possible to obtain this information. It may be that test results can only be provided during the release for administration because of the lack of maternal donor (plasma/serum) samples or the lack of reference samples of cord blood.
Listing of the CBU can be done by the CBB itself or the CBB can have an established relationship with a registry.

**Release for administration**

**Request for issuing**
The cord blood bank must receive a formal request before the work-up process starts. This can be received directly from the transplant centre, but it can also be organised by the registry or cord blood bank. The return of an unrelated cord blood unit is generally not permitted under international standards. Transplant centres need to be certain that they are prepared to accept responsibility for the cord blood unit after it leaves the inventory of the cord blood bank.

The work-up will result in a cord blood unit being released for administration. The minimum requirements for a unit to be released are set out in the WMDA form CB21 cord blood report. The cord blood bank or registry can have their own cord blood report, but this must show the same information and criteria as form CB21.

The review is often referred to as the cord blood bank’s process for ensuring that all elements of collection, processing and storage have been evaluated and found to meet established safety, potency and quality criteria, and that the cord blood unit is suitable for distribution.

**Releasing tests**
In addition to examining the characteristics of a cord blood unit, the cord blood bank must perform certain tests before the unit can leave the cord blood bank.

**Verifying CBU identity through HLA typing of a CBU**
Cord blood unit identity can be verified by performing HLA-typing on the unit, using a contiguous segment which is still connected to the bag containing cryo-preserved cord blood. The cord blood bank should have a policy in place for cases in which no remaining attached segments are available for testing.

If the minimum of four-digit DRB1-typing has not been performed before listing the unit, tests to verify the unit’s identity can be combined with extended DRB1-typing. Some cord blood banks will use other genetic markers, such as
short tandem repeats (STRs), to confirm the identity of the cord blood units. Before the unit can be released for transplantation, the STR tests must be performed a second time and the results of this second test should be compared with those form the first tests. The WMDA has accepted the definition of verification (confirmatory) typing to be, ‘typing done using material from an attached segment, using DNA methodology’.\textsuperscript{54} HLA-A, -B and -DRB1 loci must be determined using DNA-based methods, in accordance with the NetCord-FACT Cord Blood Standards.

**Cell viability or potency, as measured by viable cd34\(^+\) cells or CFU**

Testing the viability of cd34\(^+\) cells or Colony Forming Units CFU, after processing but prior to cryo-preservation, is generally required by international standards. Assessment of viability is based on intact cell membranes and active cell metabolism, excluding dyes. It is a requirement to assess the functional capacity of the cord blood unit, prior to its release to the transplant centre. CFUs are grown from functionally-viable cells and increase confidence in the quality of the cord blood unit and its ability to engraft. Therefore, it is recommended that CFU should be performed from a frozen segment of the unit, or a cord blood unit sample taken according to the cord blood bank’s alternative policy. This should be done prior to the unit’s release for transplantation.

**Additional infectious disease marker tests**

Infectious disease marker (IDM) testing of maternal samples is known as a ‘surrogate test’ and the results are strongly reflective of the infectious status of the cord blood unit, because the circulation has been shared between the mother and her child via the umbilical cord during gestation. Prior to the unit’s release for transplantation, the results of maternal donor screening tests (HIV 1/2, HBV, HCV, HTLV I/II and \textit{Treponema pallidum} (Syphilis)) should be available. Due to differing requirements set out in various national regulations, transplant centres may require additional IDM tests to the ones listed above.
Frozen transportation

Cryo-shipper
Cryo-preserved cord blood units should be transported or shipped in a liquid nitrogen-cooled dry shipper in order to maintain a temperature of −150°C or colder for at least 48 hours beyond the expected time of the unit’s arrival at the facility where it is due to be received. It is mandatory to measure and to document the temperature in the dry shipper throughout the period of transportation or shipment.

Cord blood banks need to make arrangements for the return of the cord blood unit transport container to the cord blood bank facility.

Courier and accompanying documents for shipment
The courier should be educated by the cord blood bank on how to handle the dry shipper and how to take care of the cord blood unit. A plan for alternative transportation or shipping should be available, in case of emergency. The identity of the courier must be known and documented. Tracking and tracing of the transportation of the unit in the dry shipper, from the cord blood bank to its final destination, must take place. Information about the date and time of packaging and departure from the cord blood bank should also be documented.

Information about date and time of receipt of the dry shipper and the cord blood unit must be documented to trace of the transportation of the unit. The use of a specific form to document the information is preferred and it should include questions about integrity and internal temperature of the dry shipper and the integrity of the cord blood unit upon arrival at the final destination.

The WMDA webpage lists the more frequent S(P)EARS related to cord blood. They usually involved problems during transportation including the temperature of the cryo-shipper, condition of cord blood unit cryo-bags when the unit is received at the transplant centre and post-thaw viability issues. These
issues highlight the level of attention cord blood banks should give to the transportation monitoring, reviewing the cord blood bag when packaging and assessment when the cord blood arrives at its destination, when any problem may generate delays in transplantation. It is important to note that cord blood units should be received at the transplant centre before the patient starts any conditioning procedure.

Thawing and infusion

Washing, dilution and direct infusion
It is important to ensure that the transplant centre receives information on how to handle and use the cord blood unit, including thawing and washing of the unit. Providing information about indications, contra-indications and precautions is the responsibility of the cord blood bank.

A jointly-prepared document called Circular of Information for the Use of Cellular Therapy Products has been created by the International Society for Cellular Therapy and The Foundation for the Accreditation of Cellular Therapy. It is available at www.ISCT.org or www.factwebsite.org. According to this circular, cord blood banks should be able to provide instructions for a validated thawing process of their cord blood unit. In general, there are three ways to administer the cord blood product to the transplant recipient. These are: direct infusion; 1:1 volume dilution with a hyperosmolar buffer (generally a dextran and albumin mixture); or using an additional washing step after dilution, in cases where the infusion volume is too high or the product contains an excess of red blood cells.

Clinical follow-up

For a cord blood bank, it is important to obtain clinical outcome data to analyse the quality, safety and efficacy of the cord blood bank’s production process. These data should also show the safety, purity and potency of the cord blood unit involved. Cord blood banks should have a policy or procedure to obtain the following information about each unit released: the viability and recovery of different cell populations after thawing the unit; information about adverse events associated with administration of the unit. This information should be

Measure and document the temperature throughout transportation
received as soon as possible but within six weeks of release of the unit. Within six months, information about the time taken to reach neutrophil and platelet engraftment after transplantation should be obtained and, each year, survival rate and information about chimerism and GvHD should be requested.

Cord blood bank management and evaluation

Listing and search (registry side): forms, communication

Cord blood banks can list their cord blood units directly in an international database or have an established relationship with a national registry in their country. The majority of cord blood banks operate in close association with their national registry. In such cases, all processes related to the listing and search of the cord blood units should be performed in agreement with the registry.

The cord blood bank should have policies and standard operating procedures (SOPs) for the review of the cord blood unit records, prior to the unit being listed by the registry. Once the units are HLA-typed and have been medically qualified, the cord blood bank submits the cord blood unit data to their registry. Upon request from a transplant centre or a patient’s registry, the cord blood bank registry provides an initial search report containing information about the units that have the highest grade of HLA-matching with the patient. The registry also lists the cord blood units in one central database, Bone Marrow Donors Worldwide, at www.bmdw.org.

A flowchart of the steps of a search, including the interface between transplant centre, registry and cord blood bank is featured in a WMDA white paper.47

Forms

After reviewing the search report, the transplant centre can request detailed information about the selected cord blood units by asking for a Cord Blood Unit Report. The report should include, at a minimum, the following information: gender and race of the infant donor, TNC, HLA-typing, testing done on the mother and on the cord blood unit, the cord collection date, processing
method, sample inventory and the type of bags used for cryo-preservation of the unit.

If additional testing is performed on the cord blood unit, this should be included in the report, or documented in a supplementary report form. The cord blood bank should have appropriate forms to ensure that all screening questions are documented, along with results of all testing which has been carried out. The WMDA provides a comprehensive standard cord blood unit report template, which can be used by any cord blood bank in the world. The template, as well as a supplementary cord blood unit report template, can be found on the WMDA website in the forms section.\textsuperscript{28}

\textbf{Communication}

The cord blood bank should use a validated electronic records system for uploading cord blood unit information to the registry. The cord blood bank must update the data of the cord blood units listed by the registry on a continuous basis. When a cord blood unit is removed from the bank’s inventory, this change must be reported immediately to the registry. The cord blood bank must have adequate information technology support to ensure such a system is in place.

Cord blood banks must respond to cord blood unit report requests, and to requests for additional information, within a time period which is in line with WMDA recommendations.\textsuperscript{56}

The access within the cord blood bank to information about the infant or maternal donor, as well as the transmission of this information to the registry, must be restricted. Access to and transmission of data should be structured in a way that prevents accidental or unauthorised access, destruction or modification of data and which guarantees confidentiality. Search requests for cord blood units listed by a national registry are to be accepted and processed by the responsible registry only.
Selection principles

Cord blood unit selection is performed by transplant physicians, usually with the help of transplant coordinators and the advice of HLA-experts. They must provide full information on the patient including:

- Age, sex and weight
- Diagnosis, stage of the disease and urgency of the transplant
- ABO and Rh blood group.
- Infectious diseases marker testing results.
- High resolution HLA-typing for the loci -A, -B, -C, -DRB1.

Transplant centres can send their search request to different organisations, according to national regulations and registry policies.

Selection criteria may vary between transplant centres, but there is a consensus among different organisations. For instance, in Europe, the Eurocord group created a recommendation on how a cord blood unit should be evaluated to benefit different types of patients.50

Another recommendation was also recently published by the USA registry, the National Marrow Donor Program (NMDP) and the Centre for International Blood and Marrow Transplant Research (CIBMTR).51

It is advisable to keep maternal samples in order to facilitate the HLA-typing of the mother, in order to determine non-inherited maternal antigens (NIMA) or the inherited paternal antigens (IPA), if required.52,53

Transplantation outcomes

Cord blood banks need to obtain information on transplantation outcomes to meet the requirements for accreditation related to the quality control of cord blood units. This information can be provided either by the transplant centres or through registries monitoring outcomes, such as Eurocord or NMDP-CIBMTR.
The WMDA also collects information on serious adverse reactions and events, in SPEARS and SEARS reports. In Chapter 5, information is provided how to report a serious adverse event.

Cord blood banks must provide information on cord blood unit characteristics to the registry representing the transplant centre. The characteristics must include: cord blood identity, TNC and cd34+ cell counts, HLA-typing, ABO, infectious disease markers, date of collection and details on cell processing, cryo-preservation and shipping.

The transplant centre’s registry will contact the transplant centre and collect information on transplant characteristics and outcomes, following the administration of the cord blood to a recipient. A specific form should be sent to the transplant centre by the cord blood bank, each time a cord blood unit is released. Data are typically collected by the transplant centre at three, six, and 12 months after transplant, followed by ongoing annual data collection.

The information required may include:
- Patient and disease characteristics.
- Conditioning regimen and Graft versus Host Disease (GvHD) prevention.
- Number of cells infused.
- Early adverse events.
- Date of neutrophil and platelet engraftment and chimerism.
- Acute and chronic GvHD.
- Infectious complications and toxicity.
- Relapse.
- Transplantation related mortality at three, six, and 12 months and then annually.
- Overall survival and disease-free survival.

Outcome data can be sent to the cord banks on request. Overall results are published every year by Eurocord-EBMT, NMDP-CIBMTR, the WMDA and other organisations.
Collection of outcome data assists the formulation of important guidelines on donor selection, indications, role of HLA, prognostic factors and comparison with other stem cell sources.

**International networking**

The International NetCord Foundation is a non-profit association of umbilical cord blood banks whose members make up the largest source of high-quality cord blood grafts for patients in need of haematopoietic stem cell transplantation. Initial steps to create NetCord were taken in 1995, followed by the formal creation of the organisation in 1998. In the year 2000, the International NetCord Foundation was established and chartered in the Netherlands.

The missions of the International NetCord Foundation are: 57

- To promote the highest quality in cord blood products through worldwide standards and accreditation.
- To balance global supply and demand for umbilical cord blood.
- To encourage and facilitate the use of cord blood transplants by promoting laboratory and clinical research and providing professional and public education.

The International NetCord Foundation holds the following values: 57

- An umbilical cord blood donation is a gift of health and well-being to a seriously ill patient. Donors should be held in high esteem, and the donation managed with great respect.
- Umbilical cord blood is a key component in the future of haematopoietic stem cell therapy and regenerative medicine. Its potential will be realised through basic and clinical research and greater professional and public awareness of the therapeutic value of cord blood.
- Cord blood has the greatest social value when donated to an accredited bank for allogeneic use and made fully accessible to all potential patients.
- For cord blood therapies to reach their full potential, cord blood banks must maintain high standards to assure quality products, and the process for banking, selecting and procuring stem cells must be accurate, efficient and economically sustainable.
NetCord sponsors standards and accreditation for umbilical cord blood banks. It also promotes studies and research into cord blood collection processes, the characterisation and preservation of cells, \textit{ex vivo} expansion of placental and umbilical cord blood and quality improvement of blood components for clinical cellular therapy.

To ensure high and uniform quality of all cord blood units in its inventory, NetCord began collaborating with the Foundation for the Accreditation of Cellular Therapy (FACT) in 1999.

In 2000, they jointly published the first NetCord-FACT International Standards for Cord Blood Collection, Processing, Testing, Banking, Selection and Release. New editions of the standards are published at approximately three-year intervals and contain information on the latest developments and requirements of high-quality banking.

In an effort to make high quality units available to the transplant community, NetCord has developed information technology resources to allow transplant centres to have a fast and reliable online overview of cord blood units stored at NetCord member banks. This Virtual Office system was created in 2001 and is being transformed to become a platform which is compatible with the EMDIScord system. This transition is planned for 2013.

In order to fulfil its goals, NetCord has developed strong relationships with key organisations in the industry. Examples include:

- Reciprocal agreement with the National Marrow Donor Program (NMDP) in the United States. The agreement covers searches conducted through the NetCord Virtual Office and also includes the inventory of NMDP-affiliated banks and searches conducted through the NMDP include the NetCord inventory.
- Active participation of NetCord officers in the work of the WMDA.
- The collection and analysis of clinical and treatment outcomes data is coordinated with EUROCORD and the Centre for International Blood and Marrow Transplant Research (CIBMTR).
Contribution to the Eurocord-ED educational website (www.biostor.eu/eurocordedu) and document resource, as well as to WMDA educational activities and to joint web conferences and training sessions with FACT.

**WMDA**

In collaboration with other working groups of the World Marrow Donor Association, the Cord Blood Working Group (CBWG) gathers and shares information about cord blood bank and registry activities and requirements. It also develops best practices to support and promote the safe and effective international exchange of unrelated cord blood units.

Subjects may include maternal donor recruitment and testing, cord blood unit collection, processing, testing, selection, release and shipment. The WMDA maintains an up-to-date set of guidelines and documents, which are relevant to cord blood banking and use. These are available at www.worldmarrow.org.

Keeping an overview of cord blood transplantation and monitoring of adverse events is part of the WMDA’s duties and is the subject of discussion and recommendations during its regular meetings. Cord blood-related topics are also covered in WMDA educational sessions.

**Eurocord**

Eurocord was created in 1995 by Professor E. Gluckman and currently has two distinct branches.

**Eurocord Association** aims at promoting scientific research (academic or industrial) and developing therapeutic applications and sharing knowledge related to umbilical cord, placenta, annexes and, more generally, any topic in the foeto-maternal field. The group has led numerous retrospective clinical studies in the field of cord blood transplantation.

**Eurocord Registry** became part of the French Agency for Biomedicine in July 2010. Created by Professor E. Gluckman, the registry gathers, validates and analyses clinical outcome data of patients transplanted with cord blood units in Europe and transplant centres worldwide. Active cooperation with CIBMTR allows both groups to exchange outcome data.
EUROCORD-ED
EUROCORD-ED is the European Online Cord Blood Learning Portal, for use by doctors, nurses, midwives, surgeons, umbilical cord blood processing and testing laboratories, scientists and study groups.

Funded by a European Union grant, the EUROCORD-ED project aims to inform and educate all professionals involved in the field: laboratory scientists, technicians, clinicians, transplant physicians, obstetricians, midwives and biotechnology companies involved in cord blood banking, research and clinical analysis of cord blood. EUROCORD-ED also aims to inform parents who are potential cord blood donors. The organisation also makes efforts to support decision-makers engaged in formulating health policy.

Cord blood bank sustainability
Cord blood banking is an expensive activity. It is estimated that each cord blood unit listed in a registry may cost more than US$1,000 to collect and process, but the chance of a unit being used is perhaps less than a 1% each year. Additionally, the effectiveness, in terms of being a likely match for a patient is greatest in the first thousands of cord blood units stored but decreases progressively later. This means each new unit stored once the inventory grows above a critical size is less likely to be transplanted than those stored earlier. If cord blood bank economics is based on the return of cost per unit transplanted, the above issue makes continuous growth of the inventory unaffordable. But the fact that cord blood units can be maintained indefinitely once stored, provides an advantage over the adult unrelated donor inventories that require a continuous renewal of donors. Taking this into account, a cord blood bank should limit the size of its inventory to make it sufficiently active but sustainable. In order to favour the use of its units, a cord blood bank needs to focus on storage of high-quality units, such as those fulfilling the highest standard requirements and containing the highest number of cells. Three important topics for consideration are set out in more detail below.

Cellular threshold
A typical cord blood collection contains $8 \times 10^7$ total nucleated cells (TNC). However, the median number of cells used for transplantation in children and
adults is $130 \times 10^7$ and $180 \times 10^7$, respectively. This shows that there is a need to select units with high TNC before processing, in order to ensure the unit’s engraftment potency.

It has been suggested that a TNC of $90 \times 10^7$ should be the minimum acceptable threshold to maintain a competitive level of quality. Further increase of TNC, if possible, will give advantage better transplantation results. In this regard, the use of $\text{cd}34^+$ counts as an acceptability criterion is worth considering. Altogether, these assessments will define the operational inventory of a cord blood bank, which is the most powerful predictor of the bank’s likely transplantation activity.

In order to ensure quality in the inventory, it is necessary to identify units which are below minimum cell counts or fail to meet current standards. This includes units without attached segments, without viability tests performed, without $\text{cd}34^+$ cell enumeration, with count discrepancies or which are lacking reference samples to test their safety and identity. Excluding these low-quality units allows a cord blood bank to assess the actual operational inventory available for transplantation. For all these reasons, it is advisable to invest in national cord blood inventories with appropriate size and diversity, following high quality procedures and controls.

**Size**

In spite of the fact that the distribution of HLA varieties differs between major ethnic groups, in a US study, 10,000 donors provided a four out of six HLA-match for patients in every group, using the conventional cord blood matching criteria (low resolution for HLA-A,-B and high-resolution for HLA-DRB1). This result was also shown in a UK study where a match was found for almost all patients in a study, using a pool of 10,000 randomly-selected donors. For a better match level, such as five out of six, a larger inventory was required. But enlarging the size resulted in a progressive decrease of efficiency. Only 5,000 units were required to find a donor for 50% of patients, but to achieve 65%, it was shown that the inventory size would need to be tripled to 15,000, or up to
50,000, to secure a match for 80% of patients. It shows that the large increase in inventory size does not result in a similarly large benefit.

**Worldwide cord blood banking**

In spite of the problem of sustainability, an international network of small but highly-qualified banks collecting units of highly-diverse phenotypes can achieve the goal of finding a donor for everybody. One could suggest that the optimum size of a world inventory could be achieved by the addition of 5–15,000 donors for each major ethnic group, depending on the group’s anticipated diversity. This may at least provide the option of finding a five out of six matching donor for more than half of the patients requiring a transplant, but it could also ensure a four out of six matching donor for almost all patients.

In addition, inter-ethnic cross-matching and other HLA favourable interactions, such as the use of two identical haplotypes (HLA homozygous) for mixed ethnicities and consideration of the effect of Non-Inherited Maternal Antigen (NIMA) matching, would further increase donor availability. For instance, if we consider 23 major ethnic groups as proposed by the allele frequency net database, a worldwide cord blood unit inventory would be in the region of 300,000 units.

This would be sufficient to provide a compatible cord blood unit for any patient in need. To be effective, all units within the inventory should be larger than 1.5×10⁹ total nucleated cells (TNC), in order to serve patients weighing up to 100 kg using double cord blood transplantation. The acceptable threshold should be 1.5×10⁷ TNC per kilogramme of the recipient’s weight. A central world cord blood bank may achieve this goal with a budget of USD 300 million. A proper world distribution network and adequate size of regional collection programmes and processing labs would need to be in place. According to Gonzalez-Galarza et al., once the optimum world inventory size is achieved, the maintenance cost will be minimal, suggesting a rapid return on investment depending on the future cord blood transplantation activity.
7 · Information technology and data management
Summary

This chapter aims to explain how Information Technology can be used to manage the information held by a registry or cord blood bank. The chapter gives advice on systems, software and electronic communication methods which may be used.

Introduction

This chapter covers all aspects of Information Technology (IT) and information management in a registry and cord blood bank. The first section describes how a registry develops a new software system – its business case, project plan, specification, development, quality, security and validation. The second section focuses on EMDIS – the electronic communication network of stem cell donor registries. The third section describes the design of the donor search algorithm, which is a key component of a registry’s IT system. The fourth section covers the hardware infrastructure of the registry. Finally, the last section covers routine maintenance and disaster recovery. Chapter 5 of the WMDA standards document, the WMDA IT Working Group White paper, WMDA guidelines and other publications are the primary references for this chapter.

Information System

This section outlines the main features of importance when considering an IT system either for a new registry, or for the replacement or development of the existing IT system. It aims to cover both simple and more complex computer systems.

The registry may be part of a large organisation, with a well-developed quality management system and IT development strategies, or it may be developing a completely new system. In this chapter, we have tried to pre-empt some of the issues you may face and provide helpful advice. Whether the software is an ‘add on’ IT package or a brand new system, it is essential to allow a substantial amount of time and resource for its implementation. Even development of
a relatively small system will take a substantial amount of time – experience shows at least two years as reference point. It is a mistake not to allow sufficient time and resources for such a project. Requirements for an IT system may be split into the following categories: business, architecture, data, functionality, usability, quality and security requirements.

**Business case preparation**

There are many areas involved when creating a new system which, in themselves, can take up as much time as the IT development itself. The first of these is preparation of a business case. This may be an informal or a formal document but it is the starting point for introducing new IT systems to a registry.

The business case may be a key document which needs approval before work on the IT project can begin. It will begin to identify the key stages in the introduction of a new system, as well as being a useful tool to justify funding.

Even in the absence of any formal process, these aspects are worth consideration before the start of any new IT project. A significant advantage is that additional resources, required from other colleagues or experts, may be identified at the start of the project. For example, input may be needed from finance, purchasing, quality, expert users and IT professionals, depending on the size of the project and the standards and complexity of your organisation.

The business plan document should be a high-level overview of the project and it is useful to include:

- Scope of the new or updated IT system.
- Option appraisal.
- Contracting for suppliers.
- Financial aspects.
- Key resources.
- Quality requirements.
- Incident management.
- Business continuity.
- Periodic evaluation.
Benefits realisation planning.

Scope
As part of the planning process, the registry should decide whether basic functionality is required, or whether delivery of entire registry’s functionality is required. At its simplest, according to WMDA standard 5.0, the IT system must be able to register donors and patients, search a database of HLA data of adult volunteer donors, or cord blood and provide search reports for transplant centres. A management comprehensive system may be required, which would manage all the registry’s functions with work-flow support, modules for on-line communication and finance, interfaces to enable connection with other systems, a document management system, customer relationship management (CRM) function, automated production of letters, reports and documents and the ability to monitor key performance indicators. These functions are discussed in more detail in a later section.

In both cases, the initial activity would be the production of a detailed specification of the registry’s requirements before a decision is made on which software should be selected. A User Requirement Specification (URS) should accurately describe the functions required of the computerised system and the specification should be based on documented risk assessment and Good Manufacturing Process (GMP) impact. User requirements and all documents should be traceable throughout the life-cycle of the system and its development.

By writing a concise URS for each area of the system, you ensure that the scope does not expand continuously and that it is not subject to uncontrolled changes. A lack of focus can be the single biggest cause of delay for such a project.

Option Appraisal
A registry could plan to have all or limited IT functions performed by, or with the help of, third party organisations. In these cases, the registry should ensure that the qualifications of any respective partner and the quality of the service provided meets WMDA standard 5.0.

There are few IT systems available for data management which are specifically designed for the operations of a registry or cord blood bank (see Table 7.1 for options).
Table 7.1  Options for the new IT system to be considered by the registry.

<table>
<thead>
<tr>
<th>Option</th>
<th>Advantages</th>
<th>Disadvantages</th>
<th>Example</th>
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<tbody>
<tr>
<td>Work with a ‘partner’ registry which has developed an IT system</td>
<td>• Inexpensive.</td>
<td>• The system may rely on a single entity and not support the business processes in your registry.</td>
<td>The New Zealand Bone Marrow Donor Registry and the Thai Stem Cell Donor registry use the Australian Bone Marrow Donor Registry software system.</td>
</tr>
<tr>
<td>designed for registries.</td>
<td>• partner has previously encountered potential difficulties.</td>
<td>• Partner registry may always prefer own interests and their own requests for change.</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>• IT support may be an issue after your system has been put into use.</td>
<td></td>
</tr>
<tr>
<td>Develop new software with the registries ‘in house’ IT team.</td>
<td>• ‘Made-to-measure’ solution.</td>
<td>• Costly and time consuming.</td>
<td>NMDP, ZKRD, France Greffe de Moelle (FGM), Italian Bone Marrow Donor Registry (IBM-DR) and others have their own IT team who develop own software solutions.</td>
</tr>
<tr>
<td></td>
<td>• Independence.</td>
<td>• High level of expertise is needed.</td>
<td></td>
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<td></td>
<td></td>
<td>• Often exceeds project plan and budget.</td>
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<tr>
<td>Purchase a ‘commercial’ system.</td>
<td>• Clear customer–vendor relationship (deadlines, guarantees, budget limit).</td>
<td>• Limited number of vendors exists.</td>
<td>Registries in Belgium, Finland, Sweden, South Africa and the UK (BBMR) use a commercial system.</td>
</tr>
<tr>
<td></td>
<td>• Experience of other users of the system.</td>
<td>• The prices charged may be high if the registry has limited funding.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• The supplier guarantees implementation of changes on schedules set by the community.</td>
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Contracting and suppliers
In case the option appraisal indicates that the creation of a new IT system should be outsourced, a formal competitive tendering process must include a detailed specification to cover the functionality and standard of the system and
the expectations of the registry. At the end of this process, contractual obligations should clearly state conditions placed on both parties.

If commercial third parties are used to provide, install, configure, integrate, validate, maintain, modify or retain a computerised system or related service, or for data processing, formal agreements must exist between the manufacturer and any third parties and these agreements should include clear statements of the responsibilities of the third party.

Less formal arrangements still require a service level agreement (SLA), which clearly sets out the responsibilities of both organisations. In both cases, the registry should audit the partner organisation as part of a planned quality audit programme.

The competence and reliability of a supplier are key factors when selecting an IT provider. The need for an audit should be based on risk assessments. Documentation supplied with commercial ‘off-the-shelf’ products should be reviewed by users to check that user requirements will be fulfilled. Normally, assurances would be given in the form of a response from the supplier agreeing on how the required functionality would be provided. This ensures common understanding of what is being provided by a supplier.

Sophisticated organisations, including the larger registries, understand that dependency on third party suppliers may add operational risk to themselves in the event of a major adverse event. The registry may employ the use of Escrow (a source code of software) and verification services to assure the long-term availability of software which is critical to their business needs. The use of such methods protects the business while safeguarding the intellectual property of the suppliers.

**Financial aspects**

The registry should consider the capital funding needed for a new system, including computer hardware, software and one-off costs, such as new servers to host the system. In addition, the project may need to identify the recurring system costs which could be incurred, such as licensing fees, maintenance costs and software updates, which are also very important.
Key resources
See the section ‘Project team and project plan’ for information on key resources required.

Quality requirements
There are a number of rules and regulations that should be considered regarding quality requirements for IT systems. Among these is Volume 4 of the 2011 edition of Good Manufacturing Practice Medicinal Products for Human and Veterinary Use. The key parts of these quality regulations, which apply to a computerised system, are: incident management, business continuity and regular updating. They define a computerised system as, ‘a set of software and hardware components, which together fulfil certain functionalities’.

When considering quality requirements the expertise of a quality manager is invaluable. The computerised system should be validated and the IT infrastructure should be qualified based on implementation quality (IQ) and operational quality (OQ). It is essential that, where a computerised system replaces a manual operation, there should be no reduction in data quality, functionality or quality assurance as a result. It is important that there should be no increase in the overall risk to the registry’s processes. This especially applies to the area of search algorithms, which must accurately identify all HLA-matched donors consistently.

Incident management
All incidents, not only system failures and data errors, should be reported and assessed. The root cause of a critical incident should be identified and should form the basis of corrective and preventive actions (CAPA). It is useful to keep these records for inspection for accreditation purposes. A large organisation is likely to have a pre-existing quality management system that controls these aspects. For smaller registries, some simple policies will suffice but are required for WMDA accreditation, as well as for European Union and other national regulations.
**Business continuity**

Computerised systems, supporting critical processes, should be made to ensure continuity of support in the event of a system breakdown. The time required to bring alternative arrangements into use should be based on risk and must be appropriate for a particular system and the business process it supports. These arrangements should be adequately documented and tested. This is an area that should form part of the validation exercise, discussed later. It is likely, for example, that EMDIS software downtime should be a maximum of 24 hours, or otherwise messages will accumulate in the system.

**Periodic evaluation**

Under GMP regulations, the registry system should be periodically evaluated to confirm the IT systems remain in a valid state and are GMP compliant. Such evaluations should include: the current range of functionality, deviation records, incidents, problems, upgrade history, performance, reliability, and security and validation status reports. It is advisable to plan these aspects of reporting into the system from the start. An up-to-date listing of all relevant systems and their GMP functionality is also useful for accreditation purposes.

GMP regulations have been extended to take into account Good Automated Manufacturing Practice (GAMP). Guidelines are aimed at manufacturers and users of automated systems in the pharmaceutical industry. GAMP includes a risk-based approach to compliant computerised systems and describes the life-cycle approach to an IT system.

One of the core principles of GAMP is that quality cannot simply be tested in a batch of product but must instead be built into each stage of the manufacturing process. As a result, GAMP covers all aspects of production; from the raw materials, facility and equipment to the training and hygiene of staff. Standard operating procedures (SOPs) are essential for processes that can affect the quality of the finished product.

Although this appears to apply to manufacturing processes, the IT-specific list below makes it clear that GAMP Good Practice Guide also covers IT aspects:

- A Risk-Based Approach to Compliant GxP Computerised Systems.
- Electronic Data Archiving.
- Global Information Systems Control and Compliance.
• IT Infrastructure Control and Compliance.
• Testing of GxP Systems.
• Validation of Laboratory Computerised Systems.

**Benefits realisation planning**

It is important to understand which benefits a new or updated IT system will offer to your registry. These could be either increased income or increased operational efficiency. This ‘benefits realisation’ should be considered at the start of the life-cycle of an IT project. If required, a registry can monitor these benefits after implementation of the system. Examples include increased numbers of searches per staff member and more blood samples being requested for verification typing (VT), therefore more collections and, ultimately, more income. These performance data are becoming important for registries to understand the benefits from any new or improved IT system.

**Project team and project plan**

The need for IT staff is crucial in stem cell donor registries, because of the organisations’ dependence on IT systems and infrastructures. Registries can employ IT staff, hire consultants, or depend on the support of a professional company. In each case, staff maintaining the IT systems of a registry should be adequately trained to support the registry operations. The registry must demonstrate that such trained and skilled staff exist.

A key resource to be considered at the start of the registry software project is an individual or group of people with sufficient knowledge of both the HLA system and IT. These skills are rarely found together in a single individual and it is important that expert HLA users work closely with IT experts to develop their skills.

The project team should be composed of end users, who define the registry needs; local IT infrastructure administrators, who look after the hardware, network, security and back-up and the development team or vendor. A project team may also include quality management specialists, procurement specialists and other external consultants, such as HLA experts, transplant physicians, donor recruitment staff and the finance department. It is useful to have either a project manager, or lead individual who can make decisions and who has the skills and tools to push tasks forward. There should be regular meetings...
Table 7.2  An example of the one year project plan for deployment of the commercial software solution for a middle size registry (in months). Many of the above stages will vary depending on the organisations involved. However, a version of this plan will be necessary, even if it is informal.

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or teleconferences of the project team, ideally once a week. Minutes should be documented from the meeting and an action list drawn up, with people and deadlines assigned to tasks.

Procurement of IT software may require a tender and this may involve one year’s work if the contract is of high value. Negotiations with vendors and several amendments to the agreement with the selected supplier may be required. The project plan must be shared by both parties and responsibilities for each phase of the project must be clearly defined (see Table 7.2).

**Specification of the system**

WMDA standard 5.03 requires that ‘All patient and donor communications and records must be stored to ensure confidentiality and to allow for traceability of the donors/cord blood units and steps of the donation process’. This section describes the architecture, data and functional requirements of the registry IT system.

**It is essential that the registry analyses the following:**

- What are the key modules and functions of the system?
- What information should be stored on the database and how?
- What are the business processes of the registry and how should they be supported by the system?
- Who are the end users of the system and what are their roles in the system?
- What are the interactions of the system with the outside world and what interfaces should be built?

The architecture of the system is determined by the registry organisation. There are several aspects involved:

- Situation: The registry might be completely independent, or be located in the administrative building, or be part of a hospital, blood transfusion institute or other medical organisation. If the registry belongs to the bigger medical organisation, it has to follow specified rules and usually has to be well-integrated. Very often, small registries are organisationally connected with a HLA-laboratory, which necessitates the interface between systems of these departments.
- Donor centres: The registry may be the national hub which does not recruit donors directly, but cooperates with a network of donor centres and cord blood
banks. In some countries, the registry does not have access to donor contact details, so the donors may not be contacted directly without going through the donor centre. In this case, the ‘master record’ for the donor is in the donor centre and the registry only has a copy. Other set-ups, typical for small registries, are based on integrating the registry with the donor centre. In this situation, donor recruitment is organised by the registry itself or a network of partner organisations and, after recruitment, all donor data is transferred to the registry database, which means the master record for the donor is managed by the registry itself.

- Access to the registry database is usually restricted to registry staff. Partner institutions must contact the registry in order to access the database, or changes will be visible after next off-line upload of data from a partner institution. The alternative option is to build an on-line interface or allow partner institutions to access the database directly. For example, donor centres and cord blood banks could manage their donors, cord blood unit records and transactions directly. The registry may look like a single institution to the international community when viewed through systems such as EMDIS, but it will in fact be a network of donor, transplant – and search coordination centres spread across the country.

The following is a list of key functional requirements that a registry may consider including, when considering a new or improving an existing registry IT system.

**Donor database is the key module. Donor record may include:**

- Donor identification (ID): a unique, invariant registry ID for the donor is the primary reference, but a data set can also include social security number, donor centre ID, recruitment ID, cord blood bank ID, ID of the mother of the cord blood unit, preferably ISBT128 donation code, stored sample ID, stored DNA ID, EMDIS ID and other fields.
- HLA data: separate fields for serology and DNA typing results, typing laboratory, date of typing, primary typing data, NIMA, etc. The registry should consider how HLA data will be imported into the database, as this may be from either an internal or an external source. Reference to the white paper\(^6\) has to be made regarding standardisation of nomenclature and data formatting.
- Demographics: name, title, gender, date of birth, ethnic group, insurance company and so on.
• Relationships: family or personal relations to other donors or patients, used for family reports of the patient.
• Recruitment: donor centre, date of recruitment, recruitment method (website, patient-draft, blood donor, indication of whether the donor is also a blood or platelet donor).
• Donor status: reservation of the donor, temporary or permanent withdrawal, reason of withdrawal (age, medical, personal).
• Contact details: permanent, temporary or work address, email, phone numbers, social media networks, communication language, preferred contact method, history of communication with the donor.
• Medical questionnaire: weight, height, blood group, haemoglobin, number of pregnancies, number of blood transfusions, donor consent to different types of donations, past diseases.
• Infectious disease markers: CMV status, Toxoplasmosis, EBV status, HIV status, HIV p24 antigen, antibodies to HIV, hepatitis B and C status and antibodies, Lues status, ALT status, with dates of tests and laboratories that performed tests.
• Products: information about the stored donor samples or cord blood unit product, its position in the freezer and so on.
• Cord blood unit data: volume of cord blood unit, total nucleated cells, $cd34^+$ cells, mononucleated cells, white blood cells, processing methods, fractions, and maternal tests.
• Collection: date and place of collection, date and place of transplant, patient ID, source of stem cells (bone marrow, PBSC, DLI, cord blood, other).
• Audit: who has created or modified the donor record and when, searchable history of changes to the donor record.

Patient database provides a record for both national and international patients and may include:
• Patient identification: unique, invariant registry ID, but can also include social security number, transplant centre ID, hospital record ID, EMDIS ID, physician and so on.
• HLA data: separate fields for serology and DNA typing results, typing laboratory, date of typing, primary typing data. Separate fields for historical HLA results.
• Demographics: name, title, gender, date of birth, ethnic group, insurance company and so on.
• Relationships: family or personal relations to donors, used for family reports of the patient.
• Patient status: donor search status, transplantation status, closure of the case (date, reason).
• Medical information: diagnosis, disease phase, weight, blood group, CMV status.
• Transplants: date and place of collection, date and place of transplantation, donor ID, source of stem cells (bone marrow, PBSC, DLI, cord blood, other).
• Audit: who has created or modified the patient record and when, searchable history of changes of the patient record. Both donor and patient database must be searchable by different attributes.
• Quality control: the system should control quality of data according to registry policies. There should be no expired reservations of donors, no over-age donors that are marked as ‘available for transplant purposes’ on the searches, no donors missing critical data (e.g. date of birth, gender) and HLA data should always be valid according to the latest HLA nomenclature.
• Regular update of reference tables: for HLA nomenclature and multiple-allele-codes.
• Reports: customisable reports of donor and patient details, ability to export to PDF files, ability to send letters and emails to donors through user-defined templates.
• WMDA annual report: Many registries do not systematically collect data for the WMDA annual report, leading to time being spent searching paper records or Excel spreadsheets when preparing the WMDA questionnaire. There is a huge advantage to build in this functionality to generate data automatically at the start of the IT project. This also increases the reliability of data reported to WMDA.
• Donor searches: The donor search algorithm is the key and probably the most difficult element of the registry software. It should follow WMDA recommendations and guidelines. For more information about the search algorithm see the section ‘Search Algorithm’.
• Management of requests: the system must allow users to create and track different national and international requests for donors. This includes typing requests, verification typing sample requests, infectious disease marker testing requests, donor reservation requests and work-up requests. Traceability of requests means documenting clear information about the status of the request (result, inability to do the service, cancellation, denial) and related
events (acknowledgement by the partner, contact of the donor, reminders, and invoice). Management of requests includes both:

- National requests: national patient and national donor.
- International requests: national patient and international donor or vice versa; electronic on-line requests (EMDIS or web interface) and fax requests (outside EMDIS).

- The system should support the work-flow management of requests for different scenarios, for example, the unsuccessful collection or a cancelled work-up. Each step in the search process should be documented with all relevant attributes and a time stamp, according to WMDA standard 5.03.3

- Financial module can be integrated into the request management work-flow. Closed requests are usually invoiced to the requesting institution. Integration with external economic software systems may requires synchronisation of services, which are classed as invoice items and clients, who are classed as invoice recipients.

- Transplant records, donor and patient follow-up records with automated reminders of incomplete or missing records.

- Document management system: possibility to store and maintain different kinds of electronic documents, linked to donor, patient, search and other types of records.

- International interfaces: the registry should be well integrated to the international community, mainly to assist with efficient donor searches. Interfaces may be needed with:
  - BMDW: regular export of donor and cord blood unit database to Bone Marrow Donors Worldwide (www.bmdw.org).
  - EMDIS, EMDIScord: on-line peer-to-peer network of stem cell donor registries (www.emdis.net) You will find more information about the EMDIS system later in this chapter EMDIS cord is a project in developmental stage.
  - NMDP: some international registries are listed as donor centres in the NMDP network, so they regularly export data to NMDP database (www.nmdp.org, Traxis software).
  - Netcord: member cord blood banks of this organisation regularly export data to the central database (www.netcord.org).
  - HLA: regular import of the current HLA nomenclature (http://hla.alleles.org/wmda/index.html), NMDP allele code nomenclature.
National interfaces: the registry serves as the national hub which connects different institutions and individuals within the country. The following electronic interfaces might be useful:

- HLA laboratory: registry sends electronic typing requests for its donors and patients to the laboratory and HLA-typing results are returned to the registry. The registry can also access information about donor samples stored in the HLA laboratory freezers, so registry coordinators know if they can use this stored DNA sample for the additional HLA typing.

- Donor centres: donor centres and cord blood banks in the registry network may have their own IT systems that should be interfaced to the registry system.

- Collection centre: once a matching patient-donor pair is identified, the registry may send the donor record to the collection centre’s system and get back details about the stem cell product.

- Search units: search units in the registry network may have their own IT systems that should be interfaced to the registry system.

- Transplant centres: transplant centres and hospitals need to communicate with the registry. An on-line solution instead of a fax, paper or phone solution is desirable.

- Donors: On-line web portal helps a registry to keep in contact with donors. Such portals can include an online form to amend contact details, an on-line forum, news bulletins from the registry, a reimbursement form and so on. Some registries also use social media networks such as Facebook or Twitter.

- Sponsors: On-line web portal for registry sponsors may increase their motivation. The system can manage sponsor accounts and show statistics such as how many donors were recruited thanks to the sponsorship and how many went on to be selected for verification typing or donation.

**SUGGESTION** Registry systems do not store or manage the HLA-typing results in the same format as the HLA laboratory information management system (LIMS) and, although some registries have implemented such data storage, it is a mistake to use HLA results from LIMs systems in search algorithms.

The main differences between registry database and HLA LIMS database are:

- The registry system needs fast access to the most current and comprehensive HLA typing results, which does not always mean the last test typing. This may be a combination of multiple tests performed in the past by multiple typing
techniques. The registry system always needs access to the full set of loci that should be stored in one place, while the HLA laboratory system order includes only requested tests and loci, so HLA-typing results of an individual may be spread out in multiple typing orders.

- When the HLA laboratory supervisor approves the order results, it cannot be changed in the laboratory system. However, the registry system has to keep historical HLA-typing results up-to-date, according to the latest HLA nomenclature, so amendment of the records is required on a regular basis.

**Quality and security requirements**

The system of quality management should include tools and policies to ensure that IT-related errors and problems are identified, tracked, reported and resolved. The software system development life cycle must include a quality assurance plan, as well as tracking of user testing and approval.

**Quality and Security requirements include:**

- Authentication and authorisation policies. It should be possible to configure different user roles and limit the functionalities available to certain roles. See section ‘Confidentiality and security’ for more details.

- Archiving of the data so that these cannot be changed, including log-files, for 30 years or according to national legislation.

- Traceability of changes, clear log-file of data saving, handling, changes and removal of data, including what amendments were made, by who, when the amendment took place and, if necessary, why. See section ‘Audit trail’ for more information.

- Quality management and IT-related issue tracking system.

- High level of availability for use: ideally 24 hours a day, 7 days a week.

**Confidentiality and security**

The access to donor and patient data within the registry, as well as the transmission of this information to and from the registry, must be organised in a way that accidental or unauthorised access, destruction or modification of data is prevented and confidentiality is guaranteed. Usually an IT system uses authentication with built-in access levels.
There are three types of authentication:
- What you have – such as keys, badges, ID, passes or tokens.
- What you are – such as your DNA, fingerprints, voice match or iris recognition.
- What you know – for example, passwords or phrases.

An IT system should support at least one of these three types of authentication and implementing more than one of these types makes the system more secure. If a system is secured by passwords only, it is recommended to have a password policy in place to make sure that the passwords being used are sufficiently complex. This means, for example, no dictionary words should be included; passwords should be at least 8 characters long and should include numbers or other characters.

A system may have different levels of access for different users. This means that donor and patient information can be accessed, stored, modified and destroyed, based on access control lists. The individual who is responsible for data, policy, security and database maintenance usually has an administrator level of access. It is advisable at the outset of creating a new IT system to document how records will be protected from accidental or unauthorised access, destruction and modification.

**Audit trail**

Traceability is defined in the WMDA standards as ‘to follow all the steps of a process from beginning to end. The ability to locate and identify a volunteer donor or recipient, their data and cell product, during any stage of the recruitment, testing, collection, donation, transplantation and follow-up process’. If a registry uses an IT system for its business processes, the steps towards transplantation, as mentioned in the definition, should be supported by this definition.

An IT system should log changes that are made, including a date or time stamp and the system user who has made the change. Identifiers are a key part of traceability. A unique and anonymous identifier should be assigned for:
- Each adult volunteer donor and cord blood unit
- Each patient
- Each donor cellular product
It is recommended to use an identifier to track each volunteer donor and cord blood unit, along with their associated data and biological material and their participation in the donation process, on a long-term basis and this identifier should therefore not change over time.

Identifiers should be generated automatically, for example, as an integer and a checksum digit appended for error prevention. The method used to generate identifiers could be implemented to differentiate between donors, cord blood units, patients and products. Preferably, any identifiers generated should be independent of any information related to the subject identity in order to give an additional level of privacy. The identifier should be unique and once a donor or cord blood unit, patient or product has an identifier assigned, this should not be changed, as assigning new identifiers would damage the traceability.

A registry should implement a policy for the retention of records. The policy must cover the entire life cycle of the information, from initial submission to potential removal of the donor and product information from the registry. Local laws may apply here. National laws may state that information must be stored for a number of years; however, these laws may also require organisations to delete information after this period of time. If an organisation needs the stored information after the dictated period of time, for example, for research or statistics), the data must be anonymised, in order to comply with WMDA standard 5.01.05.3.

Migration and validation

Moving data to a new system from an existing (heritage) system is also an important consideration at the start of the project. If data is migrated from the old system it would need to allow data to be immediately accessed, backed up and any risks associated with keeping the old system archived are avoided. For some organisations, such as blood banks, regulations may dictate that old records must be retained. The process of automated data migration may require specialist software and would involve both the new IT system supplier and the provider of the old software.

If data is being migrated from a heritage system, a series of validation exercises must be carried out to check that the correct data has been transferred to the
correct fields. Usually, a percentage of migrated records is selected in the new system and verified for their accuracy. The recommended method for checking data migration is a risk-based sampling plan. This should be a repetitive process.\textsuperscript{69}

A critical step in the migration process is producing a mapping table, so that old data fields are mapped to new fields. Sampling should be carried out on a defined number of data fields of different types to check that data has migrated as expected. As well as data, checks should be made on the systems themselves and their functionality, to ensure it is as described in the specification. Testing is usually carried out using a test database.

It is common practice to perform Process Critical Acceptance Testing (PCAT) to check that the IT processes function as expected. In some complex systems, there may be systems where an old, paper-based) system runs parallel with the new IT system. This allows any issues with processes or different ways of working to be identified to avoid any surprises on the date the system ‘goes live’. This also allows staff to use the new system prior to the ‘go live’ date. After this point, the IT system then goes to a ‘post go live’ phase, after which it is used every day, a period known as business as usual (BAU).

New versions of software used must be subject to version control and, for new releases of IT software, full documentation of the version content must be provided.

**SUGGESTION** New software versions should be introduced with the same rigour of testing as the first version. Validation documentation, as described above, should include change control records (if applicable) and reports on any deviations observed during the validation process.

**Inter-Registry Communication System:**

**EMDIS**

Reliable communications and data transfer of donor and patient records between all organisations involved is one of the most important factors in
successful stem cell transplantation. The internet provides great opportunities for connections between registries, including the software to support the whole process, from the preliminary search request to transplantation.

EMDIS (European Marrow Donor Information System)\textsuperscript{62,70,71,72} is an open computer network for the exchange of data between different unrelated haematopoietic stem cell donor registries. Today, it covers around 90\% of all potential unrelated stem cell donors and cord blood units registered in BMDW www.bmdw.org. It is the ‘de-facto’ standard communication system for unrelated human stem cell transplantation registries worldwide. The EMDIS community provides documentation, status information, software tools, support and a project management platform.\textsuperscript{62} You can find more information at www.emdis.net.

**Technical background**

The decrypted content of an EMDIS message is shown as text in special format, called the Flexible Message Language (FML). EMDIS emails are not read by humans, but by computer systems that break down the FML text into its basic attributes and data fields, which are then further processed.

On the basis of this technical background, about 30 message types are defined, including preliminary requests and patient updates, search results, typing requests and results, sample requests, notification of sample arrival date and sample testing results, infectious disease markers (IDM) requests and results, donor reservation requests and results, work-up requests and results.

The most advanced feature in EMDIS is the donor search process. When a national registry initiates an international donor search for a specific patient, information is sent to other EMDIS registries. Every registry’s computer which receives the data makes a donor search in the local registry database using its own algorithm and technology and replies with a set of potential donors. Then the requesting registry composes these partial results into one global EMDIS search result. In practice, these results are received within several hours.
After this procedure, the patient is at ‘preliminary status’ and no further action is taken. The local registry can change this status to ‘active’ by sending a ‘patient status change message’ to other registries. The preliminary search result could become out-dated after a few days. If the patient has an ‘active’ status, every remote registry runs a regular repeat search process for this patient and checks if the search result has changed. An update is sent back to the patient’s registry. It could contain new and more desirable donors than those previously reported or other changes in the current search result.

Finally, when the patient’s case is closed, the national registry broadcasts the patient status change message with the new status ‘stopped’ and the repeat search process for this patient comes to an end. Figure 7.1 below shows the EMDIS communication process.

**Software implementation**

The basic components of the EMDIS software include:
- An email system to send and receive messages.
- Software based on ECS (EMDIS Communication System) rules to control the sending and receipt of messages.
- Software to encrypt and decrypt messages.
- Software to validate the EMDIS FML message (the FML parser, FML = Flexible Message Language).

![Figure 7.1: EMDIS communication. HUB is a registry.](image-url)
• Functions to interpret the process and respond to messages – EMDIS message processor.
• Search engine to run preliminary and repeat searches.
• User interface to create and manage EMDIS messages.

The first four components exist outside the registry's own software and are currently available free of charge. These four form a package called ESTER (ECS message Transfer between EMDIS Registries), a platform-independent implementation of the first three components is called PerlECS, which was developed by the National Marrow Donor Program (US).

In Figure 7.2, components five, six and seven are the most complex. They are available as a separate piece of software, known as Prometheus, which links ESTER to a copy of the local registry database.

EMDIS implementation can vary from one registry to another. Typically, a registry receives a search or sample request from its own national or regional transplant centre by e-mail or fax. These are then passed, via EMDIS, to the active EMDIS nodes. Responses to these requests are sent back from the external EMDIS nodes and are then relayed by some other means to the originating transplant centre. This is patient-related EMDIS messaging.

If the local system implements the original idea of a ‘single virtual international registry’, it must maintain the same status of the patient in all EMDIS registries. This could include the national registry itself. In this situation, there is no difference between a local search and a remote search – it is only an EMDIS search. The advantage is that the local system also notifies of changes in search results, similar to the function performed for international patients.

The registry can also receive and respond to search or sample requests from other registries directly via EMDIS. This is donor-related EMDIS messaging. Not all registries have chosen, or are able, to respond to all of the available EMDIS messages and some registries process donor-related messages only.
The two-way messaging between registries follows highly-structured protocols and standard nomenclature agreed and controlled by the EMDIS community.

The EMDIS organisational structure and rules are described by the EMDIS House Rules\textsuperscript{74} and reflect the procedures of national registries which are members of...
the EMDIS network, with a high level of user involvement and a focus on practical issues.

The EMDIS User Group coordinates the advancement of EMDIS to achieve the goals of the network. It sanctions and approves new EMDIS users; validates and prioritises user needs; liaises with the EMDIS Technical Group over specifications, time-tables and feasibility of requirements.

The EMDIS Technical Group protects the integrity of the EMDIS system, technology and infrastructure and defines technical requirements for the participation in EMDIS. It defines interfacing rules and prepares the necessary documentation, reviews proposals for new developments emanating from the user group, prepares specifications and timetables for implementation by national development teams, liaises with the user group and the national development teams of the member registries.

These groups meet regularly to discuss requests for change and to oversee the implementation of new versions of EMDIS. General maintenance, training and operational issues are also supported by the WMDA IT Working Group.

EMDIS membership is open to unrelated donor registries which actively use the EMDIS system. They are known as EMDIS hubs. Membership application has to be submitted to the chair of the EMDIS User Group for review and must be approved by the EMDIS User Group.

**Search algorithm**

Information and communication technologies play a key role in the donor search process in stem cell donor registries, both nationally and internationally. One of the major challenges for registry computer systems is the development of a reliable search algorithm. This section discusses the top-down design of such algorithms and current practice.
Search algorithm requirements

The purpose of the donor search algorithm is to find and present a selected list of potential donors and cord blood units, in which the ones most likely to be an optimal stem cell source for the patient are sorted to the top of the list. Selection and sorting criteria are based on HLA compatibility and may also take into consideration secondary preference criteria, such as CMV antibody status, gender and age.

Basic requirements for the search system used by stem cell donor registries are:

- Deterministic behaviour that ensures the same results with the same input. This means the algorithm has to reproduce exact decisions at every step of the process.
- Clear ranking order of the results.
- Exhaustive — all donors available for transplantation in the source database should be included in the search algorithm. Exceptions must be clearly indicated to the end-user. For example, some algorithms exclude donors that are typed only at HLA-A and HLA-B.
- Scalable — the system should be able to handle databases of varying size and type.
- Fast — search algorithms are also used in user-interactive systems, so the results should be received in seconds.
- Configurable — search coordinator must be able to define patient-donor HLA match criteria and secondary preference criteria, such as CMV status, gender, age.
- Consistently matched — The data presented should be uniformly matched as a set for a given patient search. Different primary algorithms or matching criteria should not be used within a single patient search.

The search algorithm is usually implemented as the key component of the stem cell registry’s software system. It has several inputs and a single output. The following input data is essential:

- Patient’s data: HLA-type (minimum HLA-A, HLA-B and HLA-DRB1 typing).
- Patient’s match criteria (position and number of allowable mismatches).
- Database of adult unrelated donors (AUD) and cord blood units (CBUs) (optional).
- HLA nomenclature code-lists.
- Allele and haplotype frequencies (optional, depending on type of algorithm).
Design of the search algorithm

The algorithm itself usually follows these steps:

- Pre-processing: fast pre-selection of donors based on pre-determined internal indices.
- Processing: comparison of every (pre-selected) donor with the patient, calculation of match grades, matching probabilities and filtering.
- Post-processing: linking corresponding donor or cord blood unit details.

Search criteria

Search algorithms should allow users to define matching preferences for each individual search. EMDIS Matching Preferences define the following criteria:

- Counting method for mismatches: count graft-versus-host (GvH) mismatches only or host-versus-graft (HvG) mismatches only.
- Maximum number of antigen or allele mismatches for adult donors.
- Maximum number of antigen or allele mismatches for CBUs.
- Maximum number of antigen or allele mismatches at loci A/A*, B/B*, C/C*, DR/DRB1*, DQ/DQB1*.
- Maximum age of the donor, gender matching, CMV status matching

The IT Working group of the WMDA has issued two key resources which describe the correct handling of HLA data and key patient-donor matching procedures:

- ‘Framework for the implementation of HLA matching programs in haematopoietic stem cell donor registries and cord blood banks’.65 This article gives a bottom-up approach to the design of search algorithms: comparison of individual HLA codes, then HLA single-locus phenotypes and, eventually, HLA multi-locus phenotypes.
- ‘Guidelines for use of HLA nomenclature and its validation in the data exchange among haematopoietic stem cell donor registries and cord blood banks’.63

The algorithm has to recognise the description of HLA-typing codes, for example, multiple-allele-codes, as well as relations between HLA codes, especially DNA to serology mapping. Some algorithms even use antigen recognition site matching, amino acid sequences or nucleotide sequences. It is recommended that code-lists and code attributes are downloaded from specialist reference web sites.67,68
Validation

All implementations of the search algorithms need to be validated before being used. The Matching Validation Subcommittee of the WMDA IT Working Group runs a project comparing and validating a number of search algorithms of all participating registries. The registry should use the database provided by the IT Working Group, which is designed to evaluate the donor selection algorithm and ensures that it functions as designed.

Output

The basic system must also consider the output, which must be a search report displaying the donors and cord blood units in HLA matching order, as a minimum. WMDA standard 5.10 says that the search report should also display the date that the search request was received, as well as the date the search report was provided to the requestor.

Only active donors should appear in search reports, for example, a donor who is deceased should not appear. In general, the search output can be presented either through the user interface, or on a printed report or by being transmitted.
to other systems, such as EMDIS. A notable issue in search output design is the display of HLA-typing, which may include HLA allelic strings, which are very long. The display may also use National Marrow Donor Program (NMDP) multiple-allele-codes.68

It is common practice to highlight patient-donor HLA mismatches and to group donors by match grade categories. Some systems also display matching predictions, which show the probability of a high-resolution phenotype match.

**Hardware infrastructure**

The issue of hardware infrastructure and its reliability should be a prime consideration. The following topics must be addressed, according to WMDA standard 5.03:3

- The security of the overall data system (standards 5.03 and 5.09).3
- Documentation (standards 5.12 and 5.14).3
- Backup and disaster recovery (standards 5.10 and 5.11).3

Hardware for information systems, as used in a registry, can differ depending on the size of the registry, the financial situation of a registry, or on how a registry is organised. Depending on the size of the registry, consideration should also be given to whether the system operates on a ‘stand-alone’ PC system or on a supported network.

All registries must have documents to describe key computer systems and network infrastructures. Documentation should include a global overview and description of the key computer systems and networking infrastructure which is being used. Furthermore, for hardware used for key registry processes, back-up systems should be available. Depending on the resources available at the registry, systems may have redundant components, or back-up systems may be on stand-by, ready to be activated when the main systems fail. Registries should have policies and procedures for implementing changes to hardware.

It is also recommended, as part of the general disaster recovery procedures, to have contracts with hardware suppliers to provide replacement hardware within an agreed time frame.
Connectivity is an important consideration, as there may be a requirement for a registry to be connected with customers or other registries. Electronic connection and communication with external organisations must be organised and performed with greatest possible security.

The registry should seek professional advice regarding IT infrastructure, covering the following topics: hardware configuration, servers, workstations, monitors, printers, scanners; network architecture, routers, firewalls, VPN (virtual private network); fault tolerance, RAID (redundant array of independent disks) configuration for hard drives, electricity power backup system, duplicate internet connections, data back-up solutions; security, antivirus software, regular updates of operation system software and external connections used to access registry data.

**Backup and disaster recovery plan**

The registry must have a written policy on how its information systems are backed up. A back-up should include databases, documents and everything related to key business processes. Back-ups should be performed regularly, to a fixed schedule, with the sole purpose that key systems, databases or files can be restored in case of system failure.

Back-ups can be performed automatically, locally at the registry by IT staff, or by specialists on behalf of the registry. This policy should include a schedule and interval of back-ups. This could be daily so that, in the event of interruption to a system, no more than a single day’s data would be lost. A higher frequency of back-up would reduce the amount of data lost, but may increase downtime, when users would not be able to access the system. A back-up should be a snap-shot in time, to make sure the information being backed up is consistent.

In case of system failures or loss of information, it is necessary that the files or databases which have been backed up can be restored. It is therefore apparent that back-up should be verified and tested periodically to ensure information is recorded properly, in order to satisfy WMDA standard 5.11.³
If a major disaster strikes, even back-ups stored on-site may be lost. It is therefore also very important that back-ups are stored in a secure place off-site, at some distance from the registry's location. Considering the confidentiality of the data contained in the back-up, this off-site back-up should be securely stored – if it is stored electronically at a different location, it is recommended that the data should be encrypted.

Back-up and disaster recovery is a broad topic. For more information check the WMDA Crisis Response, Business Continuity and Disaster Recovery Guidelines, issued by WMDA Quality Assurance Working Group.\textsuperscript{78}
8 · Finance and administration
Summary

Currently, more than 45% of the stem cell donations made worldwide are shipped from one country to another country. In 2012 stem cell donations were shipped to 56 different countries. In view of the ever-growing number of donor registries and cord blood banks around the world, it is evident that a smooth and efficient cooperation between all registries is crucial for all parties involved, which will lead to the best results for the patients. Guaranteeing the best possible cooperation and striving continuously to improve it is a constant challenge.

The elements of cooperation include administrative procedures, infrastructure and communication systems, which need to be built with the ultimate goal of providing the best possible match for any patient in the world as rapidly as possible and, if possible, without financial considerations or constraints.

Whereas the laws of many countries prohibit the purchase and sale of haematopoietic stem cells, most, if not all, allow for payments associated with the collection, transportation, implantation, processing, preservation, quality control and storage of such cellular products. The relevant laws may differ from jurisdiction to jurisdiction, so applicable laws and regulations must be carefully assessed before entering into a financial transaction. You are encouraged to seek the advice of a qualified legal professional in your jurisdiction. The information contained in this handbook is for information only, and does not constitute legal advice.

Preamble

This chapter was prepared in order to define a framework for the administrative and financial aspects of the international cooperation between requesting and supplying registries. This chapter aims to define the best practice in this field and, where no unique recommendation is agreed upon; it is recommended that international organisations should try to work with one another to reach a resolution which is mutually acceptable.
**General considerations**

As clearly stated in the WMDA executive committee’s first special report on bone marrow transplantation using volunteer donors, international donor searches should be processed through a registry with responsibility for coordinating activities. Establishment of a registry in a country is a prerequisite for the efficient organisation of finances and administration. As a result, registries are fully responsible for the financial settlement of charges made for services they request on behalf of their patients and for the services they request on behalf of their donors.

The recommendations made in this chapter are not intended to take the place of specific agreements which already exist between any two parties. However, the recommendations should be taken into account where no such specific agreements exist.

**Legal entity**

The WMDA standard 2.01 indicates that: ‘A registry must be a legal entity or be contained within a legal entity operating within the laws of the country in which the registry resides’. The registry on the receiving end of payments – acting as a supplier – should complete, and submit to the requesting registry, any legal documentation needed for the requesting registry to comply with its legal filing requirements. A registry should check with national legal authorities to determine tax obligations.

**Business relationship**

As a consequence of the general considerations above, the formal business relationship governing the process of international donor search and stem cell procurement should be between one registry and another. Any international flow of information should pass through a registry. It is the responsibility of the registries to ensure that their own processes do not cause undue time delay or have any other negative effects on the search process. The registry plays the role of intermediary between the customer and supplier, facilitating financial events and transactions. The registry may also act as customer or supplier, as shown in the diagram below.
Registry responsibilities

Invoices for customers (requesting registries and transplant centres), and adjustments to invoices, should originate from the registry. Customer payments (from transplant centres and requesting registries) should be made directly to the registry. Supplier registries and medical service providers should directly invoice the registry. The registry is obligated to make payments directly to their suppliers.

Customer invoicing and payment

The registry must ensure that the invoices it issues and the payment of these invoices corresponds to services requested and rendered (e.g. extended HLA typing and/or verification (confirmatory) HLA typing, including shipping of blood samples).

The registry should invoice the customer in the currency the registry want to receive payment in. Invoicing and credit memos sent by the registry to the customer registry or transplant centre should include the following information:

- Patient identity (ID).
- Date of service performed.
- Type of service performed.
• Invoice number.
• Payment terms.
• Purchase order number, if available.
• Amount, by service line.
• Invoice date.
• Total amount due.
• Tax type, if applicable.
• Donor or cord blood unit identity (ID).

Invoices should be sorted by patient and list the type of service requested and fulfilled in relation to that patient. Customer invoices for services may be issued as soon as the service is definitely completed, for example, test results have been received by the requesting customer or transmitted by a fast and reliable medium, or blood samples are received in appropriate condition. The level of detail recorded on invoices should be sufficient to determine the service carried out and the details of the donor or patient.

Each registry should work with its suppliers and customers to determine the details required (see ‘Supplier invoicing and payment’). Invoices should be submitted to the customer within 60 days of the date of the service being completed and no later than three months from the date the service was provided.

Monthly statements should be provided listing all outstanding invoices. This practice helps confirm that payments have been received and processed correctly and it also informs the registry of any outstanding invoices. Payment should be made within terms agreed, in the currency stated on the invoice and according to the payment instructions provided by the registry. Payments should be accompanied by a remittance document provided by the registry, or the invoice or reference number or patient identification should accompany the payment.

Supplier invoicing and payment

The supplier invoice, adjustment and memos sent to the registry from supplier registries and medical service suppliers should include the following:

Develop a clear fee schedule for the services offered
information, along with a clear statement of the currency in which payment should be made:

- Patient identity (ID).
- Date of service performed.
- Type of service performed.
- Invoice number.
- Payment terms.
- Purchase order number, if available.
- Amount, by service line.
- Invoice date.
- Total amount due.
- Tax type, if applicable.
- Donor or cord blood unit identity (ID).

The registry’s payment to the supplier should follow the payment instructions given and payment should be made in the currency requested by the supplier. Payment should include all invoices due for a given payment cycle and should be accompanied by a remittance statement, referencing the invoices being paid by invoice number, invoice amount and invoice date. Any adjustments or credits taken should also be reflected in the remittance statement. Suppliers should provide monthly statements to their customers, listing all unpaid invoices. It is the responsibility of the registry requesting the services to directly pay the suppliers that provided services for search costs, product fees, donor expenses, collection centre fees and cancellation costs. See Chapter 7 for more information about building invoicing and finance into registry IT systems.

Pricing and fee schedules

Each registry is required to publish a fee schedule stating the effective date, billing triggers and price of each service offered. The fee schedule should be in the same currency as the invoicing for the services being offered. From the registry perspective the fee schedule has a dual purpose: It serves as catalogue to the customers (foreign registries and transplant centres) and it states the services and fees offered by the suppliers and foreign registries. It is common and accepted practice that a registry’s prices for services to national and international customers may vary. This variance is caused mainly by the supplier’s variation in costs, shipping and courier travel. The registry is required to invoice its
customers based on the customer fee schedule published and in effect at the time the services were performed. This also holds true for registries playing the role of supplier. Supplier registries are obligated to invoice the requesting registry according to the supplier fee schedule published and effective on the date the service is performed. Notice of changes in fee schedules should be provided via email at least 30 days in advance to allow registries adequate time to update their price catalogue. Estimated cost or prices should be listed for shipping and courier.

Services, procedures and fees

Any services requested internationally should be performed according to the recommendations of the WMDA. Registries invoice for costs associated with searching for and identifying an unrelated donor (search costs), costs incurred following the identification of a matched donor (product fees, donor expenses, collection centre fees), transplant costs and costs incurred after the work-up of the selected donor has begun and is subsequently cancelled by the requesting registry or transplant centre (cancellation costs).

Cancellation of services and requests

If any search service request is cancelled by the customer (i.e. requesting registry or transplant centre) the registry should do its best to inform the supplier (i.e. donor’s registry or medical service provider) and stop any activity related to the request. Charges to the customer (patient’s registry or transplant centre) are acceptable for any cost already incurred or caused within 21 days after cancellation of activities, if stopping was not reasonably possible. If a supplier registry fails to complete a donor work-up for whatever reason, a reasonable fee for the costs actually incurred up to that point is typically charged. If a supplier registry fails to fulfil a request, or fails to complete any other type of request for whatever reason, no charge may be levied for the efforts made by that registry in trying to provide the service requested. If a donor work-up is cancelled by the requesting registry, a cancellation fee may apply, over and above the fees for costs actually incurred up to that point.
Discrepant typing results

When unconfirmed blood samples are offered, the requesting registry is obliged to pay all fees, including the courier cost, even if re-typing of the samples gave discrepant results. Payment is required as long as the samples received were from the correct donor.

Confirmed blood samples may include a repeat HLA re-typing, performed in the country of the registry providing the donor. In case the verification (confirmatory) typing at the transplant centre shows discrepant typing results with well-established relevance to stem cell transplantation, the registry providing the sample should refund all fees, including the courier fee, immediately or an arbitration process can be used to agree a course of action.

Responsibility

The registry is only responsible for the accuracy of its own administrative services. The registry is not responsible for any service rendered by its national cooperating partners, apart from a possible refund of fees that may have been received for services provided.

Resolving conflicts

All disputes should be settled amicably. If arbitration is needed, the parties involved should agree on one or three arbitrators from registries of countries not involved in the dispute. As a last resort, any legal action must take place in the country of the defendant, according to national law.

Communication and exchange of data

All registries with a reasonably high exchange of searches should make reasonable investment into their IT systems in order to speed up searches, avoid errors and reduce costs. The aim of such projects should be to allow systems to interconnect and to limit the cost of such a challenging worldwide enterprise by adhering to established standards at all levels.
Preliminary search

Chapter 3 of the handbook explains how to start a preliminary search for patients by sending the HLA-type of the patient to international registries, so they can check to see whether potential donors are available. Preliminary searches should be free of charge for international patients.

Activation

Registries should make reasonable efforts to eliminate activation fees for international patients. Any costs to be recovered should be calculated into each actual service rendered.

Requests for tests or blood samples

Unless agreements state otherwise, a request not finally completed within 90 days should be regarded as expired and no payment can be requested, even if it is fulfilled after that date. Nevertheless, the requesting registry should be explicitly informed about the termination of work on such requests. For requests for blood samples, providing such information is mandatory.

If the requesting registry explicitly indicates that a service should be performed, irrespective of the time frame required, the registry is obliged to pay, whenever the request is completed. Such requests will be followed through until they are explicitly cancelled, the search for the patient is stopped, or the donor becomes definitely unavailable.

Sample procurement for verification (confirmatory) typing

The fee schedule should indicate if testing for infectious disease markers is included in the fee for blood sample procurement and, if so, which infectious disease markers are routinely obtained. If infectious disease markers are not included in the fee for blood sample procurement, the fee schedule should indicate whether those tests are mandatory and are to be charged for, regardless of the requesting customer’s desire to receive the results from the registry. The
fee schedule should indicate whether courier expenses are included in the fee for blood sample procurement. The results of the verification (confirmatory) typing should be made available to the donor’s registry in due course.

**Donor work-up procedure**

The complete cost of a normal donor work-up procedure should be included in the stem cell collection fee. Special charges may be levied, if there is early mutual agreement in place, in cases with exceptional donor situations or additional requirements. A fee schedule should indicate the cost of cancellation of a collection, either as a flat fee or broken down to individual cost items. Whenever deviations from the standard fee schedule are to be expected, the customer should be informed as soon as possible.

**Postponement charges**

Postponement charges should be clearly identified on the fee schedule, along with details outlining the invoicing criteria, including time frames from initial physical examination and tests being repeated.

**Transport of products**

The procurement fee should effectively include every cost incurred up until the point where the suitably-packed cell product is handed to the courier leaving the collection centre. Deciding on the courier method and paying for the cost of such transport should be the responsibility of the recipient registry or transplant centre. It is advisable to have service level agreements in place with any couriers, which should set out when payment will be required and which party (courier or registry) is liable in case of adverse events relating to the product, whether that be stem cells, bone marrow or a cord blood unit. Consideration should also be given to whether appropriate insurance is needed to cover the courier process.

Indicate if courier costs are included in the fee.
Cord blood unit

The majority of cord blood banks have a collaboration with a registry that facilitates the communication between the requesting registry or transplant centre and the cord blood bank. A registry will establish a service level agreement with the cord blood bank, describing who is responsible for packaging, labelling, shipping and invoicing of samples requested and cord blood units provided. There are several aspects a registry needs to think about related to cord blood shipment, which differ from shipments relating to products given by adult volunteer donors.

A cord blood bank needs to establish guidelines related to the samples provided to requesting registries and transplant centres. A cord blood unit is stored in liquid nitrogen and there are only a few samples available for additional testing. Cord blood banks must maintain control of available additional cord blood samples and generally charge transplant centres for any testing they request. The most critical sample is the contiguous segment because it is the only sample that can be tested to verify that the original typing reported was obtained from the cord blood unit. This segment typing only needs to be performed once. The value of a cord blood unit to a transplant centre is diminished if the unit does not have a contiguous segment. This is because the lack of segment makes carrying out necessary verification testing difficult and this can cause delays in the transplant process.

Procedures need to be developed as regards what a cord blood bank should invoice for, if a transplant centre cancels the request for the cord blood unit after it has left the cord blood bank. Thought should also be given to when to invoice for the cord blood product. Some registries invoice when the cord blood unit has left the cord blood bank, while other registries invoice when the cord blood unit safely arrives at the transplant centre.
Glossary

**Activation (of a patient)** Administrative actions necessary when the first cost incurring service is requested for a specific patient.

**Activation Fee** Fee charged upon the completion of the first cost incurring request for a specific patient.

**Activation (of a donor)** Administrative actions necessary when some specific service is requested for a donor showing that this donor is under closer consideration for a specific patient.

**Allele** An allele is an alternative form of a gene (one member of a pair) that is located at a specific position on a specific chromosome.

**Allogeneic** (genetics) Derived from separate individuals of the same species. In stem cell transplantation, this is used to refer to both sibling transplants and unrelated donor transplants.

**Apheresis** Apheresis is a technology in which the blood of a donor or patient is passed through an apparatus that separates out one particular constituent and returns the remainder to the circulation.

**Autologous** Derived or transferred from the same individual’s body.

**Blood sample** Newly-drawn sample of blood from a potential donor and shipped to the tissue-typing laboratory designated by the transplant centre responsible for a patient.

**Bone marrow** The flexible tissue found in the interior of bones, where haematopoietic stem cells are produced.

**CD34** CD34 molecule is a cluster present on certain cells within the human body. It is a cell surface glycoprotein. CD34 is also the name for the human gene which encodes the protein.

**CFU-GM** Colony-forming unit granulo-monocyte. This is a colony-forming type of stem cell and is the precursor for monoblasts and myeloblasts.

**Chimerism** A state in bone marrow transplantation in which bone marrow and host cells exist compatibly, without signs of rejection.

**Chromosome** A chromosome is an organised structure of DNA and protein found in cells. It is a single piece of coiled DNA containing many genes.

**Consanguineous** Having the same ancestry or descent; related by blood.

**Cord blood** Blood contained within the placenta and umbilical cord after birth of the child. This blood is rich in haematopoietic stem cells, which can be used in transplantation.
Donor work-up  At this stage, a volunteer adult donor has been identified as an acceptable match for a patient, agrees to donate HPC after a full donor information and counselling session, and is medically evaluated for their fitness to donate HPC.

GCSF  Granulocyte colony-stimulating factor is a cytokine that stimulates the bone marrow to produce granulocytes (white cells) and HPC and causes these cells to mobilise (move) to the peripheral blood where they can be collected from the veins for transplantation.

Graft vs. Host Disease (GvHD)  A condition which can occur post-transplantation, when the donor (graft) cells attack the recipient (host) cells. GvHD can be chronic or acute and may be fatal.

Haematopoietic stem cells  Self-renewing stem cells which are found inside the bone marrow and which form blood cell components.

Haemoglobinopathy  Inherited single gene disorders, such as sickle cell disease.

Haemolysed  The rupturing of red blood cells

Haploidentical  Sharing a haplotype; having the same alleles at a set of closely linked genes on one chromosome.

Haplotype  A haplotype is a group of genes, which is inherited together from a single parent.

Heterogeneity  The condition of being heterogeneous.

Heterogeneous  Consisting of dissimilar elements or parts.

Histocompatibility  Having the same, or mostly the same, alleles of a set of genes called the major histocompatibility complex. These genes are expressed in most tissues as antigens, to which the immune system can respond (antibodies or T cells).

Homogenous  Consisting of similar elements or parts.

Homozygous  A genetic condition in which an individual inherits the same alleles of a particular gene from both parents.

Human Leukocyte Antigen (HLA)  The human leukocyte antigen (HLA) system is the name of the major histocompatibility complex (MHC) in humans. This super locus contains a large number of genes related to immune system function in humans. This group of genes resides on chromosome 6, encodes cell-surface antigen-presenting proteins and has many other functions. HLA is essential for immune function and is the basis for donor-patient matching in transplantation.

ICD coding  The International Classification of Diseases (ICD) is the standard diagnostic tool for epidemiology, health management and clinical purposes. It is used to monitor the incidence and prevalence of diseases and other health problems. It is used to classify diseases and other health problems recorded on many types of health and vital records including death certificates and health record
**Leukapheresis** Removal of white blood cells from the blood by means of apheresis.

**Locus (pl. Loci)** The specific location of a gene or DNA sequence on a chromosome.

**Nomenclature** A system of naming in arts or science.

**Registry** An organisation responsible for coordination of the search for HPC from donors (including cord blood) unrelated to the potential recipient.

**Peripheral Blood Stem Cell (PBSC)** Progenitor cells which give rise to blood and immune system cells. These cells are found in (GCSF-stimulated) peripheral blood.

**Phenotype** The observable physical or biochemical characteristics of an organism, as determined by both genetic makeup and environmental influences.

**Polymorphism** The occurrence of different forms, stages, or types in individual organisms or in organisms of the same species.

**Preliminary search procedure** Transmission of patient data including HLA in a database in order to check the total number of potentially suitable donors or cord blood units available including their tissue types and other relevant attributes. Ideally, a list of individual donors will be returned which includes gender, age, CMV status and blood group (if known).

**Serology** The scientific study of plasma serum and other bodily fluids.

**Transplantation cell product** Includes any product derived from any donor to be transplanted into any recipient (e.g. bone marrow, GCSF-stimulated peripheral stem cells, donor leukocytes, cord blood.

**Verification (confirmatory) typing** This HLA typing includes the tests carried out on a fresh sample of a specific donor or on an attached-segment of a cord blood unit with the purpose of verifying the identity and concordance of an existing HLA assignment. This stage used to be referred to as ‘Confirmatory Typing (CT)’.
Directory of organisations


**Bone Marrow Donors Worldwide (BMDW)** An international organisation which collects and displays the HLA phenotypes and other relevant data of volunteer stem cell donors and cord blood units, to facilitate stem cell transplantation. [www.bmdw.org](http://www.bmdw.org).

**Centre for International Blood and Marrow Transplant Research (CIBMTR)** Organisation of basic and clinical scientists researching important issues in blood and marrow transplantation. [www.cibmtr.org](http://www.cibmtr.org).

**Eurocord** An organisation which aims to promote the advancement of scientific academic and industrial research, the development of therapeutic applications and dissemination of knowledge related to the umbilical cord, placenta, annexes and more generally all that is within the field of materno-foetal interactions. [www.eurocord.org](http://www.eurocord.org).

**European Federation for Immunogenetics (EFI)** Sets a series of standards for laboratories to adhere to and works to create relationships with other organisations worldwide that carry out similar work. [www.efiweb.eu](http://www.efiweb.eu).

**European Group for Blood and Marrow Transplantation (EBMT)** A non-profit organisation that was established in 1974 in order to allow scientists and physicians involved in clinical bone marrow transplantation to share their experience and develop co-operative studies. [www.ebmt.org](http://www.ebmt.org).

**European Marrow Donor Information System (EMDIS)** The EMDIS system integrates the national blood and marrow donor registries worldwide, automating all search and business processes between the national databases and networks. [www.emdis.net](http://www.emdis.net).

**Foundation for the Accreditation of Cellular Therapy (FACT)** Founded in 1996, FACT establishes standards for high quality medical and laboratory practice in cellular therapies. FACT is a non-profit corporation co-founded by the International Society for Cellular Therapy (ISCT) and the American Society of Blood and Marrow Transplantation (ASBMT) for the purposes of voluntary inspection and accreditation in the field of cellular therapy. [www.factwebsite.org](http://www.factwebsite.org).

**International NetCord Foundation** Aims to promote the highest quality in cord blood products through worldwide standards and accreditation; to balance global supply and demand for umbilical cord blood and to encourage and facilitate the use of cord blood transplants by promoting laboratory and clinical research and providing professional and public education. [www.netcord.org](http://www.netcord.org).
International Society for Cellular Therapy (ISCT)  A global association driving the translation of scientific research to deliver innovative cellular therapies to patients. Founded in 1992, ISCT is a global forum for developing and supporting innovative cellular therapies through communication, education and training. www.celltherapysociety.org.

Joint Accreditation Committee-ISCT (Europe) & EBMT (JACIE)  A non-profit body established in 1998 for the purposes of assessment and accreditation in the field of haematopoietic stem cell (HSC) transplantation. www.jacie.org.

World Health Organization (WHO)  The directing and coordinating authority for health within the United Nations system. It is responsible for providing leadership on global health matters, shaping the health research agenda, setting norms and standards, articulating evidence-based policy options, providing technical support to countries and monitoring and assessing health trends. www.who.int.

World Marrow Donor Association (WMDA)  An international association to facilitate the exchange of high quality haematopoietic stem cells for clinical transplantation worldwide and to promote the interests of donors. The WMDA works towards the goal that high-quality and secure haematopoietic stem cell products are available for all patients worldwide while maintaining the health and welfare of stem cell donors. WMDA cares for donors who save patients’ lives by concerning itself with donor safety, education, globalisation, standards and accreditation. www.worldmarrow.org.

Worldwide Network for Blood and Marrow Transplantation (WBMT)  A non-profit scientific organisation with the mission to promote excellence in stem cell transplantation, stem cell donation and cellular therapy. www.wbmt.org.
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W
Since the first successful unrelated bone marrow transplant in 1973, over 300,000 unrelated blood stem cell transplants have been performed worldwide. This would not have been possible without the existence of blood stem cell banks (also known as registries) in many countries. Still, not all patients in need of a blood stem cell transplant are able to find a suitable donor or cord blood unit even today, which motivates people to start up new registries or cord blood banks in countries which do not have one yet.

Which factors contribute to the success of a registry and how can a registry remain successful in the future? These and many more questions are answered in the first handbook for blood stem cell donation, launched by the World Marrow Donor Association (WMDA). Valuable information and guidance about setting up and running a registry can be found in this comprehensive book which is an interesting read for both registry personnel and professionals involved in blood stem cell donation, as well as people interested in setting up a new registry.

‘This handbook is a MUST for anyone who is actively involved in one of the many activities necessary for a successful unrelated stem cell transplant!’

– Jon J. van Rood, WMDA President 1988-1999