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Review of the HPC sector Final Report

Department of Health

Review of the HPC sector

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Executive summary

Haemopoietic progenitor cell (HPC) transplants, more commonly known as stem cell transplants, are an important life-saving treatment for many Australian patients suffering from certain haematological malignancies (such as leukaemias), bone marrow failure syndromes and genetic abnormalities. Clinicians prefer to rely on a genetically matched relative to provide a stem cell donation to support a patient's transplant. However, where this is not possible, a patient will have to rely on an unrelated HPC donor.

Bone marrow donor registries recruit, register and search for HPC donors. In Australia, the Australian Bone Marrow Donor Registry (ABMDR), which manages the national registry, is responsible for these activities. Cord blood banks (CBBs) bank cord blood units (CBUs), which are another source of stem cells.

PricewaterhouseCoopers Australia (PwC) was engaged by the Commonwealth, on behalf of all state and territory governments, to undertake this review to consider whether the HPC sector was efficiently, effectively and appropriately structured to meet future needs. The report considers the sector's ability to provide Australians with access to HPCs for transplantation, Australia's place in the broader international network of HPC providers, and the regulatory context. The scope of the review included:

a. assessing the current state of the sector, including clinical demand and trends, governance arrangements, costs and service delivery models

b. presenting future needs, including registry and clinical needs, and options to better meet those needs.

Current state and findings

The ABMDR has successfully operated for 27 years, acting as Australia's only bone marrow donor registry, providing unrelated donors for patients requiring bone marrow transplantation. It has done so in collaboration with the international community, building strong links to ensure Australian patients can identify the best donor for their treatment.

As a measure of success, evidence shows that very few patients don't find a match. However, many patients may find a less desirable donor (for example, a mismatched donor) or need to rely on an international donor who is a better match than an Australian donor. In some cases, a clinician may pursue an alternative treatment pathway altogether. In addition, where an international patient is looking for a donor, Australia plays an important reciprocal role, providing Australian donors for international patients.

The ABMDR is supported by transplant centres, the Australian Red Cross Blood Service (ARCBS) and pathology laboratories to coordinate and deliver the operating activities of the HPC sector.

The sector has traditionally relied on the ARCBS, which recruits blood donors, to also recruit donors to the bone marrow registry. However, over the last 20 years, a number of changes in the HPC sector have shifted its donor recruitment criteria. This is partly due to clinical advances, which mean that a greater number of older patients may now be treated. In addition, Australia's growing diversity means volunteer donors need to have broader genetic diversity to enable patients to find a match. Finally, changing clinical preferences have also driven the preference for peripheral blood, over bone marrow or CBUs, as the primary source of unrelated HPCs.

While blood donors are an important and committed cohort, many of the characteristics of these donors do not align with the clinical needs of HPC donors. The ideal donor pool is made up of young males from an ethnically diverse cohort. Currently, the states and

territories lead recruitment activities through agreements with the ARCBS; however, its blood donor recruitment pool and broader sectoral changes means these arrangements will not support the future needs of the bone marrow registry.

Contractual agreements, funding and oversight

The organisation and responsibility of entities within the HPC sector is fragmented. The Commonwealth's primary funding agreements support the ABMDR. The state governments have funding agreements with ARCBS for activities associated with recruiting, coordination and tissue typing (the type of test used to measure genetic compatibility between donor and patient). Transplant centres in public hospitals across Australia collect and transplant HPCs.

The ABMDR is funded through two primary contractual agreements. The Core Services Agreement specifies program objectives relating to the International Donor Registries Search Project and management of the ABMDR. The second agreement (the NCBCN contract) specifies objectives for managing the National Cord Blood Collection Network (NCBCN) and the Australasian Bone Marrow Transplant Recipient Registry (ABMTRR). The Commonwealth and state and territory governments have funded the NCBCN in accordance with the AHMAC cost shared arrangements (50% Commonwealth, 50% between the States and Territories) since 2001.

While the Core Services Agreement specifies that the ABMDR updates and maintains the donor registry, it does not contain clear performance indicators or reporting milestones, such as the size and composition of the registry and whether it should be self-reliant for Australian donors.

The NCBCN agreement sets out clear objectives and activities to manage the collection and banking of cord blood for Australians.

The financial and contractual arrangements underpinning the ABMDR and its operations have been largely unchanged in recent years. This review has identified that the funding appears to be insufficient to cover the registry's activities. This has meant the ABMDR has had to use funds obtained from supplying Australian HPCs internationally. In contrast, the NCBCN has sufficient funding.

The activities of the ARCBS, such as donor recruitment, tissue typing, and search and match coordination are covered by its agreements with state governments in NSW, Victoria, South Australia and Tasmania. The ACT and Northern Territory are captured under the contractual agreements in NSW and South Australia, respectively. Queensland and Western Australia hold agreements with the ARCBS to undertake donor recruitment, but hold agreements with Pathology Queensland and PathWest, respectively, to undertake tissue typing and search and match coordination. These agreements cover a number of other services provided by the ARCBS, making it challenging to extract specific details, such as the cost of providing tissue typing services, and do not set out clear performance indicators or reporting requirements for items such as recruitment targets.

All governments also fund the activities of the ABMTRR, which reports the outcomes. The funds flow through the ABMDR, while St Vincent's Hospital in NSW governs the ABMTRR's activities.

The Commonwealth, states and territories are all represented on the ad hoc Jurisdictional Haemopoietic Progenitor Cell Committee, which provides some oversight to the sector. This committee is an effective decision maker for matters relating to the NCBCN, but it is not as effective for other parts of the sector. The current arrangements do not allow the committee to provide the central oversight, coordination or strategic guidance the sector needs.

Donor pathway

A patient undergoing an HPC transplant falls into one of three categories:

- An autologous transplant which involves collection of a patient's own stem cells before treatment and returning them to the patient to re-establish their blood-forming system.
- In an allogeneic-related transplant, the stem cells of a matched related donor – often a sibling – will be used to give a patient a new blood-forming system.
- In an allogeneic-unrelated transplant, the stem cells of an unrelated donor will be used.

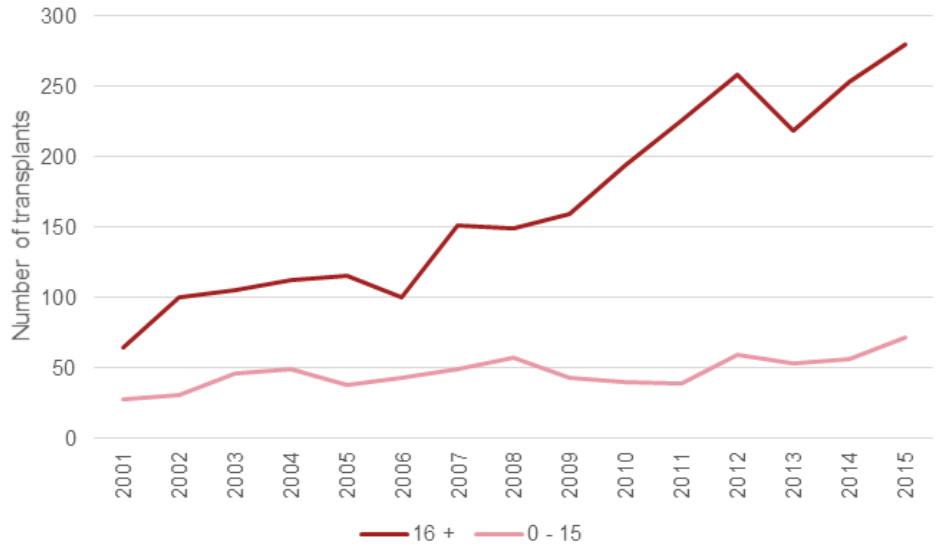
The patient's condition determines which transplant pathway is relevant to their treatment. For allogeneic transplant patients, the source of stem cells will be primarily determined by the closeness of the donor match, which is identified through tissue typing. If a patient does not have a suitably matched relative who is willing to act as a donor, the treating transplant centre will initiate a search of the registry for a match to use in an allogeneic-unrelated transplant. The match will look at the compatibility of tissue typing between patient and volunteer donors.

State Search Coordinators use the ABMDR's MatchPoint system to search for domestic and international donors who may be a potential match for a patient. They then report to the clinician on the likelihood of finding a suitable match. Donor Coordinators assist with organising the consent and testing of volunteer donors. Before a donor is selected, verification typing (additional tissue typing to confirm a match) may be performed on a number of volunteers who are a promising match.

Demand for donors

Demand for unrelated HPCs is growing as the clinical indications for their use expand, family sizes decrease and the ageing population leads to older patients being given transplants.

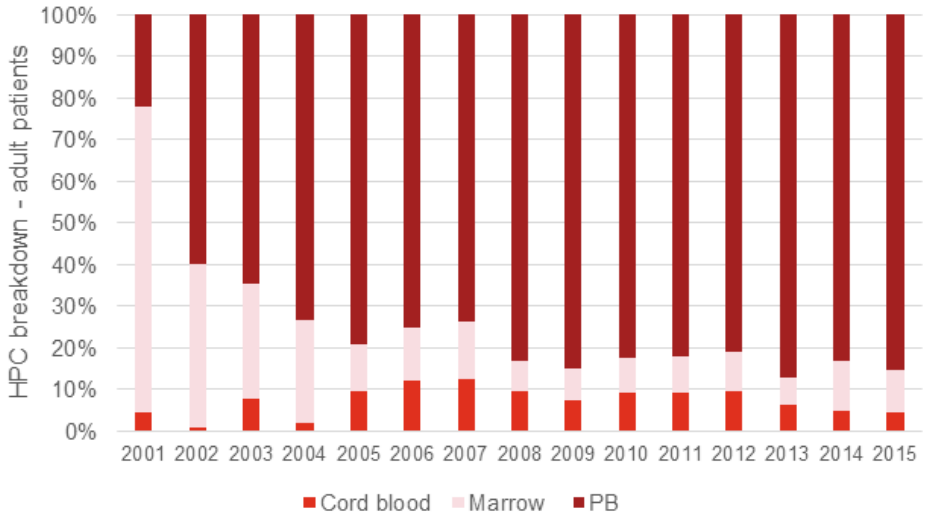
Figure 1: Paediatric and adult allogeneic transplants, 2001–15



Source: ABMTRR (2015) Matched unrelated donor HPC transplants report

The method of obtaining stem cells has changed over time, with the majority (approximately 80%) of stem cells now collected from peripheral blood using an apheresis machine (a machine which separates the HPCs from the blood and returns the blood back to the donor). Compared with other sources, the proportion of CBUs used in adult and paediatric transplantation has declined over the last few years. However, due to the overall growth in HPC transplants, the number of CBUs used has roughly plateaued.

Figure 2: HPC source over time, adult patient allogeneic-unrelated transplants



Source: ABMTRR (2015) Matched unrelated donor HPC transplants report

In 2015, 1,706 HPC transplants were undertaken in Australia. Of these, 1,133 were autologous (single or staged), 222 were allogeneic transplants supported by a related donor and 351 were allogeneic transplants supported by an unrelated donor or CBU.

Donor registry

Australia's registry has 170,791 active donors, and around 5,500 new donors are recruited each year. These donors are located around Australia and are primarily recruited through blood donor centres.

The registry make-up is 64% females and the average donor age is 45. Only 9% of the registry is aged 20–29. Donors are retired at age 60, meaning that the registry is ageing and many current donors will be retired over coming years.

Consultations and literature identify a clinical preference for young, male donors. In 2015, 61% of verification typing requests were for male donors, confirming this preference. It is particularly pronounced in requests issued to international donors, where 73% were for males, with an average age of 37.7.

Recent figures suggest that recruitment approaches are adapting to the preference for younger donors, with approximately 40% to 50% of new donors registered falling within the 20–29 age bracket over recent years.

Australian donors play a critical part in supporting patients. However, Australia is increasingly relying on international donors to support its HPC needs. The primary factor leading to the selection of international over Australian donors is the tissue typing resolution of donors available to clinicians upfront. Many international registries use high-resolution typing methods, which provide more complete and detailed information on donors. In comparison, 71% of Australian donors are typed at low resolution, which means clinicians must request additional typing to assess a donor's suitability. This can delay decision making and prompts many clinicians to search concurrently for international donor options.

In summary, we noted:

- the ageing of our registry, while clinicians prefer younger donors
- the gender split of our registry, which is skewed towards female donors, while clinicians prefer male donors due to the reduced risk of Graft versus Host Disease
- the ethnic diversity of our registry, which is largely represented by Caucasian ethnicities, but with Australia's changing demographic make-up, the registry should be genetically diverse
- that many Australian donors are typed only to low resolution, meaning clinicians do not have upfront information to assist with decision making. Western Australia recently began retrospectively typing its donors to a higher resolution, which has increased the number of its volunteers called up to donate.

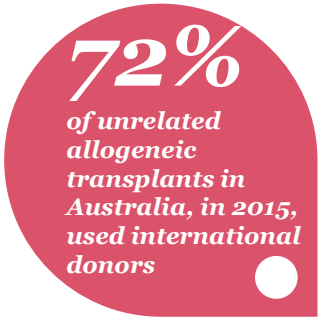
Compared to other countries, Australia maintains a large registry given its relative population numbers, ranking 22 in terms of size worldwide. For every 100,000 people, Australia has 699 registered donors. In comparison, the UK has 987 donors per 100,000 and Canada has 1,150 donors per 100,000. However, Australia has proportionally fewer donors typed across human leukocyte antigen (HLA) loci. Among all international donors, 16% are typed at six loci, while only 4% of Australian donors are typed to a similar level.

Australia holds the world's eighth-largest cord blood inventory, which is similar in size to Italy and France (33,965 as compared to 34,710 and 35,194, respectively).

Future needs

Alongside the issue of clinical preferences and the current donor sex and age profile the registry faces further challenges.

On average, only 33% of Australian donors are available for verification typing. This means there is a high chance that a potential donor will be uncontactable or unwilling to proceed. This can have significant implications in terms of effort, and for the patient, it delays finding a donor, and increases the risk that a donor will not be found.



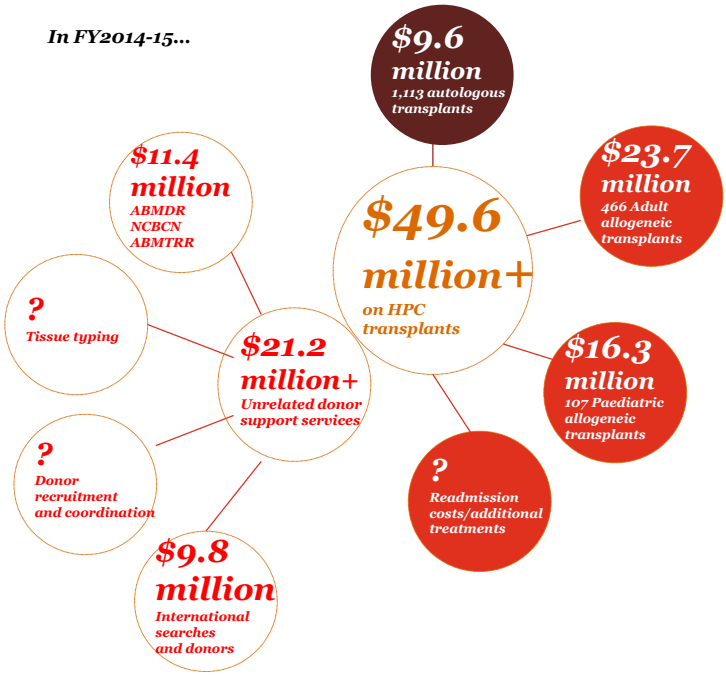
Australia relies on international donors for many of its patients. These donors are predominantly from Germany (60% of all internationally sourced HPCs) and to a lesser extent, the US and UK. Given population growth and clinical trends, as well as the increasing ability of older patients with clinical indications to undergo allogeneic transplants, the projected growth in demand for HPCs is significant.

If Australia does not address current challenges, including donor profile, resolution of tissue typing and availability, its reliance on international donors is projected to continue increasing. Based on recent trends, the number of international donors could grow from approximately 300 in 2016 to more than 500 in 2030.

Cost of the sector

The HPC sector is extremely costly. Clinical transplant activity, based on ABMTRR transplant figures and costing information from the Independent Hospital Pricing Authority, cost almost $50 million in FY2014–15, excluding readmission costs.

In FY2015–16, $11.9 million ($11.4 million in 2014–15) was spent on donor recruitment, tissue typing and maintaining Australia's unrelated donor registry. This figure includes the operation of the ABMTRR and the three CBBs. In FY2015–16, state governments spent an additional $6.3 million (FY2014–15 estimates are not available) on search and coordination activities to match and mobilise donors, and undertake tissue typing. A number of other costs associated with unrelated donors could not be identified in this review.



The Commonwealth, and state and territory governments fund the ABMDR through a series of agreements. In addition, the ABMDR draws on untied funding, which formed approximately 45% of its revenue of $1.3 million in FY2015–16, partly driven through cost-recovered funds from Australian peripheral blood and bone marrow HPCs distributed to international patients. Due to increasing costs, the funding appears to be insufficient for the ABMDR to fulfil its functions to recruit, maintain and manage the registry.

The cost of using international donors is rising as they contribute to an increasing proportion of HPC transplants undertaken in Australia. Based on trends in the number of applications, and average costs for the Commonwealth's Bone Marrow Transplant Program and International Searches Program applications, costs rose from $5 million in 2011 to $13 million in 2016. If growth continues at this pace, expenditure could reach nearly $20 million by 2029. If Australia is to reduce its reliance on international donors in the future, it is necessary to address the needs of the registry and its current challenges.

Australia's optimum registry size

The current state analysis identified a mismatch between clinical preferences and the average characteristics of donors on the registry and those selected to donate.

Additionally, the majority of donors on the registry identify as Caucasian. While ethnicity is not a definitive measure of haplotype diversity (an individual's group of genes), it is a proxy for the registry's genetic diversity and alignment with the general population, and suggests that some ethnic groups may be underrepresented.

Donor registries have two requirements: they must be fit for purpose in terms of the characteristics of their donors and they must consider the number of donors that should be maintained to support clinical need. The first requirement is largely influenced by the recruitment strategy a registry uses – including activities such as direct marketing, donor engagement, retention and ongoing communication – and the tissue typing laboratory engaged to deliver testing. The second requirement relies on recruiting sufficient donors to meet the quantum required to improve matching outcomes. To assess the number of donors

that might be needed, this review tested the suitability of the current registry's size and diversity.

To undertake this assessment, the review drew on modelling by the National Marrow Donor Program's (NMDP's) Bioinformatics Service, which assessed the Australian registry in 2016 to identify the probability of identifying a match among its 10 most represented ethnic groups. While non-Caucasian ethnic groups are important, their current representation on the registry meant their sample size was too small to be analysed in the modelling.

Leveraging the NMDP's modelling, the probability of identifying an identical (8/8) or mismatched (7/8) match for the 10 ethnic groupings was considered across the current registry size of ~160,000, as well as various registry sizes up to 2,000,000. This approach sought to understand how transplants are currently distributed among domestic and international sources of CBU, bone marrow and peripheral blood sourced from HPCs, and to consider how this might change with larger registry sizes.

The analysis, which was based on ethnicity reporting from the ABMDR and actual transplant data from the ABMTRR, identified that:

- improvements to the registry at its current size (~160,000) would increase the probability of finding a domestic (either identical or mismatched) match. These improvements include making high-resolution tissue typing information available to clinicians upfront and/or improving the donor profile (increasing the number of younger and/or male donors)
- increasing the registry size to ~720,000 would provide only marginal improvements in domestic matching. This is because the increase in size would not substantially reduce the number of international donors needed, while the number of domestic donors needed would have to be greatly increased
- across all registry size scenarios, as per the NMDP's work, most Caucasian donors can identify an 8/8 or 7/8 match. The probability of identifying an 8/8 or 7/8 match for other ethnicities is much lower, particularly for Sri Lankan, Chinese, Indian and Middle Eastern patients
- the registry is complemented by a CBU inventory that is a source of HPCs for many patients. The optimum size of Australia's cord blood inventory was considered in 2009 and 2016. It was found that an inventory of 30,000 CBUs should be achieved, with continued emphasis on enhancing HLA diversity and banking higher-quality CBUs.

To consider the gains in growing the donor registry, the relative costs of donor recruitment and typing, and of donor collections for domestic and international transplants, was assessed for each scenario. The results show that having a larger domestic registry may reduce the costs associated with international collection, but the current costs of recruiting and typing new donors to the registry are significant – and would produce relatively small gains.

Both the qualitative assessment and analysis of the cost-effectiveness of growing the registry suggest there are positive gains to be made in addressing its composition without significantly changing its size. This may result in higher usage by domestic donors and less reliance on international donors.

Given Australia's population size and the diminishing return on increasing the match probability with an expanded registry, the registry's current size aligns with our domestic needs. However, the profile of donors – mostly female, generally older and concentrated among certain ethnic groups – does not align with clinical needs. Therefore, the focus should be on improving the composition of the registry, the upfront information available to clinicians (by using high-resolution typing) and donor availability through re-engagement activities.

Potential options to meet future needs

To assess how the sector might be adapted to address these key findings, we considered the areas of donor recruitment, donor coordination, tissue typing, searching and matching activities, and the governance arrangements for the sector. The following five options were identified:

Option A – Status quo: This option assumes that activities continue as they are arranged today.

Option B – Improve tissue typing: Under this option, current tissue typing arrangements are changed to provide high-resolution results, either by centrally batching samples for processing at one preferred supplier or using 'demand hubs' around Australia. In addition, as searching and matching arrangements in most states are currently performed by the same provider that undertakes tissue typing, it is assumed that this activity should also be centralised or performed by demand hubs. Providing higher tissue typing resolution would improve utilisation of the Australian registry (where possible), and centralisation would provide an opportunity for more efficient and consistent services. However, there is a risk that expertise and the relationships between transplant centres and Search Coordinators supporting local practices and processes would be lost.

Option C – Improve recruitment and tissue typing: Under this option, tissue typing arrangements are altered in the same manner as option B, but recruitment activities are also changed to meet the needs of Australian patients. A recruitment strategy that targets the right cohort of donors (sex, age and ethnicities) would enable the Australian registry to better support the sector's needs and reduce reliance on international donors. As with option B, searching and matching arrangements would be aligned with tissue typing locations. In addition, it is likely that donor coordination would be centralised (or standardised) to align with the targeted recruitment approach. Under this option, a national approach would be taken to service delivery management arrangements for recruitment and typing, improving alignment across jurisdictions. However, wholesale change of management and contractual arrangements would not be needed. The key risks are in the contractual and funding arrangements, and the new registry operator(s) ability to provide analytics that would inform strategic recruitment efforts.

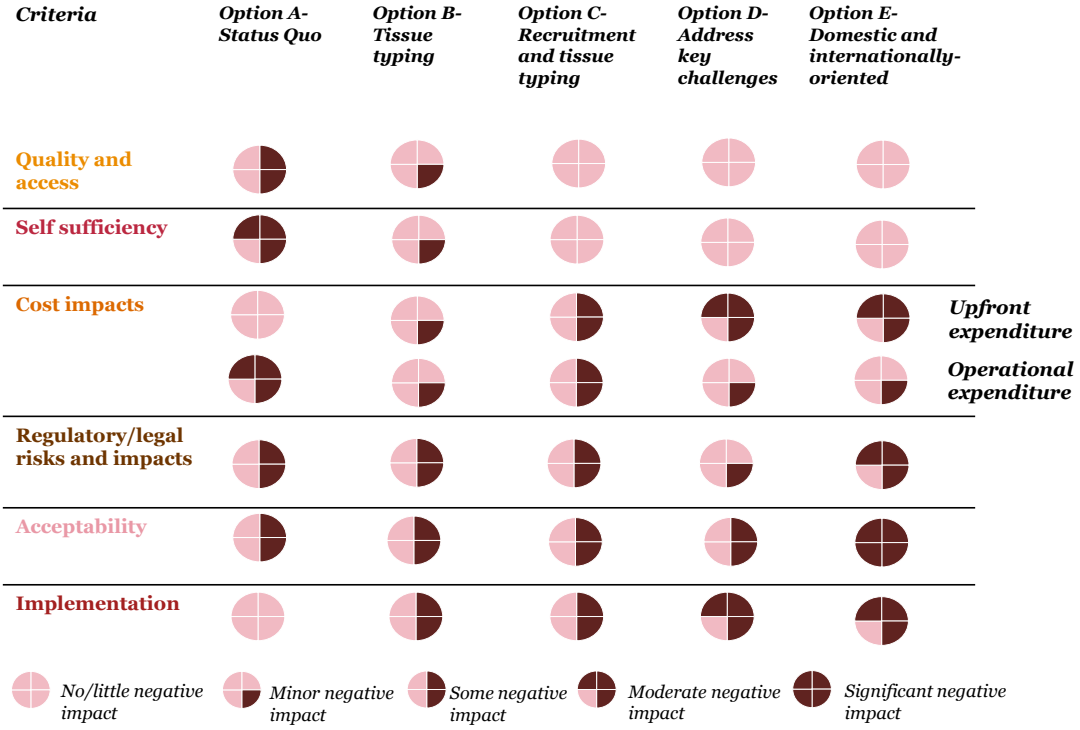
Option D – Redesign to address key challenges: This option builds on option C, changing arrangements for recruitment, tissue typing, searching and matching, and donor coordination, and also assigning responsibility for service delivery to one body. The changes cover both oversight and strategic direction provided by governments through more formal arrangements. The changes would include giving the registry manager(s) new and additional responsibilities for managing day-to-day operations through contractual arrangements, key performance indicators and performance reporting. Additional benefits include better oversight and control of the sector, gained through having a shared and coordinated strategy, and improved policy and decision making, as well as enhanced services coordination. The additional risks, beyond those outlined for option C, are governance or performance challenges associated with changed roles and responsibilities. It may also be impossible to identify a provider willing to manage some activities due to inexperience or lack of capacity, misalignment between the role and existing organisational objectives, or lack of desire to adopt new responsibilities.

Option E – Establish a domestic and internationally oriented registry: The final option builds on option D but extends into establishing a registry that addresses domestic and international needs. Collaboration with other countries to understand how the Australian registry can also support their needs, and developing a recruitment strategy that targets donors who would meet those needs would be required. Under this option, the number of donors would increase. For this reason, it is better suited to a leaner approach to service delivery, which might include batching tissue typing, allocating typing to one laboratory and providing central searching and matching, and recruitment, activities. The benefits would be enhanced international collaboration and an increase in HPCs Australia provided to donors worldwide. The latter would contribute to the financial sustainability of the administering

organisation. The risks of this option are reputational damage and loss of public trust from increasing the amount of HPCs Australia distributes to international patients, greater resourcing requirements to support more donors and collections, and higher operating costs associated with managing a larger, more active registry.

These options were evaluated against the criterion of quality and access; self-sufficiency; cost impacts; regulatory/legal risks and impacts; acceptability; and implementation. Figure 3 presents the results of this evaluation.

Figure 3: Assessment of options



In this assessment, Option A performs poorly because there are no improvements to the challenges identified in the sector and there is a growing reliance on international donors, which increases costs and means the sector does not meet its goal of self-sufficiency.

Option B addresses some of the issues identified, such as improving tissue typing activities, but it does not solve recruitment and governance challenges; therefore, it is likely to incur growing operational costs while failing to recruit donors who more closely align with clinical preferences.

Option C would cost more to implement, but it would improve tissue typing resolution and recruitment of targeted donors to address clinical needs. However, it would not address structural and process issues; therefore, it is likely to be less acceptable to key stakeholders.

Option D, which envisages changing the operation and oversight of the sector, and tissue typing and recruitment arrangements, would require greater upfront costs and effort to implement than Options B and C. However, it would better address current challenges in recruitment and tissue typing, and hand responsibility for service delivery to one entity, resolving issues with fragmentation.

Option E would be more complex and costly to implement, but by addressing structural and governance challenges, it would improve the quality of the sector and make it self-sufficient, while also cutting the cost of relying on international donors.

Option E would probably also reduce Australia's reliance on international donors. However, overhauling the sectoral arrangements and orienting activities towards providing more HPCs to international recipients would probably be less acceptable, particularly to governments and donors, and risks undermining public confidence in the sector.

Next steps

This review has outlined the importance of the many roles and activities within Australia's HPC sector. Across all organisations and individuals consulted, there was a shared commitment to supporting patients to ensure they can access HPCs for transplant treatment if needed. This cannot be achieved without altruistic donors whose commitment is vital to assisting patients who don't have a related match.

This review was undertaken to identify challenges and offer solutions so that organisations and individuals within the HPC sector can meet the future needs of clinicians and patients. It found that current arrangements are not optimal for a cost-effective and efficient HPC sector. We recommend that governments consider the options set out in this review and undertake next steps, which include:

- establishing a direction for the sector by developing an intergovernmental position that considers strategic objectives for the next 5–10 years: this position, together with a detailed costing of the preferred option(s), can then be used to agree and develop a strategy
- aligning funding and contractual agreements: governments should establish governance arrangements and high-level contractual agreements with the relevant organisations undertaking activities in the sector, in line with the preferred options
- readiness and implementation: a strategic direction should be set, and selected service provider(s) should develop implementation and business plans. The registry manager(s) should appoint service providers and establish desired service delivery arrangements. Finally, they should implement the agreed changes, which may cover organisational roles, responsibilities and reporting.

Contents

1

Background

This chapter covers...

- *brief background to the key programs and entities that support the HPC sector in Australia*
- *the scope and approach adopted to undertake this review.*

1 Background

1.1 Introduction

Australian governments support the safe, affordable and clinically appropriate provision of haemopoietic progenitor cells (HPCs) for Australian patients by funding the Australian Bone Marrow Donor Registry (ABMDR), the National Cord Blood Collection Network (NCBCN), the International Searches Program (ISP), the Bone Marrow Transplant Program (BMTP) and the Australasian Bone Marrow Transplant Recipient Registry (ABMTRR). These programs support Australians in sourcing domestic and international HPCs for clinical treatment.

The key programs and entities that support the HPC sector are described below.

1.1.1 The Australian Bone Marrow Donor Registry

The ABMDR manages a national registry of volunteer HPC donors and coordinates searches for unrelated donors through that registry and affiliated international registries. The Commonwealth government provides funding for core services.

The ABMDR also administers the NCBCN, which is funded by the Commonwealth, and state and territory health departments.

Additionally, the ABMDR provides funding to the ABMTRR, which collects and reports on outcome data relating to all autologous and allogeneic HPC transplants. The ABMTRR also receives funding from other avenues to support its activities.

1.1.2 State and territory governments

State and territory governments support the operation of the HPC sector through direct funding for tissue typing provided under service agreements with the Australian Red Cross Blood Service (ARCBS), PathWest and Pathology Queensland.

Victoria, NSW, Queensland, Tasmania, South Australia and Western Australia have agreements with the ARCBS to provide volunteer donor recruitment and initial tissue typing services to the ABMDR registry. In Victoria (which includes Tasmania), NSW (which includes the ACT) and South Australia (which includes the Northern Territory), the ARCBS is also funded through these agreements to provide tissue typing services for searching and verifying unrelated donors. In Western Australia and Queensland, these services fall under agreements with PathWest and Pathology Queensland, respectively.

Additionally, the treatment of HPC transplant patients is supported through state-based health systems, which provide integral care to patients throughout their journey from diagnosis to transplant and remission.

1.1.3 The National Cord Blood Collection Network

The NCBCN is a network of three public cord blood banks (CBBs), located in Melbourne, Sydney and Brisbane. The banks collect, test and store cord blood units (CBUs) that may be used for unrelated HPC transplants. Together, they maintain Australia's public cord blood inventory.

1.1.4 The Haemopoietic Progenitor Cell Program

The Haemopoietic Progenitor Cell Program (HPCP) is funded by the Commonwealth Government that supports access for Australians to HPCs. Many Australians have to look internationally for a donor match. HPCP supports this through two sub-programs:

- the International Searches Program (ISP), administered by the ABMDR and

- the Bone Marrow Transplant Program (BMTP), administered by the Department of Health.

The programs provide Australian patients with financial support to search for an international donor match and facilitate collection of HPCs from a donor. The HPCP also supports and administers ancillary costs, such as for travel and couriers to transport HPCs.

The International Searches Program

The ISP provides funding to the ABMDR to enable it to search international registries on behalf of Australian patients.

To access the program, transplant centres apply to the ABMDR for funding approval to search for international donors. Funding covers the cost of searching international HPC registries and the associated expenses for tissue typing that may be required to seek further genetic information on a donor, and/or to confirm they match a patient. The ABMDR structures and manages the funding, and also has relationships with the international registries.

The Bone Marrow Transplant Program

The BMTP supports Australian patients to access international HPCs identified through the ISP as a match. Once an international donor is identified for an Australian patient, the treating transplant centre will initiate a funding application to the Commonwealth, which administers the BMTP, for accessing that international donor. The BMTP supports the costs associated with an international donation (whether for a CBU, bone marrow or peripheral blood donation). This includes the costs associated with further testing of the donor, and for collection, the courier and travel.

Eligibility for the program is guided by the following criteria[2]:

- The patient must be a permanent resident of Australia.
- The patient must be eligible for assistance under Medicare (that is, they must hold a current Medicare card).
- A suitable donor is not available in Australia.
- There must be a real prospect of success.
- The treatment must be life extending.
- The treatment must be beyond the experimental stage (that is, it must be an accepted treatment modality).

The BMTP also funds some costs associated with related HPC donations when a relative of an Australian patient lives overseas and is deemed the best clinical match for an Australian patient.

1.2 Scope

The terms of reference of this review are:

- The review must have regard for governments' continuing commitment to providing Australians with access to HPCs for transplantation, Australia's place in the broader international network of HPC providers and the Australian regulatory context.
- The review will:

[2] Department of Health, Haemopoietic Progenitor Cell Programme, accessed at: http://www.health.gov.au/internet/main/publishing.nsf/content/health-organ-bmtransplant.htm, 10 January 2017.

a. analyse the present clinical demands, and existing and future trends for using HPCs for transplantation treatment in Australia

b. analyse the models, costs and funding of the Australian HPC sector, including the costs of services and activities delivered by the Commonwealth, and state and territory governments, as well as total costs over time to identify trends and forecast future costs

c. analyse the governance and regulatory arrangements for the Australian HPC sector

d. assess the HPC sector in other relevant countries (for example, Canada, the UK, the US, Germany, Spain and France), including their models, trends, costs, funding, regulatory framework and governance, to inform recommendations on future strategic directions to allow the Australian HPC sector to meet the expected needs for the next decade

e. assess the appropriateness and effectiveness of the current structure for accessing HPCs in Australia and identify the relationships between different elements of the sector; consider the costs associated with maintaining funding models for the existing programs and develop alternate, more efficient, structures or models of delivery, accountabilities and performance management mechanisms

- The review will provide findings and costed options for refining processes and/or structures for the four programs, including governance arrangements that will most cost-effectively meet governments' continuing commitment to providing access to HPCs, and an assessment of any risks associated with each option
- The review will have regard for the research and findings of the 2016 Stage Two Review of the NCBCN.
- In addition to reviewing relevant data and written information, the reviewers will consult with:
  a. Commonwealth, state and territory health department representatives on the ad hoc Jurisdictional Haemopoietic Progenitor Cell Committee (ahJHPCC)
  b. the Australian Bone Marrow Donor Registry (ABMDR)
  c. Australian network of CBB and collection centres (AusCord)
  d. the Australian Red Cross Blood Service (ARCBS)
  e. the Australasian Bone Marrow Transplant Recipient Registry (ABMTRR)
  f. Other clinical experts as advised by ahJHPCC.

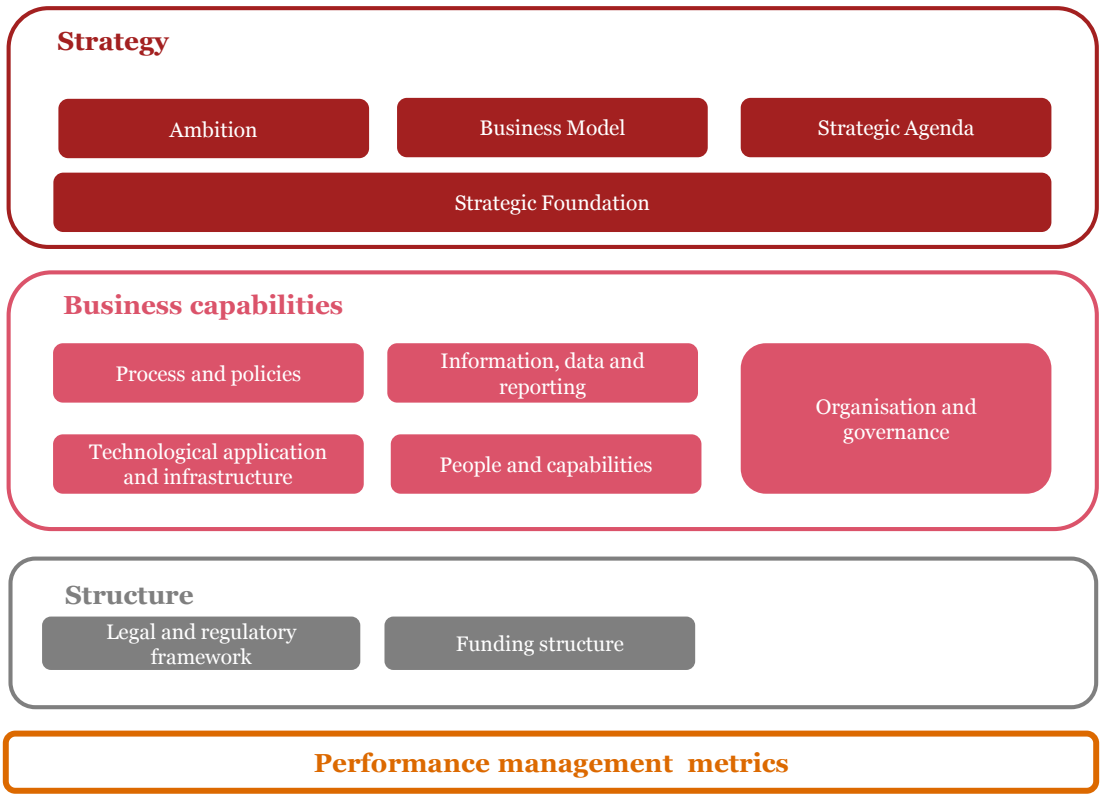
A note on scope:

- Transplants are costly, resource-intensive activities and, while important, this review does not explore the costs and clinical practices. However, it does examine the costs of collecting HPCs from volunteer donors, which is supported by bone marrow transplant units of public hospitals.
- This review has been unable to provide fully costed options due to a lack of available costing data. Costs have been presented where they have been collected through this review. This review provides an evidence base of the sector to inform future decision making.

1.3 Approach

PwC framed its approach to undertaking this review around its operating model framework, shown in Figure 4. The framework captures the elements of operational activities that the strategy, business capability, structure and performance metrics of the HPC sector are assessed against. While the ABMDR is the primary organisation of Australia's HPC sector, this review considers aspects more broadly, including the activities of other entities.

Figure 4: PwC's Operating model framework



PwC consulted with stakeholders identified by the Steering Committee and named in Appendix J. PwC collected data and other inputs from stakeholders to support the analysis in this report.

This review was also supported by the expertise of Dr Ashish Bajel, Consultant Haematologist and Bone Marrow Transplant Physician at The Royal Melbourne Hospital, and Professor Emeritus Loane Skene of the Melbourne Law School and Adjunct Professor of the Medical Faculty of the University of Melbourne. We are grateful for their contributions and guidance.

1.4 Report structure

This report has the following structure:

- Chapter 2: An outline of Haemopoietic Progenitor Cells and what they are used for
- Chapter 3: An assessment of the HPC sector
- Chapter 4: An outline of clinical indications and trends in the use of HPCs
- Chapter 5: A snapshot of HPC supply, including the characteristics of Australia's registry
- Chapter 6: A snapshot of HPC demand, including the current needs of Australian patients

- Chapter 7: Cost of HPC supply
- Chapter 8: Opportunities for the sector, reflecting Australia's future needs
- Chapter 9: An evaluation of potential options for the process, governance and structure for supporting Australia's HPC sector to meet future needs
- Chapter 10: Implementation considerations, including risks, governance and legal considerations associated with potential options.

2

Haemopoietic progenitor cells

This chapter covers...

- *the clinical needs and indications for HPC transplants*
- *the types of HPC transplants and sources of HPCs*
- *clinical decision making and donor matching to support allogeneic HPC transplants.*

Key messages:

HPCs are stem cells – sourced from peripheral blood, bone marrow and cord blood – used in HPC transplants. HPC transplants are used to treat a range of clinical indications, including haematological malignancies (such as leukaemias), bone marrow failure syndromes and genetic abnormalities.

HPC transplants can be either autologous (using a patient's own HPCs) or allogeneic (using HPCs from a donor). More autologous than allogeneic transplants are undertaken in Australia in any given year, but the indications for which type is used differ. As such, for patients requiring an allogeneic transplant, clinicians must identify an appropriate donor.

Clinicians first consider relatives, often a sibling, to donate HPCs for allogeneic transplant patients. However, for approximately 70% of patients requiring an allogeneic transplant, clinicians will need to consider unrelated volunteer donors (or cord blood units) listed on donor registries. Immunogeneticists perform the technical activity to match the human leukocyte antigen (HLA) (represented by alleles present at chromosome 6) complex of the patient with a donor. Patients can be perfectly matched to a donor, which is referred to as a 6/6 or 8/8 match (and in some instances, a 10/10). A mismatched donor is referred to as a 5/6 or 7/8 match. Current practice suggests that clinicians typically look to match a minimum of eight alleles for HPC transplants.

In addition to genetically matching a donor to a patient, clinicians also consider other aspects to identify which donor is the best match for a patient (if there are a number of genetically matched donors to choose from). This typically follows a decision hierarchy that looks for:

1. *the gender of the donor (clinicians prefer male donors)*
2. *cytomegalovirus (CMV) (a member of the herpes virus family) status (CMV negative donors are sought for CMV negative patients)*
3. *younger donors (to promote improved transplant outcomes)*
4. *blood group (when the same blood group is preferred).*

2 Haemopoietic progenitor cells

2.1 What are HPCs used for?

Haemopoietic progenitor cells (HPCs) are stem cells sourced from peripheral blood, bone marrow or cord blood for use in HPC transplants (also known as 'bone marrow transplants' or 'stem cell transplants'). A HPC is an undifferentiated cell that is capable of self-renewal and is multipotent (cells which can form into more than one cell type).[3] Other types of stem cells include embryonic and induced pluripotent stem cells, which are types of primitive cells. HPC transplants replace the blood-forming system of patients suffering from conditions including:

- haematological malignancies (types of leukaemia that are incurable with chemotherapy alone)
- bone marrow failure syndromes (for example, aplastic anaemia)
- genetic abnormalities (for example, metabolic storage disorders, haemoglobinopathies and immune deficiencies).

HPC transplant patients first undergo chemotherapy and/or radiotherapy (conditioning) to destroy their bone marrow cells, which are then replaced intravenously with healthy stem cells. These stem cells are sourced either from the patient themselves (autologous), a relative (allogeneic related match) or an unrelated donor (allogeneic-unrelated match).

2.2 Clinical need and uses

2.2.1 Clinical indications

The clinical indications that benefit from HPC transplants include[4]:

- chronic myeloid leukaemia
- chronic lymphocytic leukaemia
- acute leukaemia
- myelodysplasia
- myeloproliferative disease
- multiple myeloma
- Hodgkin lymphoma (disease)
- non-Hodgkin lymphoma
- other lymphoproliferative disorders (including hairy cell leukaemia)
- severe aplastic anaemia
- renal cell carcinoma
- paroxysmal nocturnal haemoglobinuria
- immunodeficiency diseases
- Fanconi anaemia
- inherited metabolic disorders
- marrow failure syndromes of restricted lineage
- pure red cell aplasia (Diamond Blackfan syndrome)
- congenital dyserythropoietic anaemia
- severe inherited platelet function disorder
- thalassaemia major
- sickle cell disease
- osteopetrosis

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3 *The EBMT Handbook: Haematopoietic Stem Cell Transplantation*, 6th edition, European School of Haematology and the European Society for Blood and Marrow Transplantation, Chapter 4.

4 ABMDR, 'Treatments – bone marrow transplant', accessed at: http://www.abmdr.org.au/treatments-bone-marrow-transplant/, 7 February 2017.

In addition to their traditional application in bone marrow transplants for the above conditions, there is an emerging field of applications and research for the use of stem cells. This includes regenerative medicine – using human-induced pluripotent stem cells – for tissue regeneration applications[5], cerebral palsy, myocardial infarction, spinal cord injuries and other applications, such as diabetes.

2.2.2 *Types of transplants*

There are two types: autologous and allogeneic transplants.

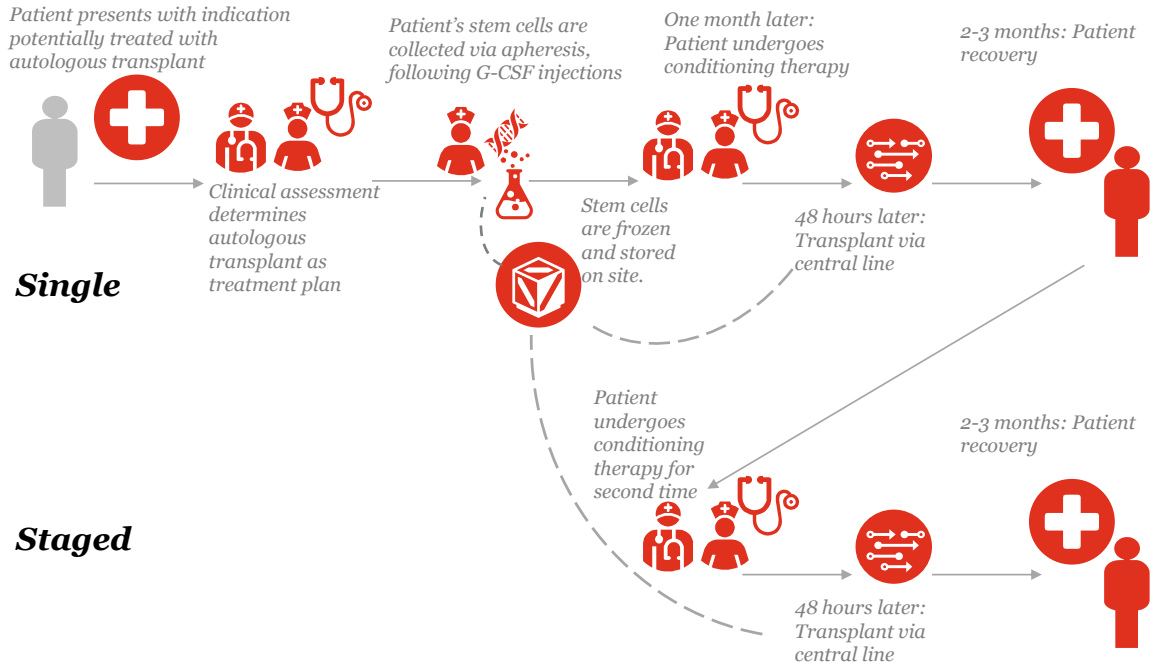
Autologous transplants

The vast majority of HPC transplants are autologous. These transplants involve collecting a patient's stem cells ahead of their treatment, and then returning the stem cells to them to enable them to reestablish their blood-forming system. Almost all collections of a patient's own stem cells are through apheresis collection (also known as 'peripheral blood collection' which is undertaken using a machine which separates the HPCs from the blood and returns the blood back to the donor). This treatment is used for patients undergoing high doses of chemotherapy.

As autologous transplants use a patient's own stem cells, risks associated with Graft versus Host Disease are not expected.[6]

Figure 5 shows a schematic of an autologous transplant patient's pathway.

Figure 5: Autologous transplant patient's pathway



Autologous transplants can either involve one transplant or staged multiple transplants.

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5 Matsumato T and Mugishima H (2009) Non-Hematopoietic Stem Cells in Umbilical Cord Blood, *International Journal of Stem Cells* 2(2) 83-89

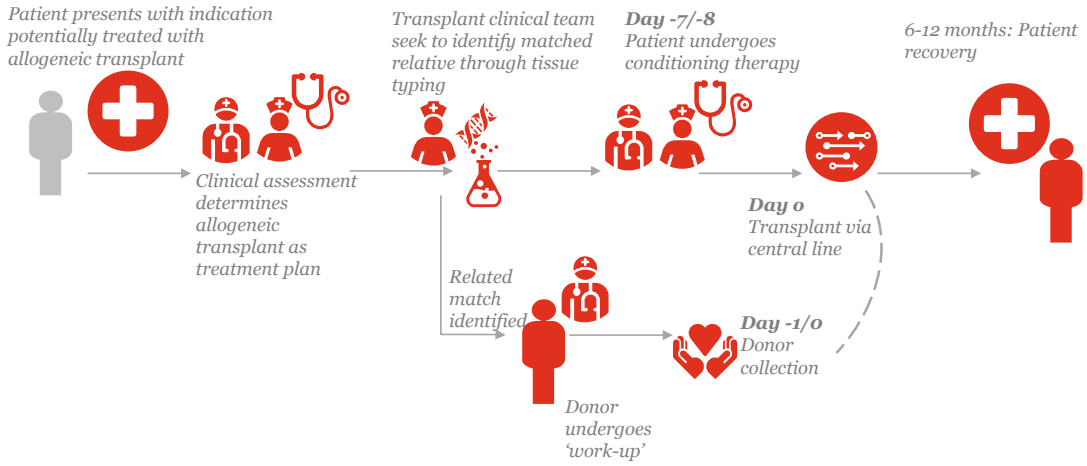
6 Department of Health and Ageing (2009) Review of demand for, and supply and use of, cord blood in Australia, prepared by HealthConsult Pty Ltd

Allogeneic transplants

Allogeneic transplants use stem cells derived from a person other than the patient. As stem cells are from another person, like blood groups, there needs to be a match between the patient and the donor. The matching process and levels of matching are described in section 2.3 of this report.

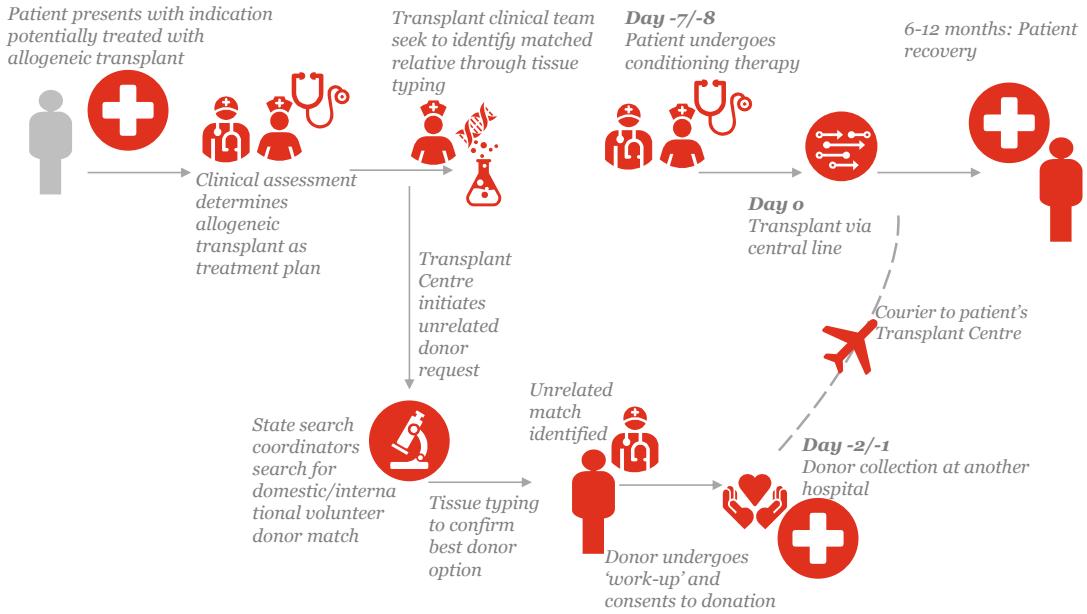
Because allogeneic transplants use stem cells from someone other than the patient, the pathway to transplant must include identifying the right stem cell source. To do this, transplant centres engage with a patient's family to identify whether there is a suitable relative who could donate to the patient. Figure 6 shows the usual patient pathway.

Figure 6: Allogeneic-related transplant patient's pathway



When clinicians cannot find a donor among a patient's relatives, they will search volunteer donor registries. Figure 7 shows the high-level pathway to transplant for these patients.

Figure 7: Allogeneic-unrelated transplant, patient pathway



2.2.3 *Transplant treatment*

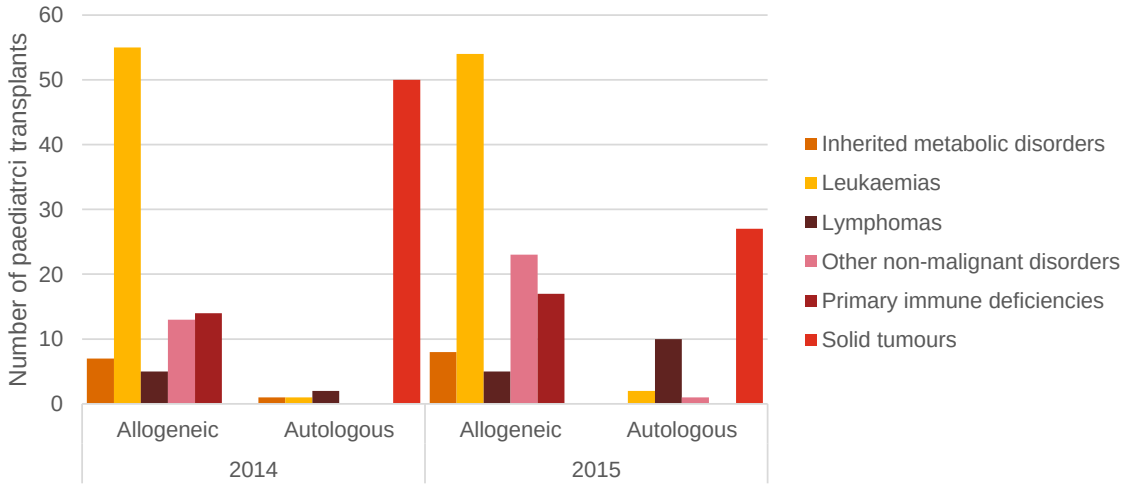
The type of transplant and treatment approaches used differs, depending on the clinical indication of the patient and their characteristics. Given the nature of diseases, this also varies between paediatric and adult patients.

Paediatric patients

Paediatric patients (patients aged 0–15) have a wide range of clinical indications that can be treated with a HPC transplant. Allogeneic transplants are undertaken more frequently than autologous transplants in paediatric patients (in 2015, 107 allogeneic transplants and 40 autologous transplants were performed).

Figure 8 shows the number of paediatric transplants performed in 2014 and 2015, by indication grouping. It shows that leukaemias (primarily acute lymphoblastic leukaemia and acute myeloid leukaemia) were the primary indications for allogeneic transplants for paediatric patients and solid tumours were the primary indication for autologous transplants.

Figure 8: Transplant type by indication grouping for paediatric patients in 2014 and 2015

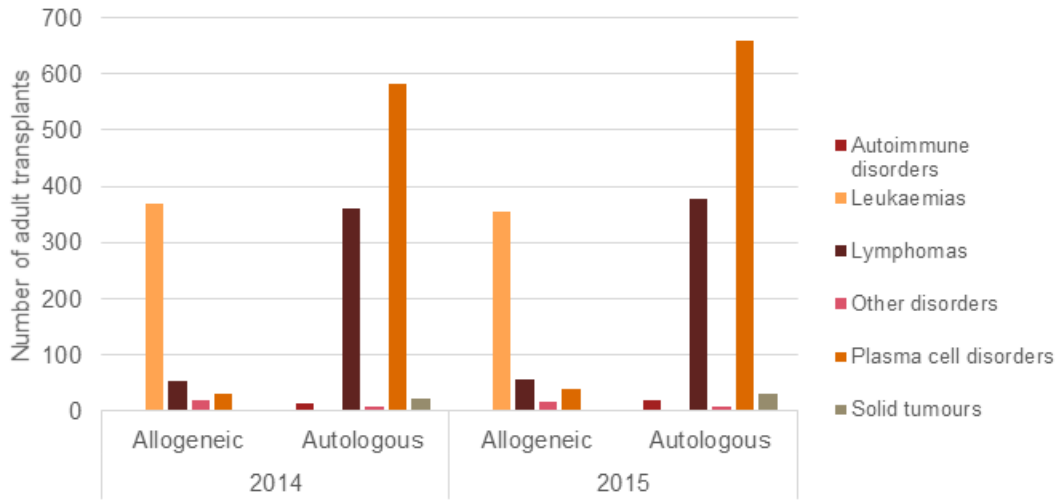


Source: ABMTRR Annual Data Summary 2014 and 2015

Adult patients

Many more adult than paediatric patients undergo HPC transplants. In 2015, 466 allogeneic and 1,093 autologous transplants were undertaken for adults. The autologous transplants were primarily for patients with multiple myeloma (614 autologous transplants in 2015) and non-Hodgkin lymphoma (309 in 2015). In 2015, almost 41% of allogeneic transplants were for patients with acute myeloid leukaemia. Figure 9 shows the number of adult transplants performed in 2014 and 2015, by indication grouping.

Figure 9: Transplant type by indication grouping for adult patients in 2014 and 2015



Source: ABMTRR Annual Data Summary 2014 and 2015

Transplant outcomes

The outcomes of HPC transplants vary by clinical indication and patient. Therefore, it is difficult to summarise outcomes, except to say that HPC transplants are clinically complex procedures and patients who are offered a transplant do not have many other options for a cure. Transplant centres report clinical outcomes data to outcome registries, including the Australasian Bone Marrow Transplant Recipient Registry (ABMTRR), the Center for International Blood and Marrow Transplant Research (CIBMTR) and the European Society for Blood and Marrow Transplantation (EBMT). These registries capture patient treatment and their clinical outcomes to inform clinical practice and research.

The *Australasian Bone Marrow Transplant Recipient Registry: Annual Data Summary 2015* reports that, of data captured within the first year post-transplant between 2010 and 2014, transplant-related mortality was 18.2% for allogeneic-unrelated transplant patients, 11.8% for allogeneic-related (identical) patients and 2.9% for autologous transplant patients.[7]

Clinical advances have overcome many risks associated with HPC transplants since they were first introduced as a treatment. Some indications have better prognoses than others, but, generally, mortality (at 300 days post-transplant) from an allogeneic-unrelated transplant is approximately 18%. For sibling matches with identical human leukocyte antigen (HLA) (siblings with an exact genetic match), it's almost 12%, while for autologous transplants, the mortality rate 300 days post-transplant is less than 3%.[8]

2.2.4 Deciding on the right HPC source for transplant

An allogeneic transplant needs stem cells that match the patient. Clinicians will first look to a patient's siblings or other relatives to identify whether they are a genetic match. This match is defined by their HLA type.

For patients who don't have a suitable related donor (approximately 70%), clinicians may pursue an unrelated donor from a donor registry. These donors have volunteered to donate and have undergone tissue typing to determine their HLA type. Donors who are matched will be contacted to prepare for donating stem cells. Stem cells are collected, either through a peripheral blood donation or bone marrow donation close to the time they are needed

[7] The ABMTRR (2015) Annual Data Summary.

[8] Ibid.

(unlike autologous transplants, allogeneic donations are not 'stored'). Alternatively, a patient may be matched to a cord blood unit (CBU), which is released from storage for transplant. Table 1 shows the key advantages and disadvantages associated with different stem cell sources.

Table 1: Advantages and disadvantages of HPC types

Type	Cord blood	Bone marrow	Peripheral blood
Advantages	• Readily available • Immunologically naive (can use mismatches) • Wider pool of rare HLA phenotypes • Collection presents less risk to donor	• Preferred source of stem cells for paediatric patients and some conditions like aplastic anaemia • Certainty in cell collection	• Faster engraftment[9] • Can be cryopreserved for later use[10]
Disadvantages	• Low HPC density (suitable for lower-weight patients)	• More difficult donation procedure, especially for children, who might require a blood transfusion[11], and risks including from anaesthesia	• Greater risk of chronic Graft versus Host Disease (GvHD)[12] • Lower risk to donors than bone marrow harvest, but still exposes donors to procedural risks

If a matched (related or unrelated) donor can't be found, clinicians may consider a haploidentical (half-matched) or mismatched HPC transplant.

Haploidentical transplants

Haploidentical transplants are transplants using a relative's stem cells that half-match the patient. That is, these donors are parents, siblings or children who have inherited or passed on half the patient's HLA tissue type.[13]

Mismatched transplants

Mismatched transplants use donors who are not a full HLA match to the patient. Typically, clinicians prefer not to use these transplant types, but may opt for them when an identical match can't be found. These transplants are managed more proactively due to a higher risk of GvHD.

Appendix C of this report describes donor pathways to transplant.

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9 European Commission (2015) *Economic landscapes of human tissues and cells for clinical application in the EU*, EAHC/2012/Health/19, p 102, accessed at: http://ec.europa.eu/health//sites/health/files/blood_tissues_organs/docs/economiclandscapes_humantissuescells_en.pdf

10 Ibid.

11 Ibid.

12 Ibid.

13 Leukaemia Foundation, 'Haploidentical Stem Cell Transplant', accessed at: http://www.leukaemia.org.au/treatments/stem-cell-transplants/haploidentical-stem-cell-transplant/haploidentical-stem-cell-transplant, 7 February 2017.

2.3 Matching a patient

Immunogeneticists perform the complex, technical activity of identifying and matching the genetics between a patient and a donor. These scientists try to match the HLA type of a patient to a donor by analysing alleles at chromosome 6. Appendix C explains this process.

Patients can be perfectly matched to a donor, which is referred to as a 6/6 or 8/8 match (and in some instances, a 10/10). A mismatched donor is referred to as a 5/6 or 7/8 match. Typically, matches are not made with fewer than one mismatch of the alleles.

To assess the match between a patient and a donor, scientists rely on tissue typing, which produces the HLA type of individuals. Tissue typing can be undertaken at different resolutions. Low-resolution typing only typically provides up to six alleles of information (can only assess up to a 6/6 match), while Next Generation typing (second-generation typing, also known as 'NextGen' or 'high-resolution typing') can assess eight alleles. Higher resolution typing reduces the ambiguity in the alleles present. Technological advances have provided for third-generation typing (which may also be referred to as 'high-resolution typing'), which provides additional allele information.

In late 2015, the ABMDR sought input from transplant centres to determine current clinical needs.[14] That review considered that a match out of eight alleles (n/8) was a minimum standard among clinicians undertaking HPC transplants.

2.3.1 Clinical decision making

As a function of genetic matching, clinicians follow a hierarchy of decision points in identifying the most suitable match for a patient.

Clinicians will always first look to relatives as donors because they are the most likely source of a match. Clinicians strongly prefer siblings, not only because they provide the most likely chance of being a match, but also because they are more easily contactable and can be worked up much more quickly (typically within three weeks). Matched related donor transplants have the lowest risk of GvHD.

However, for many patients, a suitably matched relative will not be found and clinicians will then look for an unrelated source of HPCs.

Unrelated donors are sought in the order of:

1. Matched donor from the registry
2. Mismatched donor from the registry (however, very few transplants are suited to this and it depends on the patient's clinical indication)
3. Cord blood unit (dependent on treating haematologist's preference and experience with CBUs)
4. Haploidentical transplant options

Differences do exist in the clinical approaches of clinicians. Additionally, the decision-making hierarchy may also be adapted depending on a patient's condition and their urgency for transplant.

Depending on the patient's condition, they may need a transplant within three months of diagnosis, or earlier; for example, patients who have aplastic anaemia. However, for some conditions, clinicians may follow a treatment pathway that means they have some time (four to six months) to identify a donor before performing a transplant. Each case will be treated differently and may require a clinician to adopt a different approach to identifying a suitable donor.

[14] ABMDR, *Unrelated HPC sourcing strategy* (Version 1.2, 10 May 2016), provided by the ABMDR.

2.3.2 *Matching decision making*

The treating haematologist and transplant coordinator decide which potential donor or CBU is the best option for a patient. They will analyse potential donor search reports prepared by State Search Coordinators. These reports outline details on potential matches, including their known level of tissue typing, which varies among donors. For promising donor options, the transplant coordinator will then seek confirmatory typing, at which point the State Search Coordinators and Donor Coordinators are mobilised. They will contact a donor to seek a blood sample to undertake high resolution/NextGen tissue typing and other blood sampling. Information about these donors is then fed back to the transplant centre to inform decision making.

Like decision making on a source of HPC, selecting the most appropriate donor match for a patient also varies among clinicians. Where more than one potential match (with the same tissue type) is identified, decision making typically takes into account the following factors:

1. **Gender of donor** – female donors who have been pregnant carry antibodies that can increase the risk of GvHD in transplanted patients. Due to this risk, male donors are typically preferred if an equally matched donor is available. Male donors also produce more stem cells than female donors.
2. **CMV status** – if a patient is CMV negative, clinicians will seek a CMV negative donor to reduce the likelihood of infection during the treatment's immunosuppressed period.
3. **Younger donors over older donors (aged over 60–65)** – transplant outcome data suggests that using younger donors results in faster engraftment among patients. Additionally, older donors are more likely to present with complications, such as diabetes, that may risk their ability to donate. If two equally matched donors are identified, clinicians will typically opt for the younger donor to promote the best outcome for the patient.
4. **Blood group** – for a small proportion of patients, non-matching blood groups between patient and donor negatively impact red cell production. If possible, a clinician will choose a donor whose blood group matches that of the patient.

However, even given these factors, a clinician will opt for a perfectly matched donor – noting that it is very rare to have more than a very small number of available options.

Selecting a cord blood unit

If a clinician is considering using CBUs as the HPC source for transplant, they will take into account the Total Nucleated Cell (TNC) and CD34+ counts to ensure there are enough stem cells for engraftment. CBUs can be easier to match to paediatric patients, who typically weigh less than adult patients, because clinicians can better achieve the cell counts they need for a successful transplant.

Cord blood remains an important HPC source, particularly for paediatric and difficult-to-match patients

2.3.3 *Collection of HPCs for transplant*

Peripheral blood is donated through apheresis, in which a donor will receive five days of hormone injections (granulocyte-colony stimulating factor (G-CSF)). After this time, the donor will attend a transplant centre as an outpatient, where they will be attached to an apheresis machine, and blood will be extracted using a needle inserted in a vein in their arm. The apheresis machine will separate the stem cells and return the blood to the donor through their other arm. Donors are typically attached to the machine for 4–6 hours. If the number of stem cells collected is not sufficient for transplant, the donor may need to provide a second donation the next day.

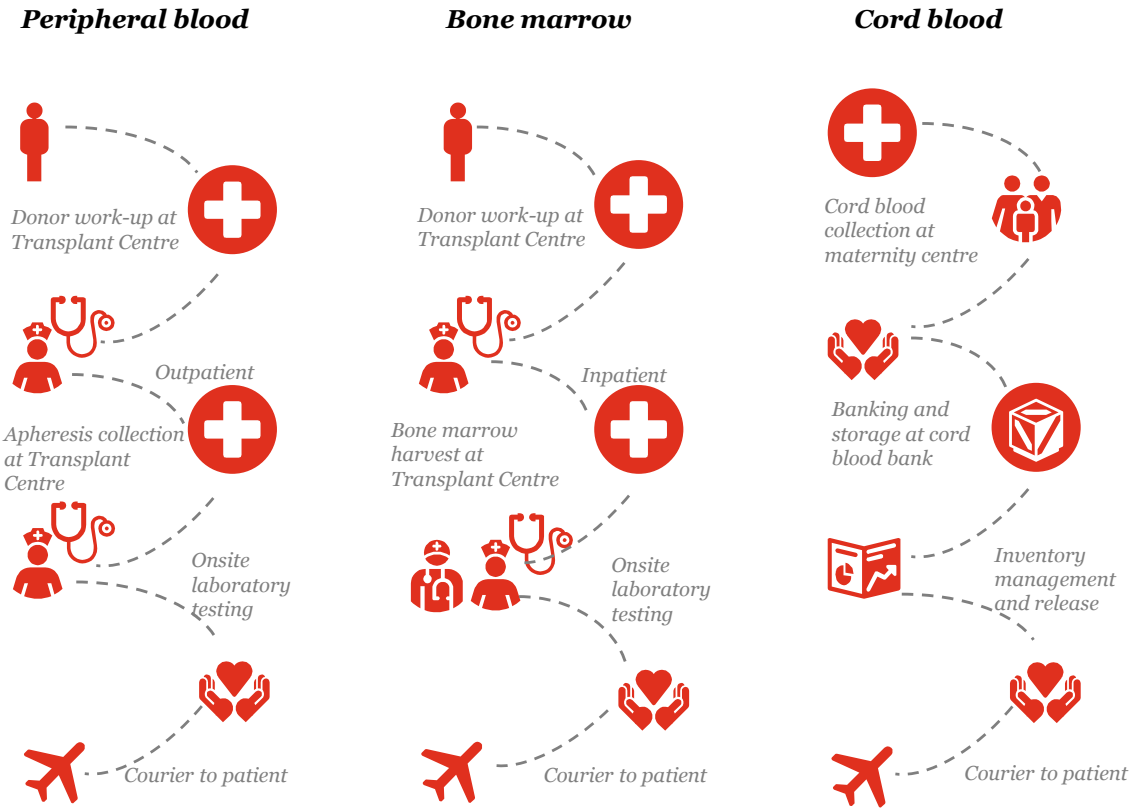
Bone marrow is collected under general anaesthetic in a surgical theatre. The donor will be scheduled for theatre (typically in the morning) for extraction of bone marrow (harvesting) by a haematologist using large hollow needles inserted into the donor's posterior iliac crests. These may be inserted at multiple sites on the donor's lower back to extract 1–1½ litres of bone marrow. The amount of bone marrow that can be safely collected is based on the patient's and donor's weight. The collection is filtered to remove bone and fat before being couriered for transplant.

Unlike peripheral blood and bone marrow, cord blood is collected from the umbilical cord following birth. The cord blood is extracted via a needle, either in utero or ex utero, and stored in a blood bag. Donations are then tested and stored in large cryogenic facilities at Australia's three cord blood banks. Once identified as suitable, which can be many years, the CBU is prepared and transported for transplant into the patient.

The role of registries in supporting related donors is increasingly being considered internationally

Some parents opt to privately bank their baby's cord blood, which will be cryogenically frozen. It may only be released at the direction of the parents, or whoever holds the contract. These units are not available through the public registry – forming an unrelated supply of donations – and so are not explored further in this review.

Figure 10: Allogeneic HPC sources and their pathway to donation



After making the original donation, both peripheral blood and bone marrow donors may be asked to also donate lymphocytes and/or blood stem cells to assist with a patient's ongoing treatment over the months following a transplant. (These donations are for the patient who received the original donation because the patient now has HLA compatibility with the donor and the donor's antigen residue.)

Autologous stem cells are typically collected as peripheral blood before being stored cryogenically on-site at the hospital treating the patient.

3

The haemopoietic progenitor cell sector

This chapter covers...

- *the history and role of the Australian Bone Marrow Donor Registry*
- *Australia's strategy for recruiting volunteer donors*
- *arrangements, funding and governance of Australia's haemopoietic progenitor cell (HPC) sector.*

Key messages:

The Australian Bone Marrow Donor Registry (ABMDR) is Australia's only registry of volunteer donors. It has successfully supported Australian patients who need a HPC transplant by recruiting volunteer donors, and facilitating matching and collection of HPCs for transplant.

Changing technology, clinical trends and preferences have driven a need for change. To date, the sector has relied on the Australian Red Cross Blood Service (ARCBS) and its core activities to recruit new donors. To support future demand, the ABMDR has identified a need to re-orient the long-term objectives of the registry to recruit younger donors and change the approach for engaging donors.

The ABMDR, as registry operator, is responsible for activities in the sector; however, it is supported by a network of parties that deliver services. The ad hoc Jurisdictional HPC Committee is the primary forum for government oversight of the activities of the National Cord Blood Collection Network (NCBCN). Governance of the sector is fragmented, with responsibilities held across many different organisations, and these arrangements do not promote strategic decision making.

The ABMDR is primarily funded through the Commonwealth Government's Core Services Funding Agreement and the NCBCN Funding Agreement (equally funded by the states and territories). The two agreements support core operations of the ABMDR, funding for international donor searches for Australian patients, the Australasian Bone Marrow Donor Recipient Registry (ABMTRR) and the operation of the NCBCN. There is limited funding available to undertake strategic planning and recruitment. Additionally, current systems and reporting lines, including the activities laid out in the funding agreements, do not promote decision making to enable governments, the ABMDR or the ARCBS to align activities with the sector's strategic needs.

Patients requiring a donor are supported by transplant centres across the country. These centres, alongside the CBBs, also collect HPCs from donors. Australian patients are also supported to identify donors internationally through the ABMDR's relationship with the World Marrow Donor Association.

3 The haemopoietic progenitor cell sector

A number of bodies are responsible for delivering activities in the haemopoietic progenitor cell (HPC) sector. The key players are:

- the Australian Bone Marrow Donor Registry (ABMDR), which is responsible for managing Australian donors on the registry and maintaining the registry system. Appendix D shows the history of the ABMDR since it was established in 1990.
- the Australian Red Cross Blood Service (ARCBS), which performs tissue typing activities, and searching and matching functions, for NSW, Victoria and South Australia; and donor recruitment and coordination for all states (including NT and Tasmania).
- PathWest and Pathology Queensland, which provide tissue typing services in Western Australia and Queensland.
- the Australasian Bone Marrow Transplant Recipient Registry (ABMTRR), which is responsible for collecting and reporting clinical outcomes of transplants.

This chapter explores the strategy, activities and funding arrangements for the sector. Under the terms of the Core Services Agreement between the Commonwealth and the ABMDR, the ABMDR's objectives include updating and maintaining the donor registry, overseeing the search for matched HPCs and cord blood units (CBUs) and supporting the ABMTRR. Given the primacy of the ABMDR in undertaking these functions, its activities are a core focus of the following analysis.

3.1 Operating model review (current state)

PwC used its operating model framework to assess the maturity of the HPC sector.

3.1.1 Strategy

Ambition

The Commonwealth's Department of Health Program 1.1 (Health Policy Research and Analysis) funds the HPC program under Program Objective D (Improving Australians' access to organ and tissue transplants).[15] The government has two primary contractual agreements with the ABMDR, which administers the NCBCN. These agreements are:

[15] Commonwealth Department of Health, Portfolio Budget Statement – Outcome 1 – Health System Policy, Design and Innovation.

- the Core Services Agreement, which funds the operation of a national bone marrow registry to identify suitably matched, voluntary donors of HPCs; operate the International Donor Registries Search Project to financially support the international search for HPC donors or CBUs; and contribute to managing the Bone Marrow Transplant Program (BMTP)[16]
- the National Cord Blood Collection Network (NCBCN) funding agreement, which supports the government's policy of developing a public cord blood banking network to provide Australian patients with access to safe, affordable and clinically appropriate cord blood.[17]

The ABMDR's aims are reflected in its Constitution's Principal Object: *To support and enhance the availability of suitably matched, unrelated voluntary donors of haemopoietic progenitor cells for patients in need of transplantation with such cells*.[18]

The NCBCN's funding agreement aligns with the operation and outputs of cord blood banking. However, the ABMDR's strategic intent and the objectives of its funding agreement diverge because its operational activities are not clearly defined.

While its Core Services Agreement specifies that the ABMDR update and maintain the donor registry, it does not contain clear performance indicators or milestones to measure progress, such as the size and composition of the registry and self-reliance on Australian donors.

Business model

With the funding agreements specifying objectives relating to cord blood banking and international searches, the ABMDR structures its activities to fulfil its funding requirements.[19] But in fulfilling its strategic role of maintaining the database and recruiting new donors to the registry, there is limited business planning. This is due to a lack of capacity and funding to do so.

Under the NCBCN's funding agreement, the ABMDR must produce a business plan for the network at the end of each financial year.[20] In turn, the ABMDR – which also oversees the ABMTRR and each of the cord blood banks (CBBs) – requires that they produce a business plan to fulfil this obligation. Planning is not consolidated across the entities, and nor are the activities of the ABMDR. Instead, activities are framed with the purpose of delivering on funding milestones.

The Core Services Agreement also requires that the ABMDR produce an annual business plan for itself and its associated entities (the ABMTRR and the three CBBs). Funding is tied to producing the plan and delivering on its specified activities. The business plans typically represent the operational activities of the ABMDR and its entities, but do not present a strategic perspective of the sector or proposed activities to achieve sectoral objectives.

The ARCBS delivers donor recruitment, search coordination and tissue typing services, in line with its contractual agreements with state governments. Each contract specifies different

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16 Australian Government Department of Health Multi Schedule Deed of Agreement between the Commonwealth of Australia and the Australian Bone Marrow Donor Registry (Core Funding, International Searches Programme and Bone Marrow Transplant Programme 2014–15).

17 Australian Government Department of Health Deed of Variation, Commonwealth of Australia and the Australian Bone Marrow Donor Registry, Funding Agreement for the National Cord Blood Collection Network, Part 6(b).

18 Constitution of the Australian Bone Marrow Donor Registry, 12 September 2016, accessed at: https://www.acnc.gov.au/RN52B75Q?ID=6EE3F24D-F1C8-440C-ABE1-BDF6C24CBA4D&noleft=1

19 ABMDR *Unrelated HPC sourcing strategy* (Version 1.2, 10 May 2016), provided by the ABMDR.

20 Australian Government Department of Health Deed of Variation No.1 between the Commonwealth of Australia and the Australian Bone Marrow Donor Registry.

activities and reporting arrangements against which governments monitor and engage with the ARCBS, to inform planning for future activities.

Strategic agenda

The strategic agenda of an organisation includes the objectives and long-term goals. These are supported by a strategic foundation, which outlines the activities that will accomplish those objectives. For the ABMDR, this would be in the form of its overall strategy, with activities such as marketing and recruitment underpinning how the strategy is achieved.

With operations and funding intrinsically tied to the activities and program delivery, it is difficult for the ABMDR to undertake strategic planning and investment. Any untied funding is typically reinvested in immediate needs (for example, the information technology (IT) system, which it has invested $1 million to stabilise it since its initial development). Future planning is left to the ABMDR executive team, which does not have the capacity or resources for long-term planning and implementation.

For example, the ABMDR developed the *Unrelated HPC sourcing strategy*[21] in 2016. The strategy is the first document of its kind the ABMDR has developed. It puts forward a five-year road map for restructuring the approach and focus of its current HPC program. It recognises that it needs to revitalise the current Australian registry and change the way it engages with donors and organises the registry. This reflects that the donor base the HPC program relies on has an ageing profile – the ABMDR estimates that within 10 years, 35% of the pool will turn 61, at which point they will be retired from the registry.[22] Ultimately, the ABMDR would like to recruit 20,000 new donors each year.

The *Unrelated HPC sourcing strategy*'s recommendations include:

- recruiting young (aged 18–30) male donors with diverse human leukocyte antigens (HLA)
- ceasing recruitment of blood donors, instead redirecting efforts to online and call-assisted recruitment, using modern approaches to communication
- performing initial tissue typing using buccal swabs or saliva collection tubes, which is a more cost-effective approach to recruiting tissue types
- contracting out a recruitment call centre, which will be supported by volunteers and managed using a new client relationship management system
- ceasing cord blood banking, and using existing inventories for releases only. Meanwhile, the existing inventory should be high-resolution typed.

As a result of not setting a strategic agenda, sectoral activities, such as recruiting, may not align with the needs of the ABMDR.

In practice, most donors (about 85%) are recruited through ARCBS blood donor centres. Regular blood donors are committed but, typically being older, Caucasian and female, do not fit the profile of the ABMDR's desired donor groups.

The ABMDR's recruitment strategy is based on a preliminary assessment made in the early 1990s, which determined that 100,000 donors would be needed to meet Australia's needs. The target was quickly surpassed as donors registered, reaching 150,000 in 1996. Since then, passive recruitment has been undertaken through blood donor centres.

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[21] ABMDR *Unrelated HPC sourcing strategy* (Version 1.2, 10 May 2016), provided by the ABMDR.

[22] ABMDR *Unrelated HPC sourcing strategy* (Version 1.2, 10 May 2016), provided by the ABMDR.

The ABMDR identified the need to look closely at the user experience of registered donors to drive recruitment. Countries that have invested in technology have increased the number of domestic donors and improved the availability rates of donors. Examples of using technology for recruitment and maintaining donor commitment included developing an online questionnaire/donor profile and online education material, and sending out commitment prompts such as emails asking donors to 'recommit'. The ABMDR could use these prompts to remind donors of the ABMDR's role and their value in remaining on the registry.

At the time of this review, ABMDR had not secured funding for its strategy, and was still finessing elements of it (for example, the needs of online technology).

Strategic foundation

Organisations have strategic foundations set by external influences that affect the environment they operate in and how they align their activities to key issues and opportunities. The ABMDR's key influences are its ability to shape recruitment, including marketing, and its funding arrangements.

Marketing

The ABMDR works with ARCBS blood donor centres to recruit new donors to the registry. However, it devotes limited resources to this marketing and recruitment. It distributes pamphlets for blood donors at donor centres, but does not use targeted engagement with potential donors.

It does not use television advertising or pursue patient awareness activities; however, it notes that it is important to educate new blood donors because they may not be called on to donate for some time, if at all. If they are called on to donate, they need to be aware of the process and commitment required to be donate. This education differs to that provided to blood donors, who typically donate more frequently. Additionally, because ABMDR wants to engage with younger generations, it needs to use social media and online channels to effectively reach these audiences and encourage potential donors to register. International registries are prolific users of this type of engagement, making significant educational material available online to educate donors on the importance of donating, and the process involved. These types of strategies have supported donor retention, leading to a donation when a match is identified.

Current recruitment practices

New donors visit a specified blood centre, where they provide consent and are given an ABMDR questionnaire. Their blood sample is taken for tissue typing, and donor centre staff enter their details into the ABMDR's online system, MatchPoint.

This strategy presents a challenge: the ABMDR is required to attract donors in line with the ARCBS's risk criteria, which can exclude some potential donors. For example, a potential donor who presents with a cold is unfit to donate blood and is excluded from testing. But this person could (or should) be tested for typing as the cold won't affect their future ability to donate. The incongruence between the enrolment criteria for blood and HPC donors remains a challenge to recruiting through blood donor channels only.

Separately, the ABMDR and blood donor centres may occasionally support patient drives. While these are valuable for promoting awareness, the return on resource investment is lower than direct recruitment activities. Organisers must have a committed number of blood donors before they can arrange a testing site, first aid and a phlebotomist. These factors all depend on volunteer hours, including the ABMDR's hours. Studies show that donors recruited in this way are typically less committed than those found through other means, mainly because donating blood is an emotive and specific activity that doesn't maintain donor commitment over time.

Blood or saliva?
Blood samples are still used to test the tissue type of a new donor, however many international registries have now turned to saliva tubes or buccal swabs which are less invasive and don't require a phlebotomist to draw blood. They also have the benefit of being a much lower cost and make for an easier method for distribution (for example, through mail-outs).

Saliva tubes are slightly more expensive than swabs, but bring the benefit of capturing more DNA than swabs. Both swabs and tubes aren't able to be tested for CMV, which can be a determinate in donor selection. However, donor CMV status changes over time and is not entered into systems regardless, so a change in recruitment approach is not likely to reduce information captured.

Another avenue for recruiting is to 'transfer' registered international donors who have moved to Australia, or to enrol siblings who have been tested for a patient and are willing to voluntarily donate. These sources account for a very small number of newly recruited donors to the Australian registry.

Additionally, engaging donors through blood donor centres does not target the audiences ABMDR is seeking to engage with (young, fit men). These factors all mean that it has limited channels to promote to new donors without extra effort. ARCBS staff are also busy and working to meet many targets. And while bone marrow donor recruitment is important, the primary tasks of collecting blood and blood products is driven by ARCBS's key performance indicators (KPIs), which do not include targets for bone marrow donors. Therefore, front-line staff don't make recruitment a priority.

Patient groups undertake awareness-raising activities to promote registration and, in particular, to make young, male donors aware that they are needed on the registry. These groups include UR the Cure, the Green Button Foundation and Fight Cancer Foundation, which all play an important, complementary role in promoting the clinical needs that the registry supports.

Proportional investment

With growing demand for HPC transplants and greater need to invest in upfront information to enable clinicians to make quicker, more informed decisions, funding is disproportionately committed to programmatic activities that do not address these needs. Challenges the ABMDR faces include:

- It is unable to influence ARCBS's recruitment strategies, KPIs and investment in tissue typing of new donors because the states and territories manage the ARCBS's contracts. The lack of central funding also hinders the ABMDR from considering activities such as batching high-resolution upfront typing, which is a more cost-effective way of undertaking high resolution typing.

- Its rigid funding arrangements dictate investment in activities. For example, much of its funding is committed to operating the CBBs, despite the low volume of their activities.

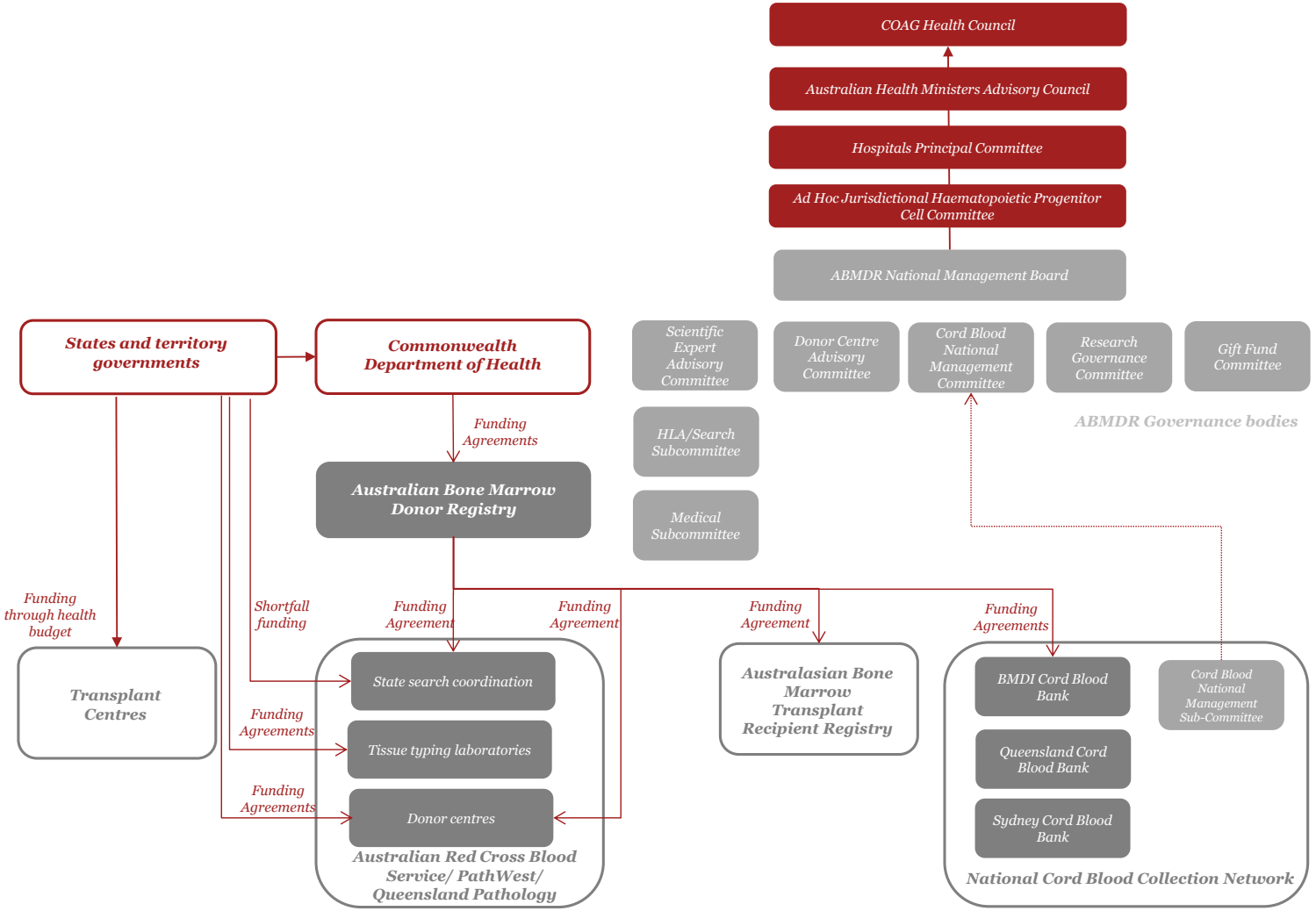
- It searches international HPC registries to match Australian patients according to demand. But as demand grows, it is dedicating greater effort to this activity, instead of using domestic strategies to reduce the need to call on international transplant donors.

3.1.2 *Business capabilities*

Organisation and governance

Figure 11 shows the overarching governance for providing unrelated HPC transplants. Governance of autologous and allogeneic-related HPC transplants fall under clinical governance arrangements, and are not explored in this review.

Figure 11: The governance and funding flows for the volunteer HPC donor sector



Government oversight and reporting

The ahJHPCC grew out of the need for jurisdictions to share ideas and agree elements of funding associated with HPCs. It was established in 2010 after the Cognate Committee on Organ and Tissue Donation and Transplantation was dissolved. (Its areas of oversight were transferred to the Organ and Tissue Authority in 2008.[23]) The Government Business Sub-Committee that reported to the Cognate Committee had brought together jurisdictions to engage on aspects of organ and tissue donation and transplantation, and cord blood; however, following its transfer, HPCs were left without a cross-jurisdictional forum.[24]

The ahJHPCC primarily focuses on the provision and operation of cord blood banking, which is funded through a joint Commonwealth-State Agreement. Representatives of the Commonwealth, and each state and territory, form the committee, which provides papers to the Hospitals Principal Committee (and ultimately, the Australian Health Ministers' Advisory Council) for consideration. However, it does so without formal terms of reference.[25]

While the ahJHPCC is an effective forum for NCBCN-related decisions, it is largely administrative, without formal authority, and lacks the ability to drive policy direction and coordinate activities. Most state and territory representatives consulted for this review cited this governance structure as ill-suited to the task of providing policy oversight and decision making for the HPC sector. This is due to the lack of clear responsibilities for strategic recruitment and providing clear direction. There is also a lack of formal reporting requirements relating to broader HPC activities or authority to direct and oversee these activities.

Additionally, the indirect role of the governments in funding and operating the ABMDR and its activities mean there are no formal lines of communication and dedicated policy areas are not apparent.

ABMDR organisational governance

The ABMDR is governed by an eight-member National Management Board. Each member represents different aspects of the sector, including in clinical work, donor recruiting, scientific updates and advances, and international representation (this includes roles with the World Marrow Donor Association (WMDA)). The Management Board brings extensive experience grounded in its members' long-term association with the ABMDR itself, including its founder and a former Executive Officer.

The Board is supported by five committees and three subcommittees, which are the:

- Scientific Expert Advisory Committee
  - HLA/Search Subcommittee
  - Medical Subcommittee
- Donor Centre Advisory Committee
- Cord Blood National Management Committee
  - Cord Blood National Management Subcommittee
- Research Governance Committee

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[23] Adhoc Jurisdictional Haemopoietic Progenitor Cell Committee (ahJHPCC), Current ahJHPCC membership as at 1 March 2017, paper provided to PwC by the Department 9 March 2017.

[24] Cognate Committee on Organ and Tissue Donation and Transplantation: Government Business Sub-Committee Terms of Reference, provided to PwC by the Department 9 March 2017.

[25] Adhoc Jurisdictional Haemopoietic Progenitor Cell Committee (ahJHPCC), Current ahJHPCC membership as at 1 March 2017, paper provided to PwC by the Department 9 March 2017.

- Gift Fund Committee

The ABMDR's Core Services Agreement stipulates that it be supported by an ethics committee, but these services are channelled through the ARCBS's ethics committee.

The ABMDR mainly engages with governments through the Cord Blood National Management Committee, which comprises representatives of government, and is managed by the Chairperson of the ABMDR Board. Additionally, members of the ABMDR executive and Board may engage ad hoc with ahJHPCC members.

International governance

Interactions with international registries are largely informal, although based on goodwill, which has led to effective operations for the last 20–30 years. The international body most relevant to HPC transplants is the WMDA. Among other roles, the WMDA is responsible for:

- the European Marrow Donor Information System (EMDIS), which is a community protocol for information-sharing and ordering processes
- Bone Marrow Donors Worldwide (BMDW), the global database of volunteer donors and cord blood products
- NetCord, an education organisation associated with cord blood banking.

The ABMDR contributes to these protocols and databases and uses them to connect to the international database of donors.

The WMDA plays an active role in addressing emerging issues and opportunities. Among these, the WMDA is starting to focus on the care and education of related donors, who are often under the care of the same transplant physician as the patient (unrelated donors are treated by different physicians to advocate for their medical interests). The ABMDR participates in the WMDA's committee activities and working groups, offering input and drawing on the development of guidelines and standards that are adopted internationally.

Additionally, the WDMA hosts the Serious (Product) Events and Adverse Reactions (S(P)EAR) database. This is a mandatory reporting system used by the ABMDR to report its adverse reactions.

The ABMDR holds five formal agreements with international registries, which stipulate the fee schedules for donor typing and HPC collection when a patient needs an international donor.

Clinical engagement

In addition to the WMDA, there are three other major international organisations:

- The Center for International Blood and Marrow Transplant Research (CIBMTR) maintains a clinical outcomes registry, which Australian transplant centres report to. The CIBMTR has an extensive worldwide dataset that provides valuable research, analytics and insights into clinical practice.
- The European Society for Blood and Marrow Transplantation (EBMT) maintains a registry that was established in the 1970s. It has captured the clinical outcomes of more than 499,000 patients in 60 centres.[26] Clinicians use the data for research and to inform clinical practice. The EBMT also has an active role in education, producing the ABMT's *Handbook on HSC Transplantation*[27], coordinating and running

[26] EBMT, 'About EBMT', accessed at <https://www.ebmt.org/Contents/About-EBMT/Pages/About-EBMT.aspx>

[27] The term 'haemopoietic stem cells' (HSC) is commonly used in the US. It is interchangeable with 'HPC' in this context.

training courses, and organising conferences on clinical practice and to promote exchanges of information.[28]

- The American Society of Bone Marrow Transplantation (ASBMT) produces medical guidance and a journal that many Australian clinicians refer to.

The newly formed Asia-Pacific Blood and Marrow Transplantation Group seeks to achieve similar outcomes in our geographical region. It is currently chaired out of Japan and Australian clinicians are interacting with the forum, which runs annual conferences.

In Australia, clinicians engage through the Haematology Society of Australia and New Zealand, which oversees the Bone Marrow Transplant Society of Australia and New Zealand (BMTSANZ). This is the main forum for Australian transplant physicians. The society was relatively dormant until recent years. It has taken a proactive role in overseeing the ABMTRR, and is expanding its activities, including considering the development of a clinical guide.

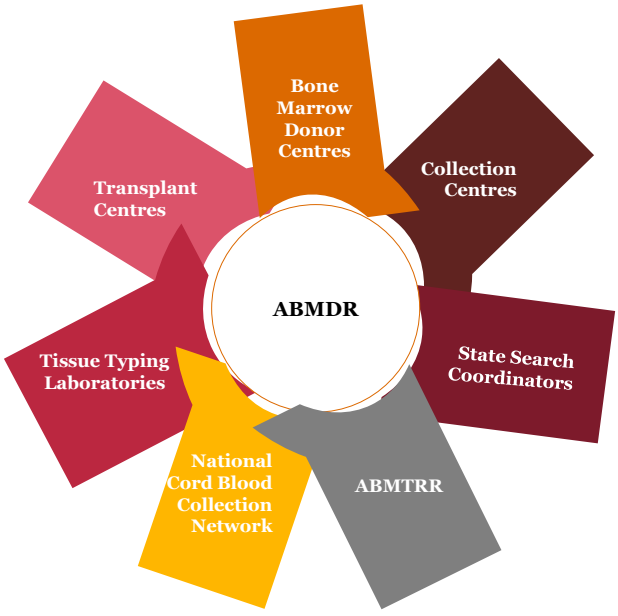
The ABMTRR mirrors the role of the CIBMTR, collecting outcomes reporting from Australian transplant centres. It operates out of St Vincent's Hospital in Sydney and is funded by governments through the ABMDR. It has had this role since 1992 and produces annual reports to assist clinicians and researchers.

As has been identified in a separate review on bone marrow transplant outcomes reporting, the ABMTRR has complex governance arrangements, is inadequately funded and operates without formally documented responsibilities. Many clinicians would like the ABMTRR to collect more data of a higher quality in Australia to further the clinical insights garnered from its work.[29]

The ABMDR network

Figure 12 shows the overarching structure of the ABMDR network and its primary organs.

Figure 12: ABMDR Network



The ABMDR has direct, contractual responsibility for managing the **NCBCN**, which is comprised of the three public CBBs that collect and store CBUs for use in HPC transplants.

In addition, the ABMDR is supported by **bone marrow donor centres**, which are based in the ARCBS's blood donor centres. The centres have a role in recruiting new donors to the registry and coordinating potential donors.

State Search Coordinators are positioned with the five tissue typing laboratories (at the ARCBS's Melbourne, Sydney and Adelaide laboratories, at PathWest and Pathology Queensland's laboratory). The coordinators manage searches for unrelated donors – domestically and internationally – to identify potential donors and liaise with requesting transplant centres. They are responsible for recommending donors who are

[28] EBMT 'Education', accessed at <https://www.ebmt.org/Contents/Education/Pages/Education.aspx>

[29] KPMG (2017) *Final report – Bone Marrow Transplant Outcomes Reporting Review*, prepared for the ABMDR.

the best option for patients. Again, they are governed and funded by all Australian governments.

Tissue typing laboratories process samples from new recruits (initial tissue typing), analysing verification typing and confirmatory typing for potential donors. This information is passed to the State Search Coordinator for their analysis. Again, they are governed and funded by state and territory governments.

Transplant centres care for patients, and initiate unrelated donor searches and identify the most suitable donor for transplant. Once identified, the Donor Coordinators at the bone marrow donor centre coordinate collection of HPCs from a **collection centre**. Functionally, transplant centres and collection centres perform the same activities (they are bone marrow transplant units located in major public hospitals). But under ABMDR accreditation of transplant centres, collection of HPCs for allogeneic-unrelated transplants is undertaken at a centre other than that where the patient is being treated. In states where the transplant centre is also the collection centre, different clinicians will manage the patient and donor to maintain privacy.

Additionally, the **ABMDR** and the **ABMTRR** play specific roles in managing the registry, and collecting and reporting on outcomes data, respectively.

Functional structure

Functionally, the roles and responsibilities for activities that support unrelated HPC donation are split among different organisations. While generally under the umbrella of the ABMDR Network, different organisations play different roles. Table 2 outlines the key activities that support allogeneic-unrelated HPC transplants.

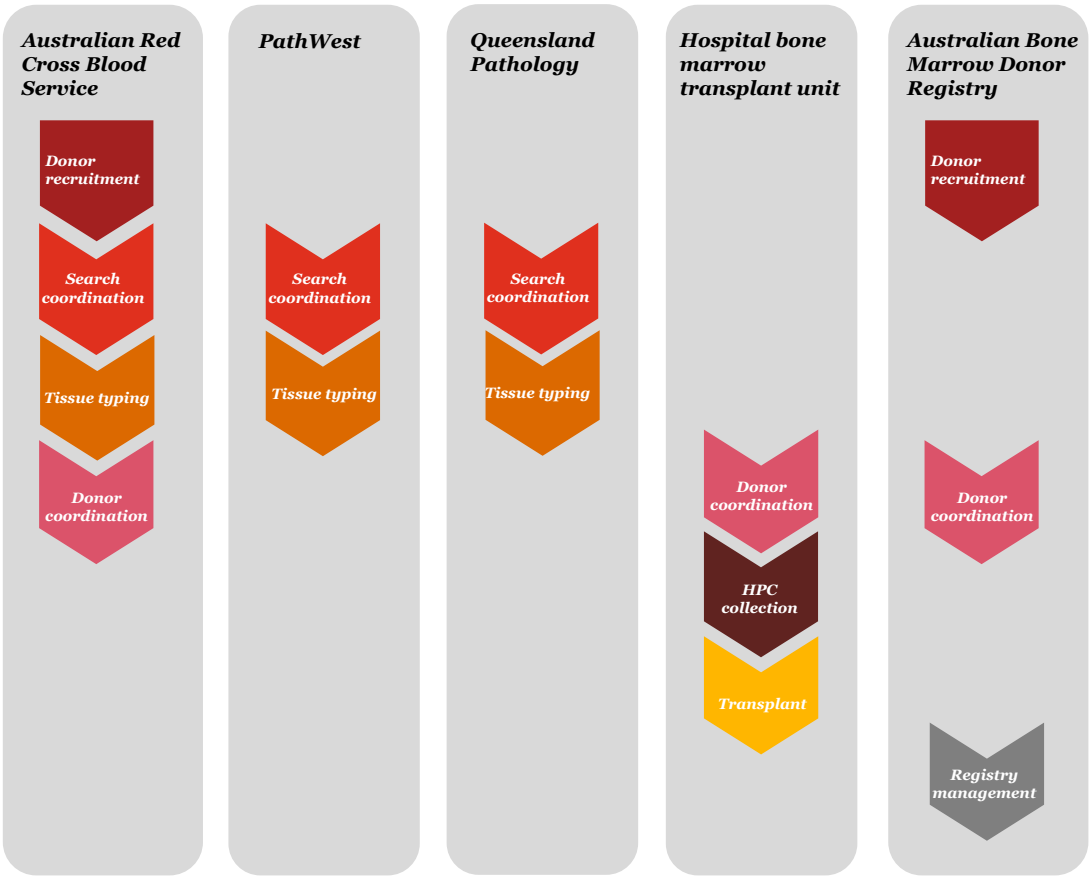
Table 2: Allogeneic HPC donation activities by stage

Stage	Key activities
1. Donor recruitment	Register donors Undertake marketing Collect donor samples and initial tissue typing
2. Search coordination	Initiate domestic searches Initiation international searches Coordinate searches Match donors
3. Tissue typing	Collect donor samples and test for Infectious Disease Markers Perform verification and confirmatory typing
4. Donor coordination	Perform work-up and obtain consent of unrelated domestic donors Coordinate donor education and domestic travel arrangements Coordinate donor education and international travel arrangements
5. HPC collection	Schedule donors, and arrange and coordinate travel Collect peripheral blood Collect bone marrow Collect international stem cells Arrange couriers for domestic transplant centre Arrange couriers for international treating transplant centres
6. Registry management	Perform donor follow-ups Administer registry and undertake ABMDR's management activities Report on outcomes

Stage	Key activities
	Issue accreditations.

These activities are shared among different organisations to support HPC donation across the states and territories. Figure 13 shows how activities are allocated among key organisations.

Figure 13: Allocation of HPC donation activities



As shown, activities are spread among a number of organisations, but functionally, the ARCBS plays a significant role in the operational activities, supported by the ABMDR. Transplant centres take on the primary role managing donors and collections to facilitate transplants. This review heard that Australia's three-tiered structure (coordinators are based in transplant centres, ARCBS and the ABMDR) for donor coordination is the only one of its kind worldwide.[30]

Operational structure

There are 41 transplant centres around Australia that provide autologous, allogeneic-related and allogeneic-unrelated HPC transplants to Australian patients. In addition, a number of centres provide autologous transplants only. These are not captured here as they are beyond the scope of the review.

[30] In addition, and as outlined in Table 2, the ABMDR manages the donor registry. The ABMTRR manages outcomes reporting.

The left column in Table 3 shows the centres that provide allogeneic-unrelated transplants (and collect HPCs on behalf of the ABMDR).

Table 3: Allogeneic transplant centres in Australia

Allogeneic-unrelated transplants	Autologous/allogeneic-related transplants[31]
NSW	

• Royal North Shore Hospital^
• Royal Prince Alfred Hospital^
• St Vincent's Hospital, Sydney^
• Westmead Hospital*
• Paediatric BMT network:
  ○ Sydney Children's Hospital*
  ○ The Children's Hospital at Westmead*
	• Concord Repatriation and General Hospital
	• Gosford Hospital
	• John Hunter Children's Hospital
	• Liverpool Hospital
	• Nepean Hospital
	• Newcastle Mater Hospital
	• Prince of Wales Hospital
	• St George Hospital
	• Wollongong Hospital

Queensland	
• Royal Brisbane and Women's Hospital^*	• Gold Coast University Hospital • Greenslopes Private Hospital • Lady Cilento Children's Hospital • Mater Private Hospital • Mater Misericordae Public Hospital • Princess Alexandra Hospital • The Townsville Hospital • Wesley Private Hospital
Victoria	
• St Vincent's Hospital, Melbourne^ • Alfred Hospital^* • Royal Children's Hospital, Melbourne^* • The Royal Melbourne Hospital^* • Austin Hospital	• Box Hill Hospital • Geelong Hospital • Peter MacCallum Cancer Centre
South Australia	
• Royal Adelaide Hospital^*	• Flinders Medical Centre • Queen Elizabeth Hospital • Women and Children's Hospital

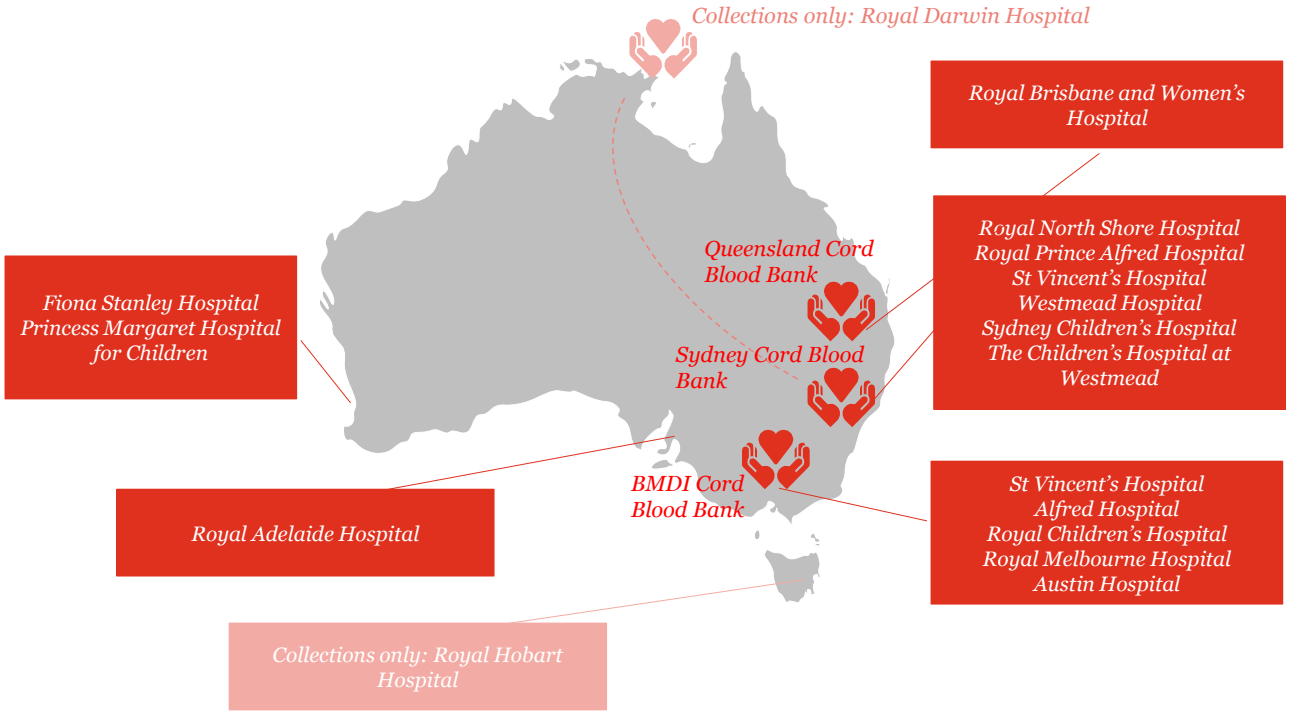
[31] Note: Not all centres listed provide allogeneic transplant services and may refer non-autologous patients to their referral centre. The table does not capture all autologous centres.

Allogeneic-unrelated transplants	Autologous/allogeneic-related transplants[31]
Western Australia	
• Fiona Stanley Hospital^* • Princess Margaret Hospital for Children^*	• Sir Charles Gairdner Hospital
Tasmania	
	• Royal Hobart Hospital
ACT	
	• Canberra Hospital

*Source: ABMTRR participating BMT centres, accessed at: http://www.abmtrr.org/index.php/centres/, and ABMDR transplant centres, accessed at: http://www.abmdr.org.au/adult-transplant-centres/. ^ annotation identifies centres which perform apheresis collection and * identifies centres which perform bone marrow harvests.*

Those centres that undertake allogeneic-unrelated transplants also support the collection of HPCs from ABMDR donors. They are further supported by collections made at the Royal Hobart Hospital and CBUs collected and stored in the NCBCN's CBBs in Melbourne, Sydney and Brisbane. The CBBs are in turn supported by collection centres at nine sites and an Indigenous CBU collection site at the Royal Darwin Hospital. Figure 14 shows a schematic collection and transplant sites in the unrelated HPC sector (the sector comprised of volunteer donors and cord blood banking). Appendix D provides a brief description of the functional arrangements and current state of the transplant centres.

Figure 14: Key elements of Australia's unrelated HPC sector



Tissue typing laboratories

The ARCBS's South Australian, Victoria and NSW tissue typing laboratories, Western Australia's PathWest and Queensland's Pathology Queensland laboratories undertake initial typing, extended typing and verification typing of donors in their respective states. Bone marrow donor centres (prescribed ARCBS blood donor centres) collect the blood samples of new registrants and send them to that state's laboratory.

Donor samples are managed and DNA is stored by the laboratories that undertook recruitment tissue typing. Where a donor is identified as a potential match to a patient, stored DNA is extracted for either extended typing (typing at greater resolution or at more loci than reported) or for verification typing in which the laboratory retests the sample at all loci to check the donor is the right match to a patient. Samples are frozen and stored on-site.

State search coordination

Working with the tissue typing laboratories, each state has an allocated State Search Coordinator (or multiple coordinators in NSW, Victoria and Western Australia).[32] The State Search Coordinator lodges a preliminary search request from a transplant centre, undertakes searches of the domestic and international registries, and provides search reports to the requesting transplant centre about potential matches. They work closely with the transplant centres to identify the most suitable match, request extended and verification typing and fill prescriptions where a donor is selected. Their role is integral to the process and requires highly technical expertise to match patients to donors.

Donor coordination

The role of coordinating potential donors is currently channelled through the state donor centres (prescribed ARCBS blood donor centres), which contact donors and seek their availability. They work with transplant centres to schedule and follow up donors. In each state, dedicated Donor Coordinators, who are ARCBS employees, undertake this task. Uniquely, in South Australia, one full-time equivalent (FTE) employee fulfils the roles of State Search Coordinator and Donor Coordinator, despite these activities slightly overlapping.

Western Australia has a role dedicated to assisting families where a relative has been matched. The role of Donor Coordinators in aiding related donors has been discussed at the WMDA and other international forums. As the role of haploidentical (half-matched) transplants expands, there may be a future need for this type of assistance.

Transplant centres, National Donor Coordinators and the ABMDR undertake ad hoc coordination of related donors who are located internationally. The ABMDR administers financial arrangements through National Donor Coordinators, who liaise with the transplant centre to align scheduling. However, often transplant centres will be directly involved in seeking typing of relatives and related donors who return to Australia for HPC collection at the centre treating their relative. Transplant Coordinators have a much larger role in these donations.

ABMDR

Aside from its role overseeing unrelated donors and operating the registry, the ABMDR has a specific role administering searches on international registries, which fall under the International Searches Program (ISP). The ABMDR approves all international search applications and facilitates contact with international registries when they are identified as having a potential donor for an Australian patient. Additionally, where an international patient has identified an Australian donor, the ABMDR acts as the first point of contact to facilitate donor testing and collection. As a function of these roles, revenue and spending relating to HPC testing and collection are funnelled through the ABMDR.

Commonwealth Government

The Commonwealth has a specific role in administering the BMTP. In this role, transplant centres (on behalf of patients) apply to the Commonwealth for funding approval to access an identified international HPC. The Commonwealth provides funding for collection costs and reimburses courier costs (or for an internationally matched relation to travel), administering

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[32] State Search Coordinators are based in WA, SA, Victoria, NSW and QLD. Tasmanian patients are coordinated through Victoria, ACT through NSW and NT through SA.

the review and approvals for doing so. This function complements the role of the ABMDR in approving and initiating international searches.

Funding arrangements and operations are fragmented as a result of the different actors within the sector.

Process and policies

The ABMDR doesn't have clinical policies, but it maintains a series of standards (formerly called 'guidelines'). It issues these to each transplant centre to standardise approaches to seeking, collecting and reporting on allogeneic-unrelated donors. Key datasets analysed lists the standards reviewed for this report.

The ABMDR's committees review its guidelines and distribute them to transplant centres that use the registry to identify potential donors (and are accredited by the ABMDR).

As previously explored in this chapter, clinical guidance is channelled through the professional societies of the clinicians. Many clinicians will also look to the international bodies of the EBMT and ASBMT for additional information.

Accreditation

The ABMDR accredits donor centres and State Search Coordinators, CBBs and transplant centres against its guidelines. Donor centres and CBBs are accredited every two years through on-site audit; however, it only makes observations.

In addition to ABMDR accreditation, the different organisations that deliver activities supporting HPC donation are accountable to[33]:

- hospitals (transplant centres), under the Australian Council on Healthcare Standards. A blood service will be licensed under the Therapeutic Goods Administration (TGA) for apheresis collections. Additionally, transplant centres must report to the ABMTRR
- laboratories (supporting transplant centres), under National Association of Testing Authorities (NATA) or Royal College of Pathologists Australia accreditation
- the American Society for Histocompatibility and Immunogenetics for accreditation and TGA licensing for tissue typing
- cord blood banks, under TGA licensing and the Foundation for Accreditation of Cellular Therapy (FACT).

The ABMDR is accredited as a member of the WMDA. Appendix E explores accreditation.

Technological application and infrastructure

Search software

To assist it in managing donors, ABMDR developed a bespoke system – MatchPoint –in 2010.[34] MatchPoint lists the details of Australian donors, including their identification, jurisdiction of registration, date of birth, date of registration, and details of tissue typing (depending on the level of tissue typing undertaken on the donor). The registry is maintained by Donor Coordinators, who are located in the ABMDR's national office, and Donor Coordinators in the states that register new donors to the registry.

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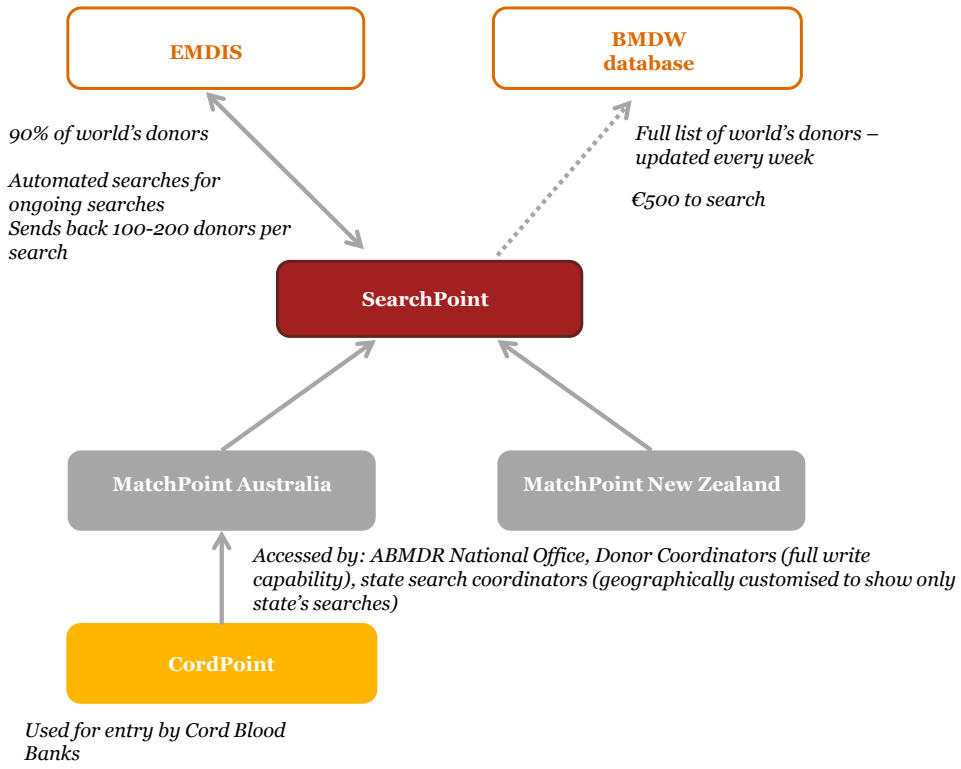
[33] ABMDR Accreditation policy, 'ABMDR-GL-OP-002-07 Accreditation.pdf', provided by the ABMDR.

[34] ABMDR, *Unrelated HPC sourcing strategy* (Version 1.2, 10 May 2016), provided by the ABMDR.

MatchPoint interfaces with SearchPoint, a platform for exchanging information with international registries. MatchPoint is also supplemented by CordPoint, which CBBs use to enter and manage the details of CBUs they are storing.

As Figure 15 shows, MatchPoint New Zealand also feeds into SearchPoint, which has a direct link to international registries that observe the EMDIS protocol. The protocol enables algorithmic searching of donors listed across the world's bone marrow registries, which account for about 90% of donors worldwide. The ABMDR has had point-to-point connectivity with other registries through EMDIS since 2007.

Figure 15: Schematic of MatchPoint, ABMDR's software system



Through SearchPoint, a Search Coordinator can register a patient's details and search international registries. The Search Coordinator will use *patient update* status in EMDIS to undertake a preliminary search of international databases, which will return around 100–200 potential donor details. If the coordinator switches the status to *patient active*, the entered search will activate the search function to continue searching international donors (this automated query will capture newly added donors to international registries to allow the coordinator to monitor new potential options for a patient). MatchPoint is designed so that it can support any search algorithm the ABMDR requires. Currently, the ABMDR has adopted a German algorithm for search activities.

Alternatively, the Search Coordinator can search the BMDW database. The database contains the full list of all internationally registered donors, allowing the coordinator to interrogate a much wider pool of donors than what might be identified in EMDIS. A coordinator may initiate a search in the BMDW database if a patient is particularly difficult to match, or the coordinator decides they need the 'full list' of potential options to make an assessment. The BMDW database is updated regularly as registries submit their most up-to-date information. Australia does this roughly every week. However, each search of the database costs €500 and relies on the information that is inputted. That is, if a registry has not updated its details, it is possible that donors who are no longer available for donation are still listed. Additionally, donors from some countries, including Malaysia, China and Hong Kong, are not available on the BMDW database. Searches for potential donors on registries not using EMDIS or not on BMDW require the Search Coordinator to undertake a manual search of those registries on

the Australian patient's behalf. This review received examples of searches initiated via email and fax.

There are 28 affiliated registries that follow EMDIS protocols, which cover approximately 90% of BMDW-listed donors.[35]

MatchPoint is provided as a free software package to Thailand and New Zealand to assist their registries. Singapore pays ABMDR an annual fee of A$50,000 to use MatchPoint. As a result of these arrangements, MatchPoint searches return Singaporean, Thai and New Zealand donors. Under changes to the EMDIS protocol standard, this cross-registry matching will be separated to return only donors from the specific registry searched in the future.

MatchPoint reclassified patient ethnicity five years ago, in line with international agreements on data-sharing protocols. As a result, as well as a data migration exercise to move legacy information from the former Search, Tracking and Registry (STAR) system, information on volunteer donors and matches before 2013 is incomplete. Despite this, the ABMDR reiterated to PwC that the lost data has not affected search functions.

Information, data and reporting

Registry management

The ABMDR has successfully supported searches and matching of Australian patients and donors for 26 years, based on information collected from donors at the time of registration and the IT platform supported. With time, changing clinical needs and technological advances, have led to changes to typing capabilities and donor access expectations.

Key challenges include the availability of upfront information on potential donors. High-resolution typing information is available for the profiles of many international donors, compared to Australian donors, who have lower-resolution typing. This means clinicians can make quicker decisions about international donors.

Contacting potential donors identified in MatchPoint can be challenging. Many donors registered some time ago, and their contact details have changed. Many entries don't include an email address, which was not captured at registration, particularly for donors registered in earlier years of the registry's operation. The ABMDR noted that the records of only around 57,000 of the 170,000 donors registered include a valid email address.[36]

Business and data reporting

Reporting extracts are not built into the current registry systems, meaning reports must be compiled manually. Around three FTEs undertake reporting in the ABMDR to fulfil its contractual obligations with governments and associated entities. Reporting of the ABMDR includes:

- quarterly reporting under the NCBCN contract, which includes compiling reports generated by each of the three CBBs and the ABMTRR, plus summary reporting
- monthly reporting on the international search program
- annual reporting under the two head funding contracts (the NCBCN Contract and Core Services Agreement, which are explored in further detail later in this chapter)
- annual reporting for the ABMDR as an organisation

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[35] UK NHS (2014) Unrelated Donor Stem Cell Transplantation in the UK, p 35, accessed at <http://www.nhsbt.nhs.uk/download/unrelated_donor_stem_cell_transplantation_in_the_uk.pdf>

[36] Note: The ARCBS maintains a database of blood donors and the ABMDR has access to the details of those who are also registered as HPC donors.

- an annual compliance report to the WMDA
- regular Board and Committee meeting reports.

The ABMDR suggested that reporting to governments often requires multiple iterations, compounding the overall reporting effort.

Additionally, lack of business intelligence (BI) means that monitoring of activities and registry statistics is relatively ad hoc. The ABMDR reports that it regularly takes a snapshot of donors on the registry to inform its internal activities, and will analyse patients in spreadsheets that capture their details. Recording a search as complete, a transplant as having taken place or a cancellation is done manually. There is no regular outward or upward reporting of KPIs or key BI metrics.

Information exchange

The process for identifying and mobilising a donor includes filling in many paper forms that require multiple-party handling. These forms present opportunities for automation and streamlining. The following table lists some of the forms.

Process	Parties
Unrelated search initiation forms (110 form)	• Transplant centre manually prepares and emails form • Search Coordinator transcribes forms and enters in MatchPoint • ABMDR provides support
BMTP application form	• Transplant centre prepares submissions, and liaises with patients and the Search Coordinator • Department of Health reviews and approves submissions
Courier reimbursement forms (BMTP)	• Transplant centre compiles receipts and follow-up with couriers • Transplant centre captures receipts for the courier are prepared and submitted • Department of Health reviews and approves submissions
ISP application form	• Transplant centre prepares submissions, and liaises with patients and the Search Coordinator • ABMDR reviews and approves submissions
Search reports	• Search coordinator prepares results, drawing on MatchPoint outputs
Recruitment and donor coordination reporting	• Blood service prepares six-monthly reports to state representatives (we understand is a separate dataset)
Outcomes reporting	• Many transplant centres report on patient outcomes to the ABMTRR and CIBMTR. While content is similar, there is some duplication.

This review identified that the ABMDR is currently undertaking business improvement activities to streamline data requests and support unrelated donor searches and approvals associated with international donors.

Clinical reporting

Additionally, the ABMTRR is responsible for capturing and reporting on clinical outcome data. The ABMTRR is governed by the BMTSANZ and operates under the auspices of St

Vincent's. The complex governance arrangements mean that the ABMDR is responsible for contractual reporting and funding management, but other entities have the true governance roles.

The ABMTRR produces an annual data summary of HPC transplants, based on reports transplant centres have lodged on its online ASTRO (Australasian Stem Cell Transplant Registry Online Database) database.[37] A handful of stakeholders reported to this review that the data collection was limited to a minimum dataset. The broader dataset reported to the CIBMTR is considered more rigorous, and potentially useful.

Transplant centres, as part of their accreditation, are required to report on patient outcomes to the ABMTRR, but the ABMTRR told us that on occasion, transplants may not be reported or are reported late, compromising its dataset.

While the merits and extent of clinical reporting captured is also currently under review, we observe that:

- there may be scope to consider how the two databases are connected (and either creating an automatic workflow/patient shell in the ABMTRR database to prompt data capture) and/or linking data capture so that transplant centres only have to report one dataset, ending duplicated reporting to the ABMTRR and CIBMTR

- donors are not systemically captured by any database, and could be incorporated into the same database as patients:

    - Currently, ARCBS Donor Coordinators conduct follow-up enquiries (within 72 hours of collection; each week until the donor is fully recovered; at three months; and then annually for 10 years); however, this information is only reported for an adverse event

    - Adverse events are reported to the ABMDR, which passes them to the WMDA

- information about patients seeking an unrelated donor – whether or not they have identified a donor – is not captured systematically, nor reported at a level that enables analysis of why a patient didn't proceed to transplant. While individual transplant centres take clinical notes, this is not aggregated in reporting

- information about the number of searches initiated, their status and outcome (including HLA level of match and time to match) is not systematically captured

- consent is sought from patients, but if it isn't captured or reported, transplant outcomes for these patients are not included in some datasets, meaning that datasets are often incomplete

- information about the number of haploidentical transplants that proceed is embedded in current data capture and reporting (allogeneic-related transplants). This information may useful for monitoring this clinical trend and its outcomes over time.

The number of transplants recorded in each year in the datasets provided for this review is a case in point. For example, the ABMDR dataset provided data on 67% of the transplants reported by the ABMTRR in 2014, but 55% of collection dates were blank. When data was assessed against ABMTRR information, it showed fewer transplants than had occurred.

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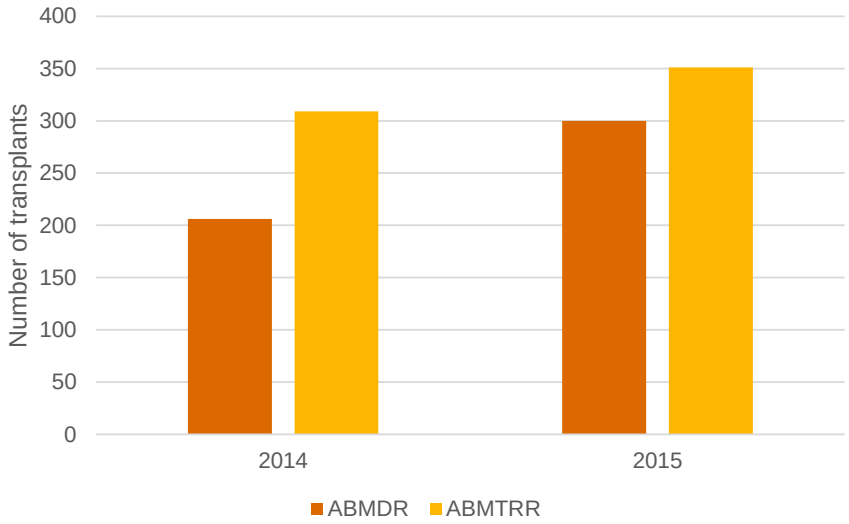
[37] With the exception of four transplant centres that have not changed practice and submit information to the ABMTRR via email.

Figure 16 shows the differences between ABMDR and ABMTRR recorded transplants in 2014 and 2015.

Figure 16: Total of recorded transplants in 2014 and 2015 (ABMDR and ABMTRR)



Source: ABMDR data – Question 4a, 4b and 4c, and ABMTRR annual data summaries

Against this discrepancy, there is a known lag in the transplant outcomes reported to the ABMTRR, meaning the total number of transplants may be under-reported. Of all transplants undertaken, the ABMTRR has captured 67% of transplant outcomes and 92.8% of one-year patient data on transplants to 2014.[38]

Some discrepancies are due to batch reporting of transplants from transplant centres, lack of dedicated resources within transplant centres to manage data, poor capture of data or lack of submissions.[39] These factors play an even greater role in the reporting of autologous transplants.

People and capabilities

Across the HPC sector, governance structures define the roles and responsibilities of individuals within organisations. Table 4 outlines some of the roles and capabilities within key organisations.

Table 4: People and capability matrix for key organisations

Organisation	Structure	People	Capabilities
Tissue typing laboratories (ARCBS, PathWest, Pathology Queensland)	Laboratories fall under the governance and organisational structures of the ARCBS, PathWest and Pathology Queensland	State Search Coordinators are located in each laboratory to initiate, assess and report on unrelated searches. Additionally, laboratory staff support the processing and	• Coordinators have tertiary qualifications in fields of immunogenetics and/or histocompatibility • Laboratory staff are also technically qualified and adhere to accreditation and

[38] ABMDR End of Financial Year Report 2015–2016, National Cord Blood Collection Network.

[39] KPMG (2017) *Final report – Bone Marrow Transplant Outcomes Reporting Review*, prepared for the ABMDR.

Organisation	Structure	People	Capabilities
		operation of laboratories	quality management standards • The roles and responsibilities of laboratories complement the skill sets of those used for typing and matching deceased and living organ donors
Transplant centres	Transplant centres are defined by the clinical governance and organisational structures of the hospitals where they are located	A number of clinical roles support a patient during the transplant process, and Transplant Coordinators are important for identifying and managing searches. Additionally, most transplant centres are supported by Data and/or Quality Managers, who support centre operations	• Transplant Coordinators are qualified clinical nurses • In addition to clinical roles, they coordinate activities in line with ABMDR protocols • Managers apply quality management systems that align with hospital standards
Cord blood banks	CBBs fall under the governance and organisational structures of the hospitals where they operate	CBB staff include scientists, laboratory technicians and researchers	• CBB Directors are highly specialised • Collectors are trained midwives
Bone marrow donor centres	Donor centres operate out of ARCBS blood donor centres and, as such, fall under its organisational and governance structures. National coordination is provided by the ABMDR national office, which also provides a reporting structure for bone marrow donor centres	Donor Coordinators are located in bone marrow donor centres (specified blood donor centres) and are responsible for recruitment, donor management and coordination	• Donor Coordinators play an important welfare role, supporting donor decisions

ABMDR office

The ABMDR is supported by a small team with significant expertise and long-held corporate knowledge about the HPC sector and operating the registry. These skills are not reflected in other industries or industry segments, except perhaps the ARCBS, which has strong capabilities in recruiting, engaging with and managing volunteer donors. As a result, staff are highly committed and knowledgeable.

The ABMDR's national office in Sydney has a small team of operational staff, who oversee the registry, manage search applications and enrol new donors onto the registry database,

and undertake reporting. It is supported by an accounts team, which undertakes all financial acquittals and reporting. The small but growing team of IT developers administer the MatchPoint program and undertake application development, including project-based activities. Additionally, two National Donor Coordinators are responsible for coordinating recruitment activities and donations. They spend the majority of their time on search activities and dedicate any spare capacity to developing guidelines and stakeholder engagement.

The ABMDR is led by a National Executive Officer, who together with the Operations Manager, undertakes analytics and measures the registry. In addition, they support the Board and provided leadership to the organisation.

Under current arrangements, the IT team risks losing capability, which is currently concentrated among very few staff. If one member in particular left the organisation, there would be limited capacity to edit MatchPoint. It would be worth considering if IT developers and administrators be separated into two teams to support new developments and the status quo of operations, respectively.

Training and professional development

In addition to accreditation activities, international bodies provide useful avenues for transplant centre staff to access professional development, training and materials to guide their practice, and to collaborate with colleagues on clinical advances and techniques. Examples provided included the CIBMTR and EBMT. In Australia, the bone marrow transplant network provides professional development opportunities for staff at its NSW transplant centres. The ARCBS used to convene a national forum to bring together Donor Coordinators and Transplant Coordinators, but it no longer holds the forums.

3.1.3 Structure

Legal and regulatory framework

The legal arrangements for the HPC sector are bound by two primary funding agreements, which govern funding flows from governments to the ABMDR. State and territory government agreements stipulate all other arrangements with the ARCBS and pathology providers, and in the health system structures where transplant centres operate.

The ARCBS and the ABMDR do not have a service-level agreement. This is despite the ARCBS housing the ABMDR within its offices, and running its recruitment and coordination. In addition, ARCBS laboratories perform a significant amount of tissue typing.

Regulation of the HPC sector

Current state

Under current arrangements, the regulation and quality and safety aspects of autologous, related and unrelated HPCs used in haemopoietic reconstitution fall under the auspices of clinical activity and the associated protocols. With the exception of cord blood banking (referred to below), the TGA does not have regulatory oversight of the HPC sector. This is because the regulation of HPCs is guided by the Therapeutic Goods (Excluded Goods) Order (2011). This order does not refer to *minimally manipulated* HPCs[40], but to 'fresh viable'

[40] The term *minimally manipulated* is defined in Regulation 2 of the Therapeutic Goods Regulations.

direct donor-to-host transplants and hematopoietic reconstitution. The order deems that HPCs are not therapeutic goods under section 4(p) of the order, and so does not fall under the *Therapeutic Goods Act 1989*.[41] This exclusion applies to HPCs collected in Australia and those sourced from international donors for Australian patients. This exclusion reflects the significant clinical role in collecting and transplanting HPCs that have not been stored or manipulated between collection and transplant.[42]

The National Pathology Accreditation Advisory Council (NPAAC)oversees the National Association of Testing Authorities (NATA), which is the body that inspects and accredits testing laboratories and transplant programs. NATA's accreditation scheme, which was updated in 2015, specifies accreditation requirements and covers directed (meaning, under clinician oversight), minimally manipulated HPCs. In doing so, it recognises the role of clinicians in ensuring the quality of donated products. Areas covered include newly harvested HPCs for allogeneic-unrelated and allogeneic-related transplants, and HPCs that are frozen and stored in hospitals for autologous transplant into patient who are supervised by the same medical practitioner who collected the cells.[43]

Cord blood banking

The TGA licenses and accredits cord blood banking activities, which are largely managed without clinical oversight (cord blood is banked and managed within banks until its release for clinical use). The TGA has licensed each of Australia's public CBBs and a number of private CBBs that are storing directed CBUs. Many private CBBs are licensed for autologous and allogeneic-related release of CBUs, but public CBBs are licensed for allogeneic-unrelated transplant purposes only (although this requirement is being removed, enabling release of CBUs for related and autologous purposes).

Additionally, the CBBs under the Australian network of CBB and collection centres (AusCord) comply with FACT-NetCord standards and maintain FACT accreditation, in line with international CBBs. The TGA does not require this, but the public CBBs, which also facilitate release of CBUs for international patients, consider it desirable. In many cases, international clinicians who treat patients look for FACT accreditation when seeking a CBU for clinical use.

Transit of HPCs

The export of blood and blood products falls under Schedule 6 of the Customs (Prohibited Exports) Regulations 1958, which requires an export permit from the TGA if the volume of a product exceeds 50mL. Under current arrangements, the ABMDR holds export permits to enable the passage of HPCs collected from Australian donors for international patients.

However, HPCs collected from international donors for Australian patients are not subject to import permits.[44]

Funding structure

The sector is funded through:

- direct funding of the key programs of the ABMDR, the NCBCN, the ABMTRR, the ISP and the BMTP, which are contained in the two primary funding agreements.

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[41] Refer to Therapeutic Goods (Excluded Goods) Order No.1 of 2011 and s 7AA of the *Therapeutic Goods Act 1989*.

[42] HPCs are regulated in a similar manner to blood, blood components and biologicals (human cells and tissues), which are exempt from oversight where a medical practitioner is involved in the collection and therapeutic application. Stem cells used for purposes other than haemopoietic reconstitution are regulated as biologicals under the TGA's Biologicals Framework.

[43] Defined as haemopoietic progenitor cells (HPC) used for haematopoietic reconstitution under s 3(a) of the *Therapeutic Goods Act 1989 Therapeutic Goods (Things that are not Biologicals) Determination No.1 of 2011.*

[44] As per the Australian Biosecurity Import Condition, Human therapeutics and medicines, effective 19 April 2017, import permits are not required for stem cells. However, consignments must be accompanied by an Importer Declaration, prescription details (for example, a doctor's letter) and a product label specifying contents. For further information, refer: https://bicon.agriculture.gov.au/BiconWeb4.0/ImportConditions/Conditions?EvaluatableElementId=214932&Path=UNDEFINED&UserContext=External&EvaluationStateId=2a7a68c4-5523-4668-9837-5fb57610d3ed&CaseElementPk=643118&EvaluationPhase=ImportDefinition&HasAlerts=False

Clinical treatment and costs of collections are supported by state and territory governments as part of state health budgets

- state-based funding of testing services of – the ARCBS (in Victoria (including Tasmania), NSW (including the ACT) and South Australia (including the Northern Territory), PathWest and Pathology Queensland – cover the cost of tissue typing and testing.

These arrangements are the outcome of changes outlined previously in this chapter. The ABMDR shifted from a model in 2001 where it had been receiving funding under the AMHAC cost shared arrangement), 50% from the Commonwealth and 50% from state and territory governments) to a model under which funding is directly provided by the Commonwealth. The states and territories now support HPC services in their jurisdictions, while the Commonwealth funds ABMDR core services the BMTP and the ISP. The NCBCN is now funded by the AHMAC cost shared arrangement. This review did not see documentation spelling out the reasoning for this shift, but we understand that the ABMDR was one of the last bodies (along with the Royal Flying Doctor Service) to be shifted from this funding mechanism. This shift was the result of the Commonwealth streamlining expenditure under Medicare agreements, instead channelling funds to state and territory governments. In turn, states adopted responsibilities for direct funding of activities associated with medical services, including donor recruitment, searching and matching, tissue typing and collections.

The change in funding and contractual arrangements between the ABMDR and different governments resulted in the states managing funding and contractual levers, leaving the ABMDR with less control over setting targets and managing activities.

This section briefly describes the current funding arrangements, including quantitative figures for recent expenditure, which are outlined in Chapter 7.1 of this report.

Primary funding sources

The HPC program is funded through the Commonwealth Department of Health's Program 1.1 (Health Policy Research and Analysis) under Program Objective D (Improving Australians' access to organ and tissue transplants.[45] In FY2016-17, the program's objective was *to provide patients in need of life-saving stem cell transplants with the best possible chance of finding a stem cell match …* and *to continue to provide funding for approved applicants to search for an international match*. It does this through the BMTP, ISP and NCBCN programs, which are administered through the two funding agreements between the Commonwealth and the ABMDR, which cover:

1. funding to the ABMDR to administer the NCBCN and to enter into a contract with St Vincent's Hospital to support it to operate the ABMTRR[46]

2. funding to operate the registry, administer the ISP program, and manage and procure international HPCs under the BMTP program.[47]

Contract - NCBCN

The NCBCN is funded through a head contract between the Commonwealth and the ABMDR. A variation on the Principal Agreement (contracted in 2012–13 and 2014–15) was put in place when the contract expired to extend its terms to cover the period 2012–13 to

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45 Commonwealth Department of Health, Portfolio Budget Statement – Outcome 1 – Health System Policy, Design and Innovation.

46 Commonwealth of Australia as represented by the Department of Health and Ageing and the ABMDR – Funding Agreement 2012–13 – 2014–15.

47 Commonwealth of Australia as represented by the Department of Health and the ABMDR – Core Funding, International Searches Programme and Bone Marrow Transplant Programme 2014–15.

2016–17.[48] The Commonwealth provides funding to the ABMDR after it lodges its annual business plan and half-yearly progress reports. Additionally, two quarterly payments are outlined in the Agreement, which are not contingent upon meeting milestones.

The states and territories have also contributed to funding for the NCBCN since 2001.

The head contract supports the operation of the three CBBs, as well as funding for the ABMTRR. Additionally, some funding is used to support the ABMDR's operating budget.

The ABMTRR was originally funded through the Arrow Bone Marrow Transplant Foundation, which a number of St Vincent's clinicians set up to establish the outcomes register. As its role grew, NSW Health began providing a small amount of funding to support a health statistician. It was later funded in 2010 by all Australian governments through the ABMDR who maintain these responsibilities.

Contract – Core Funding, International Searches Program and Bone Marrow Transplant Program 2014–15

The core funding of the ABMDR is supported by the Core Funding Agreement between the Commonwealth and the ABMDR. Payment and accounting for the ISP relies on an implicit agreement between the Commonwealth and the ABMDR that all genuine searches requested will be funded, and if a match is found, support will be provided to collect HPCs for transplant. Because it is demand-driven and demand for international donors is growing, future costs are projected to increase. Some stakeholders perceive the current funding mechanism as an uncapped liability, despite the Commonwealth recognising it as an uncapped funding pool.

The core funding contract has been varied three times to account for growing demand and the increasing costs of searching for and collecting HPCs – the Commonwealth was forced to seek supplementary funding beyond its budgetary appropriation a number of times. The contract stipulates objectives that include:[49]

- updating and maintaining the donor registry and supporting the IT system
- overseeing the search for appropriately matched HPCs and CBUs for patients needing a transplant
- supporting the ABMTRR to collect, analyse and report on clinical outcomes data for all HPC transplants and encourage transplant centres to provide patient data to the ABMTRR
- maintaining accreditation with the WMDA
- supporting the ABMDR National Management Board and its network of advisory committees and subcommittees
- meeting the regulatory requirements of the TGA where relevant, through quality assurance of the participant's activities
- ensuring financial provision for office accommodation and other infrastructure
- preparing an annual report and publishing it online.

With the exception of the activities of the NCBCN and the ABMTRR, the objectives of both agreements are process-oriented. While the agreements include historical objectives of

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[48] Australian Government Department of Health – Deed of Variation No.1 between the Commonwealth of Australia and the Australian Bone Marrow Donor Registry.

[49] Australian Government Department of Health Multi Schedule Deed of Agreement between the Commonwealth of Australia and the Australian Bone Marrow Donor Registry (Core Funding, International Searches Programme and Bone Marrow Transplant Programme 2014–15).

funding – which have not been updated since the original drafting – these objectives don't drive strategic outcomes. For example, the funding agreements' objectives are duplicated where they identify that the ABMDR is to support the ABMTRR to collect clinical outcome data (Schedule 1, Project Objective 3). Consideration should be given to the purpose and objectives of the government's funding of the ABMDR, to better craft agreements that drive outcomes of the investment.

In addition to the primary contracts held with the ABMDR, a number of other funding streams directly and indirectly support the provision of unrelated HPCs (from donors and CBUs) in Australia. These are illustrated in Figure 17 and their roles and responsibilities have been described in earlier sections of this chapter.

Figure 17: Primary funding roles across HPC sector activities

Funder		Donor recruitment: Donor registration and marketing	Donor recruitment: Initial Tissue typing	Search coordination: Search initiation	Search coordination: Search coordination	Search coordination: Donor matching	Tissue typing: Sample collection and IDM testing	Tissue typing: Verification/ confirmation typing	Donor coordination: Donor work-up	Donor coordination: Donor education, travel and coordination
Commonwealth					✓					✓
ABMDR (multiple funding sources)					✓					
State Government	ARCBS Donor Centres (state funded)	✓	✓							
State Government	Transplant centre (state funded)					✓			✓	✓
State Government	State search coordinators/ Tissue typing laboratory (state funded)			✓	✓	✓		✓		
State Government	National Cord Blood Collection Network									
ARCBS							✓			

Funder		HPC collection				National Cord Blood Collection Network	Registry management				
		Donor scheduling, travel and coordination	Bone marrow harvest/ Peripheral blood collection	Transport (courier costs)		Cord blood banking		Donor follow up	Outcomes reporting	Registry administration	Accreditation
Commonwealth			✓	✓		✓			✓		
ABMDR (multiple funding sources)		✓						✓		✓	✓
State Government	ARCBS Donor Centres (state funded)										
	Transplant centre (state funded)	✓	✓	✓				✓	✓		✓
	State search coordinators/ Tissue typing laboratory (state funded)										
	National Cord Blood Collection Network					✓					
ARCBS											✓

In addition to the state-held contracts with the ARCBS, to support the roles of the State Search Coordinators and Donor Coordinators, all Australian governments fund HPC transplantation and associated coordination activities through hospital funding. They also fund tissue typing activities, which are a major cost driver in donor-matching activities.

Tissue typing

Funding for tissue typing is fragmented across Australia's HPC sector because it is the responsibility of state and territory governments, which have established contracts under service agreements with their own tissue typing laboratories. As a result, funding contracts are:

- output-based in NSW
- core contracts in Victoria, which are supplemented by health services based on output
- capped in South Australia, which is moving towards an output-based funding model, and Tasmania
- unlimited in Western Australia and Queensland.

These contractual settings have different incentives for typing of new donor recruits, and for processing of verification typing requests. The ARCBS in NSW, Victoria and South Australia is funded under service agreements that cover both tissue typing and recruitment activities. However, these arrangements differ in Western Australia and Queensland, which fund the ARCBS for recruitment, but separately fund tissue typing laboratories, which operate independently of the donor centres.

As a result of different contractual arrangements, each laboratory has a different standard for tissue typing, which is also priced differently. These structures drive different outcomes. This review heard that laboratories in Queensland and South Australia have targets for the volume of initial tissue typing undertaken. This can result in these samples being stored in fridges until the following financial year, to meet targets for volume. It has also resulted in locally driven 'policies' that deflect potential donors if they don't meet particular criteria (for example, if they are older), so that typing is undertaken only on those donors considered most desirable.

The ABMDR has tried to incentivise tissue typing laboratories to see if they can influence the costs of typing and improve processing times. One laboratory commented that the level of incentives was too low to influence priority of processing, and as demand for typing at more loci grows, costs also grow. Incentives would need to be significantly higher to markedly shift activity.

International HPCs (the BMTP and ISP programs)

Formerly, funding to search for and collect international HPCs for Australian patients was unfunded. Funding was then covered by discretionary Act of Grace payments made by the Commonwealth Government (this power is now vested in s 65 of the *Public Governance, Performance and Accountability Act 2013*). The Act of Grace arrangements were formalised through the BMTP program, which is administered by the Commonwealth, and the process has been standardised for all Australian patients, ensuring access when needed. The ISP program provides funding for international searches and is administered by the ABMDR.

To manage the risk to the Commonwealth of uncapped searching for international donors, the ABMDR has imposed a three-tiered threshold for each patient. It has allocated a total of $12,000 for searching for each patient (made in one tranche of $6,000, and two of $3,000 each). These payments cover expenses associated with searching international registries and requesting additional testing (for example, for extended typing) to identify potential matches.[50] Funding differs between registries (for example, verification typing of a Brazilian donor can cost more than $3,000, while that for a UK donor is only a few hundred dollars), so it is difficult to quantify how many tests this amount will cover. Additionally, foreign currency fluctuations affect the calculations; however, for most patients, the threshold has been sufficient to undertake searches. Only two patients have exceeded the $12,000 threshold. On average, only about six applications per year exceed the $6,000 (first) threshold.

3.1.4 Performance management

Performance management metrics

In its Portfolio Budget Statement, the Commonwealth has qualitative targets for [51]:

- supporting the ABMDR and the NCBCN's diversity of tissue types for HPCs available for transplant
- supporting the ABMDR to search and match donors internationally.

The CBUs have quantitative targets for collections, which are:

- that 70 Indigenous CBUs were made searchable in 2016–17

[50] ABMDR-POL-OP-PAT-01 Patient funding access policy, provided to PwC February 2017.

[51] Commonwealth Department of Health, Portfolio Budget Statement – Outcome 1 – Health System Policy, Design and Innovation.

- that 50% of searchable CBUs are from people who are not of North West European (NWE) ancestry
- that of the total of 1,600 banked CBUs, at least 50 are Indigenous CBUs.

The emphasis on cord blood banking is reflected in the KPIs of the funding agreements.

The Progress and Final Report templates outlined in the NCBCN Funding Agreement specify KPIs against which the ABMDR must report.[52] The following table shows the KPIs outlined in the Agreement and progress against those KPIs, as shown in progress reports to the Department.

The NCBCN has met or exceeded its KPIs, with the exception of the proportion of CBUs transplanted that are sourced from Australian CBBs. However, the low number of transplants (43 in FY2015–16) means this percentage can vary significantly from year to year.

KPI	Target	Progress
2.1 Indigenous CBU representation	400 banked and searchable Indigenous CBUs at 30 June 2016 (Targeting 70 banked and searchable Indigenous units per year from 1 July 2016)	*Exceeded* 794 banked, 552 searchable at 30 June 2016 (Results for EOFY 2016-17 results not yet known)
2.2 Median Total Nucleated Cells (TNCs) for NWE CBUs	Median post-processing TNC count for all NWE CBUs banked in Australia annually is at least 110×10^7	*Exceeded* 113.5×10^7 at 30 June 2016
2.3 Ethnic diversity	50% of banked and searchable CBUs from births where one or both parents claim non-NWE ancestry	*Exceeded* 62–69% of banked and 60–65% of searchable CBUs were from non-NWEs in 2015–16
2.4 Suitability for Australian patients	40% of CBUs transplanted into Australian patients are sourced from AusCord	*Not met* 28% in 2015–16, which was mainly due to lower demand and typing resolution
2.5 Reasons for choosing international CBUs	During this two-year period (FY2015-16 and FY2016-17), collect data from transplanters about why they select suitably matched CBUs from international CBBs	*Met*

[52] Australian Government Department of Health – Deed of Variation No.1 between the Commonwealth of Australia and the Australian Bone Marrow Donor Registry.

KPI	Target	Progress
2.6 Accreditation	Maintain TGA licences and FACT accreditation	*Met*
2.7 Single Technical Master File (TMF)	Single TMF accepted by TGA by June 2016	*Met*
2.8 Financial management	AusCord to deliver outcomes specified by KPIs within its two-year budget	*Met*
2.9 CBU transplant reporting	The ABMTRR will continue increasing the percentage of transplant records on its database. During this two-year period (FY2015-16 and FY2016-17), it will collect and report on data, including: • average time to engraftment • survival rates • incidence of Graft versus Host Disease • the percentage of transplant records recorded on ABMTRR's database	*Met*

Source: Deed of Variation No.1 to the funding agreement between the Commonwealth of Australia and the ABMDR and NCBCN. End of Financial Year Report 2015–16.

Additionally, the NCBCN must report progress on a number of non-KPI measures, including:

- the number of searchable CBUs (banked and searchable)
- the number of CBU releases for transplant.

The Core Services Funding Agreement does not include specified KPIs. However, progress and end-of-year reporting is required to provide:

- an outline of the ABMDR's achievements against project objectives
- challenges in the project's performance
- a summary of the transplants facilitated by the ABMDR and the HPC products provided
- an overview of registry donations, including CBUs
- outcomes of the ABMDR's projects
- outline of ABMDR employees, Board members and expenditure on the ISP.

KPIs are critical to measuring outcomes

Under its contract with the Commonwealth, the ABMDR's annual report must also detail the number of searches conducted on the donor registry, although this information is not reported on.[53]

State contracts with the ARCBS, to support the bone marrow donor centres and arrangements for tissue typing, vary. We sighted contracts and information, which showed the following requirements for the ARCBS in each state and territory:

- In Tasmania, it must provide reports that specify activity levels against those agreed in the contract (although, this is not a KPI). Activities include the number of donors recruited, number of typings and requests, work-ups and the number of donations by registered donors.

- In South Australia, it must meet KPIs for newly recruited donors, volume of typing requests and number of donations, and perform a specified number of related and unrelated donor tissue typing tests.

- In Victoria, its tissue typing services are monitored for customer satisfaction, progress against the business plan and some other activities, but there are no quantitative KPIs.

- In Queensland, the tissue typing service agreement between Pathology Queensland and the Queensland Cord Blood Bank requires that it hold TGA and FACT accreditation, to meet agreed annual targets for providing searchable CBUs.

Reports are provided to the responsible departmental official, but are not shared more broadly to provide a national or even cross-jurisdictional picture of recruitment and typing activity.

53 Australian Government Department of Health Multi Schedule Deed of Agreement between the Commonwealth of Australia and the ABMDR (Core Funding, International Searches Programme and Bone Marrow Transplant Programme 2014–15).

Clinical trends

4

This chapter covers...

- *trends in paediatric and adult allogeneic transplants*
- *transplant human leukocyte antigen (HLA) matching and sources of haemopoietic progenitor cells (HPCs), including the relationship of donors to patients undergoing allogeneic transplants.*

Key messages:

The number of HPC transplants, of all kinds, continues to grow. Between 2013 and 2015 alone, the number of transplants in Australia grew from 1,551 to 1,706. However, the number of allogeneic transplants undertaken in adults is growing more quickly than for paediatric patients. This reflects that many more transplants are proceeding in older patients, due to improvements in clinical technologies and transplant outcomes, as well as a greater number of older patients being assessed as suitable to transplant.

Increasingly, unrelated donors are supporting allogeneic transplant patients as the number of HPCs from related donors decreases. Partly, this is attributable to the significant global pool of donors, which provides clinicians with more donor options, but it also relates to the older age of patients, meaning that their relatives may also be older and less suitable to donate (due to comorbidities), as well as the general trend in smaller family sizes, meaning that patients may not have a matched relative.

The vast majority of allogeneic transplants proceed with identically matched HPC donors, using peripheral blood or bone marrow. Far fewer transplants proceed with mismatched donors and, when they do, many are supported with cord blood units (CBUs). Peripheral blood remains the primary source of HPCs for adult allogeneic-unrelated transplants, while cord blood supports approximately 40% of paediatric transplants.

The Australian Bone Marrow Donor Registry (ABMDR) considers that the growing trend in allogeneic-unrelated HPC transplants is driven by:

- *underlying (absolute) growth in the number of leukaemia cases*
- *an increasing ability to transplant older and higher-risk patients*
- *improved inpatient treatment and capacity in hospitals, making it a more viable clinical pathway for patients traditionally not as well suited to transplant options.*

Additionally, there are a number of emerging applications for HPCs, including using stem cells in regenerative medicine.

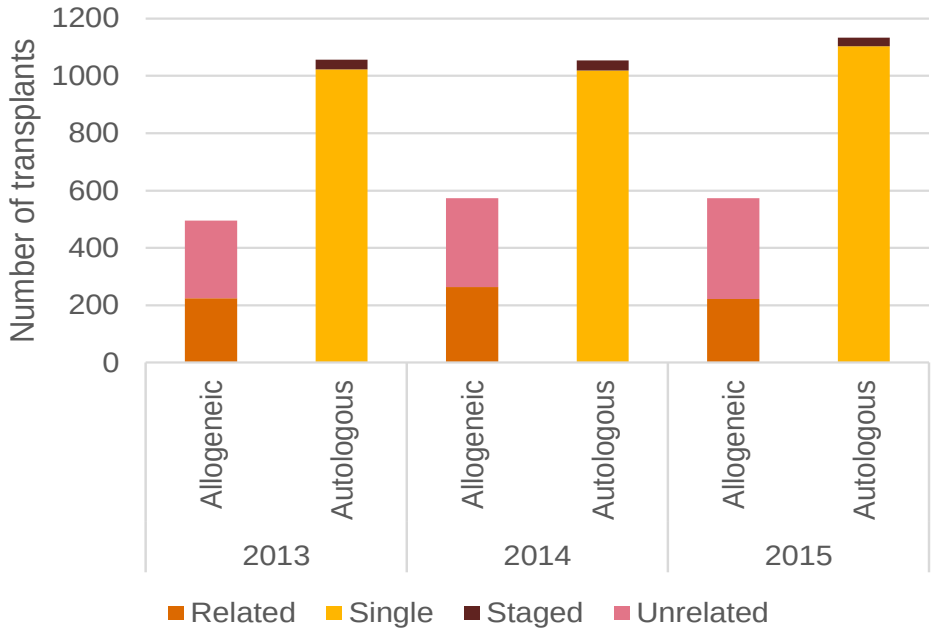
4 Clinical trends

4.1.1 HPC transplants

The number of HPC transplants undertaken each year is steadily growing. This is due to clinical advances in managing transplants, which has expanded the patient cohort considered suitable for transplant.

Between 2013 and 2015, the number of HPC transplants grew from 1,551 to 1,706. As Figure 18 shows, this is mostly represented by single autologous transplants; however, the number of allogeneic-unrelated transplants is also growing.

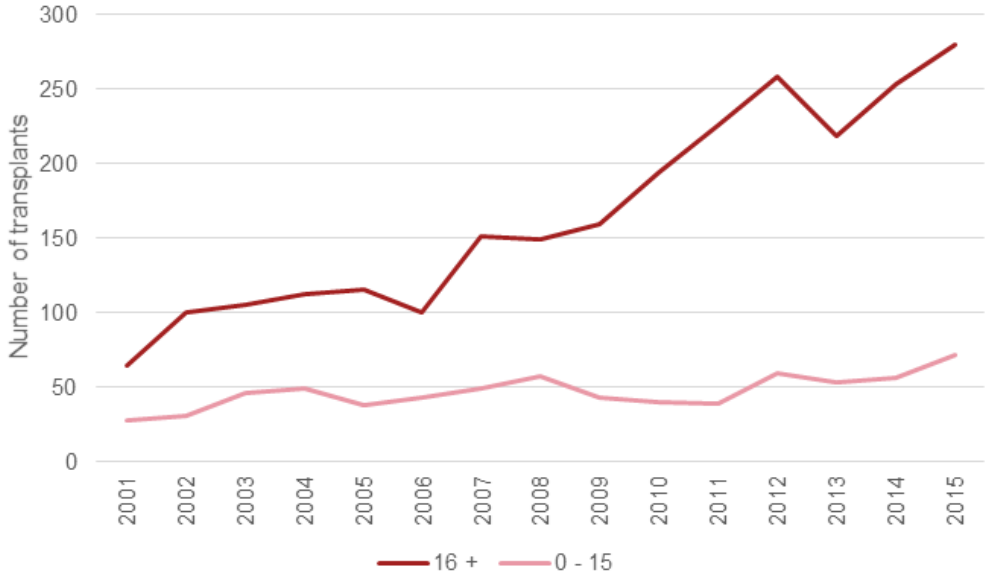
Figure 18: All HPC transplants, 2013–2015



Source: Australasian Bone Marrow Transplant Recipient Registry 2014 and 2015 annual data summaries

Figure 19 shows that over the last 15 years, the number of allogeneic transplants performed has grown. In 2015, paediatric patients accounted for 21% of all allogeneic transplants, with 279 adult patient transplants in the same year.

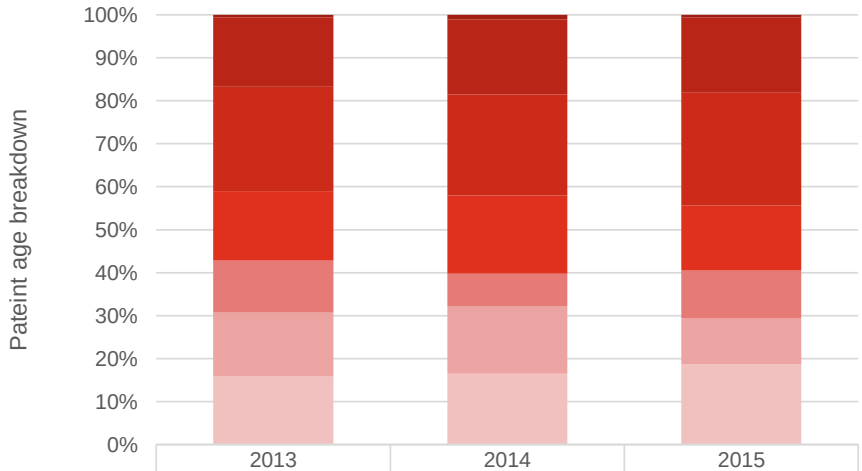
Figure 19: Paediatric and adult allogeneic transplants, 2001–15



Source: ABMTRR (2015) Matched unrelated donor HPC transplants report

Figure 20 shows the growth in the number of patients aged below 16, but even more so among patients in the 50–59 age bracket. Transplants among older patients (age 70 and older), particularly in more recent years, continues to drive demand for HPCs.

Figure 20: Allogeneic patient age groups, 2013–15

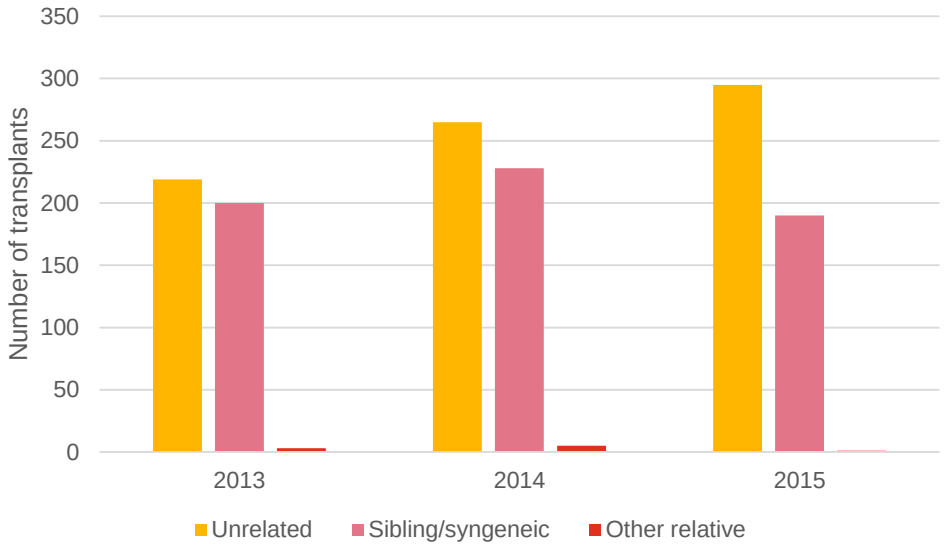


	2013	2014	2015
70 and over	3	6	4
60 - 69	80	100	100
50 - 59	120	134	150
40 - 49	80	104	87
30 - 39	60	43	63
16 - 29	73	90	62
0 - 15	79	94	107

Source: ABMTRR 2014 and 2015 Annual Data Summary

Figure 21 shows that for patients who undergo an allogeneic transplant, many will receive stem cells from an unrelated donor. Over the past three years, the number of allogeneic transplants that have used a sibling's stem cells has slightly decreased. Fewer patients use stem cells from a relative other than a sibling. It is not possible to extract information on haploidentical (half-matched) transplants from the available datasets.

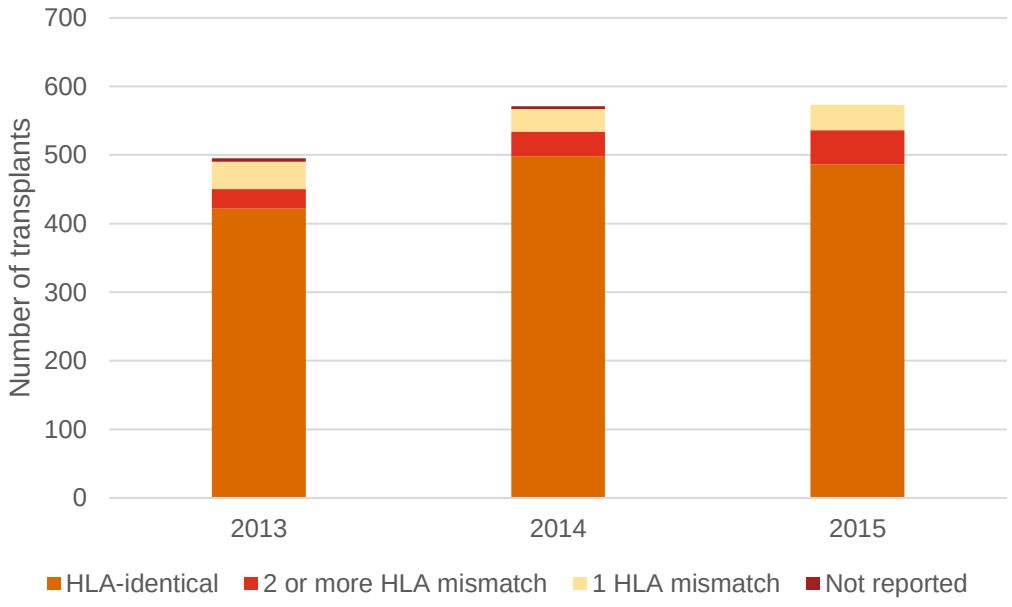
Figure 21: Relationship of donor to recipient for allogeneic transplants



Source: ABMTRR 2014 and 2015 Annual Data Summary

Figure 22 shows that the vast majority of allogeneic transplants are undertaken with donors with identical human leukocyte antigens (HLA) (HLA-identical). Second to this, transplants with two or more mismatches are undertaken (50 were undertaken in 2015), followed by one HLA mismatch (37 in 2015). The number of two or more mismatches has grown in recent years, and may indicate the trend in haploidentical transplants (for example, in 2014, 27 transplants with two or more mismatches were undertaken using a relative's HPCs, while in 2015, this number grew slightly to 31).

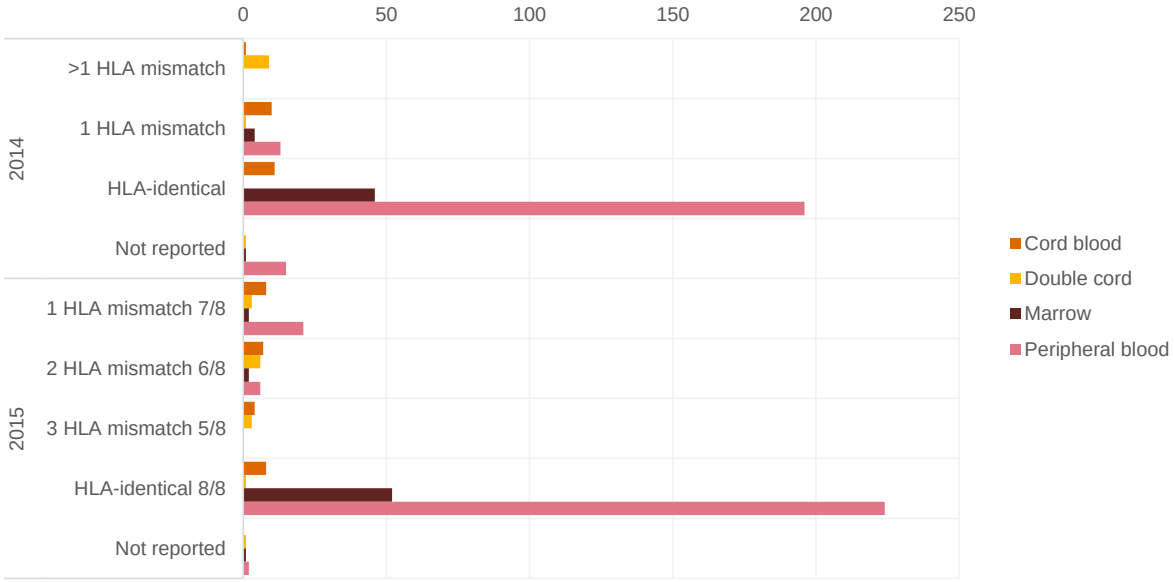
Figure 22: HLA-match level, allogeneic transplants 2013–15



Source: ABMTRR 2014 and 2015 Annual Data Summary

Figure 23 shows that by HPC source, the number of mismatches is greatest among double-cord blood and single cord blood transplant patients. Identically matched patients predominantly received HPCs from peripheral blood or bone marrow donations.

Figure 23: HLA mismatches by transplant, by HPC source



Source: ABMTRR 2014, Unrelated donor HPC transplants in Australia 2001–14 and 2015. Unrelated donor HPC transplants in Australia 2015. Note: For double-cord transplants, HLA compatibility is presented as the total mismatches for the two cords combined.

Secondary to HLA compatibility, clinicians consider the cytomegalovirus (CMV) status of donors to reduce the risks to CMV-negative patients. Between 2014 and 2015 calendar years, 74% of CMV-negative patients were paired with donors of the same status. CMV-negative status patients were coupled to a positive donor in 10% of transplants undertaken between 2014 and 2015.

Table 5: Donor–patient CMV status matches for HPC transplants

Patient CMV status	Donor CMV status		
	Negative	**Positive**	**Unknown**
Negative	176	61	2
Positive	149	167	8
Unknown	6	1	15

Source: ABMTRR Unrelated donor HPC transplants in Australia 2001–14, ABMTRR Unrelated donor HPC transplants in Australia 2015

4.1.2 Changing needs

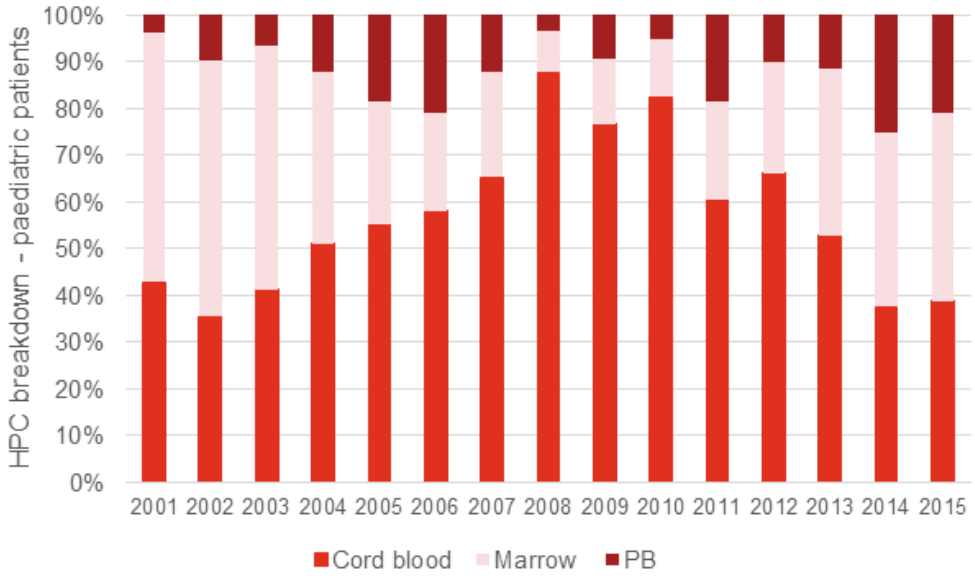
HPC source

The source of HPCs has changed over time. As practices for HPC collection have been streamlined, and more unrelated donors are sought to support patients, peripheral blood is increasingly being used for transplants.

Among paediatric patients, there was a distinct trend towards using cord blood in the mid–late 2000s, which has since tempered (see Figure 24). This reflected that at the time, cord blood was seen as more accessible and immunologically naive (and so, suited to paediatric applications). Additionally, in many cases, it provided diverse HLAs for patients who did not have a matched relative. However, the growth of global registries has reduced its relevance.

Many paediatric clinicians prefer to use bone marrow because fewer cells are needed due to their patient's lower weight. Cord blood and bone marrow remain important sources of HPCs for paediatric patients.

Figure 24: HPC source over time for allogeneic-unrelated transplants among paediatric patients

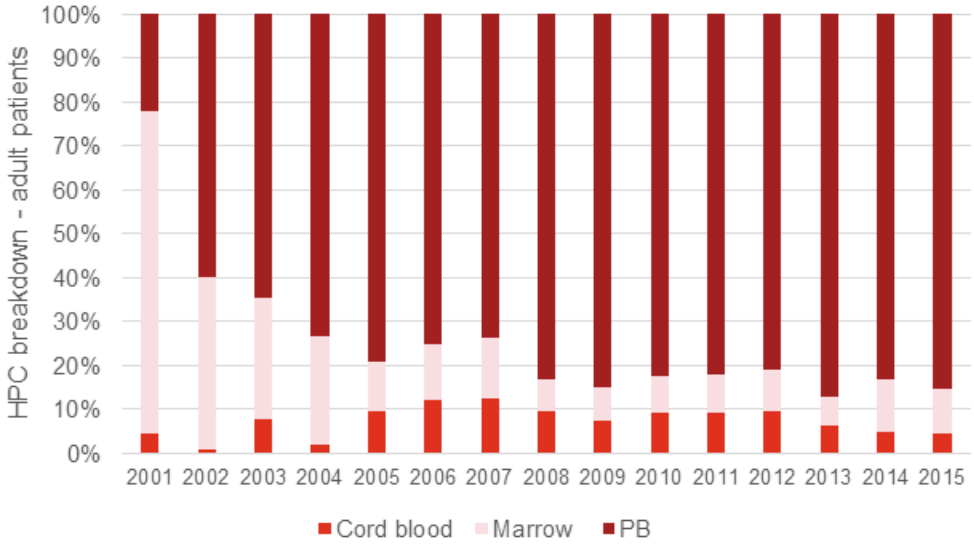


Source: ABMTRR (2015) Matched unrelated donor HPC transplants report

Among adult allogeneic transplant patients, the trend is starker. Bone marrow use has decreased since the early 2000s. At the same time, peripheral blood has grown to account for approximately 80% of all unrelated HPCs used in adult transplants.

Just as with paediatric patients, cord blood plays a small but important role in providing HPCs, particularly for patients with unique haplotypes (groupings of genes).

Figure 25: HPC source over time for allogeneic-unrelated transplants among adult patients



Source: ABMTRR (2015) Matched unrelated donor HPC transplants report

Growing demand

The Australian Bone Marrow Donor Registry (ABMDR) believes that the growing trend in HPC transplants is driven by:[54]

- underlying (absolute) growth in leukaemia cases
- an increasing ability to transplant older and higher-risk patients
- improved inpatient treatment and capacity in hospitals, making it a more viable clinical pathway for patients traditionally not as well suited to transplant options.

Importantly, demand is projected to also be driven by older patient groups who traditionally weren't suited to transplants. However, clinical advances mean that the incidence of clinical indications for a HPC transplant are expected to drive growth in HPC transplants.

The growth in clinical indications for allogeneic transplants is partly offset by increasing use of haploidentical transplants.

4.2 Emerging applications and use

The application of stem cells as a regenerative treatment is heralded as one of the next major breakthroughs in clinical sciences. Claims are being made for the use of stem cells to treat serious diseases, although their application has not yet been proven. This includes treatment for diabetes, multiple sclerosis, spinal cord injuries, neurological diseases and myocardial infarctions.

As the range of indications that might be treated by HPCs expands, registries will need to give careful thought to donor consent (currently for haematological diseases)

Applications are being promised, but in early clinical trials – and in some theoretical explorations – concerns are being raised about how information is disseminated to sick patients. Indeed, there are many anecdotal examples of patients travelling to less-regulated regions to seek unproven stem cell treatments for conditions such as Alzheimer's disease. Clinics that offer these treatments are widely criticised as exploitative and warranting ethnical interrogation.[55]

Nonetheless, applications for stem cells can only be expected to grow, possibly increasing demand for stem cells to support a wider range of treatments than are currently recognised as clinically efficacious. The extent and time frame for developing new stem cell therapies is not understood. And so, given the time frame of this review – 5–10 years – they are not considered as a demand driver.

Future applications exist for induced Pluripotent Stem Cells (iPSCs) and T cell depletion technologies. New testing approaches will also lead to more applications. Appendix B explores these issues in greater detail.

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54 ABMDR *Unrelated HPC sourcing strategy* (Version 1.2, 10 May 2016), provided by the ABMDR.

55 See, for example, the BBC's 'The Stem Cell Hard Sell' (podcast), accessed at <http://www.bbc.co.uk/programmes/p04w86gz>

Supply

5

This chapter covers...

- *clinical pathways to transplant, including the roles and responsibilities in initiating, finding and mobilising a donor*
- *Australia's supply profile, including characteristics of donors registered on Australia's registry and a breakdown by jurisdictions*
- *a snapshot of international supply and how Australia's registry compares to international registries.*

Key messages:

Australian patients who need an allogeneic-unrelated transplant are referred to one of Australia's 15 transplant centres through defined patient referral pathways in each jurisdiction. Their search for an unrelated donor is supported by the transplant centre's Transplant Coordinator, who engages with State Search Coordinators (located in the Australian Red Cross Blood Service (ARCBS), PathWest and Pathology Queensland) to search for and identify a suitable donor. Once a donor is identified, Donor Coordinators from the Australian Bone Marrow Donor Registry (ABMDR) and the ARCBS initiate contact and work-up of donors to proceed to collection.

Australia's donor registry has 170,971 active volunteer donors and 39,319 stored cord blood units (CBUs). Australia's donors are, on average, aged 45, whereas the average age of donors who are requested is 39. Australia's donors are predominantly of Northern Caucasian ethnicity (59%) and 64% of the registry is female. These characteristics do not align well with the preferences of clinicians, who want to access younger, male donors. However, more recent recruitment of donors suggests that a greater number of younger donors are being enrolled. Additionally, the make-up of the registry does not necessarily reflect the changing demographics in the general population. This can mean that some patients may not be able to identify a domestic match if they are from a poorly represented ethnicity (where ethnicity is a proxy for human leukocyte antigen (HLA) diversity).

A large proportion of Australian donors are typed only to low resolution. Newer technologies enable high-resolution typing, which provides clinicians with upfront information that assists with decision making on the likely match of a donor. Clinicians use a greater proportion of Western Australia's donors, partly because of the use of Next Generation (NextGen) typing technology.

Based on population, Australia's donor registry and cord blood inventory ranks closely with other 'like' countries.

5 Supply

5.1 Supply pathways

5.1.1 Clinical pathways

Australian patients are diagnosed each year with clinical indications for a haemopoietic progenitor cell (HPC) transplant. Their treatment pathway will differ, depending on their indication. There are defined HPC transplant patient referral pathways for the 15 transplant centres around Australia that undertake unrelated allogeneic transplants.

Common to all is that patients will be diagnosed in a hospital setting, which depending on the cancer centre treating the patient, will either manage the patient or refer them on. Referral depends on the clinical indication of the patient.

If a patient is deemed to need an allogeneic HPC transplant, clinicians will first look to siblings as potential donors. If the transplant centre undertakes allogeneic-related transplants, and the sibling is a match, the patient will be wholly managed by the transplant centre. However, if the transplant centre only undertakes allogeneic-related transplants and there are no matched siblings, the patient will be referred to a transplant centre that undertakes unrelated allogeneic transplants. In some cases, the referring centre may initiate an unrelated search. In others, the patient will be wholly referred and the receiving centre will initiate and coordinate a search to identify an unrelated donor or cord blood unit (CBU).

Many transplant centres undertake autologous transplants only. So, if a patient is diagnosed with a clinical indication and is a candidate for an allogeneic transplant, they will be referred on. These centres do not undertake typing or matching, and the receiving centre will manage all search activities.

Table 6 provides an overview of the key referral pathways for patients requiring an unrelated allogeneic transplant.

Table 6: Key cross-jurisdictional referral pathways

State/territory	Key referral pathways
South Australia	• The Women and Children's Hospital refers on all paediatric allogeneic patients to Sydney (unformalised agreement)
Northern Territory	• All autologous and allogeneic patients are referred to South Australia, but if the patient has family in Queensland or Victoria, they will be referred to Brisbane or Melbourne
Queensland	• All intra-state adult unrelated allogeneic patients are referred to the Royal Brisbane and Women's Hospital
Western Australia	• All allogeneic patients are treated at either the Fiona Stanley or Princess Margaret Children's Hospital. When multiple paediatric transplants occur simultaneously, there may be an ad hoc inter-jurisdictional transfer (but these are not formalised)
Victoria	• All Victorian patients are referred to major centres in Melbourne unless a patient requests to be treated interstate
NSW	• Northern NSW patients are referred to the Royal Brisbane and Women's Hospital • All other patients are referred to major centres in Sydney
Tasmania	• The Royal Hobart Hospital refers all allogeneic patients to The Royal

State/territory	Key referral pathways
	Melbourne Hospital
ACT	• All allogeneic patients are referred to NSW transplant centres (predominantly Westmead Hospital)

The funding of patients treated interstate is captured under cross-border flows in which inpatient case mixes are acquitted against the Australian Institute of Health and Welfare and the Independent Hospitals Pricing Authority's National Hospitals Data Collection Set. In this way, state health budgets account for treatment of residents in each state or territory. This review did not identify any agreements that explicitly outlined referral pathways, nor any funding agreements for support outside of cross-border flows.

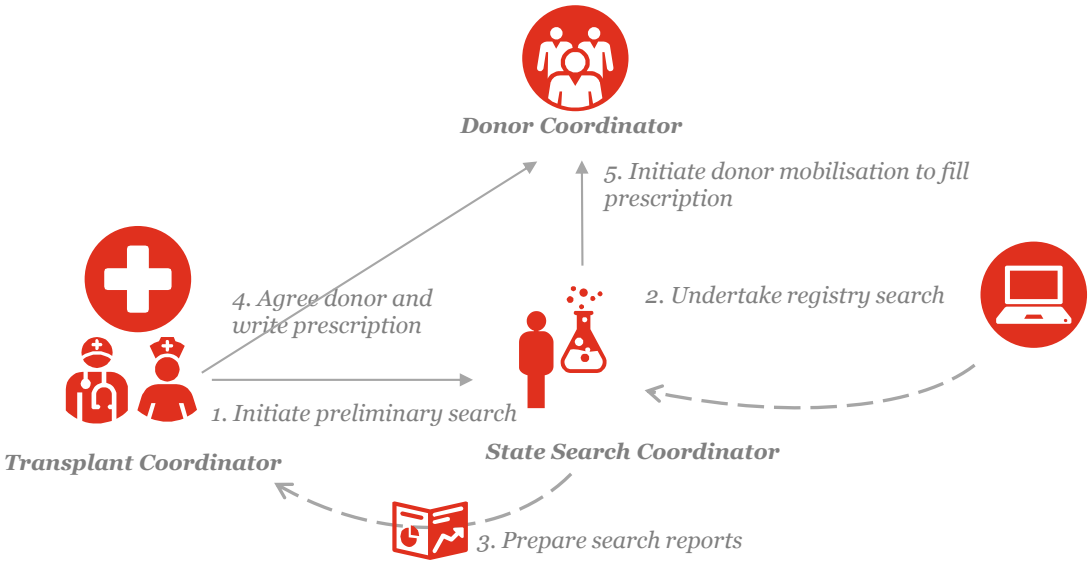
This review also observed that informal agreements for referrals are often a legacy of clinician relationships. There is also sometimes a 'centre effect', where a clinician's familiarity with the clinical team at a transplant centre, or the clinician's alignment to the centre's clinical approach, drives referrals. For example, if a clinician has been trained in using CBUs, they may refer a patient to a centre they know uses CBUs in transplants.

Referral pathways are also relevant to the timing for initiating a search application. It may be known at diagnosis whether a patient is a candidate for an allogeneic transplant; however, if the patient is not referred on until they are at the point where a transplant might be considered, the receiving centre loses time for initiating the search process.

5.1.2 Roles and responsibilities

Once a clinician identifies the need to find an unrelated donor, the Transplant Coordinator at the transplant centre will initiate a preliminary search, which is channelled through State Search Coordinators in each state. A donor may come from either the domestic or an international registry – the most suitable matches are guided by the decision making of the State Search Coordinators, who liaise with Transplant Coordinators and haematologists at the transplant centre. Figure 26 provides an overview of the key relationship pathways between coordinators.

Figure 26: Schematic of coordinator relationships



Note: All request documentation is channelled through the ABMDR to enable its central oversight

State Search Coordinators are responsible for lodging searches on the online domestic and international portals (MatchPoint and Bone Marrow Donors Worldwide (BMDW)), identifying potential donors and preparing search reports to inform a clinician's decision.

They also manage the search process and undertake matching of donors. If a potential donor is identified, they are also responsible for seeking additional typing and managing the flow of information and advice about the most suitable donor, whether the donor is domestic or international.

A Donor Coordinator's responsibilities are distinct from those of a State Search Coordinator. They mobilise a donor once a clinician and State Search Coordinator have identified them as a potential match. They will initiate contact with a donor if the donor has to provide a new sample for extended typing, or if they are a suitable match. A Donor Coordinator will start the process to work-up a donor, gain consent and book in the collection.

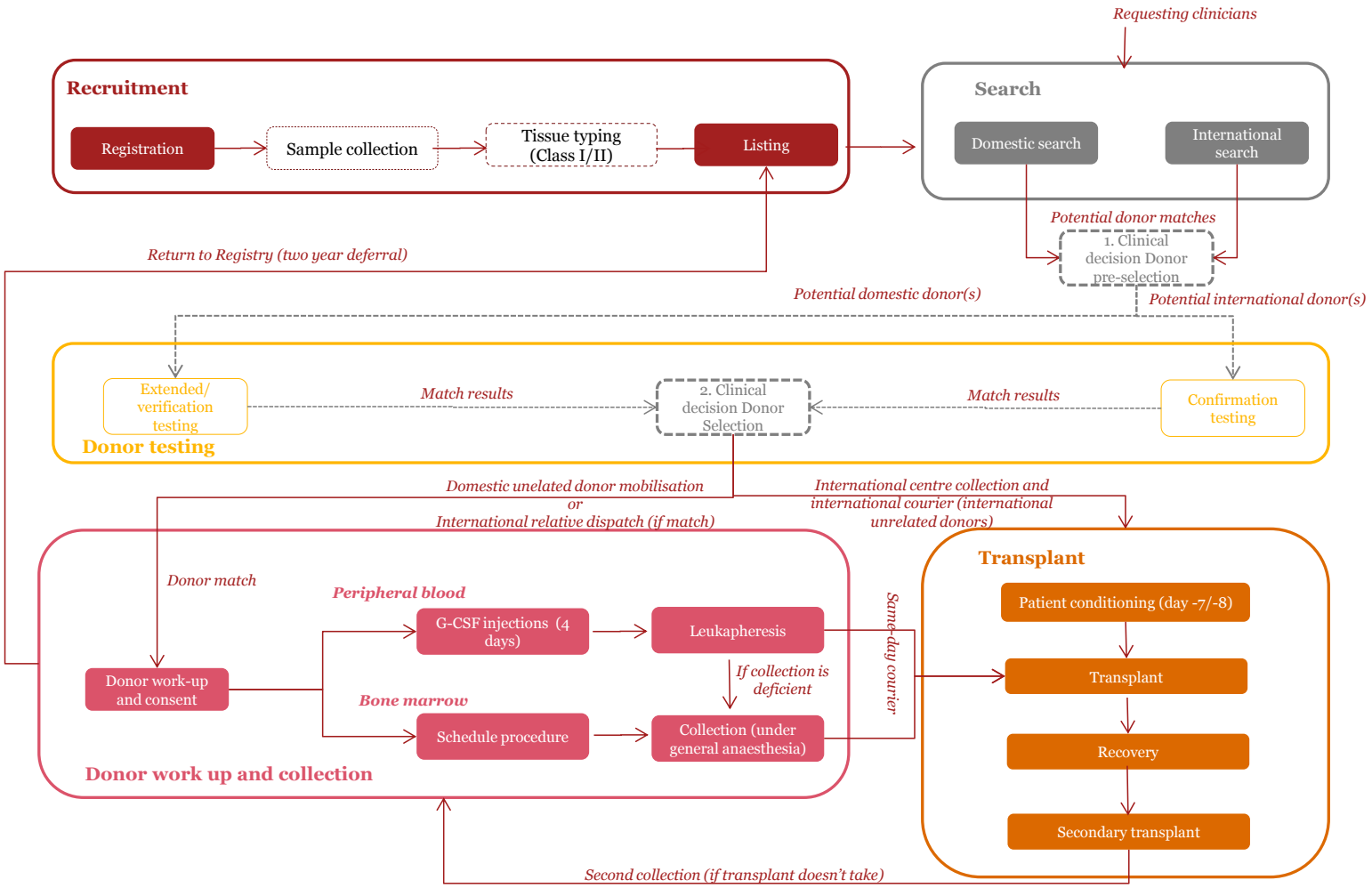
A Transplant Coordinator's role slightly straddles both, in that they act as a conduit between the clinician and a State Search Coordinator, to identify a suitable match for a patient. In addition, if a transplant centre is selected to undertake a collection from a volunteer donor, a Transplant Coordinator will work with a Donor Coordinator to arrange consultation, education and collection of HPCs.

State Search Coordinators have a dedicated role within the tissue typing laboratories in each state. Donor Coordinators work under the Australian Red Cross Blood Services (ARCBS) in each state, and are also responsible for recruiting and enlisting new donors. The exception is South Australia, where one person holds the role of both State Search Coordinator and Donor Coordinator in a 50/50 capacity. In addition to the state-based roles mentioned above, two National Donor Coordinators are based at the Australian Bone Marrow Donor Registry (ABMDR). The national team is responsible for activities associated with international donors, whereas state-based coordinators are responsible for domestic donors.

Transplant Coordinators are clinical staff members within each transplant centre. Each has different responsibilities, depending on the operating model of the transplant centre. In some transplant centres, Transplant Coordinators may be responsible for managing transplants with matched relatives as well as the process for autologous patients.

Figure 27 shows a schematic of the clinical pathway for donation to allogeneic transplants.

Figure 27: Schematic of unrelated HPC donor registration to donation pathway



5.1.3 Related matches

Related matches (including haploidentical matches (half-matches)) are wholly managed by the treating transplant centre. In a very small number of cases, a related donor may donate at a different transplant centre (for example, due to work constraints or inability to travel), but donations are largely made at the centre treating the relative. Predominantly, these donors are worked up to donate peripheral blood, although paediatric patients may require a bone marrow donation. The activities and costs associated with coordinating, scheduling and collecting from the relative is captured in their treatment episode.

5.1.4 Autologous transplants

Autologous transplants are undertaken at a wide range of transplant centres, many of which don't undertake allogeneic transplants. Autologous transplants involve collecting a patient's own stem cells through apheresis (peripheral blood collection).

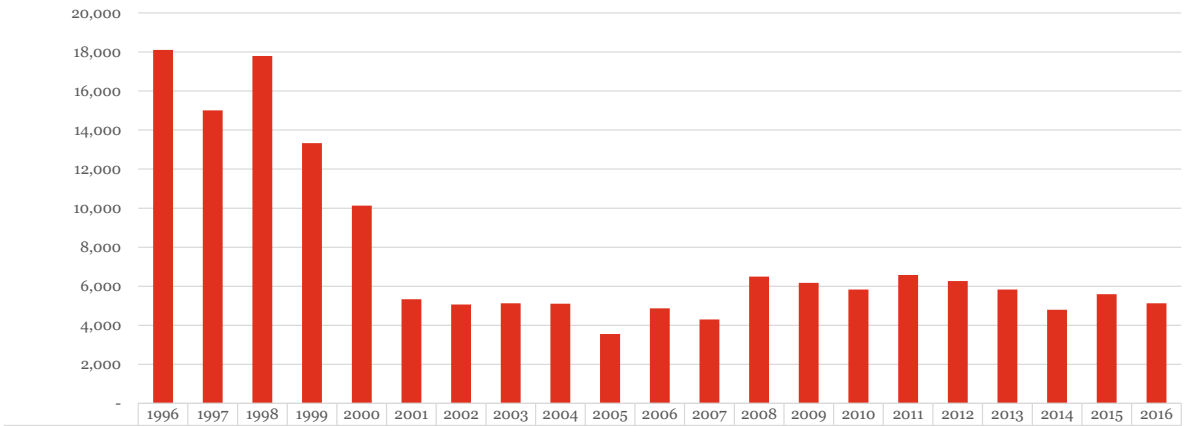
Where an allogeneic transplant is needed, these patients will typically be referred to their state or territory's nominated transplant centre. While some patients who receive an autologous transplant may require an allogeneic transplant later in life (for example, if their disease progresses and the autologous transplant is not successful), they do not form part of the 'demand pool' for unrelated donors. Due to the nature of clinical indications for requiring an allogeneic transplant (most require a transplant urgently), treating clinicians will not delay referral. Additionally, if it is known there are no potential matches among relatives, they will work with a referring centre to initiate an unrelated search as quickly as is possible.

5.2 Current supply profile

The ability to match Australian patients to local donors depends on the volume and quality of supply available to clinicians and Search Coordinators. To ensure the registry is fit for purpose, consistent recruitment is essential for maintaining the supply of young, fit donors. Figure 28 demonstrates recruitment efforts over the last 20 years. In the last five years, on average, 5,500 new recruits have been found each year, representing an incremental increase of the total registry size by around 3%. Acknowledging a large disparity between the two population sizes, the UK's Anthony Nolan register has an annual recruitment target of 80,000.

170,971 active donors on the Australian registry

Figure 28: Change in the registry over time



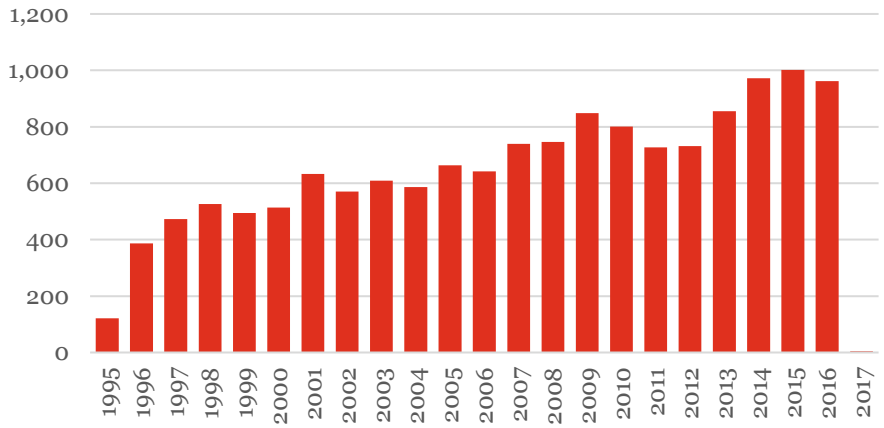
	1996	1997	1998	1999	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016
New donors	18,09	15,00	17,79	13,32	10,13	5,335	5,068	5,128	5,109	3,552	4,873	4,301	6,500	6,179	5,837	6,580	6,268	5,829	4,800	5,599	5,130
% annual growth	22%	15%	15%	10%	7%	3%	3%	3%	3%	2%	3%	2%	3%	3%	3%	3%	3%	3%	2%	2%	2%

Source: ABMDR Data 'Question_1a_to_1g – COMPLETE REGISTRY.xlsx'. Note: In 1995, 83,772 donors were added to the registry's dataset. This captured donors registered in the early 1990s and has not been included here. Note also that these figures represent available, temporarily unavailable and deleted donors (that is, those who have been retired, which form a large component of donors registered in earlier years of the registry).

Figure 29 indicates growth in the demand for Australian donors over time. In 2016, there were 962 requests for further typing on Australian donors. While the trend is growing, there

was a 4% reduction in typing requests in 2016 compared to 2015 (noting that 2017 data is incomplete in this analysis). Typing levels are also affected by the resolution of typing available on donors – the standard is low-resolution typing for 66% of Australian laboratories.

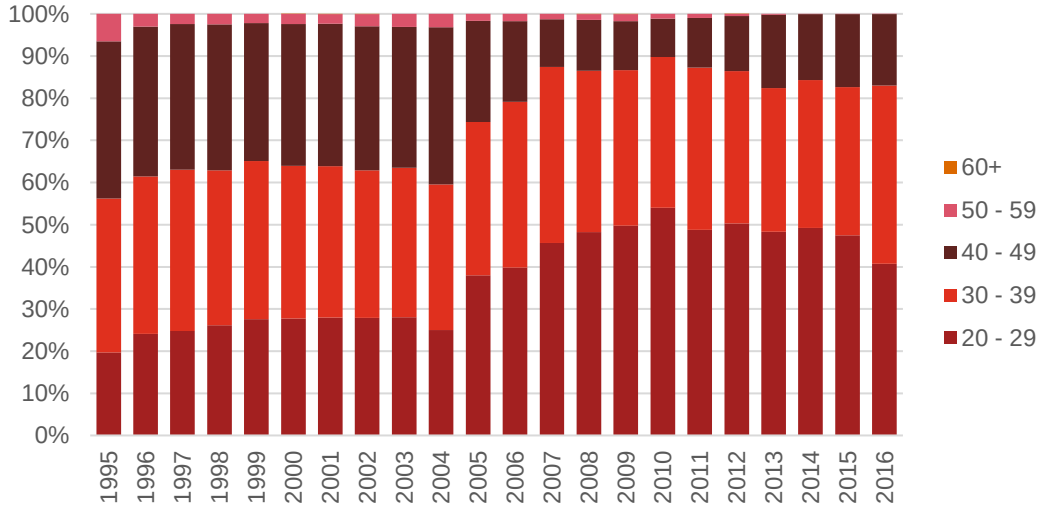
Figure 29: Number of verification typing requests over time



Source: ABMDR Data 'Question_1a_to_1g – COMPLETE REGISTRY.xlsx'

Figure 30 demonstrates the effects of age limits on donor registration, with a marked reduction in newly recruited donors aged over 60. From 2004, the proportion of newly recruited donors aged 20–29 has gradually risen.

Figure 30: Recruitment over time, by age



Source: ABMDR Data 'Question_1a_to_1g – COMPLETE REGISTRY.xlsx'

Average length that a donor has been registered

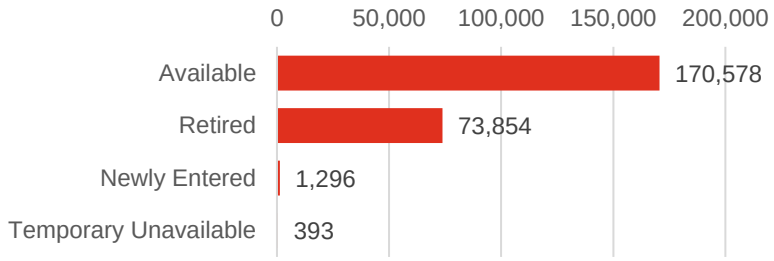
Given that the average length of time a donor remains on the registry is almost 15 years, recruiting younger donors means they are actively registered for longer periods. The current average age of a recruited donor is approximately 37.

Of these donors, approximately 0.2% are temporarily unavailable (either due to a change in their personal circumstances, or they have been identified as a match to a patient but not yet mobilised, making them unavailable as a donor to other patients for a short time). However, knowing the

true availability of a given donor remains a challenge for registries worldwide; it is common that a long time lapses between a donor registering and being called on to donate, and the donor may no longer be willing (or even aware of their registration). Chapter 6.1 discusses trends in donor commitment and retention.

Figure 31 outlines the breakdown of the status of donors on the registry (at February 2017). A total of 73,854 donors have been retired from the ABMDR. This number includes self-retired donors and those removed by the organisation after reaching the age limit of 60. Donors whose information has been collected but for whom consent information is not finalised are categorised as 'Newly Entered'. At the time of this analysis, there were more than 1,000 donors in this group.

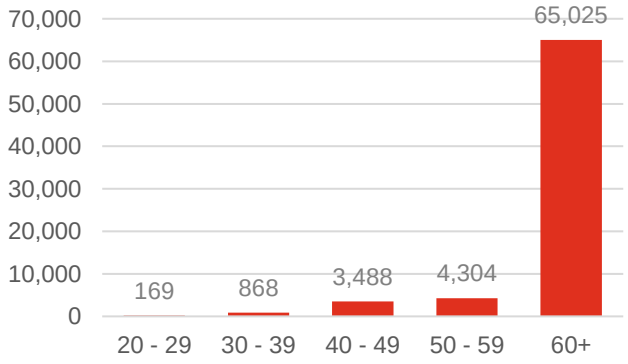
Figure 31: Registry donor status



Source: ABMDR Data 'Question_1a_to_1g – COMPLETE REGISTRY.xlsx'

The 'retirement' age of the registry is reflected in the age of deregistered donors. In all, almost 74,000 donors have been retired in the 26-year history of the registry.

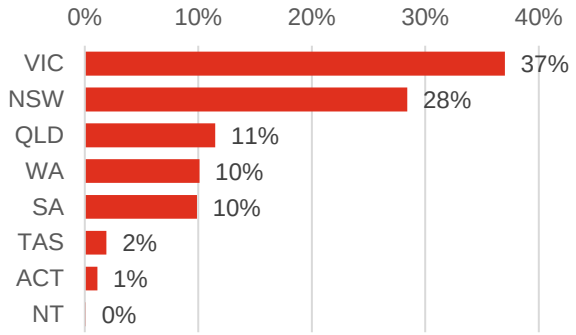
Figure 32: Retired donors by age group



Source: ABMDR Data 'Question_1a_to_1g – COMPLETE REGISTRY.xlsx'

Figure 33: Retired donors by state shows that many of those retired are from our largest states and 60% were female.

Figure 33: Retired donors by state



Source: ABMDR Data 'Question_1a_to_1g – COMPLETE REGISTRY.xlsx'. Note: NT donors are now captured in SA numbers.

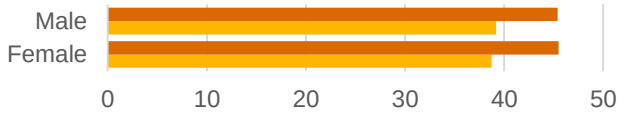
5.2.1 Donor characteristics

Who is on Australia's registry?

A large proportion of donors on the ABMDR registry are recruited through ARCBS blood donor centres. Many of these donors are older females who comprise the regular blood donor base. Currently, 64% of the registry is female, with an average age of 45, consistent with the age of male donors. While all donors are important volunteers, clinicians select a disproportionate number of male donors for verification typing, to reduce the risk of infection to patients.

Figure 34 and Figure 35 show that the donors who are selected are younger than the average age for donors. This reflects a clinical preference for younger donors. For example, in 2016, 208 donors aged 20–29 were requested for verification typing, a 12% increase since 2009. However, over the last decade, donors aged 50–59 have remained in demand. Despite this age being used less frequently, older donors remain valuable for matching to patients who need a donor.

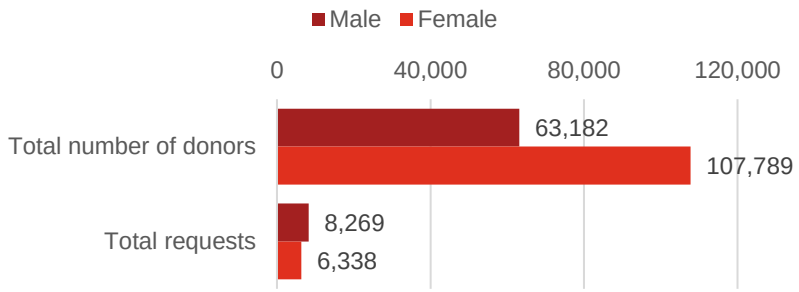
Figure 34: Average age of donors by gender



	Female	Male
Average age of donors	45	45
Average age when requested	39	39

Source: ABMDR Data 'Question_1a_to_1g – COMPLETE REGISTRY.xlsx'

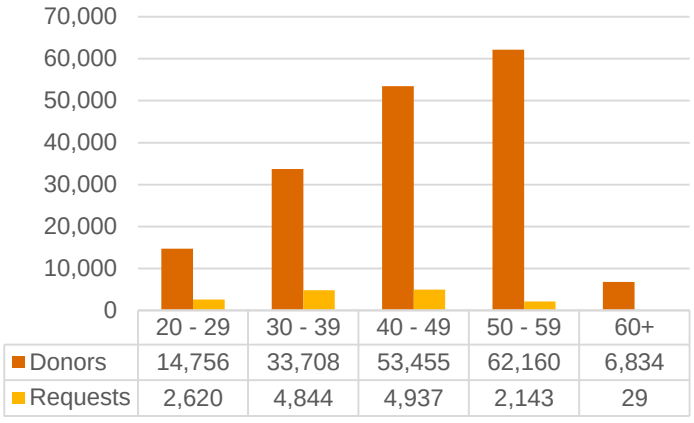
Figure 35: Donors, by gender, by request



Source: ABMDR Data 'Question_1a_to_1g – COMPLETE REGISTRY.xlsx'

Figure 36 illustrates the older age profile of the Australian registry. There are 62,160 registered donors aged 50–59, many of whom will be retired from the registry in the next five years. Recent recruitment figures suggest that current recruitment approaches are adapting to the need to bring on board younger donors, with approximately 40% to 50% of new donors registered falling within the 20–29 age bracket.

Figure 36: Donor age on registry and at time of request

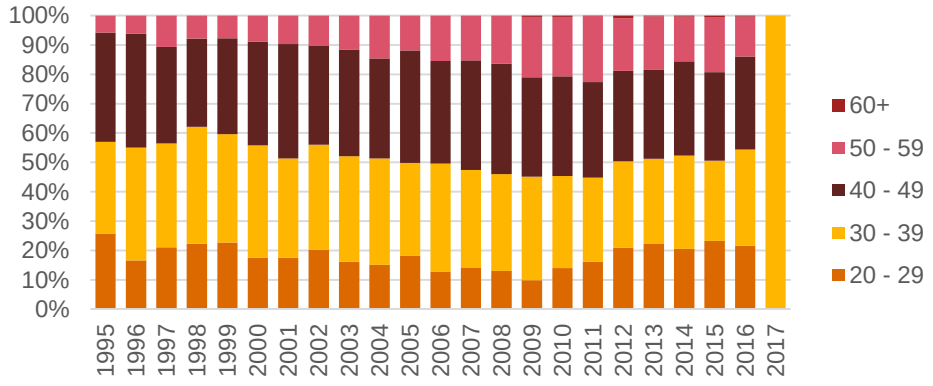


	20 - 29	30 - 39	40 - 49	50 - 59	60+
Donors	14,756	33,708	53,455	62,160	6,834
Requests	2,620	4,844	4,937	2,143	29

Source: ABMDR Data 'Question_1a_to_1g – COMPLETE REGISTRY.xlsx'

While registered donors are most likely to be in the 50–59 age bracket, donors aged 30–50 are most frequently requested for verification testing. Although there are fewer requests in total proportionally, donors aged 20–29 are used most often, representing 18% of all donors requested (see Figure 37).

Figure 37: Age at request



Source: ABMDR Data 'Question_1a_to_1g – COMPLETE REGISTRY.xlsx'

Donor ethnicity

At registration, donors are asked to identify their ethnicity. This provides insight into which haplotypes might be present on the registry, and assists search activities. While ethnicity is self-nominated, it serves as a proxy to State Search Coordinators about the potential haplotype of a donor. Table 7 shows the top 20 ethnicities represented on the Australian registry. In all, Northern Caucasian donors represent 59% of the total registry.

Table 7: Top 20 ethnicities represented on the Australian registry, by age

Ethnicity	No of donors on registry by age %					
	Total	20–29	30–39	40–49	50–59	60+
Northern Caucasian (legacy)	100,305	5%	17%	33%	41%	5%
Southern Caucasian (legacy)	6,315	6%	21%	35%	35%	3%
Jewish (legacy)	4,081	10%	31%	37%	20%	2%
North West European	6,490	40%	38%	22%	0%	0%
Aboriginal Australian/ Torres Strait Islander	2,782	15%	31%	31%	21%	2%
Asian	1,176	3%	17%	41%	36%	3%
Indian	3,218	14%	48%	27%	10%	1%
Other Middle Eastern	1,741	13%	39%	31%	16%	1%
Sri Lankan (legacy)	1,895	8%	27%	32%	31%	2%
Other Chinese Asian	1,051	19%	46%	25%	9%	1%
Maori	719	21%	30%	30%	18%	1%
Asian / Pacific Islander (legacy)	756	16%	53%	24%	7%	0%
Eastern European	955	43%	36%	21%	0%	0%
Pacific Islander (legacy)	257	1%	5%	44%	45%	5%
Vietnamese	418	17%	23%	32%	24%	3%
Southern European	645	40%	34%	25%	0%	0%
Filipino	292	26%	47%	18%	9%	1%
Indonesian	179	26%	37%	28%	8%	0%
Polynesian	172	23%	34%	30%	12%	0%
South Eastern European	299	33%	37%	30%	0%	0%

Source: ABMDR Data 'Question_1a_to_1g – COMPLETE REGISTRY.xlsx'

Of the Northern Caucasian donors on the register, 7.2% are called up for verification typing as a potential match for a patient. This is the second-highest rate for all nominated ethnicities.

In comparison, of the Aboriginal and/or Torres Strait Islander donors on the register, only 3.6% are called up, while Samoan donors have the highest rate, at over 8% of the 47 registered donors.

There is high variability in the age at which donors are requested from among ethnic groups. Among Caucasian donors, 41% are aged 50–59. However, of all verification requests made, 86% are made to younger cohorts. A larger proportion of Eastern European donors registered are younger, with 57% of verification requests made to donors aged 20–29 in this group. Figure 38 shows that a significant number of requests are also made to donors with no listed ethnicity.

Figure 38: Donor ethnicity, by number of donors, requests and length of registration

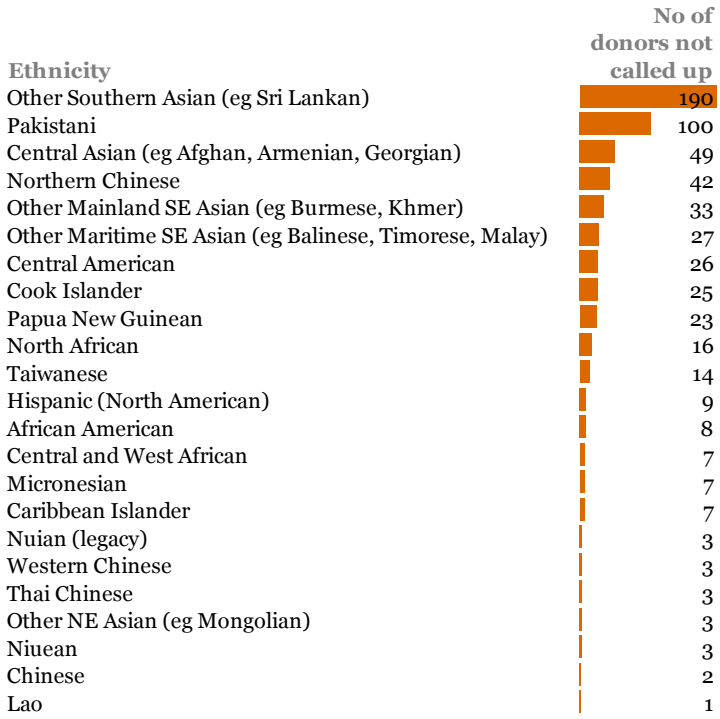
	Utilisation of donors %	Average years on registry	Total number of donors	Total requests
Samoan	8.5%	13.34	47	4
Northern Caucasian (legacy)	7.2%	16.09	100,305	7,227
Fijian	6.3%	10.27	63	4
Native North American Indian	6.3%	1.94	16	1
(blank)	5.8%	16.21	34,695	2,004
Tongan	5.7%	12.23	35	2
Indonesian	5.0%	6.83	179	9
Melanesian	4.8%	7.43	21	1
Pacific Islander (Legacy)	4.7%	18.75	257	12
Southern Caucasian (legacy)	4.6%	14.30	6,315	290
Maori	4.3%	8.21	720	31
Jewish (legacy)	4.2%	11.76	4,081	171
Polynesian	4.1%	6.49	172	7
South American	4.0%	2.10	101	4
Asian	3.9%	17.46	1,176	46
Aboriginal Australian / Torres Strait Islander	3.6%	10.57	2,784	101
Other Chinese Asian	3.5%	8.86	1,051	37
Arab	3.3%	2.45	121	4
Southern Chinese	3.1%	5.39	129	4
Asian / Pacific Islander (legacy)	2.9%	7.57	756	22
Other Middle Eastern	2.8%	9.88	1,741	49
Middle Eastern Jewish	2.8%	2.36	36	1
Filipino	2.7%	7.22	292	8
Vietnamese	2.6%	9.58	418	11
North West European	2.6%	2.19	6,516	167
South Eastern European	2.3%	2.52	300	7
Malaysian (legacy)	2.2%	9.64	230	5
Southern and East African	2.0%	2.46	99	2
Thai	2.0%	4.45	51	1
Eastern European	1.9%	2.23	959	18
Sri Lankan (legacy)	1.8%	9.19	1,895	35
Korean	1.7%	7.49	116	2
Indian	1.7%	6.71	3,221	54
Southern European	1.5%	2.19	647	10
Eastern European Jewish	1.0%	2.37	604	6
Japanese	0.9%	7.27	221	2

Source: ABMDR Data 'Question_1a_to_1g – COMPLETE REGISTRY.xlsx'

Figure 39 lists the least requested donor ethnicities. For example, there are 190 Sri Lankan donors currently registered who have not been requested for verification typing. It is important to reiterate that ethnicity is only representative and that haplotypes require genetic analysis of donors to draw conclusions. However, this review did hear examples of certain ethnic groups being more difficult to match than others as their haplotype frequency within their ethnic group was heterogeneous. For example, Sri Lankan, Aboriginal and many Asian ethnicities typically exhibit greater haplotype diversity. In contrast, some populations have relatively homogenous genetic profiles; for example, Japanese patients. This means that a match might be more likely to be found among a smaller number of donors.

Given this, while these donors may not have been called up and are relatively small in number, they represent the broad ethnic diversity of donors on the registry and are an important pillar for maintaining the representativeness of the registry.

Figure 39: Donor ethnicities not requested



Source: ABMDR Data 'Question_1a_to_1g – COMPLETE REGISTRY.xlsx'

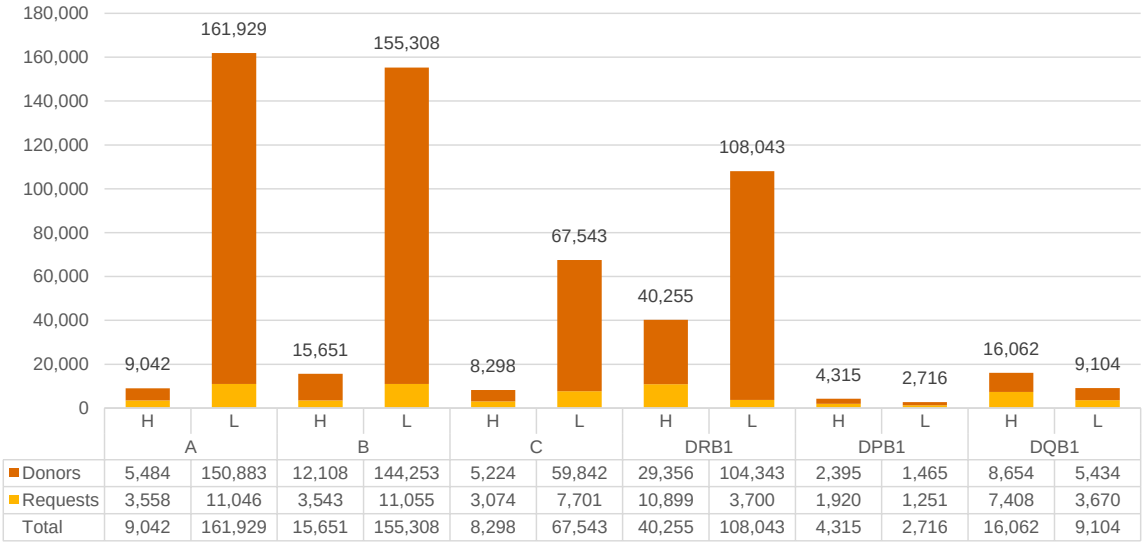
Extent of tissue typing

To provide the information to clinicians to make a match between a patient and donor, donors are tissue typed across the eight alleles of HLA-A, HLA-B, HLA-C, HLA-DRB1, HLA-DRB1 and HLA-DQB1. Tissue typing can be undertaken to different resolutions and for a different number of alleles. Further detail on alleles and tissue typing can be found at Appendix C.

Figure 40 outlines the tissue typing resolution of registered donors and those who have been called up for verification typing. It demonstrates that the vast majority of the registry is typed at low resolution (L) for human leukocyte antigen (HLA) at loci -HLA-A, HLA-B and HLA-DRB1, while high-resolution typing (H) is used for far fewer donors. Proportionally, more of the donors typed at high resolution are called up as potential matches.

For example, HLA-DRB1 has just 30% of donors typed at high resolution, while 34% of these donors have been verification typed. Typically, two or three donors are verification typed for each patient.

Figure 40: Active donor tissue type resolution profiles



	A		B		C		DRB1		DPB1		DQB1	
Donors	5,484	150,883	12,108	144,253	5,224	59,842	29,356	104,343	2,395	1,465	8,654	5,434
Requests	3,558	11,046	3,543	11,055	3,074	7,701	10,899	3,700	1,920	1,251	7,408	3,670
Total	9,042	161,929	15,651	155,308	8,298	67,543	40,255	108,043	4,315	2,716	16,062	9,104

Source: ABMDR Data 'Question_1a_to_1g – COMPLETE REGISTRY.xlsx'

The effect of high-resolution typing on donor selection is being trialled in Western Australia, which is using Next Generation (NextGen) typing. PathWest is currently retrospectively typing donors, and has identified that since doing so, these donors are called upon more often than donors with low-resolution typing. A number of registries are exploring this option to improve the matchability of donors already registered.

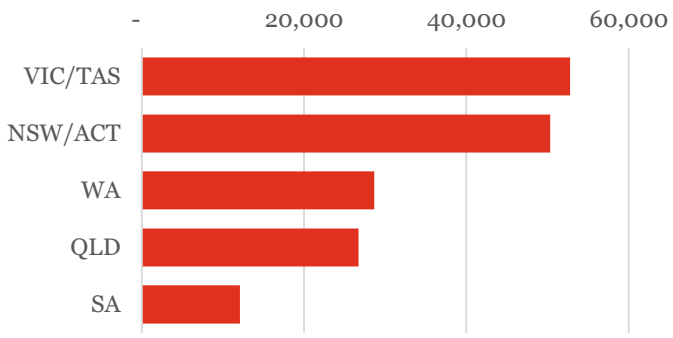
Concurrently, the ARCBS is set to introduce NextGen typing for its services in Victoria, NSW and South Australia over the coming financial year. Using NextGen typing in initial tissue typing would greatly lift the number of new donors typed to a higher resolution.

Pathology Queensland has begun introducing NextGen sequencing, which is being provided on Queensland Cord Blood Bank (QCBB) CBUs typed under a new contract. However, full implementation will take around two years. Additionally, the Sydney Cord Blood Bank (SCBB) has around 2,000 searchable CBUs with high-resolution typing.

5.2.2 Jurisdiction of donors

Figure 41 shows the breakdown by state or territory of the more than 170,000 donors on the registry. Victoria has the highest proportion, with 52,762 listed donors (including 12 Tasmanians). This is closely followed by NSW/ACT, which has just over 50,000 donors. When compared to population size, Western Australia, Queensland and South Australia all have a large number of donors registered.

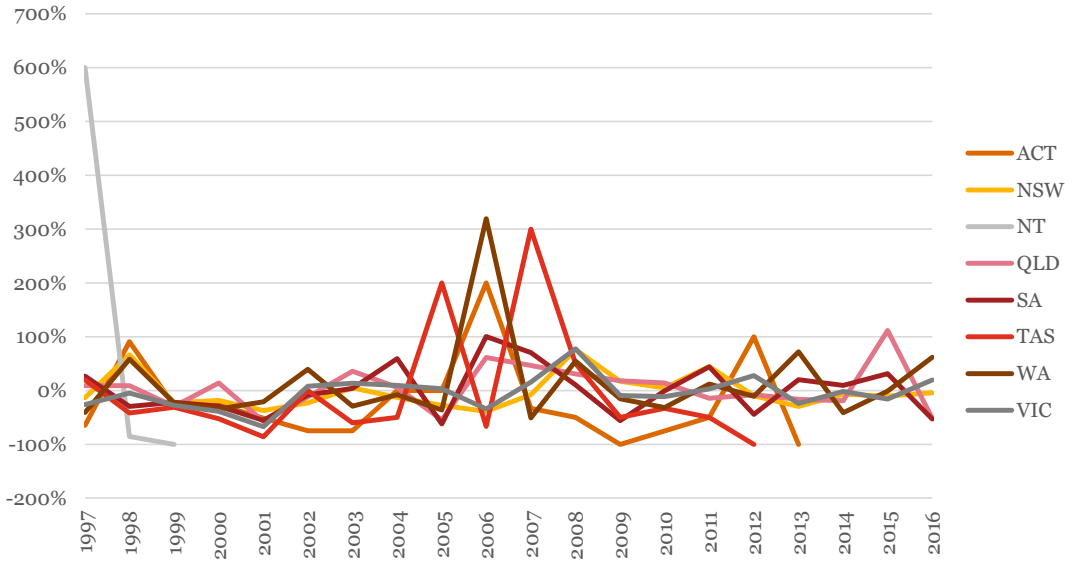
Figure 41: Number of available donors, by state



Source: ABMDR Data 'Question_1a_to_1g – COMPLETE REGISTRY.xlsx'. Note: NT donors are captured in SA numbers.

Registration of new donors changes from year to year. As Figure 42 shows, there can be significant variability between calendar years. This is primarily due to donor drives, where a large number of donors are registered at the same event (or events). In this graph, there is a slight change in data transcription, with Tasmanian donors now captured in Victoria's numbers and ACT donors included in NSW numbers.

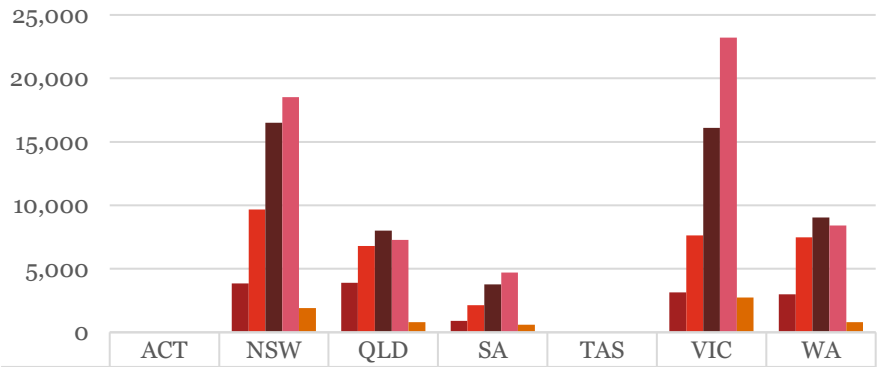
Figure 42: New donors to the registry over time, by jurisdiction



Source: ABMDR Data 'Question_1a_to_1g – COMPLETE REGISTRY.xlsx'

While Queensland does not have the highest total number of donors registered, it has the greatest number of donors aged 20–29. Victoria has a large pool of ageing donors, with approximately 26,000 aged over 50, who will soon be retired from the registry. Western Australia has the highest reported use of young donors, at 20.8% for those aged 20–29.

Figure 43: Registered donors, by state and age



	ACT	NSW	QLD	SA	TAS	VIC	WA
20 - 29		3,840	3,900	896		3,134	2,986
30 - 39	1	9,665	6,811	2,129	1	7,624	7,477
40 - 49	5	16,511	8,007	3,779	7	16,094	9,052
50 - 59	8	18,515	7,272	4,718	4	23,225	8,418
60+		1,898	798	591		2,750	797

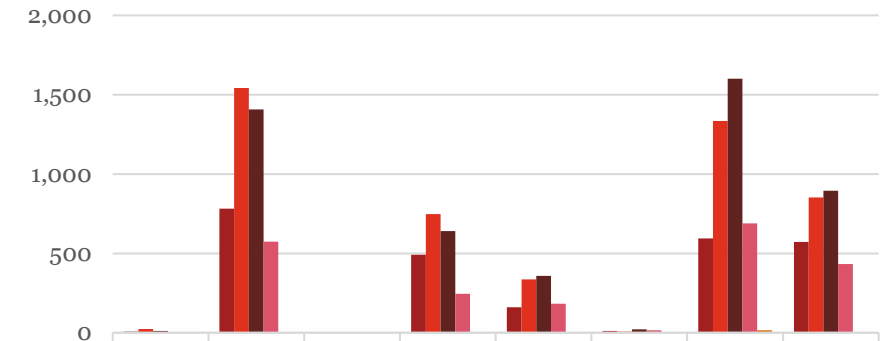
Source: ABMDR Data 'Question_1a_to_1g – COMPLETE REGISTRY.xlsx'. Note: NT donors are captured in SA numbers.

Requested donors

Figure 44 shows a breakdown of the donors – and their age brackets – on the Australian registry who have been requested by a transplant centre. Over the operation of the registry,

Transplant centres have requested donors from all states and territories, but the majority are from NSW (4,310), closely followed by Victoria (4,233). However, many younger donors (aged below 40) are requested from Western Australia and Queensland.

Figure 44: Donors requested, by state and age

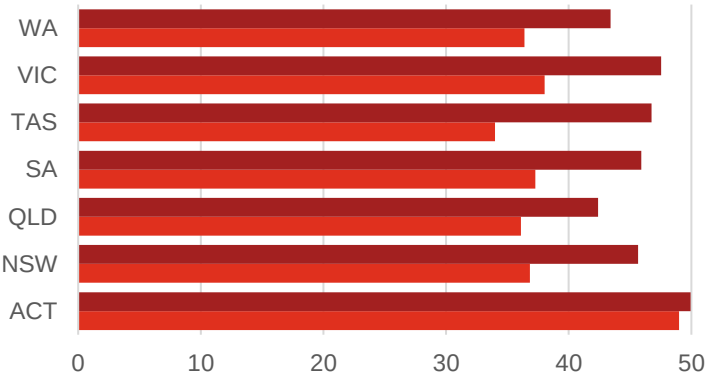


	ACT	NSW	NT	QLD	SA	TAS	VIC	WA
20 - 29	8	781		492	160	12	594	573
30 - 39	23	1,543		747	336	8	1,334	853
40 - 49	12	1,407	2	641	359	21	1,601	894
50 - 59	3	575	1	245	182	15	689	433
60+		4		2	3	2	15	3

Source: ABMDR Data 'Question_1a_to_1g – COMPLETE REGISTRY.xlsx'. Note: NT donors are captured in SA numbers.

Figure 45 shows the mean age of donors and those who are requested for verification typing in each state and territory, and demonstrates the trend for requesting younger donors. It shows that the average age of donors requested for typing is younger than the average age of donors in each state. The ACT is an outlier, with donors who are nearer to age 50 at request.

Figure 45: Mean age of donors, by state and gender

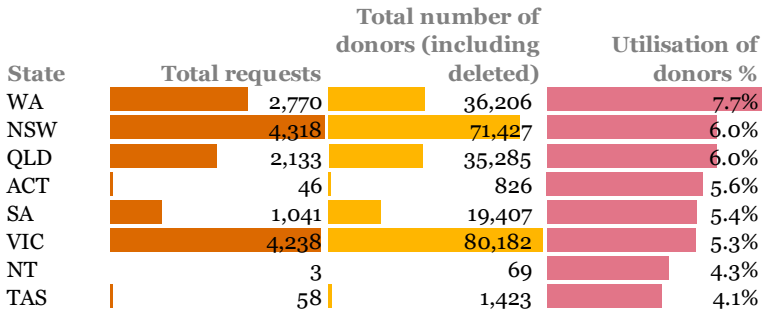


	ACT	NSW	QLD	SA	TAS	VIC	WA
Average age of donors	50	46	42	46	47	48	43
Average age when requested	49	37	36	37	34	38	36

Source: ABMDR Data 'Question_1a_to_1g – COMPLETE REGISTRY.xlsx'. Note: NT donors are captured in SA numbers.

Figure 46 compares the number of requests to the number of donors registered. It shows that Western Australian donors are used more often than donors elsewhere in Australia. This is likely to be due to the use of using NextGen tissue typing, which reduces ambiguity in results and enables clinicians to decide more quickly about which donors might be a suitable match to a patient. In 2016, Western Australian donors experienced a 13% increase in requests.

Figure 46: Utilisation of donors by state



Source: ABMDR Data 'Question_1a_to_1g – COMPLETE REGISTRY.xlsx'. Note: NT donors are now captured in SA numbers (having previously been reported separately).

5.2.3 Cord blood units

Australia's HPC program is supported by the three public cord blood banks (CBBs), which collect, test, bank and store CBUs for domestic and international patients. Table 8 shows a snapshot of Australia's current inventory.

Recently, the CBBs made many more CBUs searchable. Previously a large number of CBUs were non-searchable due to the CBBs inability to contact the mother for a 180-day follow-up. However, the TGA issued approval to make these CBUs available for transplant without the follow-up. The CBBs are expecting more of their units to be made searchable following this approval.

Table 8: Australia's cord blood inventory, as at 2017

Inventory	*Sydney Cord Blood Bank*	*Queensland Cord Blood Bank*	*Bone Marrow Donor Institute (Melbourne) Cord Blood Bank*	*Sub-total of all Cord Blood Banks*
Total	15,564	11,346	12,409 (approximately)	39,319
Searchable	14,110 (plus an additional 393 from the NT program)	9,910	10,517	34,537
Non-searchable	578 (plus 25 from the NT program)	1,326	892	2,796
Non-compliant (predominantly used as quality control units)	853	110	500–1,000	1,463–1,963

Source: SCBB figures provided as at 30 April 2017, Bone Marrow Donor Institute CBB and QCBB figures provided May 2017.

There are 4,830 CBUs recorded on the ABMDR that were banked before 2001, while the CBBs report a little over 6,500 (this difference is partially accounted for by those withdrawn from search).

CBUs are characterised by their volume, cell concentration (Total Nucleated Cell (TNC) count) and cell viability (measured by the CD34+ count). The clinician has discretion to decide on the necessary TNC and CD34+ counts for a patient, but generally, the higher each is, the better the quality of the CBU.

Table 9 breaks down total collections and average CBU statistics by bank in 2016. Sydney collected the highest number of CBUs in 2016, with 221 units. Queensland, which collected fewer units, made a greater number available due to extensive efforts to conduct 180-day follow-up, enabling the CBB to list previously non-searchable CBUs. Consistent with previous years, Melbourne and Sydney recorded higher CD34+ and TNC counts for units collected in 2016. The Bone Marrow Donor Institute (BMDI) collected units with an average TNC count of $128x10^7$.

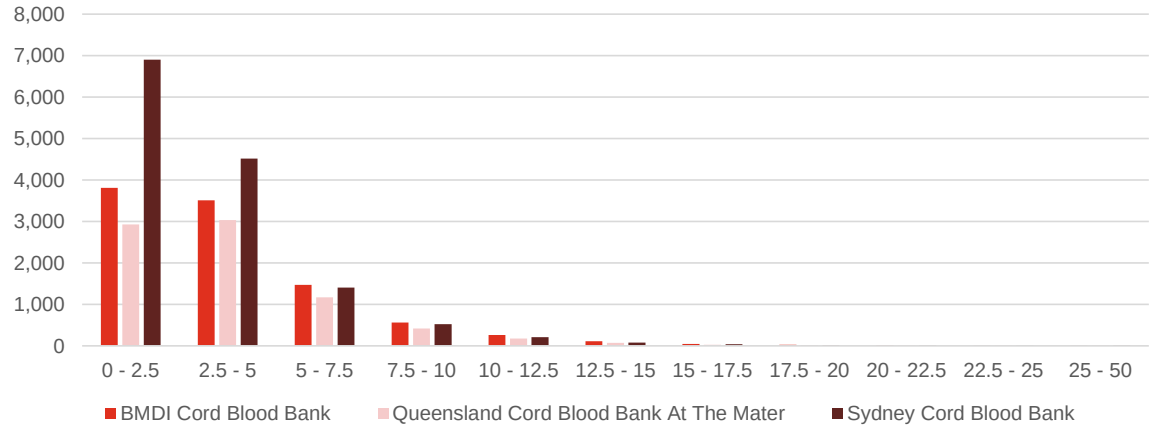
Table 9: CBUs collected over 2016

Cord blood bank	Total collected in 2016	Total made available in 2016	Average CD34+ count (10^6)	Average TNC (10^7)
BMDI Cord Blood Bank	87	595	4.7	128
Queensland Cord Blood Bank at The Mater	215	1,080	3.9	105
Sydney Cord Blood Bank	221	535	4.1	116

Source: ABMDR: Question 2.xlsx

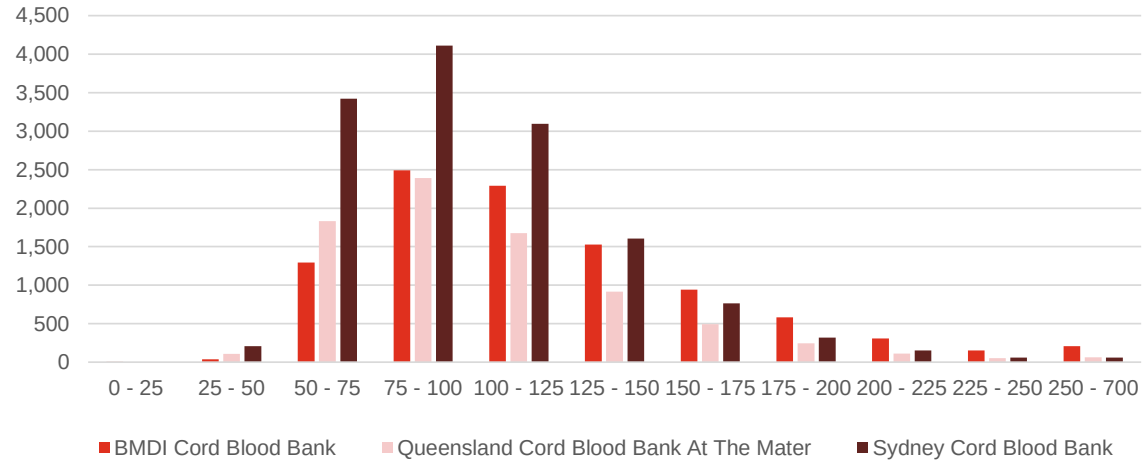
The entire inventory and its characteristics are shown in figures 47 and 48.

Figure 47: Number of CBUs by CD34+ count band (searchable CBUs only)



Source: ABMDR: Question 2.xlsx

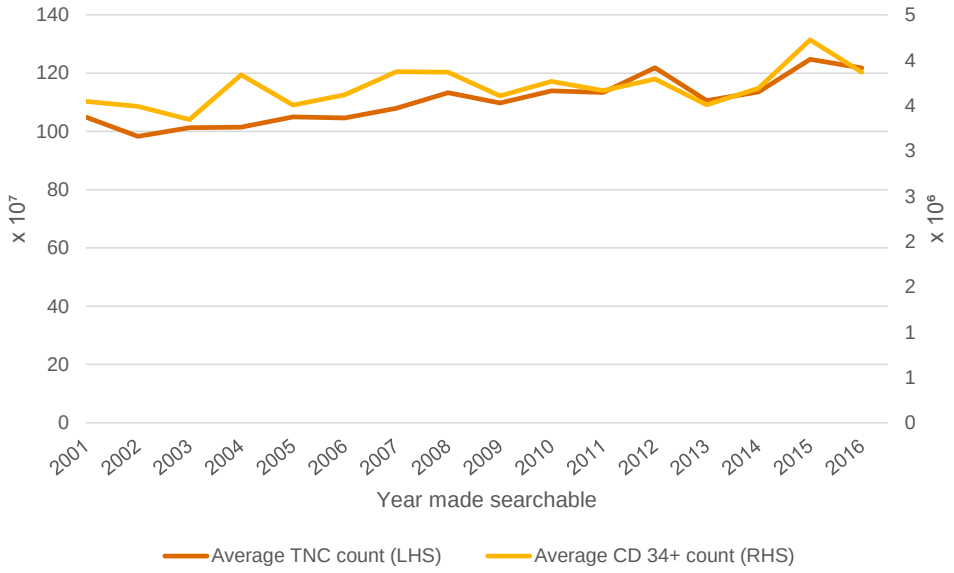
Figure 48: Number of CBUs by TNC count band



Source: ABMDR: Question 2.xlsx

Over time, the quality of banked CBUs has been growing, with increases in both CD34+ and TNC counts. Of those that are searchable, the average TNC count of a banked CBU now exceeds 120x10^7, while the average CD34+ count is around 40x10^6.

Figure 49: CBU characteristics (by year they were made searchable)



Source: ABMDR: Question 2.xlsx

Since 2001, the top nominated ethnicity for CBUs has been North West European. In 2016, 148 North West European units were collected, representing only 3% of total collections for that ethnic group. A total of 343 units have been collected from Aboriginal and/or Torres Strait Islander donors since 2001, the third-highest volume across listed groups. In 2016, 7.8% of CBUs were recorded with Southern Chinese ethnicity.

Figure 50: Top nominated ethnicities for collected CBUs

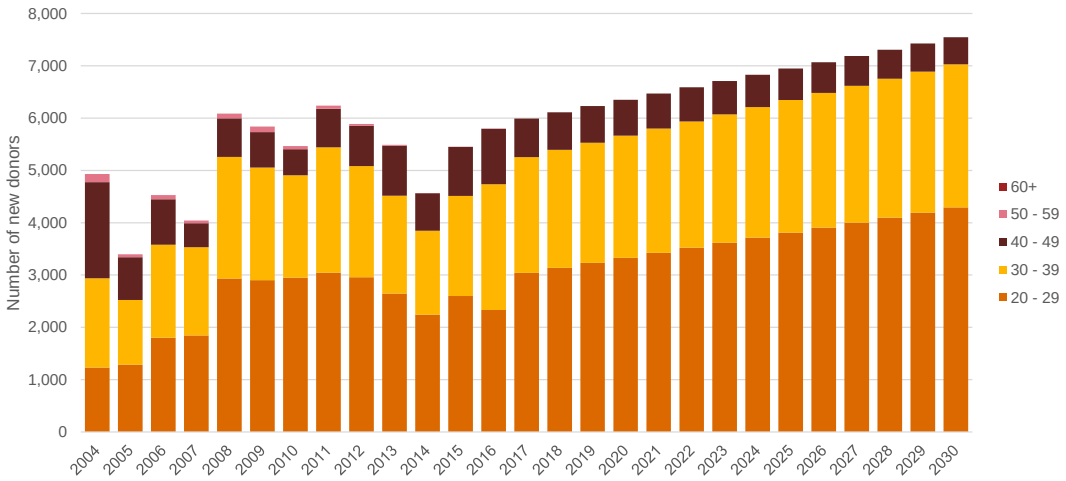
Ethnicity	Number of CBUs collected
North West European	5,195
Northern Caucasian (legacy)	365
Aboriginal Australian / Torres Strait Islander	343
Eastern European	182
Southern European	157
Maori	157
Indian	145
South Eastern European	139
Greek (legacy)	137
Italian (legacy)	112

Source: ABMDR: Question 2.xlsx, Note: Combined CBU files

5.2.4 How will Australia's registry change over time?

If the current strategy for recruiting through ARCBS blood donor centres is maintained, it is estimated that the proportion of young donors on the registry will continue to increase, while donors aged 40–49 will decrease. Figure 51 shows projections for the number of new donors to the registry, and their age at registration, with the trend for recruiting younger donors. Recent trends suggest that the strategy to recruit in the younger age brackets is succeeding. If current trends continue, by 2030 a little over 4,000 new recruits aged 20–29 will be captured, compared to only a little over 500 people aged 50–59. This compares to the current 5,799 new donors recruited in 2016, of which only 2,330 were aged 20–29.

Figure 51: Forecast age of donors, under current recruitment approach (age at registration)



Source: ABMDR Question 1, applying forecasting tool to project age at registration of donors following recruitment activity over the past 10 years

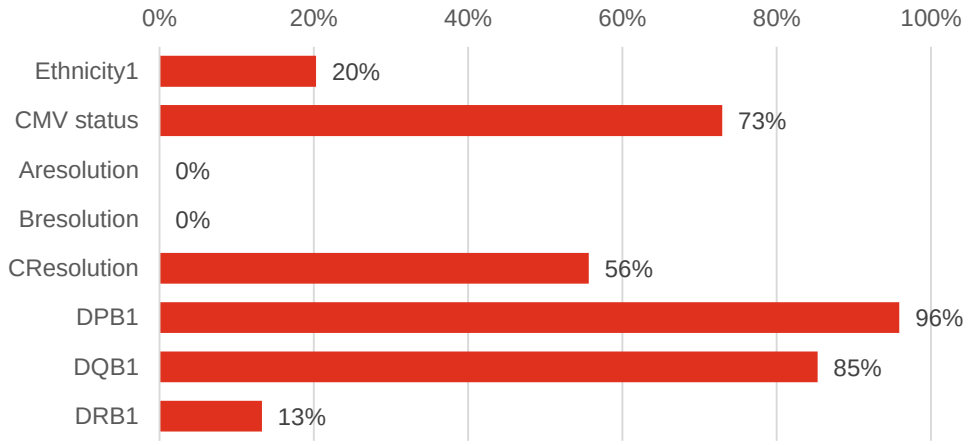
If the number of younger donors registered each year is not increased, the Australian registry's profile will quickly age, presenting significant challenges for developing a donor base that will meet clinical expectations.

Registry information completeness

The ABMDR's objectives include improving the overall standard of data held on donors on the registry. Many of the attributes clinicians seek when undertaking initial identification of potential donors is missing. Of registered donors, only 44% have information about the HLA-C loci (either high or low resolution). Most donors are not typed at HLA-DPB1 or –DQB1 (96% and 85%, respectively). Additionally, 13% are not typed at HLA-DRB1, which is increasingly a standard used to identify an 8/8 donor. Of all donors registered, only 80%

have an associated ethnicity and for the majority, their CMV status is not recorded. Improving the level of information will be integral to assisting fast, informed decision making.

Figure 52: Attributes missing (as a percentage of donors registered)



5.3 International profile

Australia forms a small, but important component of the international landscape of volunteer donors. Globally, the ABMDR is connected with more than 30 million donors. This pool of donors increases the likelihood that a patient will identify a match. Likewise, it enables international patients to identify matches in Australia. The role of international registries is increasingly important to registries worldwide.

With such a wide network of registries that are members of the World Marrow Donor Association (WMDA), more than ever, patients can search more widely for a potential match. Not only has this increased the chances of identifying an unrelated donor, it also allows clinicians to choose between multiple donors based on other selection criteria, such as sex, age, CMV status and blood group. This shift heralds the international community's successes in progressing stem cell registries and better meeting patient needs.

Of about 160,000 searches undertaken every year globally, Search Coordinators look at various parameters when identifying potential matches. The number of international donors for patients has risen globally. In 1997, international HPCs comprised only 30% of transplants, compared to 49% in 2016. In all, 16,904 transplants were reported to the WMDA in 2015, of which 12,831 were collected from peripheral blood. Of the world's regions, Europe provided more than twice as many HPCs as North America and Asia in 2015.

72%
of transplants in Australia use international donors

Of the 30 million donors registered with BMDW, approximately 57% are female and are typically in older age brackets; only 44% are under age 35. Approximately 2.3 million donors were added to the international database in 2015, and 2.2 million in 2016. Additionally, there were 715,580 CBUs on the database in 2016, up from 680,360 in 2015.

5.3.1 How does Australia's registry compare?

HPC donors are concentrated in Europe, North America, China and Brazil. Of the 30 million donors listed on the BMDW database, the US leads the number of registered donors, with more than 8.3 million on the National Marrow Donor Program (NMDP) registry alone. While Australia doesn't carry this number, it compares well for its population size, ranking 22nd globally in terms of total donors, with almost 171,000 donors registered at the time of data extraction from the BMDW website. In respect of the number of donors for our

population, Australia is on par with the UK, while Germany, the US and Israel have significant representation among their populations.

Table 10: Top 10 registries by number of donors, BMDW

Organisation	Number of registered donors	Donors per 100,000 population
National Marrow Donor Program's Be The Match Registry (US)	8,316,963	2,567
ZKRD (Germany)	7,365,288	9,124
REDOME (Brazil)	4,178,768	2,030
DKMS (Poland)	1,022,742	2,655
China Marrow Donor Program	993,132	72
Ezer Mizion Bone Marrow Donor Registry (Israel)	848,119	10,375
Anthony Nolan (UK)	636,047	987
Japan Marrow Donor Program	468,561	370
OneMatch Stem Cell and Marrow Network (Canada)	406,507	1,150
CEDACE (Portugal)	394,332	3,640
ABMDR	170,985	699

Source: https://www.bmdw.org/numberofdonors/. Note: These figures report upon each registry that has reported to the WMDA. It does not aggregate figures within countries (for example, where multiple registries exist in the one country). Population statistics drawn from the Australian Bureau of Statistics and the Central Intelligence Agency's The World Factbook*: https://www.cia.gov/library/publications/the-world-factbook/rankorder/2119rank.html*

Registries worldwide are managing the reality of their own achievements; each new donor added to registries represents only a marginal addition to the global database of haplotypes. In 1990, every second donor provided a new HLA-A, -B and –DR combination to the global database, but by 2010, this was reduced to one new haplotype for every 15 donors added.[56]

When considering CBUs, Thailand (26.3%) and Brazil (19.8%) have the greatest relative percentage of unique phenotypes. While Australia has approximately 3.5% unique phenotypes in relative terms.

Many registries want to type new donors at even more loci. Increasingly, this is done at all six loci, with a significant number of donors now typed at HLA-C, -DRB1, -DQB1 and –DPB1. Table 11 shows the extent of typing combinations. Compared to the global average, Australia has a similar proportion of registered donors typed at HLA-A and HLA-B, and HLA-A, HLA-B and HLA-DRB1. However, the proportion of donors typed at all six or eight loci is below the global average.

[56] Lown RN and Shaw BE (2013) Beating the odds: factors implicated in the speed and availability of unrelated haematopoietic cell donor provision, *Bone Marrow Transplantation* 48 pp 210–219.

Table 11: Comparison of global and Australian typing combinations

Typing level	HLA-A, -B	HLA-A, -B, -DRB1	HLA-A, -B, -C, -DRB1	HLA-A, -B, -C, -DRB1, -DQB1	HLA-A, -B, -C, -DRB1, -DQB1, -DPB1
BMDW average	6.6%	48.3%	14.8%	14.3%	16.0%
ABMDR average (high or low resolution)	7.6%	43.8%	28.1%	6.6%	4.0%

Source: WMDA Annual Report slide pack 2015 and ABMDR Data 'Question_1a_to_1g – COMPLETE REGISTRY.xlsx'

5.3.2 International cord blood units

Of the nearly 730,000 CBUs listed on the BMDW database, the US leads the number held in inventory. However, Australia's CBBs store the ninth greatest number of CBUs globally, with almost 34,000 at the time of data extraction from the BMDW website.

Of all the listed CBUs, approximately 20% on the BMDW database are typed at HLA-A, -B, -C, -DRB1, -DQB1 and –DPB1. Australia's CBBs are working to improve the tissue typing resolution and extent of typing on its CBUs to assist clinical decision making.

Table 12: Top 10 registries by number of CBUs

Cord blood bank	Number of CBUs
National Marrow Donor Program (US)	167,389
REDMO (Spain)	64,566
National Cord Blood Program (US)	60,492
BIONET Corporation (Taiwan)	39,046
Korean Network for Organ Sharing (Korea)	37,302
Greffe de Moelle (France)	35,194
Italian Bone Marrow Donor Registry	34,710
ABMDR	33,965
British Bone Marrow Registry (UK)	22,838
StemCyte Inc (US)	22,517

Source: https://www.bmdw.org/numberofdonors/. Note: These figures report upon each CBB that has reported to the WMDA. It does not aggregate figures within countries (for example, where multiple CBBs exist in one country)

In summary, we have observed that:

- the registry is ageing, while clinicians prefer younger donors
- the registry is skewed towards female donors, while clinicians prefer male donors due to the reduced risk of Graft versus Host Disease
- the ethnic diversity of our registry is largely represented by Caucasians, but with demographic changes in the general population, there is a need to ensure genetic diversity is represented on the registry
- many Australian donors are typed only to low resolution, meaning information is not immediately available to assist clinicians with decision making.

There is a continuing need to focus on the donors recruited to the registry to ensure they align with clinical needs. Additionally, a strategy should be developed that will assist with building an overall registry profile that addresses some of the key challenges relating to donor age, gender and the extent of tissue typing information available on registrants.

Demand

6

This chapter covers...

- *the characteristics of Australian patients requiring allogeneic-unrelated transplants*
- *search, transplant and collection activities across states and territories*
- *details of transplants supported by Australian and international donors and international transplants supported by Australian donors*
- *projected demand for unrelated donors and international supply.*

Key messages:

Of the 1,706 haemopoietic progenitor cell (HPC) transplants in 2015, 351 were supported by an unrelated donor or cord blood unit (CBU). The most transplants of any kind were undertaken in NSW. On a population basis, Victoria undertakes the most allogeneic transplants. Comparatively, Western Australia undertakes the most collections from volunteer donors and NSW initiates the most unrelated donor searches, compared to other states.

Consultations identified that there are very few instances of a patient not finding a match; instead, if a search is initiated and no suitable match is identified, clinicians will look to other treatment options for the patients, which could include a CBU, a haploidentical transplant or alternative treatment altogether. For approximately 70% to 80% of patients, an international search will be undertaken, reflecting the growing number of donors sought from international registries (which comprised 72% of all allogeneic-unrelated transplants). Many of these donors are young, male donors from Germany. Conversely, Australian donors support international patients (30 in 2016), who are predominantly located in the US and New Zealand.

Against clinical trends, population growth and an increasing ability to provide a transplant treatment pathway to older patients, the number of allogeneic transplants is projected to grow. To fulfil this demand, there will be a growing reliance on volunteer donors. Given the high proportion and trend in using international donors, Australia will need to consider how its registry can better meet the future needs of clinicians.

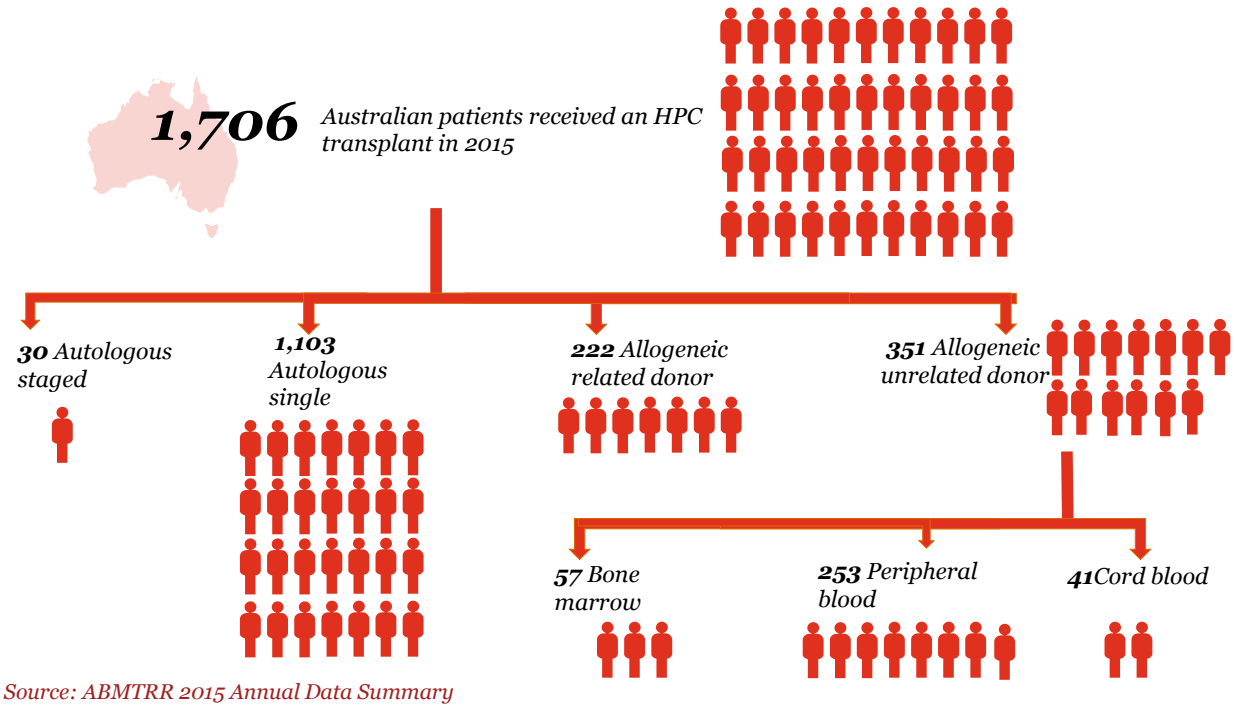
6 Demand

6.1 Current demand

Demand, as measured in this review, stems from three sources: Australian donors supporting Australian patients, international donors for Australian patients and Australian donors for international patients.

6.1.1 HPC transplants in Australia

The most recent, fully compiled dataset on transplants is for 2015, when 351 allogeneic transplants were undertaken in Australia. The vast majority of these (253) used peripheral blood donations.

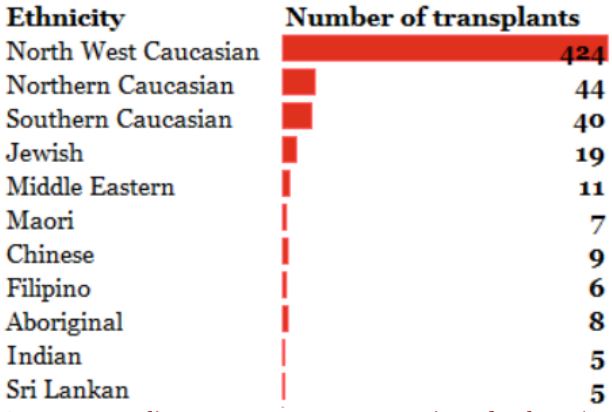


Source: ABMTRR 2015 Annual Data Summary

As explored in Chapter2, the number of allogeneic transplants undertaken in Australia and internationally is growing. This trend reflects a growing population and broadening of the types of patients suited to transplant due to clinical advances (for example, older patients). Against this trend, clinical preferences are changing, with more clinicians using peripheral blood sources for haemopoietic progenitor cells (HPC), as well as haploidentical transplants. With more transplants and older patients, there is a growing need for volunteer donors.

Ethnicity can be a preliminary indicator of a patient's haplotype, and is captured in early stages of search applications. Between 2013 and 2016, patients who underwent allogeneic-unrelated transplants were from 22 unique ethnicities. Of patients who captured their ethnicity, 86% identified as Caucasian. In 2015, six patients who identified as Middle Eastern and three who identified as Chinese underwent transplants.

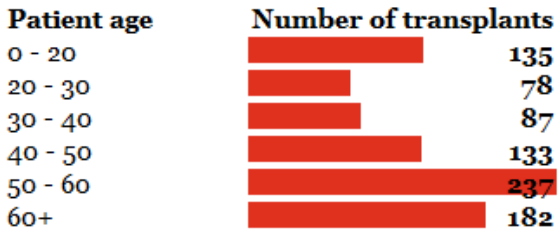
Figure 53: Top patient ethnicities for HPC transplants in Australia, 2013–16



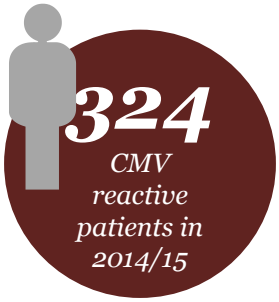
Source: Australian Bone Marrow Donor Registry database, 'Question 4', transplants between 2013-2016

The majority of patients who undergo allogeneic transplants using unrelated donors are aged 50–60. The growth in older patients undergoing allogeneic transplants is a key driver of the need for unrelated donors, as these patients may not have 'fit' siblings who can donate.

Figure 54: Patient age brackets, 2013–16



Source: ABMDR database, 'Question 4', transplants in 2013–16



The number of CMV reactive patients increased by **17%**, from 149 in 2014 to 175 in 2015.

As outlined earlier, a secondary consideration for matching HPC transplant patients is their cytomegalovirus (CMV) status. While a reactive patient can be paired with a donor who is CMV positive or negative, clinicians may seek to match patients not yet exposed to the virus to donors who are also CMV negative. Donors who are CMV negative can be matched to any patient. The number of CMV positive patients in Australia remains relatively high.

6.1.2 *State-based activity*

Transplants in each state

The total number of transplants performed in Australia has increased from 503 in 1992 to 1,904 in 2016. NSW, Victoria and Queensland undertake the largest number of transplants, and collectively have recorded an average 7% annual increase in transplants each year since 1992. In South Australia and Western Australia, transplants grew at 6% per annum on average over the same period. Tasmania and the ACT recorded the strongest annual growth, at 14%.

Figure 55: Total number of transplants by state, 1992–2016

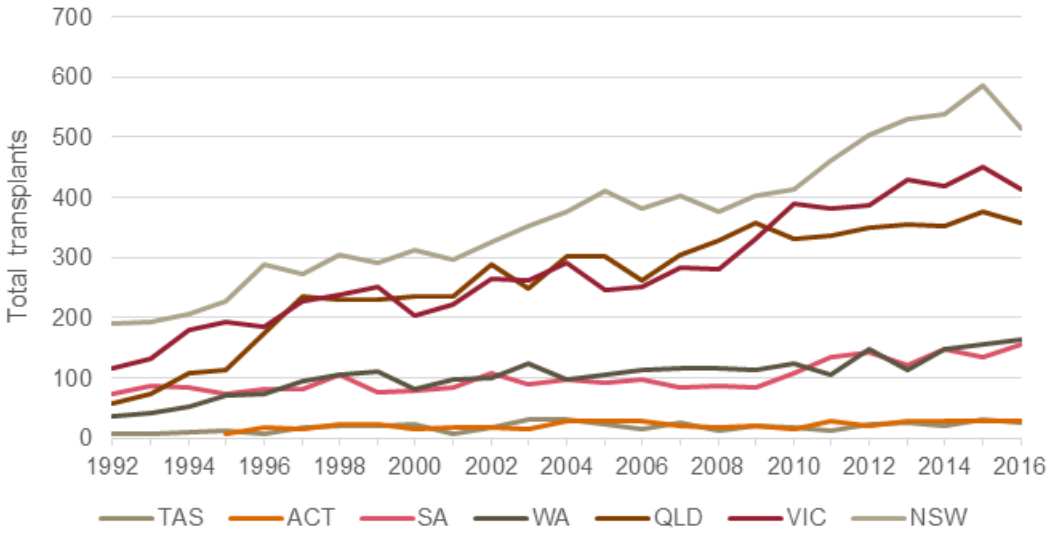
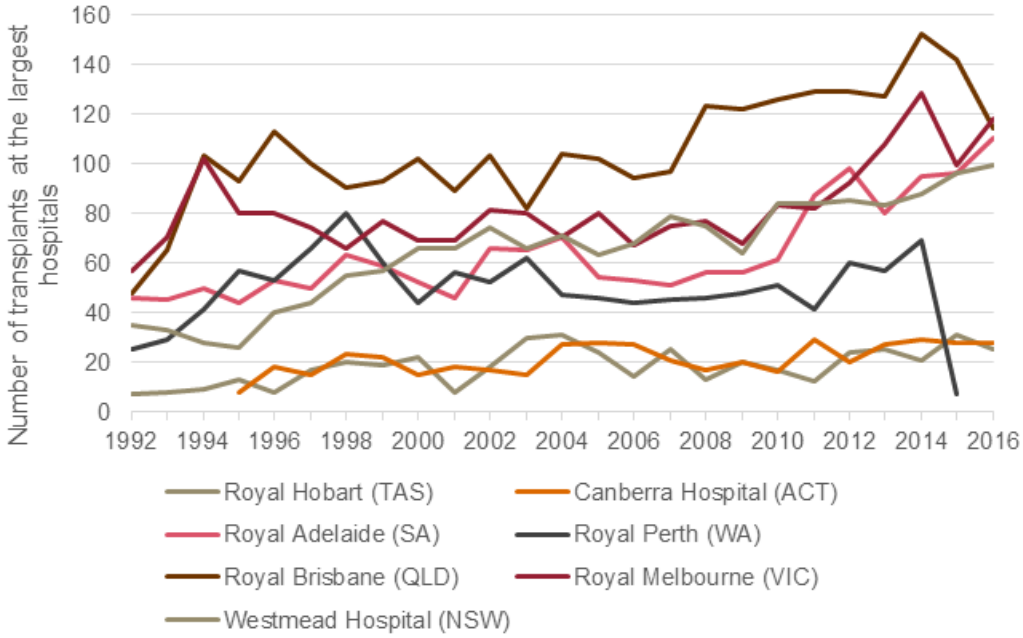


Figure 55 shows the hospitals performing the largest number of transplants in each state. The Royal Brisbane and Women's Hospital in Queensland has performed 106 transplants on average annually since 1992, 24 more per year than The Royal Melbourne Hospital in Victoria.

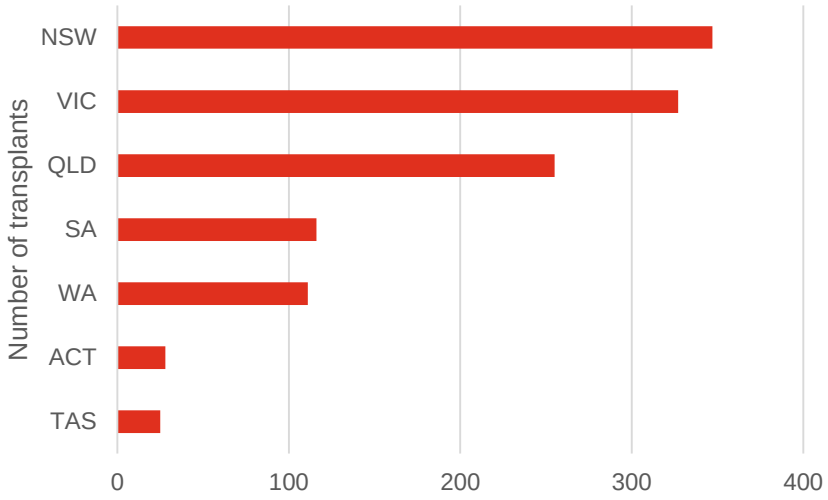
Figure 56: Total number of transplants performed by the largest hospital in each state, 1992–2016



Autologous transplants

More autologous transplants are performed than allogeneic transplants – averaging 118% more in 2016 – and the number is growing. Figure 57 shows that of all states, NSW recorded the highest number of autologous transplants, with 347 undertaken at 15 autologous transplant centres in 2016. In comparison, Princess Margaret Children's Hospital in Western Australia performed 118 autologous transplants in the same year.

Figure 57: Autologous transplants by state, 2016



Source: ABMTRR 2016 transplants.docx

Table 13: Top five autologous transplant centres, 2016

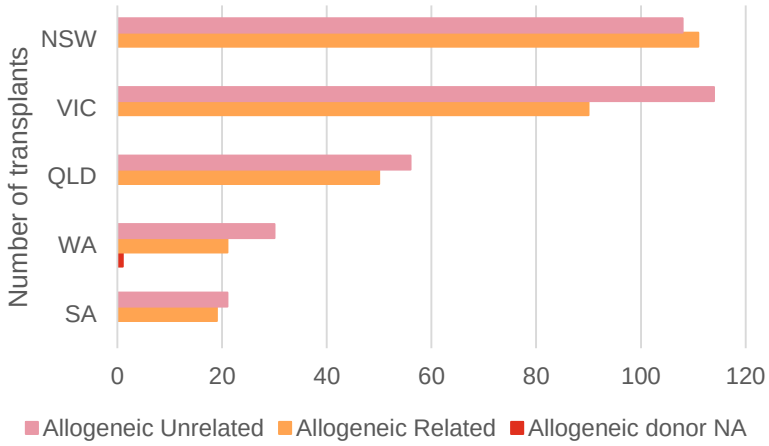
Transplant centre	Total transplants
Peter MacCallum Cancer Centre, Victoria	118
The Alfred Hospital, Victoria	74
Royal Adelaide Hospital, SA	70
Sir Charles Gairdner Hospital, WA	63
Royal North Shore Hospital, NSW	59

Source: ABMTRR 2016 transplants.docx

Allogeneic transplants

In 2016, the Australasian Bone Marrow Transplant Recipient Registry (ABMTRR) recorded 2,124 HPC transplants in Australia, of which 34% were allogeneic. Figure 58 demonstrates the breakdown of these transplants, by state, and the nature of patients' relationships with their matched donor. Victoria performed 114 allogeneic-unrelated transplants, 443% more than those performed in South Australia that year. In Victoria, 49% of allogeneic transplants took place at The Royal Melbourne Hospital, which performed more of these transplants than any other centre in Australia. Where HPCs were sourced from a related donor, NSW recorded the highest number compared to other states, with 111 in 2016.

Figure 58: Allogeneic transplants by state, 2016



Source: ABMTRR 2016 transplants.docx. Note: Allogeneic donor NA means that the related status of the donor is unknown

Table 14: Top five allogeneic transplant centres, 2016

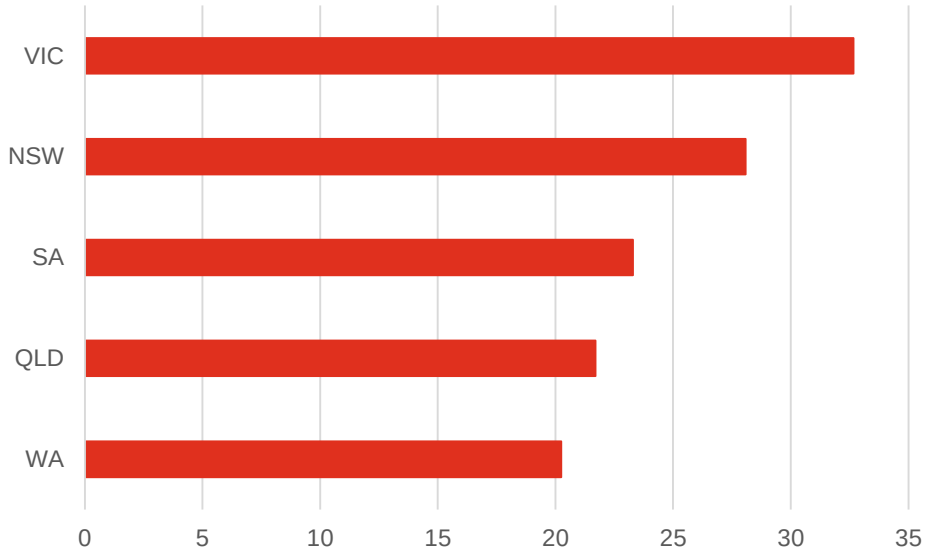
Transplant centre	Total transplants	Related transplants	Unrelated transplants
The Royal Melbourne Hospital, Victoria	100	50	50
Westmead Hospital, NSW	72	36	36
Royal Brisbane and Women's Hospital, Queensland	70	26	44
The Alfred Hospital, Victoria	50	18	32
Fiona Stanley Hospital, WA	45	16	28

Source: ABMTRR 2016 transplants.docx

When considering state-based populations, Victoria performs the highest number of allogeneic transplants per capita (see Figure 59). Given its population of about 6.2 million, Victoria performs approximately 32.7 transplants per million people. NSW, with the largest population, performs an estimated 28.1 transplants per million people. Western Australia undertakes fewer transplants per capita, at 20.3 transplants per million people. This compares to a European average of 29.3 HPC transplants per million people.[57]

[57] The EBMT Handbook 'Haematopoietic Stem Cell Transplantation' 6th edition, European School of Haematology and the European Society for Blood and Marrow Transplantation, Chapter 2.

Figure 59: Allogeneic transplants per million people by state, 2016

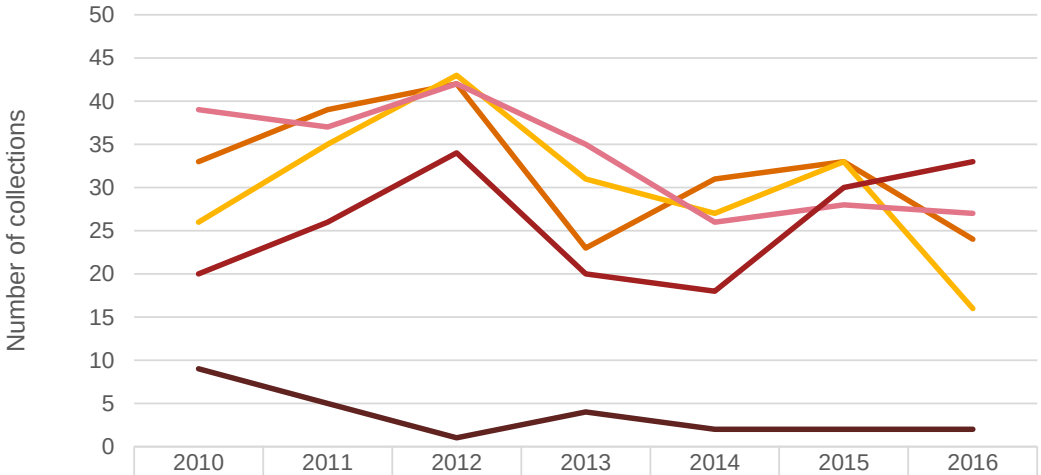


Source: Australian Bureau of Statistics population data: http://www.abs.gov.au/AUSSTATS/abs@.nsf/mf/3101.0, transplants: ABMTRR 2016 transplants

Collections in each state

Figure 60 outlines the number of collections from volunteer donors for domestic and international patients, in each state over the past six years. In 2016, there were 90 collections, of which 40% were in Western Australia. Since 2014, Western Australian donors have been typed at Next Generation (NextGen) resolution, which has driven growth in the number of collections made from donors in this state. When transplant time lines are critical, clinicians may prefer to use these donors because they are better able to decide on a potential match. In comparison, fewer collections have involved donors in Queensland in the last couple of years.

Figure 60: HPC collections in Australia, by state



	2010	2011	2012	2013	2014	2015	2016
NSW	33	39	42	23	31	33	24
QLD	26	35	43	31	27	33	16
SA	9	5	1	4	2	2	2
VIC	39	37	42	35	26	28	27
WA	20	26	34	20	18	30	33

Source: Request for PWC transplant-GSH.xlsx

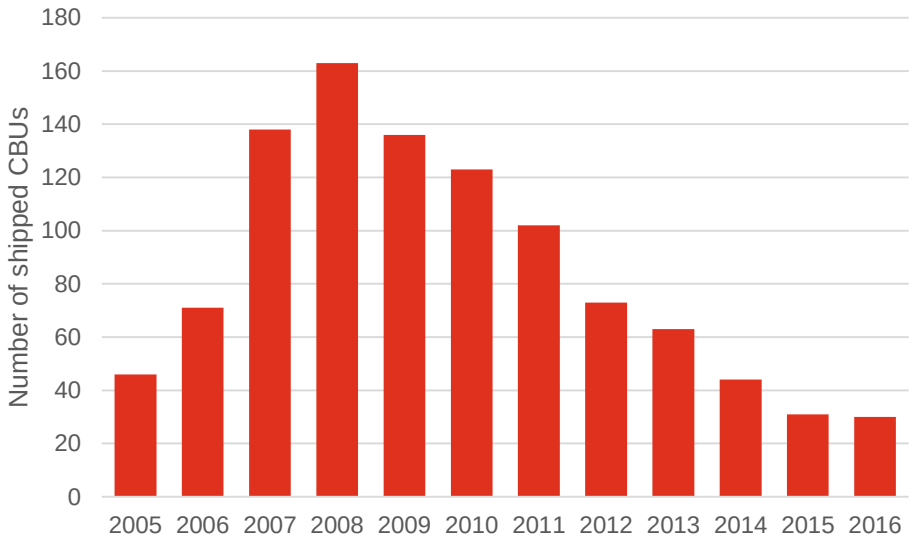
6.1.3 Cord blood units

In line with global trends, the use of cord blood units (CBUs) for HPC transplants continues to decline. The number of CBUs shipped since 2008 illustrates this trend. For example, in 2015, 42% fewer CBUs were used than in 2014. Figure 61 shows the release of CBUs from Australian banks over time.

With the adoption of NextGen tissue typing, and acceptance of emerging clinical trends, such as performing haploidentical (half-matched) transplants, preferences are moving away from using CBUs. Reduced intensity conditioning (a conditioning regime which uses less chemotherapy and radiotherapy than myeloablative conditioning) and T cell replete protocols have enabled clinicians to better manage the risks of Graft versus Host Disease, which is traditionally associated with haploidentical transplants. However, for lower-weight patients, including paediatric patients, and those with rare haplotypes, CBUs will continue to be a valuable source of HPCs.

Recently, CBUs held at Australian Cord Blood Banks (CBBs) have been made accessible on the European Marrow Donor Information System (EMDIS), which provides the international protocol for searching international registries. To date, Australian CBUs have not been entirely visible to international clinicians, meaning they may not be considered for transplant. From 2017, Australia's CBUs are expected to be available on EMDIS to countries including France and Spain, which may increase international demand for Australian CBUs.

Figure 61: Total CBUs shipped

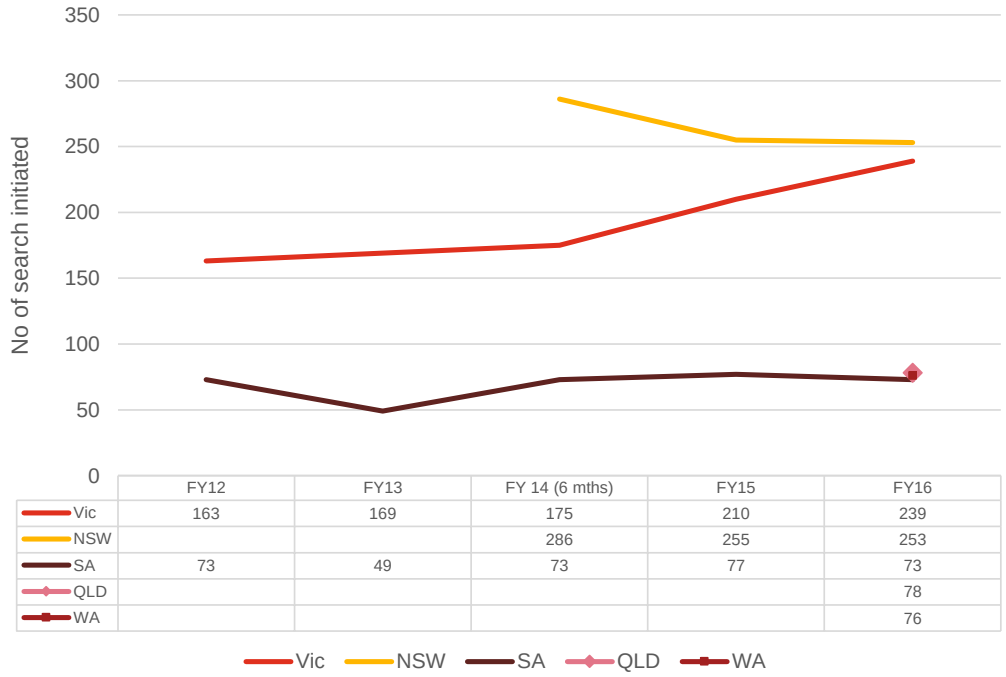


Source: CBUData-PWC-2016-02-29.xlsx, and ABMDR Question 2.xlsx

6.1.4 Patient searches

The number of unrelated donor searches initiated over the past four financial years has grown. In FY2015–16, 239 new searches were initiated in Victoria, 41% more than in FY2012–13. South Australia, which performs fewer searches than Victoria, due to its smaller patient base, recorded a 49% increase in activity for the same period. Queensland and Western Australia undertook similar levels of search activity, activating 78 and 76 new unrelated donor searches in 2016, respectively.

Figure 62: New unrelated searches initiated



	FY12	FY13	FY 14 (6 mths)	FY15	FY16
Vic	163	169	175	210	239
NSW			286	255	253
SA	73	49	73	77	73
QLD					78
WA					76

Source: ARCBS data 'PWC Combined search statistics 2011-2017.xlsx' and 2016 information provided by Pathology QLD and PathWest.

For approximately 70% to 80% of patients, an international search will also be undertaken.

For each patient matched to an unrelated donor, two to three requests for verification typing are typically issued. However, for some patients, the search may not succeed. This can be due to a variety of factors, including not finding a suitable donor, the patient becoming unwell and the search is suspended, the patient passing away or their clinician using a different treatment approach. Some of these factors are attributed to a patient not finding a suitable match due to delays in matching.

Consultations identified that there are very few instances of a patient not finding a match at all; instead, if a search is initiated and no suitable match is identified, the clinician will look to other treatment options, which could include using a CBU, haploidentical transplant or alternative treatment altogether. Patients are never left 'untreated' if a donor is not found. For this reason, a patient who would otherwise be classified as 'not finding a match' is captured as a patient treated in a different way. As such, in the current data, it is difficult to distinguish between unsuccessful searches and those that would have been unfulfilled even if a donor was identified.

Table 15: Unsuccessful searches (no verification typing sought) as a percentage of all initiated searches, 2016

State	FY2015–16
Victoria	21%
NSW	25%
South Australia	51%
Queensland	23%

Source: PWC Combined search statistics 2011–017.xlsx, provided by the Australian Red Cross Blood Service on 10 April 2017 and information provided by Pathology QLD.

Additionally, clinicians may lodge a 'book search' early in the treatment of a patient. This enables Search Coordinators to identify the likelihood of there being a match for a patient, to guide clinical decisions. However, book searches can cloud the total number of searches fulfilled because they may not be 'closed out' due to a patient not seeking a donor in the near

future. As such, a number of searches remain in the system for some time. In Queensland, there were 37 inactive/book searches in 2016. Additionally, many searches will be fulfilled in a different year to that in which the search was initiated. For example, of the 76 searches initiated in Western Australia in 2016, 44.7% proceeded to transplant, although this doesn't suggest that the remaining searches went unfulfilled.

Verification typing requests are issued to potential donors to inform decision making about potential matches. However, the number of available donors varies and depends on a number of circumstances, including the health of the donor, their willingness to donate and whether they can be contacted.

The average availability of Australian donors at the verification typing stage is 33% (using NSW, Victoria and South Australian data). This means that when a potential donor is identified, the majority won't be contactable or are unwilling to proceed. This can have significant implications for time delays and effort expended, and also creates the risk that a patient will not be able to identify a suitable donor.[58]

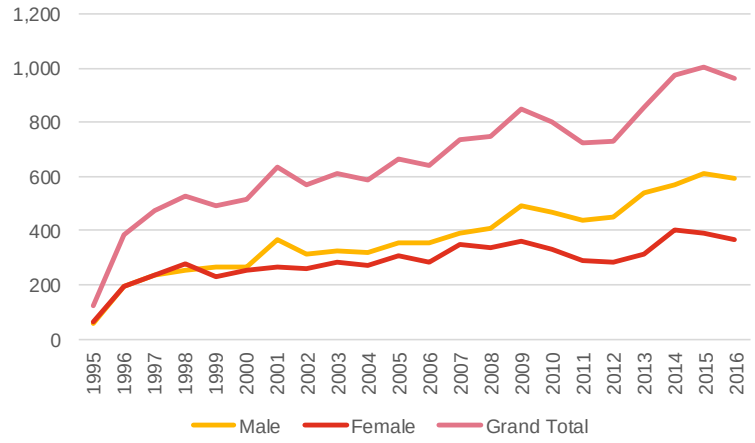
Among international donors identified as a potential match to an Australian patient, approximately 36% are available. In comparison, in Germany, an average of 85% are available. Availability also varies according to the ethnicity. For some donors, cultural or family views may intervene before collection.

The average length of time taken to produce preliminary search results (measuring the time between request for search to completing high-resolution testing and generating a donor list) is seven days. This period is relatively consistent across Victoria, NSW and South Australia. However, time taken to secure results for patient tissue types varies between labs. For example, Victoria has an estimated turnaround time of 11 days, but South Australia averages 31 days.

Verification typing

The number of requests for verification typing is driven by the demand for HPCs. Figure 63 shows the increasing number of requests, particularly over the last five years. The demand for male donors has exceeded that for female donors consistently since 2001. In 2015, there were 1,002 requests for verification testing, 61% of which were for male donors.

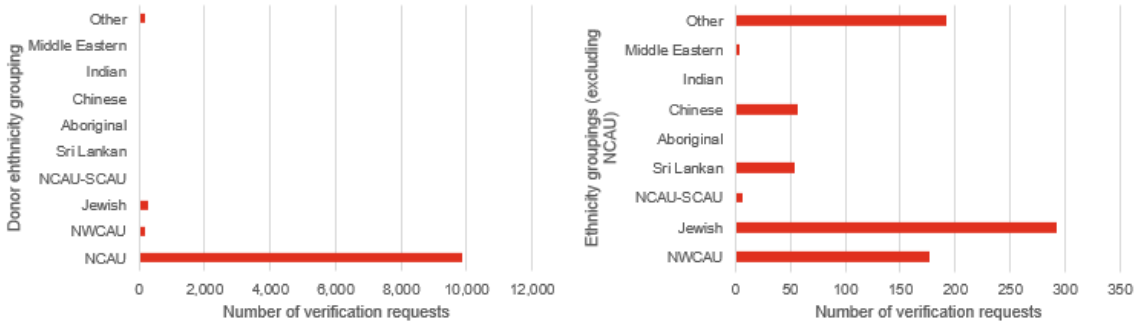
Figure 63: Number of verification requests over time, by donor sex



Source: ABMDR Question 2.xlsx

[58] Note: The Australian Bone Marrow Donor Registry is able to access the ARCBS's database of blood donors who are also registered HPC donors, and the ARCBS regularly maintains their contact details.

Figure 64: Number of verification requests by top ethnicities, 2013–16



Source: ABMDR Question 2.xlsx, grouped to key ethnic groupings

Laboratories in Australia differ in their capacity to turn around verification typing and reports. These differences are also observed in tissue typing laboratories, where, anecdotally, larger laboratories have the capacity to process recruitment samples more rapidly than laboratories in smaller states. Across global registries, extended typing requests are typically fulfilled within seven days.

Table 16 shows that verification typing requests are typically filled much more quickly. On average, Australia's laboratories sit slightly above the average in terms of turnaround times.

Table 16: Average verification typing turnaround time

	Within 7 days	8–14 days	15–21 days	More than 21 days	Unknown
Bone Marrow Donors Worldwide average	39.4%	33.8%	10.7%	7.3%	8.8%
Average turnaround for verification typing					
Victoria			18 days		
NSW			18 days		
South Australia				28 days	

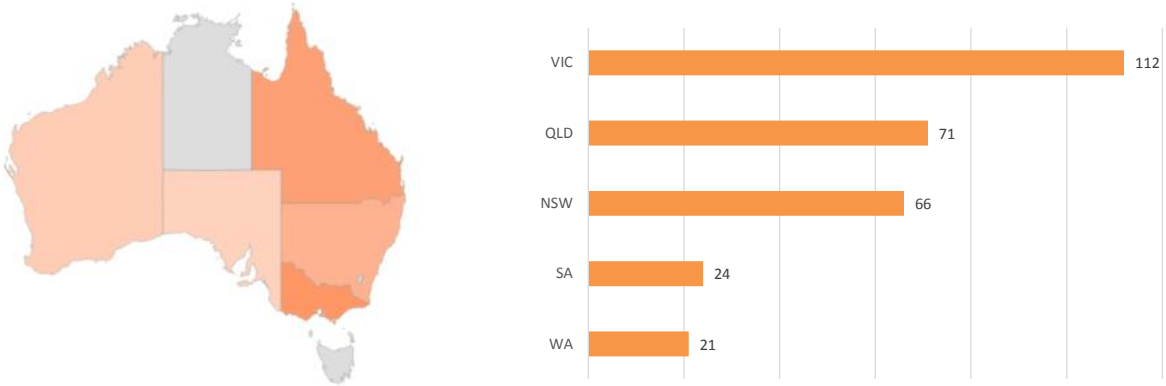
Source: WMDA Annual Report slide pack 2015 and PWC Combined search statistics 2011-2017.xlsx, provided by the ARCBS on 10 April 2017.

On average, verification typing of CBUs is turned around much more quickly than other sources of HPCs. Globally, 43.6% are typed within seven days, with a further 11.2% typed within three days and another 21% in 8–14 days.

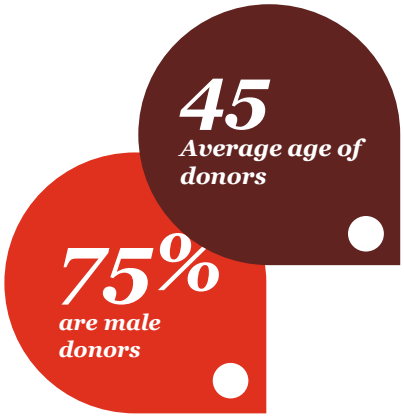
6.1.5 Allogeneic transplants in Australia

Where patients present with a unique haplotype, challenges arise with identifying suitable donors. Depending on a patient's condition and the urgency of the need, clinicians may opt to source HPCs from CBUs or a mismatched relative (haploidentical) (if either of these is not already the clinician's preferred transplant treatment). In 2015, 13 patients aged over 15 were treated with cord blood. In 2015, 5% of all adult HPC transplants used a CBU (or multiple CBUs), which is a decrease from 9.7% in 2012.

Figure 65: Transplants using domestic donors, by jurisdiction (October 2013 to December 2016, ABMDR)



Among all transplants undertaken in Australia over the last three years, demand has been growing for international HPCs.



When initiating an unrelated donor search, Search Coordinators consider domestic donors before international donors. By procuring cells locally, clinicians and Transplant Coordinators can reduce the risks associated with transporting units, and increase the ease and likelihood of performing secondary collections if required.

According to the Australian Bone Marrow Donor Registry (ABMDR), Victoria performed 112 transplants where patients where matched to Australian donors between October 2013 to December 2016.[59] Western Australia used the smallest number of domestic donors over the same period, transplanting 21 patients in all.

Figure 66 shows that the proportion of transplants using an overseas donor has increased over the last three years. In 2015, there were 261 international collections, representing 72% of total transplants for the year, a 4.3% increase from 2014.

[59] Between February 2000 and December 2016, 1,051 transplants in Australia involved domestic donors. Of these, data for 66 did not include an assigned transplant centre. Therefore, for purposes of comparison with the following sections, October 2013 to December 2016 was analysed, as all data was available across these dates.

Figure 66: Donor source, Australian unrelated transplants, ABMTRR

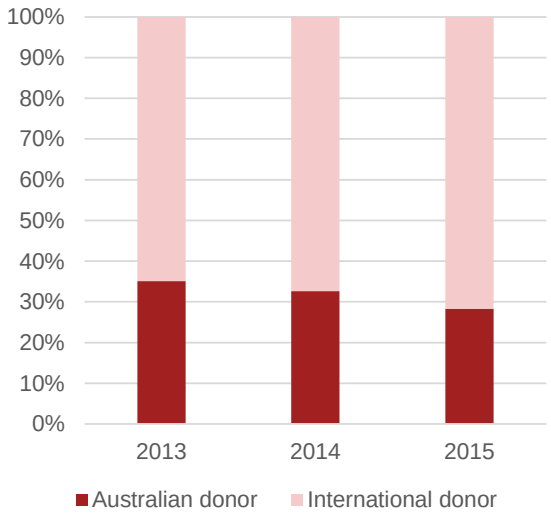
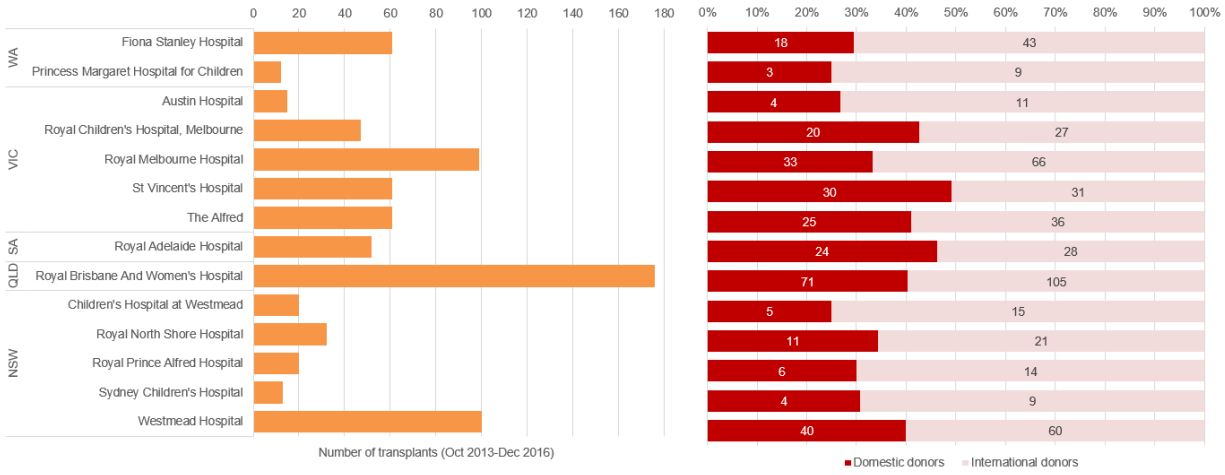


Figure 67 breaks down total transplants captured by the ABMDR between October 2013 and December 2016. It also details the proportions of HPCs sourced from Australian and international donors. Queensland's Royal Brisbane and Women's Hospital performed the greatest number of transplants in Australia over this period, undertaking 176 allogeneic transplants. Of these, 71 transplants used matched donors in Australia. Of all transplant centres, Westmead Hospital for children and Princess Margaret Children's Hospital undertook the greatest proportion of transplants involving an international donor (75% of transplants). On average, 65% of transplants performed in Australia between October 2013 and December 2016 used cells from an international donor.

Figure 67: Total transplants October 2013 to December 2016, ABMDR



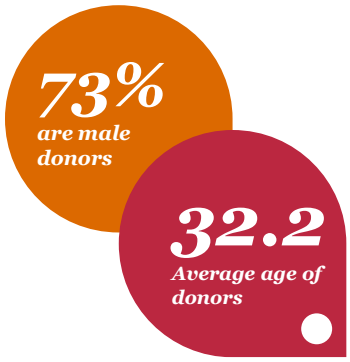
Source: ABMDR Matched datasets: file: 4a-.xlsx, 4b-.slsx, 4c-.slsx. Note: Royal Perth Hospital data is included in data reported for Fiona Stanley Hospital, and Royal Children's Hospital in Brisbane is included in Royal Brisbane and Women's Hospital figures.

The average age of Australian donors at the time of transplant is 45. While a greater portion of donors on the registry are female, 75% of those matched to patients were male in 2013–16.

HPCs are most often requested in the form of peripheral blood. In 2016, there was a 9% increase in the proportion of apheresis requests compared to those for HPCs from bone marrow.

The most commonly listed ethnicity among Australian patients matched with Australian donors was Northern Caucasian (217 patients), with a further 16 North West Europeans and one Aboriginal or/or Torres Strait Islander.

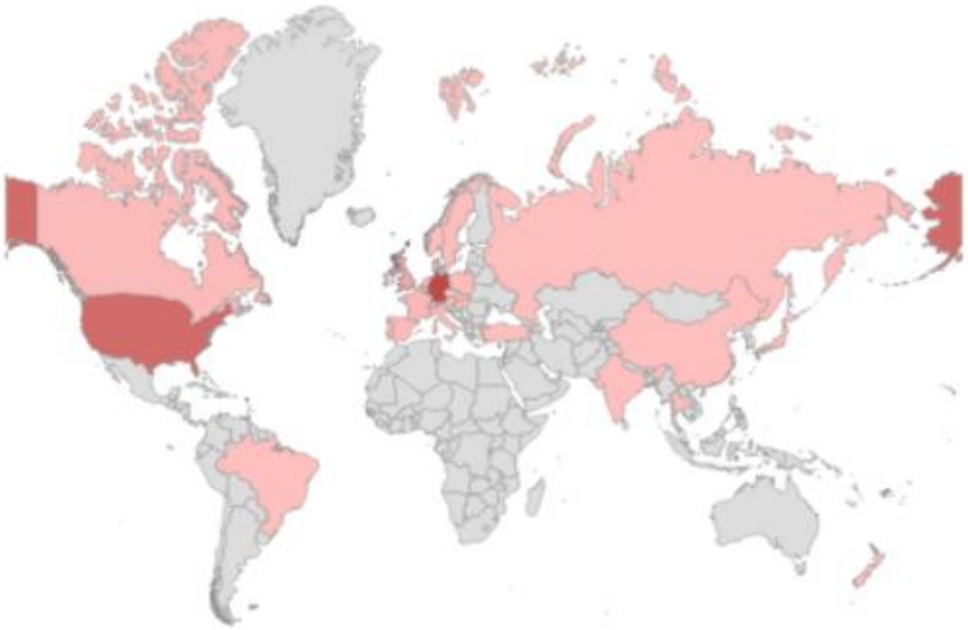
6.1.6 *International donors for Australian patients*



For patients not readily matched to donors listed on the ABMDR, a search may be initiated to source HPCs from overseas. The number of internationally sourced HPCs used in transplants has steadily increased since 2009. In FY2015–16, there were 734 applications for search requests on international registries, 47% of which were actioned to fill prescriptions for HPCs, a 7% increase on FY2014–15.

Germany is the largest donor of HPCs for Australian patients, making 285 donations since 2013 (60% of all internationally sourced HPCs). As identified among Australian donors, there is a strong preference for male donors, with 73% of all international donors to Australian patients being male. The leading ethnicity Australian patients requested from international registries was Caucasian, which may include donors with ancestry from mainland Europe, Greenland or Western Russia.

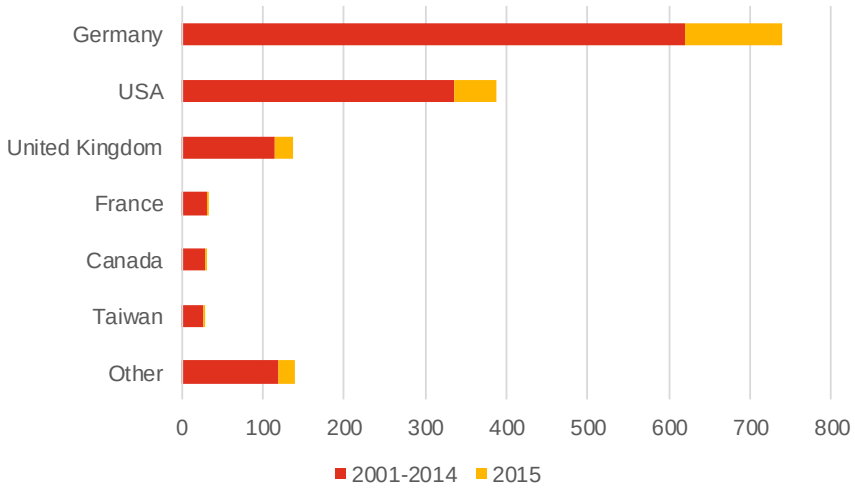
Figure 68: Origin of international donors (peripheral blood and bone marrow), 2001–15



Source: ABMTRR Unrelated HPC donor report 2015, excluding CBUs

Since 2001, Australia has relied on 1,492 bone marrow or peripheral blood donors from other countries. In 2015, 119 German donors supported Australian transplants. Figure 69 shows the leading six donor countries for peripheral blood and bone marrow donors. Countries that provided less than 25 donations to Australian patients were grouped into the category 'other' (27 unique donor countries).

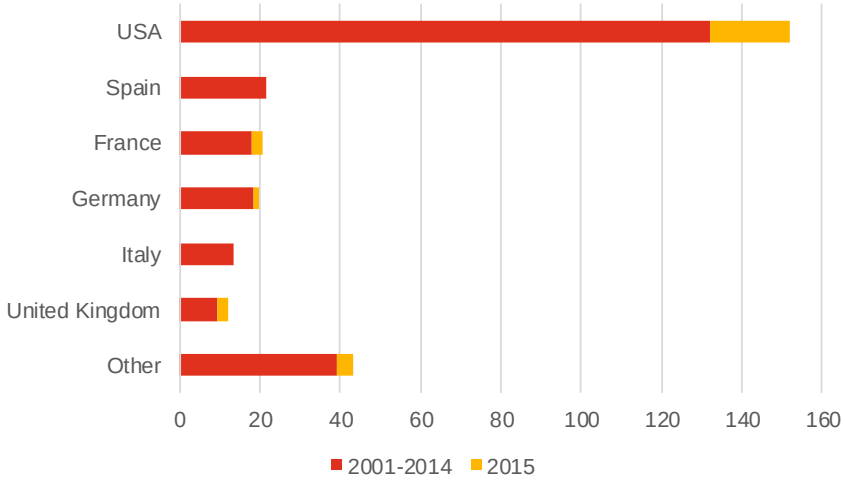
Figure 69: Comparison of leading donor countries for peripheral blood and bone marrow donations



Source: ABMTRR: Unrelated donor HPC transplants in Australia in 2015. Note: This excludes CBU transplants (available) and Australian donor statistics (2015 data was captured separately to 2001–14, as records may not be complete)

The leading countries for internationally sourced CBUs vary from donors of peripheral blood or bone marrow. The US is our primary donor country of CBUs, donating 132 units in 2001–14. Germany is Australia's fourth-highest donor for CBUs (see Figure 70).

Figure 70: Comparison of top donor countries for CBUs



Source: ABMTRR: Unrelated donor HPC transplants in Australia 2015. Note: This excludes CBU transplants (available) and Australian donor statistics (2015 data was captured separately to 2001–14, as records may not be complete)

Figure 71 shows the growth in demand for internationally sourced HPCs for Australian patients. For example, demand for German HPCs from peripheral blood or bone marrow donors grew from 86 to 119 between 2013 and 2015. The number of CBUs sourced from the US has grown from 16 in 2013 to 27 in 2015.

Figure 71: HPCs sourced from international donors, 2013–15

Source: ABMTRR Annual Data Summaries 2014 and 2015

International donors supply Australian patients with a wider pool of ethnically diverse haplotypes than Australian donors. Of requested donors, most identify their primary ethnicity as Caucasian; however, Australia's requests are diverse, including for Hispanic, Asian and African donors. There is a strong clinical preference for male donors, regardless of ethnicity. This is most strongly apparent among Caucasian donors requested, of which 78% were for male donors.

Figure 72: Breakdown of requested HPCs from international registries, by gender and ethnicity

Source: ABMDR: Matched datasets: file: 4a-.xlsx, 4b-.slsx, 4c-.slsx. Of the 475 international donors between October 2013 and December 2016, 89 donors did not list an ethnicity (or it was unknown).

6.1.7 *Australian donors for international patients*

Australia plays an important role in assisting international patients who are matched to an Australian donor. In 2016, 30 donors (peripheral blood or bone marrow) supported international patients. Due to gaps in data (such as the year of collection), this figure may be understated. Since 2013, the leading ethnicity nominated by international donors is Northern Caucasian, with requests for 64 Australian donors.

73%
are male donors

37.7
Average age of donor

Figure 73 and Figure 74 outline the leading countries sourcing Australian HPCs. Since 2013, the ABMDR has reported 26 HPC donations (excluding CBUs) to the US, the country where we distribute the most HPCs. New Zealand has requested the second-highest number of collections, totalling 24 since 2013.

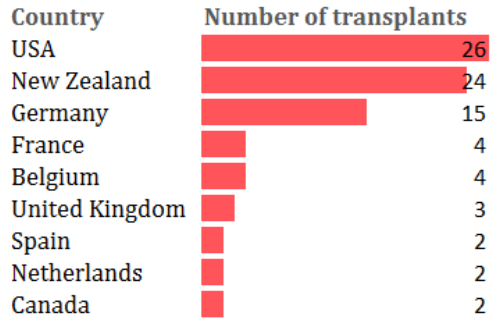
New Zealand has a unique arrangement with Australia, using MatchPoint to search for donors. Additionally, its own registry only captures its unique Maori and Pacific Islander populations.[60] This means that New Zealand patients may first seek an Australian donor if they are not matched to a donor from those ethnicities.

Figure 73: Countries to which Australia donates HPCs

Source: ABMDR provided information 'Question 4'

[60] New Zealand Bone Marrow Registry, accessed at < http://www.bonemarrow.org.nz/join-now>

Figure 74: Leading countries sourcing Australian HPCs, 2013–16



Source: ABMDR provided information 'Question 4'

The demographics of domestic donors requested by international patients is consistent with Australian demand. With an average age of 37.7, 73% of HPCs were collected from male donors between 2013 and 2016. This clinical preference is visible across numerous donor types and is detailed in Figure 75. Caucasian is listed as the leading ethnicity, with 64 donors of HPCs bound for international recipients having Northern Caucasian ethnic background. The most common request is for peripheral blood donations, which represented 90% of all HPC requests in 2016, excluding cord blood.

Given the low-resolution typing of Australian donors on the ABMDR, and the rapid adoption of more advanced typing techniques used by other countries, the number of HPCs distributed internationally has been declining in recent years.

Figure 75: Breakdown of requested HPCs (by international registries) by gender and ethnicity, 2013–16

Ethnicity	Number of	Female	Male
Northern Caucasian (legacy)	75	19	56
Southern Caucasian (legacy)	2		2
North West European	8	2	6
Jewish (legacy)	1		1
Sri Lankan (legacy)	1	1	
Indian	1		1
Tongan	1	1	
Aboriginal and/or Torres Strait Islander	1		1
Eastern European	1		1
Asian	1		1

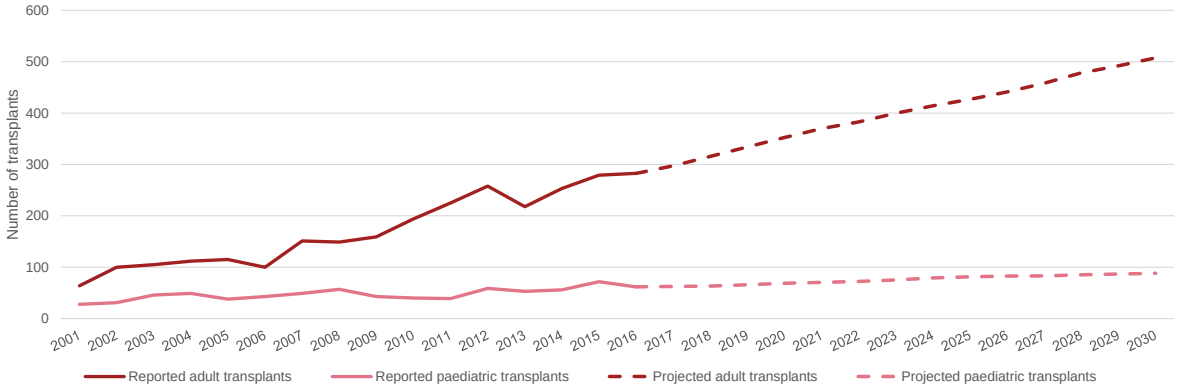
Source: ABMDR: Matched datasets: file: 4a-.xlsx, 4b-.xlsx, 4c-.xlsx. Note: 17 donors are listed without an ethnicity.

6.2 Projected demand

Clinical trends, population growth and an increasing ability to provide a transplant treatment pathway to older patients mean the number of allogeneic transplants is projected to grow. Reliance on volunteer donors to support those transplants is also likely to increase with the growing trend toward smaller family sizes and older patients with older siblings, who are perhaps not fit for donation.

Using historical growth rates, Figure 76 shows the potential future transplant demand for adult and paediatric patients. It shows that by 2021, almost 375 adult allogeneic-unrelated transplants will be undertaken. By 2030, this figure may exceed 500, compared to the almost 300 transplants undertaken in Australia today. Paediatric transplants might be expected to more closely align with growth in clinical indications, which is growing at a slightly slower rate than for adults.

Figure 76: Projected unrelated transplant figures

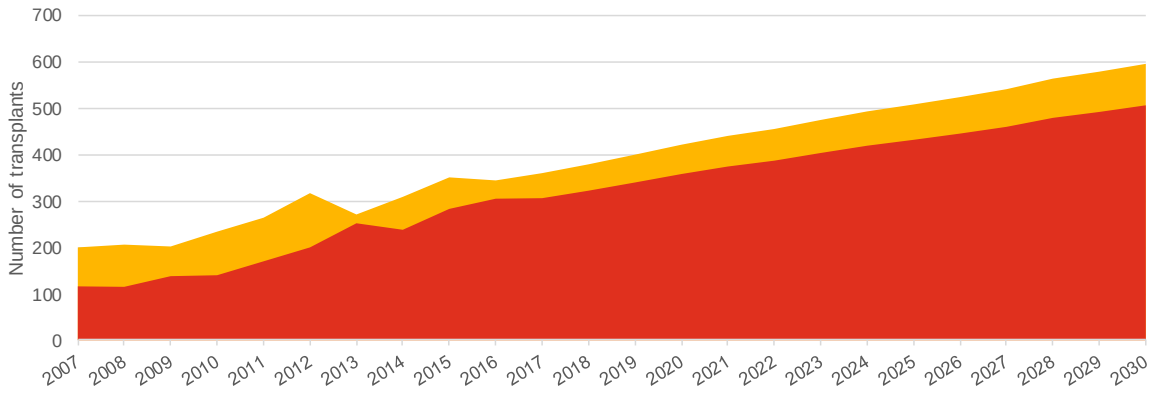


Source: ABMTRR Unrelated donor report 2001–2014 and ABMTRR 2015 report. Note: Paediatric patients are categorised as aged 0–15 and adults are aged 16+. The number of transplants represents unrelated transplant figures only. Projections were calculated using the forecast tool in Microsoft Excel.

To fulfil the growing demand for unrelated donors, Australia will have to address the current trend towards using international donors, which includes considering how the Australian registry can better meet the future needs of clinicians. Steps include enhancing the tissue typing resolution used for new and retrospectively typed donors; improving donor engagement to reduce unavailability; and broadening the ethnic diversity of donors to reflect Australia's changing demographics.

In the absence of action, current trends of using internationally sourced HPCs can be expected to continue. Figure 77 scales the historical trends for using international and domestic HPCs for Australian transplants. Assuming an upper threshold of 85% – based on it always being possible to source at least 15% of HPCs from Australian donors – the number of international donors is expected to grow from almost 300 in 2016 to more than 500 in 2030.

Figure 77: Projected transplants and proportion that rely on international donors (red graph area)



Source: Transplant numbers: ABMTRR data summaries for 2014 and 2015 for HPCs sourced from international donors; HPCP – Annual report 2015–16. Note: An upper boundary was imposed on projections of international HPCs to limit supply to 85% of transplants.

6.3 Future needs

The World Marrow Donor Association (WMDA) has observed a number of trends and needs relevant to the HPC sector, which include the following:

- Registries will continue to need information technology (IT) infrastructure that enables better access to information to support clinical decision making and reporting, and to provide standardisation across platforms.

- Increasingly, clinicians are looking for greater breadth of information when they search the database. To make a good decision on the best potential donor or CBU, clinicians would like to see more than the initial human leukocyte antigen (HLA) typing information about CMV status and donor blood group, or information about processing CBUs. Finally, to reliably calculate a match, the ethnicity of the donor is crucial.
- Extended HLA typing is important. As a result, many registries have outsourced their HLA typing during initial recruitment to commercial laboratories. More than 21% of donors and cord blood products in the BMDW database are now typed at all six loci (HLA-A, -B, -C, -DRB1, -DQ1 and -DP1).
- In some countries, clinicians are using related donors more often in transplants, while use of unrelated donor transplants is flattening out. This trend prompts a need for registries to consider greater engagement in related donor care.

- Use of unrelated donor transplants is continuing to grow in South America and Asian countries, and is supported by a number of new registries in those regions. Given this demand, the use of cord blood continues to rise, particularly in Asia, although the driver for this trend is not well understood.
- The growing number of mixed marriages is leading to more patients with difficult haplotypes to match. Recruiting minorities is important for finding a match for these patients.
- Donor availability is important. Registries are developing strategies to stay connected with their donors, to be sure that a donor is fit to donate when asked. Online technology could better support engagement with donors.
- An increasing percentage of donors are recruited online.

The quality of typing and donor availability will continue to affect which donors are preferred during the initial search.

Cost of HPC supply

7

This chapter covers...

- *expenditure of governments on haemopoietic progenitor cell (HPC) programs and unrelated donor activities, including international donors*
- *operational expenditure and staffing of the Australian Bone Marrow Donor Registry (ABMDR), the Australasian Bone Marrow Transplant Recipient Registry (ABMTRR) and the National Cord Blood Collection Network (NCBCN)*
- *operational revenue to sector entities and cost-recovery mechanisms*

Key messages:

Around $11.4 million was spent in FY2014–15 and $11.9 million in FY2015–16 on donor recruiting, tissue typing and maintaining Australia's unrelated donor registry. This expenditure includes the operation of the ABMTRR and the three Cord Blood Banks (CBBs). In addition, state governments spent $6.3 million in FY2015–16 (FY2014–15 estimates are not available) on search and coordination activities to match and mobilise donors and undertake tissue typing. A number of other costs associated with unrelated donors could not be identified in this review. Across the sector, there are approximately 102 full-time equivalent staff working for the Australian Bone Marrow Donor Registry (ABMDR), the Australian Red Cross Blood Service (ARCBS), PathWest, Pathology Queensland, the three CBBs and transplant centres that directly support donors and patients needing an unrelated donor.

Collections from international donors are a leading expense; in 2016, the Commonwealth spent $13.3 million on international searches and international donor collections. These costs are projected to grow and could reach $20 million by 2029. Against this, the decline in collections from Australian donors for international patients has reduced the fees recovered, which are a source of untied funding for the ABMDR.

7 Cost of HPC supply

7.1 Costs of HPCs

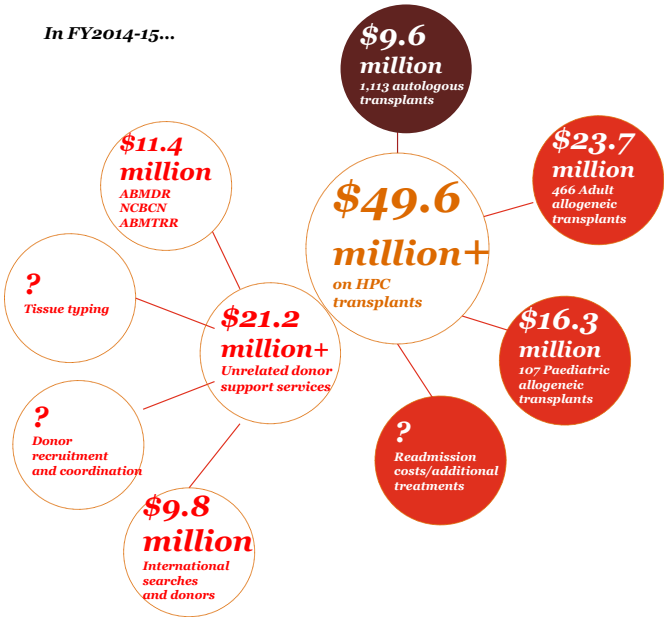
The HPC sector is extremely costly. Almost $50 million was spent on clinical transplant activity in FY2014–15, excluding readmission costs. The cost of recruiting donors, tissue typing (initial and verification) and maintaining Australia's unrelated donor registry was around a further $11.4 million in FY2014–15 ($11.9 million in FY2015–16). This spending includes the operation of the ABMTRR and the three CBBs. State governments spent an additional $6.3 million in FY2015–16 (FY2014–15 estimates are not available) on search and coordination activities to match and mobilise donors, and on tissue typing. In addition, the Commonwealth funds international searches and international donor collection costs, which were a further $9.75 million in FY2014–15 ($13.29 million in FY2015–16). The total costs associated with international donors continue to grow, as do the costs of maintaining the registry. Given this, current challenges need to be addressed if Australia is to reduce its reliance on international donors.

7.1.1 Cost of HPC transplants

Due to their complexity, HPC transplants are expensive hospital activities. In FY2014–15, clinical transplant costs reached almost $50 million.[61]

This figure excludes readmissions – a common occurrence among transplant patients – and much of the treatment pathway, which is captured as separate episodes in hospital costs data.

Additionally, leukaemia patients are among the biggest users of donated blood, and transfusion costs are not captured.



Source: ABMTRR 2015 Annual Data Summary, IHPA DRG Round 19 2014–15 National Hospital Cost Data Collection

With the number of transplants projected to rise, so too will the costs to the health system.

To capture costs to hospitals, the Independent Hospital Pricing Authority (IHPA) defines a number of treatments via diagnosis-related groups (DRG). Of these, HPC transplants are covered by four codes, for which actual costs and the National Efficient Price (NEP) are established. IHPA calculates the NEP for these treatments each year, based on the average costs incurred across the country, which are submitted as part of the National Hospital Cost Data Collection. The DRG price column in the following table shows the average cost for a HPC transplant in FY2014–15.

[61] Note: 2015 figures are used as these are the most complete datasets for both transplants and hospital costs. Additionally, conservative estimates have been adopted (that is, only the costs of autologous transplants of minor complexity are used).

DRG title	DRG code	DRG price (FY2014–15)
Allogeneic Bone Marrow Transplant, Age <16	A07A	$152,173
Allogeneic Bone Marrow Transplant, Age >=17	A07B	$50,943
Autologous Bone Marrow Transplant, MAJC	A08A	$41,869
Autologous Bone Marrow Transplant, MINC	A08B	$8,593

Source: IHPA DRG Round 19 2014–15 National Hospital Cost Data Collection

7.2 Expenditure

7.2.1 Expenditure across the unrelated HPC sector

The total spent on unrelated donor support services in FY2015–16 is estimated to be near to $31.5 million, excluding clinical costs associated with transplantation. This figure also excludes the total cost of patient tissue typing, which cannot be extracted in full under the current funding arrangements.

Over the last three financial years, the ABMDR's expenditure has grown, from $3.6 million in FY2014–15 to $4.2 million in FY2015–16. Commonwealth expenditure on the International Searches Program (ISP) and the Bone Marrow Transplant Program (BMTP) has also risen, with $13.2 million spent in FY2015–16. As Table 17 shows, the overall cost of activities is growing.

Table 17: Reported expenditure, unrelated HPC sector activities

Organisation	FY2013–14	FY2014–15	FY2015–16
ABMDR	$3,134,920	$3,523,404	$4,235,096
International Searches Program (managed through the ABMDR)	$1,467,000	$1,500,000	$1,704,000
Commonwealth (BMTP)	$6,304,000	$8,249,000	$11,588,000
ABMTRR	$394,295	$425,460	$342,345
National Cord Blood Collection Network (NCBCN)			
Sydney Children's Hospitals Network (Sydney CBB)	$2,133,226	$1,986,307	$2,220,901
NT collection centre (through Sydney Children's Hospitals Network)	$388,620	$412,288	$371,849
Mater Misericordiae Service Brisbane (Queensland CBB)	$2,488,392	$2,500,368	$2,243,783
Bone Marrow Donor Institute (Melbourne CBB)	$2,390,702	$2,504,369	$2,510,000
Coordination and typing			
Donor recruitment, coordination and search coordination	*Unknown*	*Unknown*	$1,602,578*
Tissue typing	*Unknown*	*Unknown*	$4,703,217*
Total	**$18,306,860**	**$21,101,196**	**$31,521,769**

Source: ABMDR: PWC HPC Sector Review Data Request - Financials.docx, ABMTRR: Finance-ABMTRR-1314 Template Projected quarter4.xlsx, Finance-ABMTRR-1415 Template Q4.xlsx, ABMTRR-1516 Finance Report.xlsx, NCBCN: PWC HPC Sector Review Data Request - Financials.docx, Commonwealth: BMTP - Half yearly report 2016-2017 (D17-1069372).DOCX
*Note: NCBCN expenditure does not include costing of alignment project. *Tissue typing costs have been captured in different ways and exclude WA costs*

Table 18 shows the breakdown of state and territory spending on Donor Coordinators, State Search Coordinators and tissue typing functions. This information is captured in different ways across jurisdictions due to the different funding agreements in place. Notably, there are differences in tissue typing, which is presented in columns A and B. For NSW and Queensland, total expenditure for patients and donors is captured, so costs include initial,

extended and verification typing. In Victoria and South Australia, typing costs are captured in state-wide agreements and are calculated according to the advice of the Australian Red Cross Blood Service (ARCBS). This review did not access spending on tissue typing in Western Australia.

Table 18: Jurisdictional breakdown of expenditure on recruiting, coordination and tissue typing

Jurisdiction / organisation	FY2015–16			
	Recruiting and search coordination	***Tissue typing***		***Description***
	Donor and search coordination and recruiting	*A- Donor typing costs*	*B- Donor and patient typing costs*	
NSW (including the ACT)	N/A	N/A	$2,605,572	Expenditure includes 2.1 Donor Coordinators and 2 State Search Coordinators. Tissue typing costs capture coordination and recruitment costs, and donor and patient typing (initial, extended and verification typing) costs (column B).
Victoria	$696,614	$419,530	N/A	Expenditure includes 2.4 Donor Coordinators and 1.8 State Search Coordinators. Initial typing is captured in donor recruitment costs. Column A costs capture extended and verification typing costs for donors. *This cost is estimated based on ARCBS advice on expenditure as a proportion of the state's tissue typing contract (which includes deceased and living organ typing activities).*
Tasmania	$129,676	N/A	N/A	Expenditure supports Donor Coordinators and initial tissue typing of donors.
South Australia (including the NT)	$114,083	$262,130	N/A	Expenditure supports one person acting as Donor Coordinator and Search Coordinator. Column A costs capture initial typing of donors. *This cost is estimated through ARCBS advice expenditure as a proportion of the state's tissue typing contract (which includes deceased and living organ typing activities).*
Queensland	$175,950	N/A	$1,415,986	Expenditure covers 1.8 Donor Coordinators. Column B costs cover initial, extended and verification typing of patients and donors, and cord blood unit (CBUs).
Western Australia	$220,000	*Unknown*	*Unknown*	Expenditure covers 2 Donor Coordinators
Commonwealth	$266,255	N/A	N/A	Contribution to State Search Coordinator roles (provided through the Core Services Agreement)
Total	**$1,602,578**	**$4,703,218**		

Source: State government responses to request for information and ABMDR financials. Victorian and South Australian tissue typing costs are approximated using ARCBS guidance on proportional expenditure, while NSW information is output-based expenditure for all bone marrow tissue typing (excluding cord blood typing). Queensland tissue typing expenditure includes all tissue typing for bone marrow patients and donors, including CBUs.

State governments support the State Search Coordinators, who initiate searches, match recipients with donors, and manage unrelated donor searches. Donor Coordinators, on the other hand, are located within the ARCBS in each state. They have a dual role, coordinating donors – including the contact, consent and welfare of identified donors – and recruiting new donors to the registry. The ARCBS estimates that Donor Coordinators spend approximately 75% of their time on coordination activities, and the remaining 25% recruiting.

7.2.2 ABMDR's operating expenses

The ABMDR's operating expenses have continued to grow, reaching just over $4.2 million in FY2015–16. Salaries and wages represent the largest proportion of spending, totalling $2.3 million in FY2015–16. Software and licensing costs increased by 53% to $139,611 in FY2015–16 from $91,175 in FY2014–15. An additional $358,510 was spent enhancing information technology (IT) in FY2015–16. Expenditure on the ABMTRR and NCBCN is also channelled through the ABMDR. However, it is not represented here, except for spending in FY2013–14 and FY2014–15 on the ABMTRR, which was previously partly drawn from the ABMDR operating budget. This spending has since been transferred to a streamlined contract with the Commonwealth.

Table 19: Breakdown of ABMDR operating expenses

Line item	FY2013–14	FY2014–15	FY2015–16
Staffing (17.1 FTEs)	$1,885,135	$2,404,230	$2,295,521
Accommodation	$51,950	$51,950	$52,710
International registry fees	$42,972	$36,668	$55,649
Other overheads (donor material, teleconferencing)	$14,979	$15,129	$15,871
IT costs (software licensing, enhancements, assets)	$357,700	$91,175	$498,121
Outcomes reporting (ABMTRR)	108,800	92,400	–
Depreciation and amortisation	$502,099	$625,221	$675,706
Consultancy and agency	$77,150	$7,600	$507,151
Other expenses	$202,935	$291,431	$134,367
Total	**$3,243,720**	**$3,615,804**	**$4,235,096**

Source: PwC HPC Sector Review Data Request – ABMDR financials

7.2.3 ABMTRR

Echoing the ABMDR's weighting of costs, ABMTRR's expenses are largely for staff salaries. In FY2015–16, the $0.3 million salary bill accounted for 88% of the organisation's costs. Efforts are largely focused on reporting, so resources are directed toward highly labour-intensive tasks. Roles include data coordinator, data analyst, senior statistician and database manager, which account for three full-time equivalent (FTE) staff. The ABMTRR's administration costs include IT expenses and ad hoc purchases such as stationary and printing. The Arrow Bone Marrow Transplant Foundation also endows $35,000 every second year for research activities.

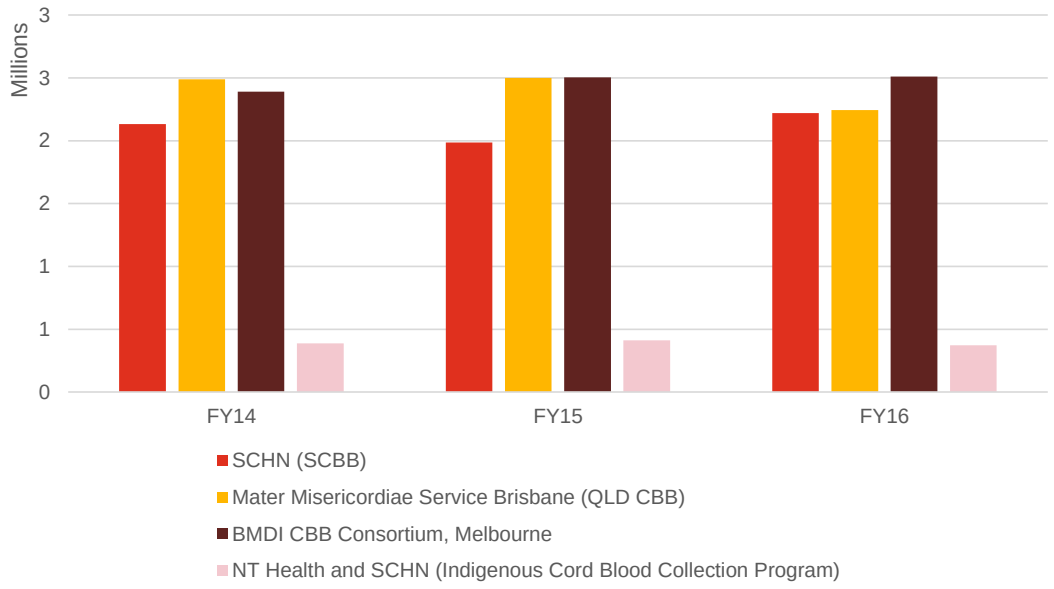
A separate review has been conducted into the sector's outcomes reporting. We concur with the review's findings that current staffing levels and funding are insufficient to deliver adequate reporting for the sector.

7.2.4 NCBCN

In FY2015–16, the NCBCN spent $7.3 million. The three CBBs incurred approximately similar expenses (between $2.2 million and $2.5 million), while an additional $371,849 was

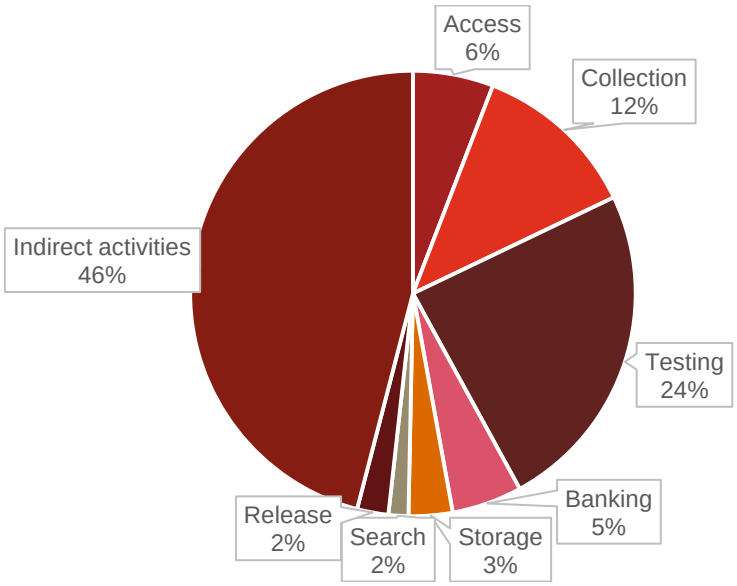
spent on the NCBCN's Indigenous cord blood collection program at the Royal Darwin Hospital.

Figure 78: NCBCN spending, by cord blood bank and financial year ($ millions)



As a previous review found, NCBCN expenses largely relate to operating activities, including capital expenditure, salaries, regulatory compliance, and training and oversight activities. In terms of effort, the NCBCN's leading activity is testing, followed by collection and cord blood banking. Capital expenditure, such as for replacing equipment and replenishing liquid nitrogen stocks, drive the overhead costs of CBBs. Salaries form the largest element of total costs, accounting for 58% of expenditure in FY2015–16. Over the last three financial years, of all the cord blood banks, the BMDI CBB spent the most on salaries.

Figure 79: Activity expenditure, FY2014–15



Source: Stage 2 Review of the NCBCN

7.2.5 Staffing in the sector

Workforce profile

The HPC sector is comprised of many hard-working individuals. Among those who support the delivery of unrelated donations for Australian patients, there are dedicated staff members at the ABMDR, the ARCBS, the ABMTRR, PathWest, Pathology Queensland, transplant centres and the CBBs. Together, there are nearly 102 FTE staff working across the sector to maintain the registry, support searches, coordinate donors, type blood samples, bank CBUs and report on outcomes. This excludes the many clinical staff who work with patients and the HPC sector to identify the right match so that a patient can have a transplant.

Table 20: Unrelated HPC sector workforce profile

Organisation and role	FTE
ABMDR	
Executive team	1
National Donor Coordinators	2.3
Accounts and operational staff	9.8
IT team	4
ARCBS	
Search coordinators	4.3
Donor Coordinators	8.75
PathWest	
Search Coordinators	2
Pathology Queensland	
Search Coordinators	1
Cord Blood Banks	
BMDI CBB	16.9
Queensland CBB	14.7
Sydney CBB	14.5
NT collection program	3
Transplant centres	
Transplant Coordinators	16
ABMTRR	3
Total	**101.5**

Source: PwC HPC Sector Review Data Request – ABMDR financials, State Government and Transplant Centre consultations, Stage 2 Review of the NCBCN, ABMDR Financials Draft Final Report – Outcomes Registry Review, provided by the Commonwealth.
Note: Transplant Coordinator roles may also support activities for related donations, as well as other activities in a transplant centre.

Allocation of staff expenditure

The ABMDR office is growing, with an additional 2.3 FTE staff joining between FY2013–14 and FY2014–15. The office expansion is managed against a backdrop of growing wages, which have increased the ABMDR's operating expenses. This effect is amplified by declining cost recovery fees from distributing HPCs to international patients. These fees provide the ABMDR with untied funds. To remedy this situation, the ABMDR has been forced to draw

additional funding under the NCBCN contract, to cover operating activities.[62] The ABMDR's core funding for its operating expenses appears to be insufficient to fulfil its functions of recruiting donors, and maintaining and managing the registry.

Search and donor coordination

Table 21 shows that the number of FTE staff working as State Search Coordinators and Donor Coordinators varies by state.

Table 21: Coordinator breakdown by state

	NSW	Qld	SA	Vic	WA	Total
Search Coordinators	2	1	0.5	1.8	2	7.3
Donor Coordinators	2.1	1.8	0.45	2.4	2	8.75

Source: ABMDR Final Report-2013-2014.pdf, End of financial year report ABMDR 2014-15.pdf, End of financial year report ABMDR 2015-16v2.pdf and ARCBS consultations

The ABMDR provides $266,255 from its Core Funding agreement with the Commonwealth to the ARCBS to fund State Search Coordinator positions. As reported in ABMDR's end-of-financial year report, which is required under its Core Funding agreement, this contributes to the cost of coordinator staff.

The states and territories pay the balance of funding for State Search Coordinators. We could not identify the exact amount paid to the ARCBS as this is embedded in contracts.

7.2.6 Expenditure on collections

The ABMDR funds transplant centres to collect HPCs for international patients as follows:[63]

- $1,141 for a donor work-up
- $2,141 for a peripheral blood or donor lymphocyte collection (including work-up)
- $3,976 for a bone marrow harvest (including work-up)
- $945 is also reimbursed to the ARCBS for donor expenses and a donor work-up information session. If the donor only participates in the work-up session, $420 is reimbursed.

Table 22 outlines the number of reimbursements made in the past three years, which mostly cover peripheral blood collections.

Table 22: Number of ABMDR reimbursements for collections made, by state, 2014–16

	Apheresis and work-up			Bone marrow harvest and work-up		
State	**2014**	**2015**	**2016**	**2014**	**2015**	**2016**
NSW	4	7	5		2	2
WA	2	8	6		1	1
Tas	1	1				
Vic	9	3	9	1	1	

[62] 'ABMDR End of Financial Year Report (Core Funding) for Commonwealth 2013–2014', 'ABMDR End of Financial Year Report (Core Funding) for Commonwealth 2014–2015' and 'ABMDR End of Financial Year Report (Core Funding) for Commonwealth 2015–2016'.

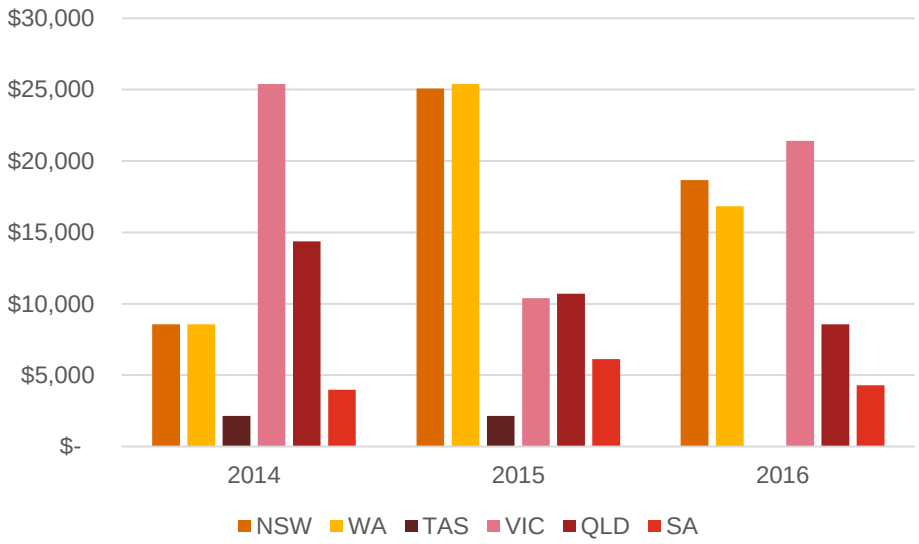
[63] 'PWC HPC Sector Review Data Request-Donor reimbursements 2014-16.xlsx', provided to PwC 19 April 2017.

	Apheresis and work-up			Bone marrow harvest and work-up		
State	**2014**	**2015**	**2016**	**2014**	**2015**	**2016**
Qld	3	4	4	2		
SA		1	2	1	1	
Total	**19**	**24**	**26**	**4**	**5**	**3**

Source: PWC HPC Sector Review Data Request-Donor reimbursements 2014-16.xlsx

In addition to HPC collections, three donors were worked up in Western Australia in 2014 and 2015, but did not proceed to collection. Another five donor lymphocyte collections were also reimbursed in 2014–16. Figure 80 shows the total reimbursements made to states (via transplant centres).

Figure 80: Reimbursements, by state 2014–16 (excluding ARCBS reimbursements)



Source: PWC HPC Sector Review Data Request-Donor reimbursements 2014-16.xlsx

However, data shows that ABMDR has not reimbursed transplant centres for all collections performed. In 2016, 29 collections were reimbursed but collections were undertaken for 41 international patients. Only $69,735 was reimbursed to transplant centres in 2016 for unrelated HPC activities. It is possible that transplant centres are not issuing invoices for collections or accounts are still being settled.

In addition to the collections not being reimbursed, the ABMDR does not cover the cost of the collections performed by transplant centres, which is estimated to be between $5,000 and $10,000. Appendix F provides an estimate of the costs associated with collections. As collections for domestic patients are covered by transplant centres under reciprocal arrangements, there is a risk that jurisdictions with more donors requested wear a disproportionate cost burden.

7.2.7 Expenditure on international HPC sources

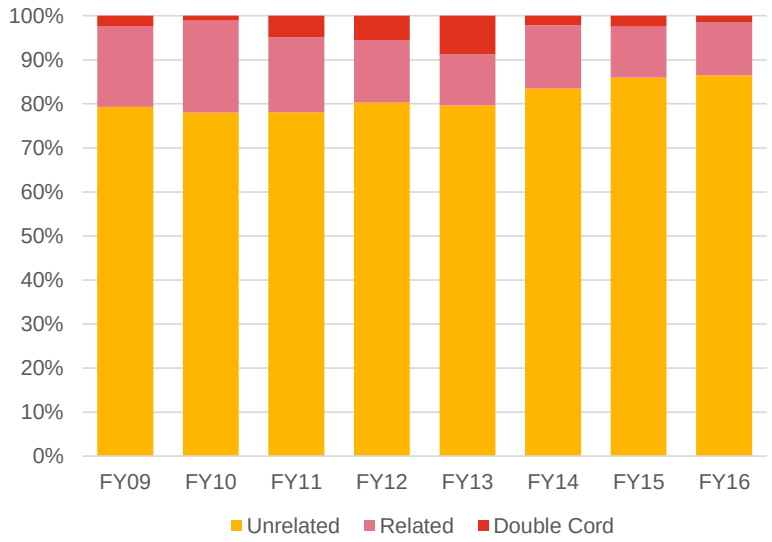
The ISP allows Search Coordinators to tap into global registries to identify potential matches. Once a donor has been identified and selected, the BMTP funds the collection and provision of HPCs from an international donor for an Australian patient. It is a demand-driven funding model, collectively known as the Haemopoietic Progenitor Cell Program (HPCP).

While the ISP's activities and associated costs are concerned with confirmatory testing and filtering of donors, BMTP expenditure reflects the realised number of collections. In FY2015–16, 734 ISP applications, at a cost of $1.7 million, and 347 BMTP applications, at a

cost of $11.6 million, were submitted to the Commonwealth. The growth in demand for international HPCs is driving expenditure on the program.

In the last eight financial years, 41% of ISP's searches have resulted in the collection of suitable HPCs for Australian patients. Of BMTP-approved applications, 82% have been for unrelated donors. For example, in FY2015–16, 734 ISP applications were made, but only 347 were submitted for BMTP support. This resulted in 42 related approvals, 300 unrelated and five double-cord units. Unrelated donors continue to represent the majority of overseas supply. Figure 81 shows a year-by-year breakdown of BMTP-approved activities.

Figure 81: BMTP-supported collections by donor relationship status



Source: HPCP Annual Report 2015-2016

Peripheral blood stem cells consistently represent the majority of HPCs collected, indicating a strong clinical preference for this extraction method. However, CBUs are often collected for patients who are unable to find a suitably matched donor. These figures are represented by double-cord blood data for adults and single CBUs for paediatric patients. The increased demand for double-cord units could indicate the increasing difficulty of finding donors on the Australian registry. In FY2013–14, BMTP received only six applications for double-cord units. The number tripled in FY2014–15, but declined to 10 requests in FY2015–16.

Clinicians may request donor lymphocytes as a secondary collection activity for patients who require lymphocytes for ongoing treatment post-transplant. Currently, Search Coordinators must submit separate applications for these collections, which partly distorts figures for the number of patients requiring transplant in the BMTP figures. In FY2015–16, there were 14 applications for donor lymphocytes.

Donor and patient locations

As part of its global network, the ABMDR accesses international donors once a patient's ISP application is approved. The application enables Search Coordinators to request extended and/or verification typing of potential donors, to inform clinical decision making. If an international donor is identified as a patient's most suitable match, the transplant centre will fill out a BMTP application to the Commonwealth to access funds for collecting and transporting the HPCs for the patient.

State-based analysis of internationally sourced HPCs

In 2015, BMTP requests were concentrated in NSW and Victoria. Figure 82 outlines the number of requests for international HPCs, by each state, in 2015. NSW initiated the most requests, representing 38% of all requests. Where a patient is unable to seek treatment in their home state, they must travel to a centre with the appropriate transplant facilities. For example, Victoria listed 84 transplants in which HPCs were sourced from international

donors. However, this number is inflated by patients from Tasmania who lodge BMTP requests from Victorian transplant centres. Similarly, NSW applications include patients from the ACT. South Australia also supports patients referred from the Northern Territory.

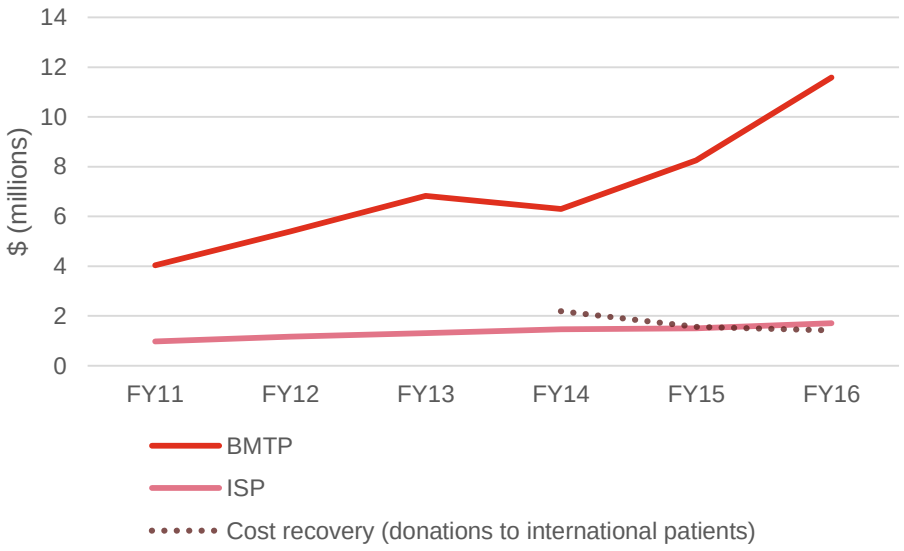
Figure 82: 2015 BMTP funding requests, by state

Source: HPCP Annual Report 2015-2016

HPCP expenditure

Spending on the HPCP has steadily increased over time. The collection of overseas units cost $11.59 million in FY2015–16, representing 87% of HPCP expenditure for the year. While FY2012–13 and FY2013–14 experienced a small decline in demand, the current trend appears to be growing steadily, with a 40.5% increase in expenditure in FY2015–16 from the previous year. Figure 83 illustrates this trends.

Figure 83: Cost of overseas donor programs



Source: Costs: HPCP Annual Report 2015-2016, Income: ABMDR Final Report-2013-2014.pdf, End of financial year report ABMDR 2014-15.pdf, End of financial year report ABMDR 2015-16v2.pdf

With demand growing for international HPCs, it can be difficult to calculate projected expenditure. We understand this means that, at times, the Commonwealth must seek additional funding to support the HPCP when applications spike. In its reporting, the Commonwealth prepares half-yearly and annual reports that capture how applications are trending and measures expenditure against appropriated funds. The ABMDR, which is responsible for ISP applications, also reports monthly to the Commonwealth on received and approved applications, to inform expenditure and as part of the ISP's monthly invoicing procedures.

Between FY2010–11 and FY2015–16, the BMTP spent an average of 3% more than its allocated funding. On average, the ISP underspent by 31%. However, in more recent years, the both the BMTP and ISP has been allocated more than it has spent.

Table 23: Percentage differences in HPCP's spending and allocated funding

Program	FY2010–11	FY2011–12	FY2012–13	FY2013–14	FY2014–15	FY2015–16
BMTP	7%	43%	9%	-16%	-6%	-20%
ISP	-18%	-20%	-35%	-35%	-35%	-42%

Source: HPCP Annual Report 2015-2016

BMTP program

Table 24 shows the breakdown of BMTP expenditure. The sums represent the largest portion of costs incurred, accounting for more than 80% of expenditure over three financial years. Commercial courier costs have increased by 237% since FY2013–14, totalling $1.21 million in FY2015–16.[64] Airline costs, on the other hand, are declining.

Table 24: BMTP expenditure breakdown, by financial year

Expenditure	FY2013–14	FY2014–15	FY2015–16
Collection costs	$4,708,000	$7,303,000	$9,559,000
Commercial courier costs	$359,000	$670,000	$1,210,000
Airfare	$502,000	$400,000	$316,000
Courier reimbursement	$90,000	$142,000	$55,000
Overseas expenses	$76,000	$94,000	$2,000
Living expenses	$56,000	$49,000	$35,000
Overseas tests	$2,000	$3,000	$5,000
Insurance	-	-	$1,000

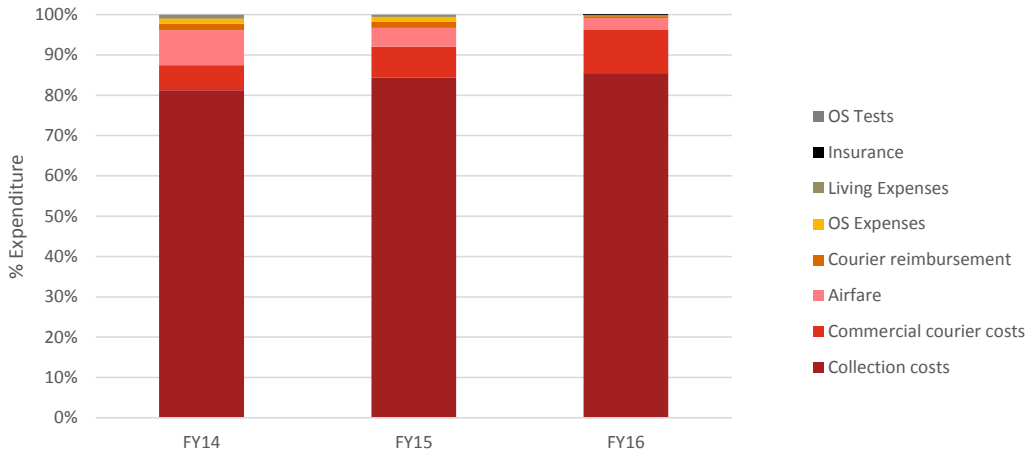
Source: HPCP Annual Report 2015–16

[64] *The ABMDR has a contract with a travel company to assist with booking international travel for couriers carrying international HPC donations for Australian patients. Travel Beyond manages the relationship with Qantas, which provides a special assistance service to the ABMDR, reserving two return flights for the courier in case of delays in collection/a need for expediency. Qantas also assists with clearance and carriage during the flight. Hospitals are able to access this service for couriering domestic HPCs to other domestic centres, but most hospitals make these arrangements directly. Commercial couriers used for international flights are based in Germany.*

Collection costs

The high costs of HPC collection itself is reflected in the proportional expense for collections under the BMTP (see Figure 84).

Figure 84: BMTP expenditure, by cost category (%)



Source: HPCP Annual Report 2015-2016

For Australian patients requiring international HPCs, the rate the ABMDR is charged depends on the country and the HPC type requested. Reciprocal agreements exist between the Australian and major registries, which set prices for different activities. For example, the cost of international donations of bone marrow can range from $21,000 for German donors to $48,000 for US donors. The ABMDR shared the costs for four countries that it relies on most frequently for collections (listing the price *Australia charge* to the international registry). Table 25 shows the average cost per activity listed in the agreements.

Table 25: Average cost of HPCs distributed to/from international registries (using ABMDR fee schedules)

HPC	Activity	Average $
–	Tissue typing	$323
Peripheral blood	Collection	$33,275
Bone marrow	Collection	$33,858
–	Verification typing	$773
–	Cancellation	$6,714

Source: ABMDR provided price lists: Fee schedule - DE Germany ZKRD 1 Jul 16.pdf, Fee schedule - NZ New Zealand 1 June 2015, Fee schedule - UK Anthony Nolan 1 June 2015, Fee schedule - US NMDP 1 August 2016, Note: costs are averaged across countries. Tissue typing is averaged across low and high resolution.

Collection costs are heavily affected by changes in exchange rates, and are reviewed and adjusted every few years. As these are the ABMDR's fees, these figures do not necessarily represent actual costs.

In addition, arrangements exist for accessing international CBUs and providing CBUs to international patients. Table 26 outlines the costs associated with CBUs for an Australian patient seeking a donor.

Table 26: Cost of international CBUs

HPC	Activity	Average $
Cord blood unit	Tissue typing	$223
Cord blood unit	Collection – single cord	$39,000

HPC	Activity	Average $
Cord blood unit	Collection – double cord	$58,000
Cord blood unit	Verification typing	$490
Cord blood unit	Cancellation	$3,900

Projected costs of internationally sourced HPCs

Under current trends, the proportion of international HPCs used in transplants for Australian patients is expected to grow.

The average cost per BMTP application over the past six financial years was $24,778, while an ISP application averaged $1,955. Using these averages and trends in applications for both the BMTP and ISP, the projected costs of each program is shown in Appendix F. In all, following current trends, the HPCP, as a whole, is expected to cost close to $20 million by 2029 if the level of reliance on international donors is not addressed.

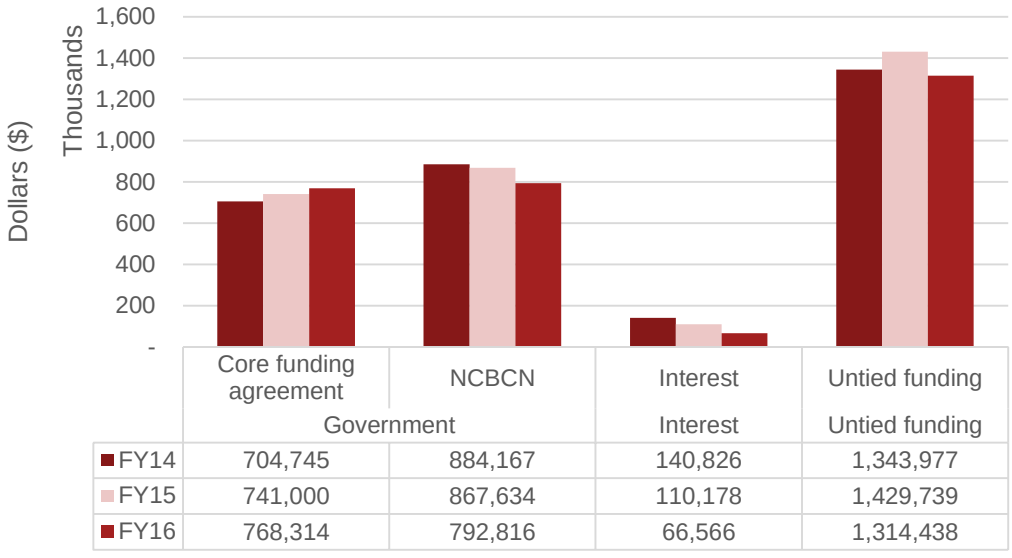
7.3 Revenue

7.3.1 Operational revenue

Over the past three years, Commonwealth Government funding provided through the core funding agreement, has grown. Overall, government revenue as a percentage of operational revenue for the ABMDR has increased from 51.1% in FY2014–15 to 53.1% in FY2015–16. Interest revenue is declining and made up only 2.3% in FY2015–16.

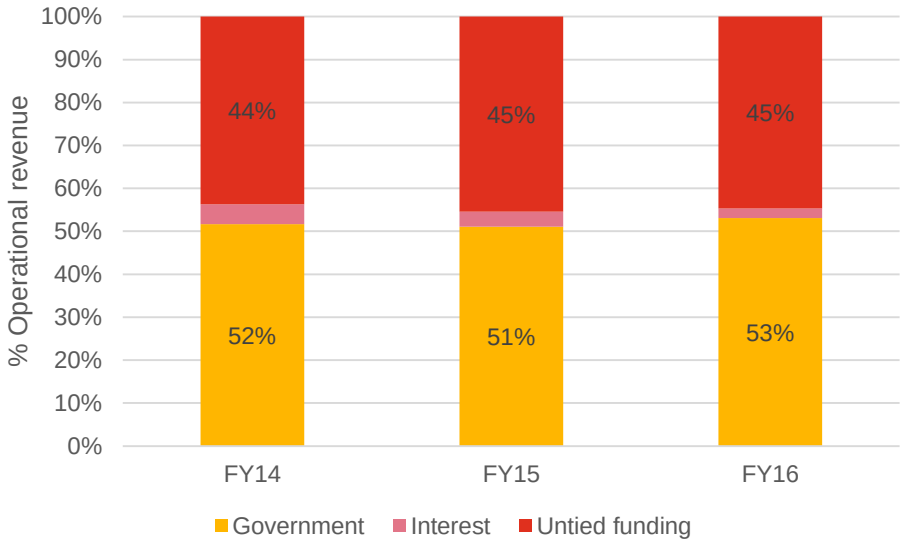
Untied funding, mainly from HPC cost recovery fees from international patients, accounts for a large portion of the ABMDR's income. The fees represented approximately $1.3 million in FY2015–16, or 44.7% of operational funds. However, this figure is inflated as the fees are cash flow to the ABMDR that it expends on invoices for collections and typing costs associated with Australian donors requested by international patients, which comprised an estimated $400,000 to $500,000 of flow-through expenditure in FY2015–16.

Figure 85: Line item view of ABMDR operating revenue



Source: 'PwC HPC Sector Review Data Request – Financials.docx'
Note: This excludes one-off payments, including IT revenue of $221,461 in FY2013–14, Enhancement revenue of $358,510 in FY2015–16 and alternate yearly donations of $30,000 in both FY2013–14 and FY2015–16

Figure 86: Breakdown of ABMDR operating revenue



Source: 'PwC HPC Sector Review Data Request – Financials.docx'

7.3.2 Cost recovery from providing HPCs to international registries

The number of HPCs distributed to international patients has steadily decreased over the last three financial years. With few Australian states typing new donors at high resolution, other registries are better positioned to provide more granular results upfront when searching for donor information. As high-resolution typing becomes widely used among international registries – its use is one of the main reasons Australian clinicians seek international donors – the number of Australian donors identified for international patients is declining.

However, due to Australia's diverse population, the ABMDR can provide HPC donations for international patients, which is a principal feature of collaboration. Just as Australia attracts fees when issuing search requests for an international donor, the ABMDR lists fees for tissue typing, verification typing and collection of cells for international patients. Price lists not only differ among activities but fluctuate between countries. Table 27 represents a selection of countries that receive Australian HPCs.

Table 27: HPC costs, by country, 2016

Country	Tissue typing (high resolution)	Peripheral blood collection	Bone marrow harvest	Verification typing	Single cord blood unit collection
Germany	$370	$20,770	$20,770	$585	$39,000
NZ	$300	$24,000	$24,000	$550	$39,000
UK	$555	$42,190	$42,190	$690	$39,000
US	$810	$46,140	$48,470	$1,265	$39,000

Source: Fee schedule - DE Germany ZKRD 1 Jul 16.pdf, Fee schedule - NZ New Zealand 1 Jun 15, Fee schedule - UK Anthony Nolan 1 June 2015, Fee schedule - US NMDP 1 Aug 16. Note: Double CBUs have been excluded from the calculation and attribution as individual units can be sourced from different countries

Cost recovery fees from HPCs distributed internationally is highly variable.

Australia charges the US the highest cost per collection for both bone marrow and peripheral blood (on average, $47,305). The US is also our primary destination for internationally distributed HPCs. The US is charged more per activity than any other country, including for high-resolution typing, which reflects the on-average higher collection fees the US charges Australia, compared to other countries. Countries are typically charged for tissue typing a

number of potential donors, verification typing of selected donors, collection of HPC units and cancellation fees if donors are worked up but no collection is made.

Price lists for each country are continually reviewed and updated. With the exchange rate variability, the true costs may vary significantly for each country.

New Zealand relies upon the Australian registry for donors as it does not have a representative registry itself

New Zealand also relies heavily on Australian donors and is the second-highest destination for Australian HPCs.

It is difficult to specify the level of funds received from internationally distributed HPCs, due to variations in each request, as well as the flow-through funding provided to tissue typing laboratories and transplant centres that perform the activities associated with the collection. However, we understand cost recovery fees account for approximately two-thirds of the ABMDR's operating expenditure.

Excluding fees for tissue typing and verification typing that would accompany a request, the average collection cost for a bone marrow harvest or peripheral blood collection is $34,754 (across the four fee lists PwC sighted). For the 41 collections from Australian donors bound for international patients in FY2015–16, this represents an estimated $1.4 million in cost recovery fees. For each collection made, Australian transplant centres are reimbursed $2,141. A further $945 is reimbursed to the ARCBS for donor expenses and a donor work-up information session. Together, this represents $3,086 reimbursed for each (on average), while $34,754 is recovered from international registries. In FY2015–16, this crudely represents almost $1.3 million of untied funding to the ABMDR.

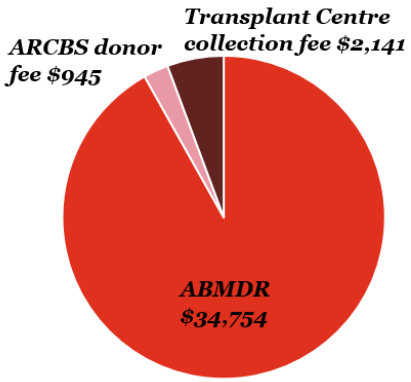
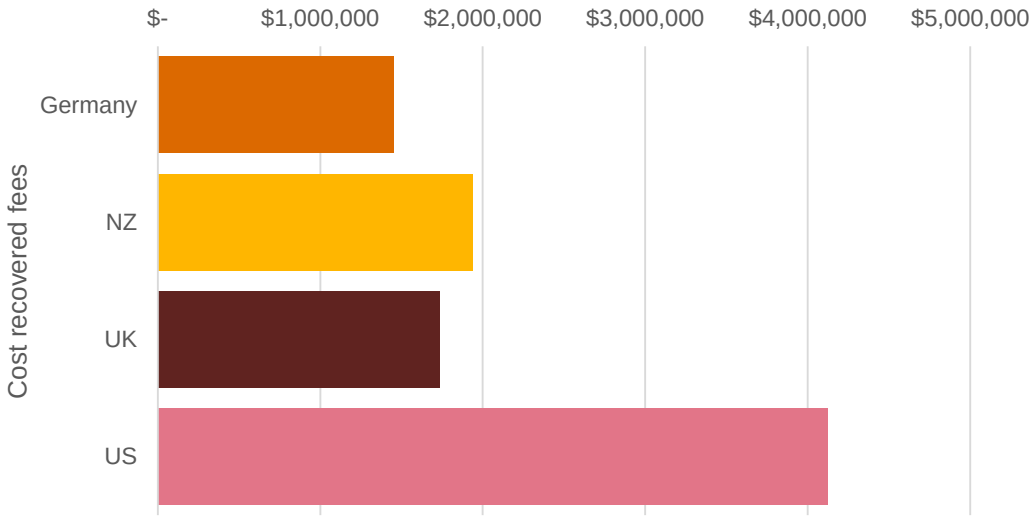


Figure 87: Potential cost recovery fees to the ABMDR from October 2013 to December 2016 from top destination countries (by cost of collection only, not accounting for foreign exchange or follow-on expenditure)



Source: ABMDR transplant dataset. 10/2013 – 12/2016. Note: Income has been calculated by multiplying total number of internationally distributed HPCs by the total cost of collection activity under the ABMDR fee list price.

Cord blood trust account

Unlike cost recovery fees for internationally distributed peripheral blood and bone marrow, fees accruing from distributing Australian CBUs are committed to the Cord Blood Trust. The Trust held $14,482,646 at 31 December 2016, and is reported against as part of the ABMDR

ledger.[65] Trust funds are available for use by the NCBCN, with the agreement of all Australian governments. The Commonwealth can authorise funding for up to $1 million, following consultation with the ahJHPCC. The Cord Blood National Management Committee can also refer proposals (accompanied by a business case) to access funds to the ahJHPCC for consideration. For funding requests above $1 million, authorisation is sought from the Hospitals Principal Committee. Funding is released in line with the priorities set for the Trust Account, which are:[66]

- for one-off costs of complying with regulatory requirements
- to offset or supplement government funding
- to implement new or upgrade existing IT systems that enhance search or data storage capacity and support more efficient and timely access to CBUs
- to implement or investigate strategies to improve efficiencies
- for one-off equipment purchases or to buy equipment required to harmonise processes between the CBBs
- for laboratory refurbishment and fit-out
- other one-off expenditure to improve access to CBUs.

The Cord Blood Trust has been accessed six times since it was established. Funds were released:[67]

- twice to offset government funding
- once to supplement government funding
- once to fund the Operational Alignment project ($1.78 million to standardise and alignment activities between the three CBBs)
- twice to support government reviews.

The Trust continues to grow as it accrues interest and internationally distributed CBUs produce income. Over the past six years, it has accrued almost $8 million.

7.3.3 Other sources of funding

In addition to cost recovery fees through government contracts and untied funding from internationally distributed HPCs, other non-government funding sources include:

- a $35,000 biannual endowment from the Arrow Bone Marrow Transplant Foundation to the ABMTRR for expenditure on specified research activities
- a $30,000 biannual gift to the ABMDR, which is used for research, only upon approval by the ABMDR's Gift Fund Committee.

The ABMDR is also supported by streams of in-kind support, including:

- approximately $44,000 per year of software support provided by the Microsoft Software for Charities program
- human resources, health, safety, recruitment, payroll, security, training, marketing and advertising services provided by the ARCBS

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[65] The Cord Blood Trust Account is not a 'Trust' in the legal sense, but is a bank account controlled solely by the ABMDR.

[66] Cord Blood Trust Account – Access and Priorities – AHMC agreed policy (D14-959799), provided by the Commonwealth Government.

[67] Cord Blood Trust Account Summary (D17-1460069), provided to PwC by the Commonwealth Government.

- phone, internet, desktop and server housing and connection support provided by the ARCBS
- subsidised rent through the ARCBS. The ABMDR spent a little over $50,000 in FY2015–16 on rent and outgoings.

8

Future opportunities

This chapter covers...

- *an assessment of the optimum size of Australia's registry*
- *the cost impact of growing the registry.*

Key messages:

The optimum size of a donor registry is one that is 'fit for purpose', meaning the characteristics of its donors and the number of donors support clinical needs. A registry's recruitment approach influences the former, while the latter relies on recruiting enough donors to meet the quantum required to improve matching outcomes. The 'right size' of a registry has been considered by a number of countries. Leveraging the UK's approach, this review considered the potential impact of having several registries of different sizes on haemopoietic progenitor cell (HPC) sources for Australian transplants.

The Australian Bone Marrow Donor Registry (ABMDR), through the NMDP Bioinformatics Services, analysed the Australian registry in 2016 to assess the match probabilities for patients across Australia's top 10 ethnic groups. This information was used in this assessment.

Given Australia's population size and diminishing return on increasing the match probability, the current size of the registry appears to align with our domestic needs. This conclusion also reflects the marginal return on the significant investment required to grow the registry (measured as a net cost per additional domestic transplant facilitated). Improving the availability of existing donors and better aligning the profile of donors – generally female, older and concentrated among certain ethnic groups –with clinical needs would both bring gains.

Additionally, in line with the Stage Two Review of the National Cord Blood Collection Network (NCBCN), the current size of Australia's cord blood unit (CBU) inventory is likely sufficient to support Australia's ongoing needs. However, there is a need to focus on enhancing the quality of CBUs available. This could include limiting collections to higher-quality units, enhancing the human leukocyte antigen (HLA) diversity of any newly banked units and undertaking a stocktake of non-compliant CBUs and CBUs that are unlikely to be used.

8 Future opportunities

8.1 What are Australia's future needs?

Previous chapters of this review explored the current registry make-up and clinical preferences for HPCs. The registry has 170,791 donors, and our analysis found that 64% are female, with an average age of 45.

Our analysis found that 57% of requests for further typing are for male donors on the Australian registry. When a match is found, male donors are used in 76% of transplants for Australian recipients. The average age of Australians who go on to donate is 37.5, while international donors for Australian transplants are younger, with an average age of 32.2. This demonstrates a mismatch between the average characteristics of donors on the registry and those selected for transplant. The misalignment of donors with the clinical needs of patients is also reflected in the fact that 72% of all transplants in Australia use international HPCs.

Stakeholders in this review also identified that Australia's registry profile diverges from clinical preferences. In addition to being predominantly female and older, 71% of donors on the registry were typed at low resolution only, meaning clinicians do not have upfront information to support their decision making. Consistent with our findings, in its recent draft strategy for unrelated donors, the ABMDR defined an optimum donor as someone aged below 30, ideally male, with high-resolution tissue typing, and who is available immediately to clinicians.[68]

An analysis of donor ethnicity on the registry was also conducted and found that the majority were Caucasian. While ethnicity is not a definitive measure of haplotype diversity, it is a proxy for the diversity and alignment of the registry to the general population. Some ethnic groups are underrepresented, suggesting that the ethnic diversity of the registry needs to be enhanced to improve patients' chances of being matched to a donor.

Therefore, donor registries have two requirements: they must be fit for purpose in terms of the characteristics of donors and the number of donors needed to support clinical needs. The former point is largely influenced by a registry's recruitment strategy, including whether it uses direct marketing and engages donors, as well as the tissue typing laboratory it uses to test donors. The latter point relies on recruiting enough donors to meet the quantum required to improve matching outcomes.

To calculate the 'ideal number of donors', in the early 1990s, the ABMDR performed an analysis that concluded 100,000 donors would support Australia's needs.[69] During our review, we considered the suitability of the registry's current size, given the significant population growth and demographic changes since the 1990s. Our approach to determining the ideal size of the registry to meet future needs is consistent with international studies.

8.2 Considerations for 'the right size registry'

As previous chapters demonstrated, the optimum size for a registry means different things in different countries. For some countries, a homogenous population can mean that a registry needs fewer donors to capture a representation of genetic diversity. For others, due to changing demographics around migration and family structures, a larger registry is needed to capture a broader genetic profile if the principle of self-sufficiency is to be achieved. For countries with a diverse population, like Australia, registries often focus on 'replicating the

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68 ABMDR *Unrelated HPC sourcing strategy* (Version 1.2, 10 May 2016), provided by the ABMDR.

69 ABMDR *Unrelated HPC sourcing strategy* (Version 1.2, 10 May 2016), provided by the ABMDR.

face' of the country. They do this to try to provide the best possible representation of all ethnic groups, increasing the chances of achieving a match.

While demand for HPCs in Australia is expected to grow, the demand effect does not drive registry size. This is because the number of transplants performed is far fewer than the number of potential donors and so, unlike a traditional supply–demand analysis, it is not correlated in this way. Instead, assessing the probability of finding a match against a growing registry is a better approach to determining the right registry size. In this way, the likelihood for matching ethnic groups represented in the community can be considered when determining an appropriate size.

However, due to the complexity and diversity of genetics, there is no ideal registry size that will provide a 100% guarantee that everyone can find a perfect match. Additionally, without requiring the whole population to enrol – and accounting for the very young, very old and the unwell – the registry will always be smaller than the total population of the country. This means that the optimum size for a registry will be the point at which marginal returns on probability are reached (that is, adding more donors will provide only a small increase in the chance of a match), and adding many more donors will be less cost-effective.

Instead, in keeping with international approaches, it would be better to improve the presence of underrepresented ethnic groups on the registry and increase its size to strengthen the chance of achieving a match.

8.3 Best fit approach to defining Australia's optimum supply

To determine an approach for quantifying the effect of different registry sizes, the review examined methods used by other registries worldwide. Each approach had common themes, including the need to:

- assess the likelihood of a patient finding a match within a registry
- consider the level of unmet demand
- assess the trade-offs for different registry sizes (often guided by the cost-effectiveness of growing the registry).

Appendix G provides an outline of the approaches considered.

In consultation with the ABMDR, this review identified that the NMDP Bioinformatics Service analysed the Australian registry in 2016, assessing the probability of finding a match for the top 10 ethnic groupings on the registry. The ABMDR kindly provided its findings, which this review used to establish the probability of finding a match on a number of modelled registry sizes.

The NMDP's analysis considered 10 ethnicities that were adequately represented on the current Australian registry. The NMDP used genetic mapping to define the ethnicities, which were NCAU (Northern Caucasian); NWCAU (North West Caucasian); Jewish; NCAU-SCAU (Northern-Southern Caucasian); Sri Lankan; Aboriginal; Chinese; Indian; Middle Eastern and SCAU (Southern Caucasian). PwC has drawn on the probability assessments to judge relative transplant outcomes across different registry sizes for these ethnicities. This approach maps Australian Bureau of Statistics population data (taken from the Census) to the NDMP ethnicities to assess their likelihood of finding a match (being a 7/8, 8/8, 9/10 or 10/10 match) (see Appendix G for further information on this approach and how ethnicities were defined).

The NMDP determined ethnic grouping by clustering the 902 unique ethnicities into 10 broader ethnic groups. Each group had to have a minimum sample size of 500 donors typed at human leukocyte antigen (HLA) -A (HLA-A), -B and –DRB1. An algorithmic assessment was performed on haplotype frequencies among the nearly 60,000 donors in these 10 groups, to resolve ambiguity in the haplotypes and assess the probability of achieving a

match. The NMDP then assessed the genetic distance of haplotypes among groups to determine cross-matching opportunities (that is, the ability to match a patient of a given ethnicity to a donor from a different reported ethnicity).

Because the minimum sample size was 500, the NMDP were unable to assess the matching probability for many ethnicities, due to their smaller representation (for example, the NMDP identified 350 populations with only one donor).

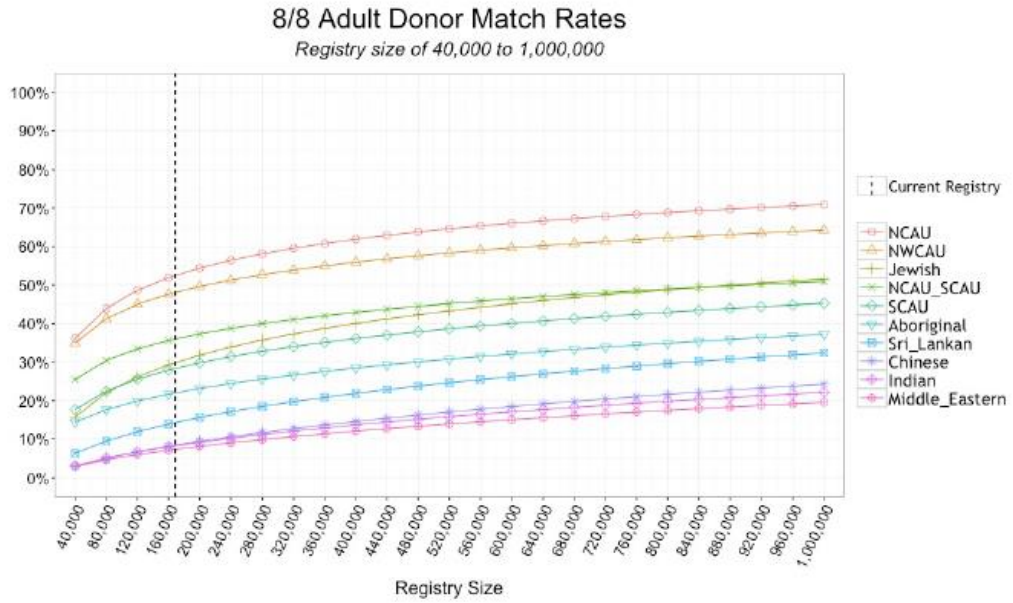
Based on the above, four caveats to our analysis should be considered:

1. The 10 ethnic groups only represent 97% of the registry (in absolute terms), according to our mapping of donors and their self-reported ethnicities against the NMDP's 10 ethnic groups. Accordingly, further expert analysis is required to assess the likelihood of finding a match among ethnic groups not represented. Additionally, many donors don't have a reported ethnicity; therefore, the haplotypes of these donors have not been considered by the NMDP or in the following analysis.[70] As such, this analysis is quite limited and should be considered as a high-level guide of the suitability of the registry against the population's needs.
2. Ethnicity is used as a proxy to identify a suitably matched donor; however, the probability of identifying a match for a particular patient will depend on their genetics.
3. This review has drawn on the NMDP's modelling outputs, which assume 100% donor availability and identify the highest potential match probability of an individual in a given ethnic group (that is, a match within their own ethnic group, although for some, a match may be identified from a different ethnic group). While the NMDP did model for 75% donor availability and for matching among other ethnic groups, for reasons of simplicity, these analyses were not drawn on (as the best possible scenario will be captured by 100% donor availability, and matching a patient's and donor's ethnic group).
4. Registry growth is based on the current registry profile (its population size and composition). This means that larger registries will be proportional to the current registry composition (that is, being largely comprised of Caucasian donors) and have not been adjusted for a changing demographic (that is, changing ethnicities within the population and those enrolling to the registry).

Figure 88 shows an example of the NMDP's modelling outputs.

[70] Almost 35,000 registered donors do not have ethnicity listed on the registry.

Figure 88: NMDP modelled 8/8 match rates for different registry sizes



Source: ABMDR NMDP Models Report (2016), kindly provided by the ABMDR with the permission of the NMDP Bioinformatics Services

8.4 Registry size scenarios

Given the current representation of ethnic groups on the registry and the number of individuals of those group's within the Australian community, for some ethnicities a very large number of those communities would need to be enrolled to support larger registry sizes if the registry were to reflect the matching outcomes modelled. A comparison between the ethnicities captured by the ABS against the ABMDR ethnic groups is shown in Appendix G.

Given Australia's population size and diminishing return on increased match probability, the current size of the registry appears aligned with our domestic needs. Additionally, while matching outcomes improve and our reliance on international donors reduces with larger registry sizes, the current costs of recruiting and typing new donors to the registry are significant, meaning that there appears to be limited economic value in supporting recruitment strategies focused only increasing the registry sizean enhanced recruitment strategy much above the current registry size. However, gains might be found in addressing rates of donor availability and in targeting recruitment of donors to better align with clinical preferences.

To judge the differences in outcomes for different registry sizes, the theoretical distribution of transplant types that would proceed has been assessed. This approach leverages the analysis undertaken in the UK, which sought to estimate the number of additional transplants facilitated by different registry sizes. This analysis was undertaken under the current registry size of ~160,000, as well as registry sizes of 240,000, 400,000, 720,000, 1,040,000, 1,520,000 and 2,000,000. Figure 89 shows the approach used, which is explained below.

Figure 89: Approach to assessing the relative gains of different registry sizes

1. Understand current number of transplants performed

To provide a baseline against which registry gains can be assessed, the total number of transplants performed and their source was considered. Information about the number of transplants that have proceeded and patient ethnicity is held in separate datasets that aren't linked. Because of this, the number of transplants and transplant type for each ethnic group has been inferred, to develop the baseline in the following way.

The ABMDR data on patients with self-identified ethnicities (between 2013 and 2016) was analysed first and these ethnicities were allocated to the 10 NMDP ethnic groups. The data was assessed for information the ABMDR had recorded on the number of transplants facilitated by domestically sourced or internationally sourced HPCs.

Of the 222 domestic HPC transplants with ethnicity reported in 2013–16, the relative percentages for each NMDP ethnic group were identified.

Table 28: Distribution of domestic HPCs across NMDP ethnic groups, 2013–16

	NCAU	NWCAU	Jewish	NCAU-SCAU	Sri Lankan	Aboriginal	Chinese	Indian	Middle Eastern	SCAU	Other
Percent	10.4%	76.1%	3.6%	1.8%	0.0%	2.7%	1.4%	0.0%	0.9%	1.8%	1.4%

Source: PwC analysis of ABMDR data

Of the 475 domestic transplants that used international HPCs in 2013–16, 134 (28%) did not list a patient ethnicity. For the remaining 341, the percentage in each NMDP ethnic group was again analysed.

Table 29: Distribution of international HPCs in NMDP ethnic groups, 2013–16

	NCAU	NWCAU	Jewish	NCAU-SCAU	Sri Lankan	Aboriginal	Chinese	Indian	Middle Eastern	SCAU	Other
Percent	5.3%	68.9%	3.2%	6.7%	1.5%	0.0%	2.3%	1.5%	2.6%	2.9%	5.0%

Source: PwC analysis of ABMDR data

The Australasian Bone Marrow Transplant Recipient Registry (ABMTRR), which records the total number of transplants that have proceeded, was then drawn on to re-establish the baseline, including how many of the domestic transplants were perfectly matched and how many were mismatched. Using 2015 data, the following was used to establish the baseline.

Table 30: Key assumptions and inputs, ABMTRR data, 2015

HPC type	Number	Source
International donor transplants	219	ABMTRR Matched unrelated HPC report *Assume distributed as per ABMDR distribution of transplants across ethnicities*
Cord blood unit (CBU) donor transplants	41	ABMTRR Matched unrelated HPC report 2015, Adult + Paediatric, single + double cords *Assume equally distributed across all ethnicities*
Domestic donor	91	ABMTRR Matched unrelated HPC report, 2015

transplants		*Assume distributed as per ABMDR distribution of transplants across ethnicities*
Percentage identical	0.88	ABMTRR Annual Data Summary, 2014 and 2015 *Assume each ethnicity has this ratio of HLA-identical transplants (from domestic donors)*
Percentage mismatched (of any kind)	0.12	ABMTRR Annual Data Summary, 2014 and 2015 *Assume each ethnicity has this ratio of HLA-mismatch transplants (from domestic donors)*

With ABMTRR data from 2015, the total number of transplants and their source (international, CBU, domestic, identical and mismatched transplants), and the percentage of transplants for each ethnic group (from ABMDR data) were used to establish a current state distribution of HPC transplants as represented in Table 31. Paediatric transplants are not assessed separately and are captured in totals.

Table 31: Current state distribution of HPCs across ethnic groups, 2015

HPC source	NCAU	NWCAU	Jewish	NCAU-SCAU	Sri Lankan	Aboriginal	Chinese	Indian	Middle Eastern	SCAU	Total
CBU	3	3	3	3	3	3	3	3	3	3	28
International	12	151	7	15	3	0	5	3	6	6	208
Domestic: identical	8	61	3	1	0	2	1	0	1	1	79
Domestic: mismatch	1	8	0	0	0	0	0	0	0	0	11
Total	24	223	13	19	6	5	9	6	9	11	326

Source: PwC analysis of ABMDR and ABMTRR data

2. Adjust total demand

As the total number of transplants that proceeded only indicates supply that has been fulfilled, the baseline for each ethnicity is adjusted to account for unmet demand.

This review was not able to capture exact information on unmet demand for patients seeking a match but who didn't succeed, because it is not regularly reported upon. Instead, this review relied on research studies[71] that have considered a supply gap, identifying that between 2% and 5% of donors have a unique phenotype not represented in the global database. Drawing on this research, and anecdotal information obtained from our stakeholder consultations, it's assumed that 2% of patients seeking a match currently do not identify one.

In assessing how registry size affects transplant outcomes, the UK undertook a similar analysis; however, it drew on a sample study of patients that identified a much larger unmet need. As there was no evidence for this size of unmet need in Australia, the assumption that 2% of patients do not identify a match was adopted. Additionally, our approach may not properly capture discrepancies among ethnic groups, as there is likely to be greater unmet demand among underrepresented ethnicities compared to those well represented on the registry.

[71] Tiercy JM (2012) Unrelated Hematopoietic Stem Cell Donor Matching Probability and Search Algorithm *Bone Marrow Research* Volume 2012.

Table 32 shows the adjusted baseline, accounting for unmet demand. Note that numbers have not been rounded in this analysis. This is due to the small numbers being handled and the effect of compounding rounding, which would skew the analysis.

Table 32: Adjusting for unmet demand

HPC source	NCAU	NWCAU	Jewish	NCAU-SCAU	Sri Lankan	Aboriginal	Chinese	Indian	Middle Eastern	SCAU	Total
Total with unmet demand	24.4	228.7	13.5	19.7	6.2	5.4	9.4	6.2	9.6	11.1	334.2

Source: PwC analysis

3. Assess number of theoretical domestic HLA-identical matches

Taking the total demand for each ethnic group (based on the sum of CBUs, international, domestic identical, domestic mismatched and unmet demand), the number of patients who should theoretically receive an identical match (8/8) is assessed using the NMDP's modelled match probabilities for each registry size.[72] Table 33 shows an extract of the theoretically domestic matched 8/8 patients for a registry of 240,000. This shows that, for example, of the 24.4 NCAU patients needing a match, 13.8 are matched to an identical domestic donor in a registry with 240,000 donors.

Table 33: Theoretical domestic HLA-mismatch matches, 240,000 on registry

HPC source	NCAU	NWCAU	Jewish	NCAU-SCAU	Sri Lankan	Aboriginal	Chinese	Indian	Middle Eastern	SCAU
Patients who get an 8/8 domestic match	13.8	117.2	4.6	7.6	1.1	1.3	1.0	0.6	0.9	3.5
Patients who do not get an 8/8 domestic match	10.6	111.5	8.9	12.1	5.1	4.1	8.4	5.5	8.8	7.6

Source: PwC analysis

4. Assess number of theoretical international HLA-identical matches

Acknowledging that a clinician is likely to consider international donors if an identical donor cannot be found in Australia, it is assumed that 65% of patients who do not find an identical domestic donor will identify an identical international donor (this is based on 2015 ABMTRR figures, which identify that 62.4% of all transplants used an international donor). This also reflects the findings in this review that many clinicians opt for international donors. Applying this to the same 240,000 registry size scenario as above, of the 10.6 NCAU patients who did not find an identical domestic match, 6.9 would be matched to an international donor.

[72] Matches out of 10 are not assessed as the clinical standard (and the ABMTRR's reporting standard) for an identical match is out of 8, so, an out-of-10 analysis may overrepresent the number of identical (10/10) transplants proceeding.

Table 34: Theoretical international HLA-identical matches, 240,000 on registry

HPC source	NCAU	NWCAU	Jewish	NCAU-SCAU	Sri Lankan	Aboriginal	Chinese	Indian	Middle Eastern	SCAU
Patients who get an identical international match	6.9	72.5	5.8	7.8	3.3	2.6	5.5	3.6	5.7	5.0
Patients who do not get an identical international match	3.7	39.0	3.1	4.2	1.8	1.4	2.9	1.9	3.1	2.7

Source: PwC analysis

5. Assess number of theoretical domestic HLA mismatches

Of the patients who didn't receive a theoretical HLA-identical match (domestic or international), the number who should theoretically receive a domestic mismatch (7/8), again using the NMDP's match probabilities against each registry size, was assessed.

Using the 240,000-registry size scenario, 3.4 of the 3.7 NCAU patients who were not matched to an identical domestic or international match would theoretically be matched to a domestic 7/8 match.

Table 35: Theoretical domestic HLA-mismatch matches, 240,000 on registry

HPC source	NCAU	NWCAU	Jewish	NCAU-SCAU	Sri Lankan	Aboriginal	Chinese	Indian	Middle Eastern	SCAU
Patients who get a 7/8 domestic match	3.4	34.3	2.3	3.3	1.0	0.9	1.3	1.0	1.4	1.9
Patients who do not get a 7/8 domestic match	0.4	4.8	0.8	0.9	0.8	0.5	1.7	1.0	1.7	0.7

Source: PwC analysis

6. Donor unavailability

However, for each match identified, not all donors would be available to donate due to their health, pregnancy or personal circumstances. It is assumed that 25% of identified donors do not proceed to donation. This is a conservative estimate, given this review's findings that the average availability of Australian donors at the verification typing stage is only 33%.

Using the 240,000-registry size scenario, the revised-down estimates for transplants that would take place with domestic identical or mismatched donors, or with an international donor, are outlined in Table 36.

Table 36: Theoretical initial matches, 240,000 on registry

HPC source	NCAU	NWCAU	Jewish	NCAU-SCAU	Sri Lankan	Aboriginal	Chinese	Indian	Middle Eastern	SCAU
Total 8/8 domestic transplants	10.3	87.9	3.4	5.7	0.8	1.0	0.7	0.5	0.7	2.6
Total 7/8 domestic transplants	2.5	25.7	1.7	2.5	0.8	0.7	1.0	0.7	1.0	1.5
Patients who get an identical international match	6.9	72.5	5.8	7.8	3.3	2.6	5.5	3.6	5.7	5.0
Domestically matched patients now without a donor (total)	4.6	42.6	2.5	3.7	1.3	1.1	2.2	1.4	2.3	2.1

Source: PwC analysis

7. HPC substitution

30% of remaining patients are assumed to be matched with CBUs

70% of remaining patients are assumed to be matched with international donors

The patients who are not matched, or their donor is unavailable, are then assumed to be matched with a CBU or an international donor (perhaps, a mismatched international donor but it could also be an identical donor who wasn't first identified in international searches).[73] It is assumed that 30% of these patients would be matched to a CBU and the other 70% would be matched to an international donor. This is based on a broad assumption from the ABMTRR's 2015 data that, of the 260 transplants that proceeded with either an international donor or CBU, 84% used an international donor and 16% used CBUs. Given some patients in this analysis were already matched to an international donor, Table 37 represents the additional international matches made at this step and the total international matches (including the previous identical international matches assessed). Note that CBUs can be sourced domestically or internationally.

Table 37: HPC substitution for unmatched patients, 240,000 on registry

HPC source	NCAU	NWCAU	Jewish	NCAU-SCAU	Sri Lankan	Aboriginal	Chinese	Indian	Middle Eastern	SCAU
CBU	1.4	12.8	0.8	1.1	0.4	0.3	0.7	0.4	0.7	0.6
International (additional)	3.2	29.8	1.8	2.6	0.9	0.7	1.6	1.0	1.6	1.5
Total patients matched to an international donor (identical and mismatched)	*10.2*	*102.3*	*7.6*	*10.4*	*4.2*	*3.4*	*7.0*	*4.6*	*7.3*	*6.4*

Source: PwC analysis

[73] Note: No distinction is attempted between the proportion of international matches that are identical or mismatched, due to the absence of data that would provide this granularity. Anecdotally, international matches are typically identical matches. Some international searches can be delayed due to the need to undertake extended/verification typing or to search additional databases, which can mean that not all potential international donors are identified upfront. Additionally, CBU information is not broken down into domestic or international sources in outcomes reports.

Matching to a CBU

CBUs also provide an integral and important source of HPCs to Australian patients. While they are important, it should be noted that CBUs are not explicitly considered in respect of matching rates in this analysis for three reasons. First, CBUs are typically matched as 6/6, 5/6 or 4/6 matches. While matching levels are changing, it is difficult to establish the differences between 8/8 matching for donors as compared to 6/6 matching for CBUs in a comparable way. Second, the needs of patients for whom clinicians are seeking a CBU match are often different and third, this Review is not aware of any contemporary studies that have assess the match probabilities of the Australian inventory that would enable easy incorporation against the NMDP's modelling work. For this simple analysis, CBUs have therefore been considered through the lens of an assumption rather than attempting to assess matching rates. Expert analysis is required to establish the probability of being matched to an Australian CBU.

8. Unwell patients

A number of patients who identify a match for transplant will be unable to proceed due to their disease progressing or being too unwell to undergo a transplant. It is assumed that 2.5% of matched patients do not proceed to transplant.

The UK estimates that 12% to 33% of unwell patients who are matched don't proceed to transplant. However, as the unmet demand is unclear (and could include unwell patients), a lower assumption is adopted, acknowledging that this figure may be higher in Australia.

Table 38: Summary of transplants that proceed (accounting for patient who don't proceed due to disease progress or patient being too unwell), 240,000 on registry

HPC source	NCAU	NWCAU	Jewish	NCAU-SCAU	Sri Lankan	Aboriginal	Chinese	Indian	Middle Eastern	SCAU
Total 8/8 domestic transplants	10.1	85.7	3.3	5.6	0.8	1.0	0.7	0.5	0.6	2.6
Total 7/8 domestic transplants	2.5	25.1	1.7	2.4	0.8	0.7	0.9	0.7	1.0	1.4
Total CBU transplants	1.4	12.5	0.7	1.1	0.4	0.3	0.7	0.4	0.7	0.6
Total international transplants	9.9	99.7	7.4	10.1	4.1	3.3	6.8	4.5	7.1	6.3

Source: PwC analysis

Findings of analysis

Undertaking the analysis (steps 1 to 8 above) over the current state transplant distribution for different sized registries provides the outputs shown in Table 39 and Figure 90. They show that with a growing registry, more domestic than international donors would be selected.

Table 39 shows that for the same registry size as the baseline (~160,000), theoretically, there would be far less reliance on international donors and CBUs, and more domestic matches. Potential reasons for this outcome include:

- improving the current registry to increase the probability of finding a domestic (identical or mismatched) match. For example, based on the registry's current size, our model shows that 50 additional domestic transplants, including 23 HLA-identical transplants, should be available. Improvements to the registry could include clinicians having access to better information upfront, and higher-quality donors (younger and/or male donors). However, the gap between current availability

and our analysis may also be explained by limitations in this analysis, such as it focusing on the 10 ethnic groups assessed

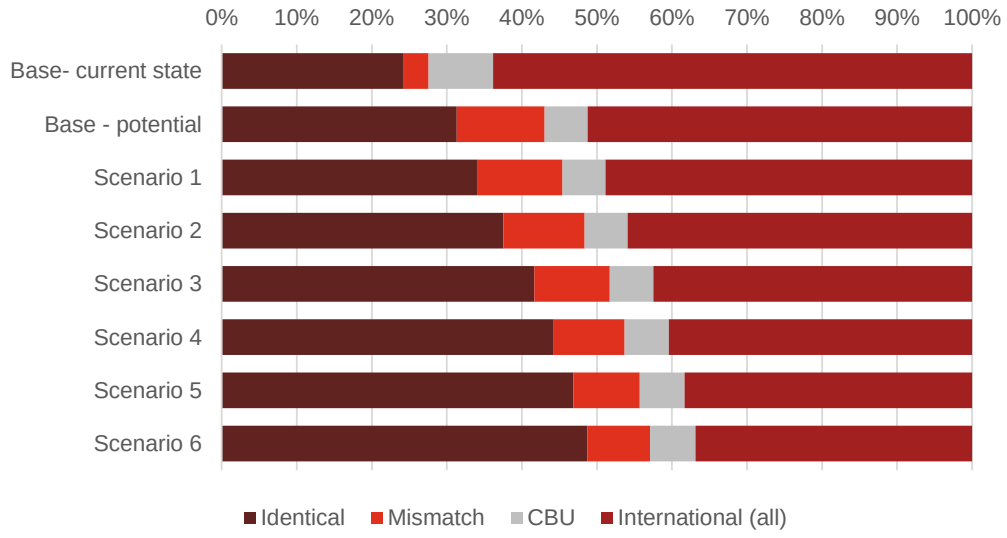
- the effect of matching to CBUs, which is not well understood. There are likely to be cases where a clinician opts for a CBU over a mismatched donor; for example, when treating a paediatric patient. As such, it is a limitation of our model that it is likely that matching to CBUs is underrepresented.

Another important point not explored here is the impact of haploidentical (half-matched) transplants on demand. Definitive data is unavailable in Australia on how many haploidentical transplants proceed, so this is not incorporated into the model. However, increasingly, clinicians are opting for this type of treatment over other options. For this reason, this review is generous in its assessment of mismatches, which is a proxy of sorts for non-identical matches, including haploidentical transplants.

Table 39: Transplant outcomes for n/8 donor-matching scenarios

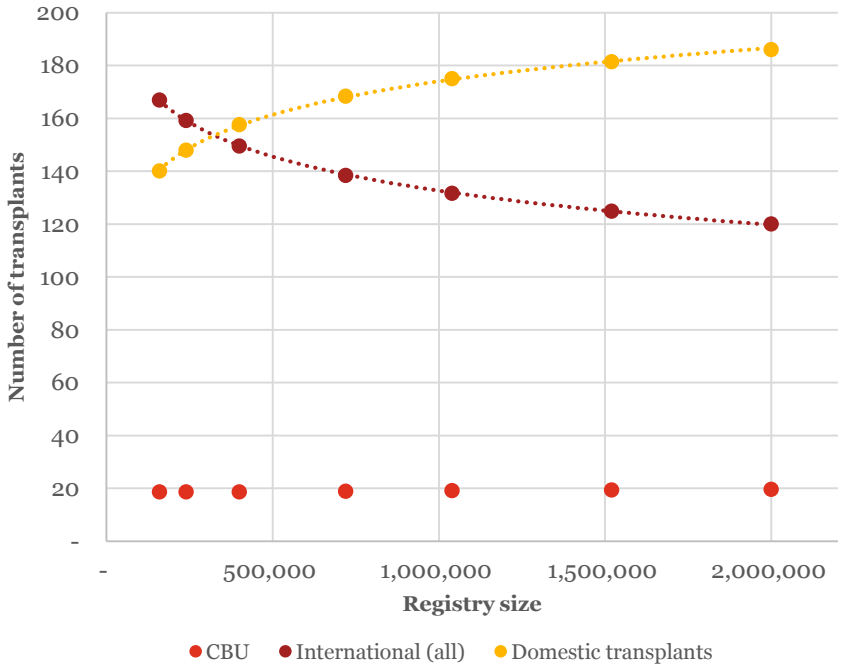
Scenario	Registry size	Domestic (identical)	Domestic (mismatch)	CBU	International	Total
Base – current state	160,000	79	11	28	208	326
Base – potential	160,000	102	38	19	167	326
Scenario 1	240,000	111	37	19	159	326
Scenario 2	400,000	122	35	19	150	326
Scenario 3	720,000	136	33	19	138	326
Scenario 4	1,040,000	144	31	19	132	326
Scenario 5	1,520,000	153	29	19	125	326
Scenario 6	2,000,000	159	27	20	120	326

Figure 90: Relative distribution of HPC source under different scenarios



An important aim of growing the registry is reducing Australia's reliance on international donors. Figure 91 illustrates the impact on the number of transplants proceeding with a larger registries. It shows that with a registry of 400,000 donors, the number of domestic and international donors facilitating domestic transplants would converge, with 158 domestic (identical or mismatched) matches and 150 international matches.

Figure 91: Impact of registry size on HPC source



Donor availability

Five additional scenarios were modelled, reducing the estimate of donor unavailability to 75%, 50%, 25%, 15% and 10%. Note that these reductions had a substantial impact on the total number of domestic transplants that would proceed across all registry sizes. This suggests that, independently of growing the registry size, addressing donor availability could significantly increase the number of domestic donors called on to support Australian patients. This is particularly relevant, given this review's findings that the average availability of Australian donors at the verification typing stage is only 33%.

Table 40: Total number of domestic transplants (identical and mismatched) that would proceed under different donor unavailability rates

Scenario	Registry size	75%	50%	25%	15%	10%
Base – current state	160,000	90	90	90	90	90
Base – potential	160,000	72	106	140	154	161
Scenario 1	240,000	74	111	148	163	170
Scenario 2	400,000	76	117	158	174	182
Scenario 3	720,000	78	123	168	187	196
Scenario 4	1,040,000	79	127	175	194	204
Scenario 5	1,520,000	80	131	182	202	212
Scenario 6	2,000,000	80	133	186	207	218

How big is big enough?

Looking at the number of transplants facilitated under registries of different sizes, it appears that registries of 160,000–720,000 donors would provide access to more domestic donors, reducing our reliance on international donors. Marginal gains in domestic matching would be achieved by having substantially larger registries, but this would not significantly reduce the reliance on international donors. For example, in this analysis, a registry of 400,000 donors and one with 2,000,000 would yield 155 and 186 transplants, respectively. So, for the

31 additional transplants that wouldn't involve an international donor, Australia would need to add 1.6 million donors. Without even considering the costs of doing so, this clearly represents a much larger recruitment effort and investment in the Australian population.

Another observation from this exercise is that gains can probably be made with the current registry of approximately 160,000. This could involve focusing on improving the information available to clinicians upfront (that is, donor typing resolution) and donor availability through re-engagement activities.

As discussed in the chapters on the current state of the registry, it is worth focusing on its composition. While this analysis is based on modelling that assumes the same registry representation as it grows, certain ethnicities could benefit from improving the composition. Figure 92 shows the additional domestic (identical or mismatched) transplants for each registry size considered. It shows that NWCAU patients would benefit from a larger registry. However, for other ethnicities, gains are much more incremental (recognising that under the current state, there are fewer patients in these groups than in NCAU and NWCAU).

Figure 92: Total additional domestic transplants (compared to current state), by ethnic group

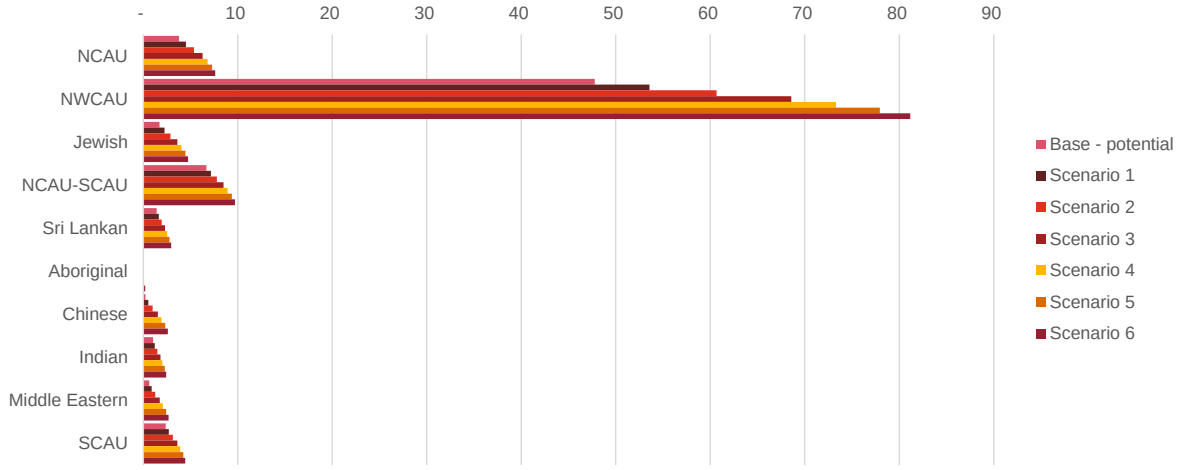


Figure 92 shows that, as per the NMDP's work, most Caucasian donors are able to identify an 8/8 or 7/8 match. The probability of identifying an 8/8 or 7/8 match for other ethnicities is much lower, and for Sri Lankan, Chinese, Indian and Middle Eastern patients, in particular, is very low. For example, a Sri Lankan patient has a 14% chance of identifying an 8/8 match for a registry of 160,000, which only grows to 42% under a registry of 2,000,000 donors. This compares to a 52% and 77% chance, respectively, for an NCAU patient.

As such, for many underrepresented groups, the likelihood of identifying a perfect match is not ideal under most registry scenarios considered here. This suggests, that despite any major recruiting campaigns, some patients would still need to rely on the international community. The Australian registry should continue to collaborate with the international community to determine how it can best contribute to optimise the chance of Australian patients from all ethnicities identifying a match. Specifically, Australia should continue working to understand where haplotypes are well represented in the international donor community to address supply gaps in poorly represented haplotypes on our own registry. It should also keep working to understand which are the best haplotypes Australian donors can offer to international patients. For example, Australia's geography and history of immigration might mean that we are better positioned to enlist donors of Asian and Pacific ethnicities than other major international registries, and could offer better support to international patients of those ethnicities. Equally, other registries may be better able to locate donors with ethnicities that are underrepresented on the Australian registry (for example, the Brazilian registry could enrol donors of South American ethnicity).

This review recognises that under all scenarios, Australia will have to rely on international donors, at least to some extent. As with most major registries, Australia has access to the significant pool of international donors through the World Marrow Donor Association

(WMDA), increasing the likelihood of a patient identifying a potential match. Registries can rely on each other to grow the overall donor base. The role of the WMDA is not superseded under any registry size and should be considered complementary to any recruitment strategy.

And cord blood?

The optimum size of Australia's cord blood inventory has been previously considered. A 1997 study cited in the 2009 HealthConsult Review of the National Cord Blood Collection Network (NCBCN) estimated match probabilities of 51%, 70% and 80% for 5/6 or 6/6 matches under inventories of 5,000, 10,000 and 20,000 donors, respectively. In 1997, Health Ministers adopted an inventory size of 20,000 as a minimum for Australia's population.[74] The 2009 review reconsidered the available evidence and assessed that Australia should have an inventory of 30,000 CBUs.

In 2016, PwC assessed Australia's future need for CBUs and identified that, even if demand grew or under a strategy that focused on addressing underrepresented ethnicities, there was no need to increase the size of the current inventory, reflecting that clinical demand is unlikely to rise in the near future. That review found that an inventory of approximately 30,000 CBUs was likely to be sufficient to meet future needs if access to international registries was maintained. However, the review recommended continuing to enhance the HLA diversity of collections to optimise matching probability. Additionally, banking of higher-quality CBUs should remain a focus, including enhancing the CD34+ and Total Nucleated Cell (TNC) counts and CBU volumes, in line with international standards.

8.5 Assessing the cost impact of the registry size

To guide the relative benefits of growing the registry against maintaining its current size, this review assessed the relative costs associated with using domestic versus international HPC sources. In doing this, it considered the costs associated with domestic sources including:

- donor recruitment
- initial tissue typing
- donor work-up
- donor collection.

These costs were then compared to the costs of an international collection, based on the average fee paid for a peripheral blood or bone marrow harvest, as provided by the ABMDR.

While this approach was originally intended to adopt a health economics approach to considering the quality-adjusted life year (QALY) benefits of growing the registry, no supply gap could be validated, meaning that assertions about additional transplants proceeding could not be qualified (as stakeholders consider that all patients seeking a transplant in Australia will receive one). Further, this review was unable to distinguish how many patients matched to international donors found a perfect match – this data is aggregated with domestic transplants – and data could not be used to deterministically assess patient outcomes. Given this review is not aware of studies that present improved patient outcomes between identically matched donors – international or domestic – our analysis focused on the *distribution* of transplants between identical, mismatched, international and CBUs, which have a cost rather than a quality impact.

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74 Department of Health and Ageing (2009) Review of demand for, and supply and use of, cord blood in Australia, prepared by HealthConsult Pty Ltd.

This review has also not considered other qualitative factors such as convenience, control over the process or improved time to transplant between a domestic or international HPC, as there was no clear evidence of these. Additionally, there was no literature to suggest a domestic HPC provides a better outcome than an international HPC, all else being equal.

Table 41 outlines the key cost components that differ between the two sources (domestic and international).

Table 41: Key cost components, domestic and international HPCs[75]

Cost component	Estimated cost	Source
Donor recruitment	Approximately $50 per donor	ABMDR *Unrelated HPC sourcing strategy* (Version 1.2, 10 May 2016), provided by the ABMDR
Initial tissue typing	$479.56 Allelic Real time LinkSeq ABCDRDQ	Allelic-level HLA-A, -B, -C, -DR and –DQ SA Tissue Typing Service Agreement (currently this cost is embedded within service agreements)
Donor work-up cost	$1,141	ABMDR, personal communications (G Healey) (Assume all worked-up donors go on to collection)
Domestic collection cost	$1,000 apheresis, $2,835 bone marrow harvest (assuming 80% peripheral blood/20% bone marrow collections): approximately $1,367 per collection	ABMDR, personal communications (G Healey)
Cost of international collection	Average of international fee schedules (peripheral blood and bone marrow) $33,857	ABMDR fee schedules

These figures show that the total estimated cost for a domestic HPC is approximately $2,508 compared to $33,857 for an international HPC. It should be noted that these costs are estimates only and exclude costs associated with donor education, second sample collection, verification typing, infectious disease marker testing, donor travel and courier costs. While these other costs are important, they will be incurred regardless of the registry size and so were not drawn into this assessment comparing relative costs.

Taking these figures and applying them to the registry supply scenarios considered, the relative costs of the registry sizes are analysed. Figure 93 shows the high-level collection costs associated with domestic and international donor transplants under different registry sizes.

[75] Note: Appendix F shows a breakdown of current work-up and collection cost estimations.

Figure 93: Comparative costs of registry supply scenarios (collection costs)

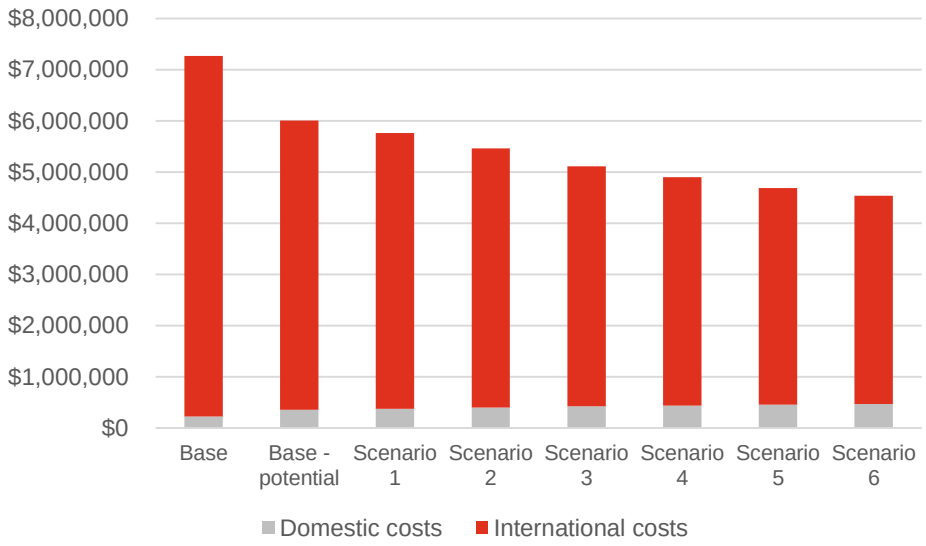

Table 42 outlines the recruitment costs associated with each registry size, and then, accounting for the reduced expenditure on international collections, the approximate net cost associated with each scenario.

Table 42: Relative costs of different registry size scenarios

Scenario	Registry size	Recruitment costs	Net costs (compared to base case)	Net cost per additional domestic transplant
Base – current state	160,000	N/A	N/A	N/A
Base – potential	160,000	N/A	($1,264,773)	($25,098)
Scenario 1	240,000	$42,364,800	$40,857,470	$702,175
Scenario 2	400,000	$127,094,400	$125,282,429	$1,846,919
Scenario 3	720,000	$296,553,600	$294,393,513	$3,741,769
Scenario 4	1,040,000	$466,012,800	$463,639,392	$5,439,286
Scenario 5	1,520,000	$720,201,600	$717,614,783	$7,821,689
Scenario 6	2,000,000	$974,390,400	$971,653,655	$10,091,262

The table shows that, while the costs associated with international collections may be reduced with a larger domestic registry, the current costs of recruiting and typing new donors to the registry drives expenditure. This expenditure is significant given the cost of initial tissue typing and suggests that relatively small gains are achieved in growing the registry when considered against the significant expenditure required to recruit enough donors to support those outcomes.

Under a 240,000-registry size scenario, $42.4 million is required to recruit the additional 80,000 donors. The larger registry would reduce reliance on international donors, but the $1.7 million saved in international collection costs does not outweigh the $42.4 million spent. This scenario requires that $700,000 is spent to attain each additional domestic donor transplant – the incremental gains in increased domestic donor matches does not outweigh the costs of investment. However, the scenario for a 160,000-registry size (Base – potential) provides more benefits than costs, saving $25,000 per additional domestic donor transplant it facilitates. As the analysis earlier in this chapter shows, improvements to the current registry could bring gains.

This assessment, of course, assumes there would be no growth in the number of HPCs Australia provides to international donors, which in practice, would be likely to grow. With

growth, Australia would increase the cost recovery it receives for providing international HPCs, potentially further lowering the cost of provision. While this growth may partially offset expenditure, it is unlikely to balance the upfront investment needed to grow the registry, given each internationally provided HPC only recoups approximately $30,000.

Without a mechanism to significantly reduce the upfront costs associated with recruitment and initial tissue typing, there appears to be limited economic value in enhancing the recruitment strategy to increase the registry much above its current size.

In summary

Given Australia's population size and diminishing return on increased match probability, the current size of the registry appears to align with our domestic needs. However, the profile of donors – currently more are female, generally older and concentrated among certain ethnic groups – could be better aligned with clinical needs.

Further, given Australia's international obligations to promote the principle of self-sufficiency, it needs to ensure that the HPC sector aligns with our future needs. This should remain a tenet and a driver of future investment and reform activities.[76,77]

Additionally, in line with the Stage Two Review of the NCBCN, the current size of Australia's CBU inventory is likely sufficient to support Australia's ongoing needs. However, there is a need to continue focusing on enhancing the quality of CBUs available. This could include limiting collections to higher-quality units, enhancing the HLA diversity of any newly banked units and undertaking a stocktake of non-compliant CBUs and CBUs that are unlikely to be used.

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[76] World Health Organization (2012) Expert Consensus Statement on achieving self-sufficiency in safe blood and blood products, based on voluntary non-remunerated blood donation (VNRBD).

[77] Declaration of Istanbul on Organ Trafficking and Transplant Tourism (2008), Principle 5, World Health Assembly.

9

Process, governance and structure options

This chapter covers...

- *the potential scenarios for how each of the sector's activities could be arranged to address challenges, including key considerations in exploring those scenarios as future options*
- *the potential options for sector reform (which are combinations of the scenarios) and their key benefits and risks*
- *a qualitative evaluation of the different options.*

Key messages:

This review has identified a number of key challenges in the areas of donor recruitment, donor coordination, initial tissue typing and verification typing, searching and matching, and governance and service delivery management. To address these challenges, consideration can be given to how the sector is arranged to support revised strategic objectives.

Five options have been assessed: Option A (status quo), Option B (improve tissue typing), Option C (improve recruitment and tissue typing), Option D (redesign to address key challenges) and Option E (establish a domestic and internationally oriented registry). Each option provides different benefits and risks, with options B and C focusing on improving recruitment and tissue typing services, and options D and E proposing significant changes to the way in which service delivery is managed across the sector. These options bring greater benefits by addressing key challenges, but they also bring risks associated with cost and implementation effort.

In summary, Option A performs poorly due to its inability to address key challenges and the growing reliance on (and cost of) international donors. Option B goes some way to addressing these issues in its improved tissue typing activities, but does not address recruitment and governance issues. Option C is more expensive to implement, but will support improved typing resolution and recruitment of targeted donors. Option D, which envisages changing the way the sector operates, will require higher upfront costs and a greater effort to implement, but it provides better outcomes. Option E is more complex and costly to implement, but in addressing structural and governance challenges, it will provide better quality and self-sufficiency outcomes, while addressing ongoing cost impacts associated with a high reliance on international donors under current arrangements. Options B, C and D provide the greatest opportunities to address sectoral challenges.

9 Process, governance and structure options

The scope of this review included presenting options for governance arrangements and structures to provide the most effective means of meeting governments' continuing commitment to providing access to HPCs, including identifying risks associated with each option. To consider some of the options, this review reflects on the key findings so far, which are:

1. The primary funding agreements do not include objectives, activities and milestones that reflect the registry's future needs or strategic goals.
2. The Australian Bone Marrow Donor Registry (ABMDR) can improve its marketing approach and communication with donors to promote their engagement.
3. The current recruitment approach is mismatched to clinical needs in respect of donor demographics, age and sex, and mostly relies on blood donors who do not fit the profile of donors preferred by clinicians. Additionally, there is little focus on marketing to promote the registry and donor recruitment centres use different techniques.
4. The governance of the haemopoietic progenitor cell (HPC) sector is fragmented and responsibilities are spread across many different organisations.
5. Current systems and reporting lines do not promote comprehensive data capture, or inform business analytics to support strategy development, monitoring and implementation.
6. Corporate knowledge and understanding of the sector and the operation of the registry is concentrated in a few key staff at the ABMDR, which exposes the registry to operational risks if that knowledge is lost.
7. Reporting of recruitment and tissue typing activities and drivers of demand (for example, number of searches and newly recruited donors) is not centrally captured or reported because it is not required under current arrangements.
8. The resolution of initial tissue typing of donors is different around the country and is mostly low resolution, meaning clinicians do not have upfront information to inform decision making.
9. Given Australia's population size and the diminishing return on increased match probability with an expanded registry, the current size of the registry aligns with domestic needs. However, the profile of donors – more are female, generally older and concentrated among certain ethnic groups – is not well aligned with clinical needs.

9.1 Potential options

To assess how the sector might be adapted to address the implications of these key findings, this review has developed options across the five key activities of the sector. These options reflect the natural boundaries in capabilities, activities, functions and future needs to support the registry's operation. These are:

1. donor recruitment
2. donor coordination
3. initial tissue typing and verification typing
4. searching and matching
5. governance and service delivery management.

9.1.1 Donor recruitment

Donor recruitment activities includes actively recruiting, enrolling and educating new and potential donors. It also includes donor engagement (such as marketing) and coordinating donor drives. As the key interface with the public, this role ultimately drives alignment of recruiting with clinical needs. Donor recruitment is currently embedded in National and State Donor Coordinator roles.

Key challenges that exist in donor recruitment include:

- lack of coordinated recruitment or strategic recruitment across the country
- using a passive recruitment approach that largely relies on committed blood donors, who are assessed against blood donation risk criteria that may not be relevant for HPC donation (for example, if a potential donor has a cold or the flu, they can't be sampled). These donors are also typically older, female and predominantly Caucasian, which doesn't align with clinical preferences
- manual enrolment and follow-up with new volunteers.

Through this review, a number of considerations were raised for improving donor recruitment or changing approaches to help address some of the challenges regarding donor availability and registration. Among these were:

- introducing donor leave and/or compensation – some stakeholders raised the issue of financial support as a potential barrier to donors participating in the registry. Other stakeholders saw it as an opportunity to raise commitment to donation. For example, business owners or donors with casual or part-time jobs are likely to receive less or no support if called on to donate as they would not get sick leave. There may be opportunities to better support these donors to encourage their commitment to donation.[78]
- marketing – to encourage registration of younger donors, many jurisdictions undertake targeted promotional campaigns and engage with potential donors via social media channels. These avenues improve provision of information and two-way engagement, and enable access to wider cohorts of the community. Early sections of this report highlighted the current limitations of the existing marketing approach. Lessons might be learnt from overseas jurisdictions about approaches to use and successful campaigns to enable the Australian registry to better connect with its intended audience.
- using volunteers – many international registries use volunteers to enhance engagement and recruitment activities with potential donors. Volunteers are trained to promote the core messages of the registry, and in methods and approaches for engagement, as well as the minimum amount of information to provide to a donor. While volunteers need to be coordinated, using them enables the participation of individuals who may be unable to donate (for example, older volunteers who do not meet the donor registration age criterion but who are willing to assist the registry in

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78 The issue of donor leave is quite contemporary. The Fair Work Commission received a number of submissions through its four-yearly review of modern award wages calling for the inclusion of a clause that supports blood and bone marrow donor leave. It was proposed that the clause be included in the General Retail Industry Award 2010; Fast Food Industry Award 2010; Pharmacy Industry Award 2010; Hair and Beauty Industry Award 2010 and the Mannequins and Models Award 2010. The hearings were scheduled to take place in July 2017. (See more at https://www.fwc.gov.au/awards-agreements/awards/modern-award-reviews/4-yearly-review/common-issues/am201636-blood-bone?page=1).
Examples of adoption are seen in the explicit inclusion of paid donor leave as a feature of some employment agreements in Australia. For example, Clause 39 of the McDonald's Australia Enterprise Agreement 2013 outlines employee rights to three days leave for these purposes. (See more at http://www.sda.org.au/download/enterprise-agreements/MCDONALDS-AUSTRALIA-ENTERPRISE-AGREEMENT-2013.pdf)

another way), while reducing resourcing pressures on other aspects of the registry's operation.

- opt-out recruitment schemes – like with organ donation, some stakeholders raised the option of using an opt-out scheme to improve the number of donors registered. The issues of implementing an opt-out scheme, in which all Australian donors would be automatically enrolled as a potential donor unless they opt-out, have been explored in many forums. The challenges include commitment of donors, ability to legislate a scheme and the need for donor education, which in the case of bone marrow donors is potentially more pertinent given the time commitment and invasiveness of the collection procedure. Opportunities might exist for developing opt-out arrangements through partnerships with specific enterprises. Examples could include the military, emergency services and the police, which are examples of workforces with higher representation of younger males (a number of international registries use opt-in style partnerships). Appendix I outlines additional ethical considerations.
- targeted recruitment – ethnically diverse communities may understand the need to enhance the representation of many of the haplotypes on the registry, and recruitment efforts could concentrate on attracting individuals from these communities. Additionally, clinical preferences for male donors means targeting male volunteers may be warranted (a practice widely used internationally). The practice of targeted recruitment was identified as a complex activity that may affect the willingness of other donors, while marginalising certain communities that aren't well represented. Appendix I explores these legal and ethical considerations.
- goodwill of donors – many stakeholders identified the importance of maintaining the goodwill of donors. As an altruistic act, donor faith that the registry is acting in the best interests of patients and donors is integral to their retention and commitment. If recruitment were oriented to grow the donor base to distribute more HPCs internationally, there is a risk that it may break donor goodwill and unravel the volunteer base. Engagement with donors is important to ensure messages about strategic decisions and the purpose of activities is properly communicated and understood.

Appendix I provides more information on the ethical and legal considerations of changing the recruitment approach.

To address these challenges, the review considered the following four scenarios.

1. Donor recruitment

1a – Status quo

State-based Donor Coordinators, no national strategy

Under current recruitment arrangements, each state funds Donor Coordinators as part of its Australian Red Cross Blood Service (ARCBS) contract. They are supported by a National Donor Coordinator in the ABMDR's national office. The Donor Coordinators are responsible for engaging with (primarily) blood donors to encourage them to register as a HPC donors, providing education and enrolling them in MatchPoint. They also support ad hoc donor drives to register new volunteer donors. Without a central strategy or centralised performance measures, recruitment is not necessarily aligned to the strategic objectives of the registry. Note: donor coordinators have a dual role, delivering recruitment and donor coordination activities (the latter is explored in the next activity).

Under this scenario, no additional resourcing is considered and the number of donors registered is consistent with the current number of new donors registered every year (approximately 5,500).

1. Donor recruitment
1b – Target (to meet domestic need) *Targeted recruitment directed at specific groups (ethnicity/young/male) or at rates to maintain or fulfil local need* Under this scenario, State Donor Coordinators would be encouraged to meet targets that would seek to fulfil domestic needs. Targets would be centrally set, specifying the number of donors and their characteristics to better shape the registry to meet clinical needs. This may mean expanding and undertaking targeted recruitment among certain age groups and/or ethnic groups. Under this scenario, additional resourcing would be required to support marketing and recruitment campaigns, which would likely involve engaging with potential donors outside the ARCBS blood donor channels. Additionally, more resources would be required to meet an ongoing need to continually assess the registry make-up and search requests against clinical needs, to ensure recruitment is aligned with those needs. With more donors, our domestic needs would be better fulfilled, meaning more local collections and less reliance on international HPCs.
1c – Target (to meet domestic and international needs) *Targeted recruitment to meet domestic and international supply needs* In this scenario, State Donor Coordinators would be responsible for delivering on centrally determined recruitment targets that enhance Australia's registry to fulfil our domestic needs and also those of the international community. In doing so, recruitment activity would be enhanced to engage with the wider community and may involve large campaigns. This scenario includes even more additional resourcing than 1(b) as it assumes a higher rate of registration, marketing and recruitment, as well as closer collaboration with international registries to identify how the Australian registry might be able to better support international needs. Additionally, like 1(b), more resources would be required to meet an ongoing need to continually assess the registry's make-up and search requests against clinical needs to ensure recruitment aligns with those needs. The increase in registration is likely to have a flow-on impact from greater numbers of domestic collections for local and international purposes. The number of internationally sourced HPCs Australians use would correspondingly reduce, while costs recovered from internationally distributed HPCs would be likely to grow.
Disregarded options
Stop – *No recruitment of Australian donors (untenable)* The scenario of stopping new recruitment was assessed; however, it was considered untenable. This is due to our obligation to meet the needs of Australian patients and maintain our global role in the international network of registries. Finally, given that many of our current donors will soon be above the current age threshold and will be retired from the registry, this option is not viable.

The key costs associated with donor recruitment include:

- resources (full-time equivalent (FTE) staff) for activities such as donor recruitment; analysis of current registry make-up and Australian demographics; marketing; donor education; and donor engagement

- collection of DNA samples, including consumables and resources (FTE) to supervise or undertake collections (which, for blood samples, may require a phlebotomist)
- consumables associated with marketing material, recruitment equipment (saliva tubes or buccal swabs) and batching of samples
- information technology (IT), such as media campaigns and donor engagement emails and websites.

The following table presents the estimated costs for some of these items, where this information was discussed or identified during the review.

Cost component	Estimated cost	Source
Donor recruitment	Approximately $50 per donor	ABMDR *Unrelated HPC sourcing strategy* (Version 1.2, 10 May 2016), provided by the ABMDR
Donor recruitment roles	Donor Coordinators/recruiters spend approximately 75% of their time on donor coordination and 25% on recruitment activities (there are 8.75 state-based FTEs)	ARCBS advice – 3 April 2017
Sample collection (blood sample)	$220	ABMDR NZ Fee Schedule (currently this cost is embedded in service agreements)
Consumables		
Saliva tube	*~$15 – $20*	Spit kit published cost (~£10 per kit) https://www.anthonynolan.org/8-ways-you-could-save-life/give-money/where-your-money-goes
Buccal swabs	*~$15*	ABMDR consultation Anthony Nolan consultation, ~20 pence per swab (excluding collection/other material costs)
Batching/ storage/ shipment	*~$60/sample*	Estimate provided by the ABMDR through consultations (storage costs are also captured in *Tissue Typing* below, as samples are currently held in Australian tissue typing laboratories)

9.1.2 Donor coordination

Donor coordination involves the activities of national donor engagement and management. Donor Coordinators exist at the national and state levels. State-based Donor Coordinators have a dual role in delivering recruitment activities, which was explored above.

If a donor is identified as a potential match for a patient, a National Donor Coordinator is responsible for passing a referral to a State Donor Coordinator to activate the donor in their state. Coordinators then engage with the donor to seek their participation, schedule their appointments (liaising with transplant centres to allocate a collection), and follow their progress through to collection. They are also responsible for donor education and welfare, much of which is undertaken by Transplant Coordinators at the transplant centres. National Donor Coordinators also coordinate international donors for Australian patients; allocate collections to transplant centres (to work-up and collect HPCs from a donor); coordinate activities between transplant centres (to ensure the scheduling of the collection date meets the patient's transplant preparation schedule, which requires careful planning and coordination with the receiving transplant centre); and undertake donor follow-up.

Challenges in current donor coordination arrangements include:

- inefficiencies in handling information and engagement with the donor (which is partly undertaken by transplant centre staff and National and State Donor Coordinators). This can include recapturing information from the donor, booking, discussing and handling travel arrangements, and conveying or arranging appointment schedules and timing to coordinate the collecting and receiving transplant centres
- lack of a central point of contact for the donor due to responsibilities being held between coordinators
- an ad hoc approach to allocating the transplant centre responsible for donor collections. If many more collections were undertaken, this may result in a disproportionate collection workload for some transplant centres.

A core consideration for changing the approach to donor coordination is the impact it may have on donor relationships and the local knowledge held by State Donor Coordinators. While donors may not be called upon to donate often (if at all), having a local contact may assist in engaging with some donors. Additionally, the relationship between local staff and transplant centres in the donor's state may assist in achieving outcomes.

The following two scenarios are considered as future options.

2. Donor coordination
2a – Status quo In this scenario, the current arrangements apply in which selected donors are first managed by National Donor Coordinators, who allocate the transplant centre that will undertake the work-up and collection. Donors are 'handed over' to State Donor Coordinators, who then take on the role of contacting and seeking the consent of the selected donor. State Donor Coordinators work closely with the patient's transplant centre and allocated collection centre to schedule work-up and collection. Under this scenario, no additional resourcing or activity is considered.
2b – Centralise coordination In this scenario, coordination of a selected donor is revamped to introduce a centralised process with a standard approach to coordination. Coordination activities could be undertaken by a central office or supported by the State Donor Coordinators. Coordination activities would be standardised to introduce a common approach across states and territories, and address current challenges in communicating with donors and transplant centres. The activities captured include donor activation, work-up and collection, scheduling and engagement with transplant centres, ongoing engagement with donors and donor follow-up activities (following collection and on an ongoing basis to capture longitudinal donor outcome information). This option clarifies the roles of different coordinators and supports the central office to manage and deliver recruitment and collection strategies. Under this scenario, additional resourcing would probably be needed to assist the central office to develop a standard approach and for ongoing coordination support. Upfront investment would also be required to revamp internal systems to better manage coordination and donor outcomes, and to establish and disseminate new operating procedures. This scenario may also be more efficient, depending on resourcing arrangements for coordinator staff (for example, whether they were state- or centrally based).
Disregarded options
Stop

A scenario in which all donor coordination is stopped has not been considered, as Donor Coordinators will always be need for Australian patients, even if recruitment was halted and Australia sought to only use international donors.
State-based recruitment and coordinator teams A scenario in which all donor engagement and coordination was funnelled through state-based Donor Coordinator teams was also ruled out. In this scenario, State Donor Coordinators would be responsible for recruitment and donor coordination activities, which could risk the development of different recruitment and coordination processes and procedures across states, further fragmenting operations. This scenario also risks poor alignment to the national registry and inhibits the ability to support cross-jurisdictional coordination activities.

The key costs associated with donor coordination relate to resources for donor education and FTE Donor Coordinator roles. The following table shows the estimated costs, where this information was obtained.

Cost component	Estimated cost	Source
Donor Coordinator roles	There are 2.3 FTE National Donor Coordinators	ABMDR 2015–16 End of Financial Year report and consultations
	Donor Coordinators/recruiters spend approximately 75% of their time on donor coordination and 25% on recruitment activities (including supporting donor drives, marketing and communicating with donors) (there are 8.75 state-based FTE Donor Coordinators)	ARCBS advice – 3 April 2017

9.1.3 Tissue typing

Tissue typing covers the breadth of activities associated with typing potential donors. Activities include initial tissue typing associated with new donor samples (collected at registration); storing DNA samples; extended typing of samples upon a clinician's request to determine whether a donor is the right match to a patient; and verification/confirmatory typing of fresh samples from an identified potential donor (either domestic or international). Laboratories provide reports to State Search Coordinators and clinicians to guide decision making. Tissue typing laboratories type to different extents and are responsible for their accreditation against testing requirements.

As has been highlighted, challenges associated with current tissue typing arrangements include:

- a large proportion of the Australian registry only contains information typed at low resolution, which lacks the upfront information clinicians need to inform decision making. Only 4% of Australian donors are typed at higher resolution across six loci (compared to 16% of international donors). While some laboratories in Australia have the capability to undertake Next Generation (NextGen) typing, this is not used for all new recruits to the registry
- they are spread among the states, which hold agreements with the ARCBS (or in Western Australia and Queensland, PathWest and Pathology Queensland, respectively). This has resulted in different fees for typing, and different standards for the required resolution of upfront typing and the volumes to be handled across

states. Additionally, these laboratories service solid organ typing needs, which influences priorities, capacity and operational costs

- the demand-driven model. Due to the capped funding model in some jurisdictions, some laboratories have a backlog of new samples for processing and/or cannot manage volumes associated with recruiting. An uncapped recruitment model means that the volumes laboratories can manage (or that are funded) may not support recruitment activities, and result in typing not being undertaken on some new donors.

There are a number of policy considerations associated with tissue typing, including:

- tissue typing resolution – consultations and evidence suggest that the registry should orient to provide NextGen typing of donors. This review identified that a number of laboratories are already pursuing NextGen typing; the impact on HPC donor typing and extent of resolution should form part of governments' consideration of options. Preferred resolution standards (which specify the number of loci to be typed to given resolution levels) should be established to support providers with the capacity to undertake typing to this resolution. This would need to be reflected in any existing or future service agreements, as well as in the ABMDR's protocols
- impact on solid organ transplantation tissue typing – all tissue typing laboratories that are typing HPC donors also support typing of solid organs for transplantation. The impact on those laboratories of any new arrangements for typing HPC donors should be considered, as it could affect the volume, equipment needs and cost of operations. These needs have not been considered here and the options below do not suggest that solid organ typing needs be bundled into the approaches proposed
- sample type – currently, all samples are collected as fresh blood samples. Moving to using buccal swabs or saliva tubes could bring significant cost savings.[79] The type of sample used is closely related to the recruitment strategy (for example, for new donors who enrol online, a buccal swab could be the obvious method for collecting DNA from them). Furthermore, if an international supplier became the provider of initial tissue typing services, export permits would be required to move blood samples through customs, which would be both costly and prohibitive in terms of resources needed
- supplier(s) – the approach and selection of a preferred supplier may depend on their fee schedule and capacity to manage the volumes necessary and at the resolution needed. Shortlisting or targeted expressions of interest may be based on market-informed decisions about which suppliers are capable of providing the services needed
- standardised funding – given the discrepancies in the funding per test across states, there may be merit in exploring whether a nationally standardised fee could be developed for different typing tests. This would encourage transparency and efficiency across services, although it would depend on the option pursued
- sample storage – currently, each of the larger states has a laboratory and if blood samples are taken in another state, they are transported to one of the state laboratories. If an international or domestic laboratory located a hub that was a long way from a recruitment location or testing laboratory, samples may need to be stored and batched for dispatch for typing. This could delay testing and increase the costs associated with transporting and storing samples. Storage costs could also increase

[79] Buccal swabs are small swab sticks – much like an ear bud – used to swab the inside cheek of a donor to collect DNA. They are then put into a moisture-resistant envelope to be sent for testing. This is a lower-cost method for collecting DNA. International registries often mail kits to individuals, enabling them to swab and send their DNA from home. Saliva tubes are a small container used to collect spit from a potential donor. Like buccal swabs, they are a lower-cost method for collecting DNA and can be used without supervision. The benefit of saliva tubes is they often collect more DNA than buccal swabs (if collected without supervision), reducing the risk of a non-viable test.

due to the need to batch samples before sending them for testing. Buccal swabs and blood samples would both need to be stored.

- retrospective typing – many stakeholders identified that there may be opportunities to retrospectively type existing donors to a high resolution to improve the current registry. Similar approaches have been adopted internationally, and are currently being trialled in the Western Australia and Queensland cord blood banks (CBBs). The CBBs are also exploring retrospectively high-resolution typing stored cord blood units (CBUs). However, decisions would need to be made about which donors should be typed at the NextGen level and how this might be funded
- Therapeutic Goods Administration (TGA) requirements if an international supplier is pursued – there may be a requirement to seek TGA approval for using in-vitro diagnostic devices (IVDs) (the category of tests and associated accessories used to analyse samples of blood, tissue and DNA) during tissue typing, which falls under TGA regulatory oversight. Therefore, international providers may need to seek certification to provide these services. This requirement should be fully investigated before approaching or engaging any international supplier
- technology change – with continuous development of testing technologies, resolution capabilities are likely to increase over the next 5–10 years, which may affect decisions about the initial resolution of samples and changes in international and clinical preferences. For example, a number of international registries are exploring or implementing third-generation typing.[80] Market providers should be engaged to understand whether it might be possible to undertake typing to a resolution enabled by newer technologies at a cost-competitive rate.

The following three scenarios were considered to address these challenges.

3. Initial tissue typing/verification typing
3a – Status quo Under a status quo scenario, the model of state-held contracts with state-based laboratories is maintained. This means that laboratories would continue to undertake initial typing on a demand-driven basis, while states would need to specify resolution needs in their contracts. This strategy risks continuing a fragmented approach to the volume and quality of typing of new registrants. It may result in further cost inefficiencies and inequality across jurisdictions over time (as higher-resolution jurisdictions, such as Western Australia, are called upon disproportionately to recruit, type and mobilise donors). No additional resourcing or change in activities is assumed under this scenario.
3b – NextGen central laboratory (batch samples) In this scenario, all samples would be batched and sent to one preferred supplier for initial tissue typing at NextGen resolution. This approach ensures that all new recruits will be typed at the highest resolution and to the same standard across the registry. A preferred supplier would be engaged centrally (through the registry or by government) to enable a competitive tender process and direct contractual management through one focal point. Using one supplier would ensure that typing was aligned, and deliver on the strategic objectives of the

[80] Third-generation sequencing is a newer technology than NextGen sequencing (also known as second-generation sequencing). Sequencing is undertaken at the single molecule level, avoiding the DNA amplification and synthesis methods used by NextGen sequencing, and providing greater allele accuracy. See, for example, Heather JM and Chain B (2016) The sequence of sequencers: The history of sequencing DNA *Genomics* 107 (1).

Third-generation sequencing is not yet widely used, but was recently introduced by the Anthony Nolan registry to type its donors. See: https://www.anthonynolan.org/news/2016/01/06/new-generation-lifesavers-anthony-nolan-launches-pioneering-technology

3. Initial tissue typing/verification typing
registry, including managing volume and achieving economies of scale through engagement. The supplier could be domestic or international. This approach may require that governments' pool funding currently distributed across state providers and nominate a contract manager. Alternatively, contracts could be redefined to support shared targets and enable central engagement. Additionally, extended and verification typing would still need to be maintained in local laboratories, in line with donor procedures, which require that fresh samples be typed at the laboratory serving the transplant centre.[81] There is also a risk that a single supplier would be able to monopolise typing services, leading to other laboratories losing capability, which would affect the national skills distribution for typing providers. Under this scenario, it is assumed there would be upfront spending on procurement and engagement activities, with the potential to reduce initial typing costs through batching and economies of scale. Costs associated with extended/verification typing undertaken in Australia may be affected by clinical time frames and laboratory capacity.
3c – NextGen demand hubs (east and west) Like with scenario 3b), in this scenario it is assumed that some consolidation in the engagement of initial tissue typing is undertaken. However, this review suggests that instead 'demand hubs' (perhaps one each on the eastern and western seaboards) are established that are responsible for managing and processing all initial tissue typing and extended/verification typing. With two or so preferred suppliers, economies of scale might be achieved, driving down costs while better managing volumes. This scenario may still require a new funding model to pool expenditure so that it is proportionally captured, as well as requiring that a number of focal points be established to manage contracts. In this scenario, it is assumed there would be more than one provider, reducing the risk of losing local capability, although it may require some consolidation of the skills base among laboratories. It is also assumed the costs would likely be greater than in scenario 3b) as it remains a partly distributed model and may not achieve the efficiencies of one laboratory. Benefits may also exist in relationships between local hubs and the State Search Coordination and transplant centre roles, which depend on, and engage with, laboratories.
Disregarded options
Stop Stopping tissue typing has not been considered because it is necessary to manage samples of newly recruited donors and those already registered, as well as type potential donors for Australian patients.

The key cost drivers associated with tissue typing include:

- those associated with initial, extended and confirmatory tissue typing, and infectious disease marker testing

[81] As per the ABMDR protocols: Chapter 4: Donor Enrolment, Extended HLA typing and verification typing (ABMDR-GL-OP-004-12) and Chapter 5: Tissue typing Standards (ABMDR-GL-OP-005-08).

- storing samples, including consumables, accommodation and equipment costs within a tissue typing laboratory
- transport, such as shipping DNA samples interstate or internationally (for initial typing or verification typing so that donor and patient samples are tested in the same laboratory to ensure accuracy in typing outcomes).

The following table shows estimates of some of the costs, where this information was obtained.

Cost component	Estimated cost	Source
Initial tissue typing	$217.04 + $195.78 Serologic ABGT and DRGY (bone marrow) $479.56 Allelic Real Time LinkSeq ABCDRDQ	Serological HLA-A, -B and –DR Allelic-level HLA-A, -B, -C, -DR and –DQ SA Tissue Typing Service Agreement
Sample collection (blood sample)	$220	ABMDR NZ Fee Schedule (currently this cost is embedded in service agreements)
Sample storage	$8 per DNA sample	SA Tissue Typing Service Agreement (note, a batching approach for samples may mean that storage is not in an Australian tissue typing laboratory as described in *Donor Recruitment*)
Sample shipping (interstate)	$75 per sample	SA Tissue Typing Service Agreement
Extended typing cost	Between $132.97 and $207.18 per allele	High-resolution typing SBT-HR (HLA-A, -B, -C, -DR, –DQ or –DP) SA Tissue Typing Service Agreement (currently this cost is embedded in service agreements)
NextGen typing (domestic)	*~$180/sample*	PathWest consultation
NextGen typing (international)	*~€30/sample*	ABMDR consultations (estimated cost in Germany)

9.1.4 Searching and matching

Searching and matching activities include initiating a patient search, ongoing engagement with Transplant Coordinators and clinicians, initial matching and reporting of potential donors, and processing requests for extended or verification typing. As this function is currently carried out by State Search Coordinators, searching and matching also involves analysing typing results provided by laboratories to genetically match potential donors and provide recommendations to clinicians about the best match/es to a patient.

Issues in current searching and matching arrangements include:

- some inefficiencies in manual/duplicated entries to initiate a search, including data entry to initiate unrelated searches, provide search reports and relay information among parties
- output reporting is non-standard and is largely relationship-based in the preliminary search stages. These methods have been adequate for small volumes, but if donor or patient volumes significantly increase they may come under stress

- a lack of central oversight or monitoring of search activity that is spread across multiple organisations. This can limit the ability to inform future activities and affect resource allocation (in peak periods).

Changes to searching and matching arrangements should consider:

- the risks associated with diminishing the relationships between State Search Coordinators and clinicians
- the interconnectedness of searching and typing and laboratories. Many of the skill sets and current arrangements benefit the relationships between coordinators and laboratories, and they collaborate in seeking and accessing typing outcomes and reporting the outcomes (for example, Search Coordinators are scientists, making them an important conduit between laboratories and hospitals). However, Transplant Coordinators and Search Coordinators also have close relationships. This means Search Coordinators could either be based in hospitals or the same location as the laboratories, which may require consideration when selecting an option.

The following three scenarios have been developed for evaluation.

4. Searching and matching
4a – Status quo Under the status quo, State Search Coordinators who undertake searching and matching functions are funded through state-held contracts with local laboratories (with the ABMDR making a smaller contribution through its Commonwealth funding agreement). State Search Coordinators manage relationships in each jurisdiction in different ways, which has resulted in different processes for each transplant centre.
4b – Centralise (national provision) This scenario considers providing all searching and matching functions nationally. It would mean that all searches would be channelled through one national contact point, and matching, requesting and reporting activities would be provided by the same office. Central provision would promote cost-efficiencies and likely improve oversight and linkage with the registry. It may also require a revised funding model to pool government funding. However, this scenario risks the loss of specialist skills through consolidation, and the loss of relationships between Search Coordinators and clinicians in the same state. This scenario assumes unchanged spending on coordination, and upfront investment in changing protocols and management. Once these arrangements are fully established, greater efficiencies may reduce operating costs.
4c – Demand hubs This scenario assumes that two or more demand hubs are established to support all search initiation and matching for patients. It's likely that these hubs would be based on existing referral pathways and volume in each state, to distribute service demand and maintain a single contact for each transplant centre. It's also logical that this scenario be implemented if scenario 3c) (Demand hubs for tissue typing) was pursued, as it has inherent linkages in service delivery and could act as a 'one-stop shop' for transplant centres. This scenario may require a revised funding model that makes use of pooled government funding. Benefits could include cost-efficiencies and better linkages to the registry and its objectives. Drawbacks include that it risks loss of specialist skills and staff through consolidation, as well as existing local relationships between Search Coordinators and clinicians. This scenario assumes unchanged spending on coordination, and upfront investment in changing protocols and management. Once these arrangements are fully established, greater

4. Searching and matching
efficiencies may reduce operating costs.
Disregarded options
4a – International provision Any scenario in which an international provider delivers searching and matching activities has been disregarded, due to the need to align with Australian clinical practice and to maintain a level of local engagement.
4b – Integration into existing tissue typing roles As the skill set for searching and matching closely aligns to that used in deceased and living organ matching, there may be opportunities to integrate the role of State Search Coordinator with these activities. However, this scenario was not explored further as it would not reduce costs (the allocation of effort would be spread rather than concentrated in 1–2 roles per state) and could mean less communication with, or availability of, coordination staff dedicated to individual searches.

The key cost drivers associated with searching and matching include resources (FTEs) to deliver these activities.

The following table sets out estimates for these costs, where this information was obtained.

Cost component	Estimated cost	Source
State Search Coordinator roles	In 2017, there were 7.3 FTE State Search Coordinators. Coordinators currently comprise: 1.8 FTE in Victoria, 2 FTE in NSW, 2 FTE in WA, 0.5 FTE in SA and 1 FTE in QLD.	ARCBS, PathWest and Pathology Queensland consultations

9.1.5 Governance and service delivery management

Governance and service delivery of the HPC sector are dealt with separately to provide options for governments when it is considering the oversight of the sector, and the optimal structures for service delivery that sit beneath the governance structure.

Options include activities relating to the overall management of the registry and service delivery. These are set against the strategic direction for recruitment and registry operations to ensure they align to clinical needs for HPCs. These activities also include service delivery in elements of the sector such as recruitment, tissue typing, cord blood banking, outcome reporting and donor follow-up. Service delivery management also includes ongoing clinical, government and international community engagement, to deliver on and inform the strategy for the whole sector.

Governance responsibilities (provided by governments) include providing policy direction and oversight, as well as the structure the sector is accountable to (through reporting and progress reviews). Governance also incorporates the role of governments as policy makers who provide funding.

Challenges in the current arrangements include:

- enhancing the strategic objectives of the registry through contractual arrangements between the ABMDR and ARCBS, and oversight provided by the ahJHPCC
- the ABMDR's perceived lack of control in driving recruitment and strategic direction, due to an absence of contractual arrangements between the ARCBS and other bodies delivering services
- funding arrangements made complex by a fragmented approach
- limited proactive registry management to ensure it is 'fit' for clinical needs by recruiting new donors, managing those donors on the registry and implementing policy to drive strategic outcomes
- limited oversight and outcome-oriented reporting that would drive accountability and inform strategy development and decision making.

Key considerations in determining the most appropriate scenario for governance and managing service delivery include:

- the different entities delivering services within the sector and responsibilities for managing those services
- governance committees and funding. The role of government, governance and funding arrangements will need to be agreed to support any change of arrangements. The specific structures and reporting lines will require careful consideration to formalise roles and responsibilities. There is scope to streamline current reporting arrangements to the ahJHPCC, to address some of the existing governance challenges, without the need to change funding arrangements
- engaging a new provider to undertake specific or all service delivery, after researching the market to discover whether there are capable and equipped vendors.

The following three scenarios were considered for governance and managing service delivery.

5. Governance and service delivery management
5a – Status quo The status quo scenario maintains existing arrangements for governance and service delivery management of the sector. This means the ARCBS or other pathology laboratories deliver recruitment, donor and state search coordination and tissue typing activities, and report to state governments. The ABMDR retains responsibility for maintaining the registry and search software. The ABMDR also manages or oversees the operation of the National Cord Blood Collection Network (NCBCN) and the Australasian Bone Marrow Transplant Recipient Registry (ABMTRR). This scenario assumes the current operating or capital expenditure are unchanged.
5b – Assign service delivery responsibility to one body In this scenario, one body would be responsible and accountable for all activities within the sector. These activities could include recruitment, donor coordination, tissue typing, searching and matching, registry maintenance, contractual administration and reporting. They could also include aspects such as administering changed service delivery of recruitment, tissue typing, searching, the NCBCN and the ABMTRR. The body would have full oversight and contractual control over how services are best delivered to align with strategic objectives – centrally managing these activities, rather than existing across funding agreements held by different entities. The governance arrangements for overseeing the sector and giving it direction would need to change. The ahJHPCC would need clear terms of reference and responsibilities for setting a national strategy and direction. These conditions would allow the ahJHPCC to oversee the activities of the entity responsible for service delivery. Funding and contractual

5. Governance and service delivery management
arrangements would also need to change, and may need to be pooled to flow to the one entity. Having one entity would improve accountability across the sector, increase transparency and ensure a national approach to service delivery. Drawbacks might include the one entity not having the capacity or practical knowledge necessary for a smooth transition. Additionally, it would require a substantial change in funding, governance and reporting arrangements. Under this scenario, if responsibility for managing service delivery in the sector was handed to one of the existing organisations, it would need additional resources and capabilities.
5c – Government-led activity In this scenario, the governance structure (through the ahJHPCC) and the service delivery structure (through the ABMDR, ARCBS and other bodies) would not change. However, the governments would change. They would have to collaborate to develop a national strategy and assign state-based responsibilities for achieving targets; for example, the national strategy could include establishing a national donor recruitment target, and each state would allocated responsibility for driving and monitoring its relationships with the ARCBS, PathWest or Pathology Queensland. This does not require a change in contractual arrangements or the funding flow, but it may result in changes to these factors. While the benefits of this scenario include a centralised strategy, it may further fragment service delivery and presents risks for successfully implementing the strategy. These risks could arise from contracts being siloed and providers being able to deliver services in different ways. It may also lose efficiencies achieved through centrally managing service delivery, and spread control and decision making across entities. Upfront investment would be required by governments to establish an agreed strategy and possibly change funding arrangements.
Disregarded options
International third party Any scenario in which a third party manages the registry was not considered. This is due to the greater risks associated with managing an international provider and the need to deliver on our domestic objective of giving Australian patients access to HPCs.

The key costs associated with governance and related activities include:

- resources (FTEs) to support the registry, including executives and staff involved in operations, office administration, IT support, finance, donor engagement (for example, updating donor contact details) and outcomes reporting
- office and overheads, including accommodation, business support, utilities and equipment
- international registry membership fees to access international IT systems, and WMDA membership
- software licensing fees for the provider of the software that operates the registry database and outcomes reporting
- donor engagement material to educate new and selected donors and, potentially, to maintain the website and social media channels

- IT uplift, which captures upfront expenditure periodically incurred to support the registry database.

The following table sets out estimates for these costs, based on the ABMDR's and ABMTRR's current expenditure, where this information was obtained.

Cost component	Estimated cost	Source
Registry office staffing	ABMDR currently employs 17.1 FTEs (excluding National Donor Coordinators) at a cost for 2015–16 of $2,295,521.	ABMDR End of Year Financial Year Report 2015–16 and ABMDR financials
Registry office and overheads	$1,375,065	ABMDR financials (excluding IT and staffing) 2015–16
Outcomes reporting	$342,345	ABMTRR financials 2015–16
International registry membership fees	$55,649	ABMDR financials 2015–16
Software licensing	$139,611	ABMDR financials 2015–16

9.1.6 Options considered

Table 43 presents the different scenarios under each category (including governance and recruitment), and logical pairings of options. For example, a central laboratory for tissue typing (3b) is paired with a central office for searching and matching activities (4b), enabling consideration of fewer options to inform decision making. Centralised donor coordination (2b) is paired with targeted recruitment (1b or 1c) because this activity would require central oversight.

Table 43: Outline of potential scenarios across sector activities

1. Recruitment	2. Donor coordination	3. Initial tissue typing/verification typing	4. Searching and matching	5. Governance and service delivery management
1a – Status quo	**2a – Status quo**	**3b – Status quo**	**4a – Status quo**	**5a – Status quo**
1b – Target (to meet domestic need)	**2b – Central office**	**3b – NextGen central laboratory (batch samples)**	**4b – Centralise (national provision)**	**5b –Assign service delivery responsibility to one body**
1c – Target (to meet domestic and international needs)		**3c – NextGen demand hubs (east and west)**	**4c – Demand hubs**	**5c – Government-led activity**

Note: coloured cells represent paired options, where one scenario is selected after adopting the same-colour scenario in other sectoral activities.

The five resulting options are described and evaluated below.

A. Option to maintain status quo

The status quo option captures all activities as they are arranged today.

1. Recruitment	2. Donor coordination	3. Initial tissue typing/verification typing	4. Searching and matching	5. Governance and service delivery management
1a – Status quo	**2a – Status quo**	**3a – Status quo**	**4a – Status quo**	**5a – Status quo**

Table 44 summarises the key benefits and risks of maintaining Option A.

Table 44: Option A key benefits and risks

Pros	Cons/risks
No need to manage the impact of organisational change	Registry resolution and donor base are not aligned to clinical needs
Search Coordinators, transplant centres and governments maintain current relationships with local laboratories	Potential for increasing reliance on international supply
	Cost risks include: • the existing fragmentation of the cost of coordination, recruitment and searches is unchanged, and there is a risk costs will increase • international HPC costs remain large and may grow • exposure to currency fluctuations from continuing to rely on international HPCs

B. Option to improve tissue typing

The option to improve tissue typing considers changing the current tissue typing arrangements to instead batch samples for processing at one preferred supplier or through demand hubs. Ideally, searching and matching activities should mirror these arrangements, and either be centrally provided or supported by demand hubs. This option leaves all other aspects of the sector unaddressed.

1. Recruitment	2. Donor coordination	3. Initial tissue typing/verification typing	4. Searching and matching	5. Governance and service delivery management
1a – Status quo	**2a – Status quo**	**3b – NextGen central laboratory (batch samples)**	**4b – Centralise (national provision)**	**5a – Status quo**
		3c – NextGen demand hubs (east and west)	**4c – Demand hubs**	

However, without addressing recruitment, there are key risks associated with only addressing the extent of initial tissue typing. Table 45 summarises the key benefits and risks.

Table 45: Option B key benefits and risks

Pros	Cons/risks
Local clinicians make better use of domestic registry due to improved information on domestic donors	Potential loss of expertise (staff and range of providers) under changed arrangements. This effect may be amplified if an international provider was selected, dissuading local laboratories from investing in newer-generation technologies for typing
Achieves better economies of scale from changing typing arrangements, potentially reducing typing costs	Potential for prolonged or increased reliance on international supply due to not recruiting underrepresented ethnic groups and an ageing donor pool (NWE donors)
Ensures a more consistent and coordinated approach to search initiation and matching that enables central oversight, reporting and resource allocation	Loss of local relationships between Search Coordinators and transplant centres, which, due to differences in processes may affect some jurisdictions more than others. These impacts include the approach Search Coordinators use to identify a match (Search Coordinators who understand a clinician's preference are able to conduct searches in line with those preferences) and the way search results and progress are communicated back to a transplant centre (which can be frequent or ad hoc). Centralisation may replace these informal activities with process-based arrangements.

	Cost risks include: • the existing fragmentation of the cost of coordination, recruitment and searches is unchanged, and there is a risk costs will increase • international HPC costs remain large and may grow • exposure to currency fluctuations from continuing to rely on international HPCs

This option does not address a number of residual risks associated with the key challenges identified in this review, including:

- the lack of a coordinated recruitment strategy and approach that addresses the need to recruit donors preferred by clinicians
- problems with donor coordination, such as a lack of a central point of contact for donors and ad hoc collection allocation arrangements
- complexities in current funding and governance arrangements, which are fragmented and lack shared strategic objectives. There are also limitations in proactively managing the registry so that it is fit for purpose, and in the level of oversight of national activities.

C. Option to improve recruitment and tissue typing

Under Option C, the current recruitment and tissue typing arrangements are altered to address key challenges relating to recruitment strategies and the typing resolution of new donors. In this option, 1b supports using a more robust domestic recruitment approach and is paired with 3b or 3c (batch typing or demand hubs) for typing donors. As searching and matching arrangements are currently aligned to typing arrangements in most states (using the same provider), it is assumed these activities would also follow the selection for 3 (using a central laboratory or demand hubs for searching and matching activities).

The status quo scenario for donor coordination has been excluded because a targeted recruitment approach would require central oversight of coordinator activities, and 5c (government-led activity) supports changing the service delivery management arrangements. These changes would be undertaken in line with a national approach to recruiting and typing, but it wouldn't be necessary to make wholesale changes to management and contractual arrangements.

1. Recruitment	2. Donor coordination	3. Initial tissue typing/verification typing	4. Searching and matching	5. Governance and service delivery management
1b – Target (to meet domestic need)	**2b – Centralise coordination**	**3b – NextGen central laboratory (batch samples)**	**4b – Centralise (national provision)**	**5c – Government-led activity**
		3c – NextGen demand hubs (east and west)	**4c – Demand hubs**	

Table 46 outlines the key risks and benefits of Option C.

Table 46: Option C key benefits and risks

Pros	Cons/risks
As per Option B, the likely benefits of improving tissue typing arrangements include: • local clinicians making better use of the domestic registry • reducing the cost of typing • using a more consistent and coordinated approach to search initiation and matching	As per Option B, the risks from improving tissue typing arrangements include: • loss of expertise and relationships associated with tissue typing and search coordination • increased reliance on international supply • exposure to the increasing costs of internationally sourced HPCs
Recruitment activities will be targeted and aligned to meet national needs, and they will	Requires the ABMDR (or another registry manager) to proactively manage coordination (a role not currently adopted), which may

Pros	Cons/risks
follow a more strategic vision	introduce implementation and change risks
More efficient donor coordination from using a centralised approach	Capabilities in analytics, using a central approach, are needed to inform strategy and collaborate on recruitment
More aligned national approach to managing service delivery across jurisdictions	While undertaken centrally, or in a standardised manner, there is a risk that aspects of coordination – such as donor consent, travel arrangements and lodging of forms – are increasingly devolved to transplant centres, placing a burden on hospitals. This situation would arise from a desire to localise engagement (or a perception that it would be more efficient to devolve these aspects of coordination)
	New risks associated with contractual and funding arrangements if government funding is pooled, or if new managers are appointed to support changed coordination, typing and searching activities, which are currently state-funded
	Upfront implementation costs will be required to reshape coordination, typing and searching functions

This option doesn't address a number of residual risks associated with the key challenges identified in this review, including:

- complexities in current funding and governance arrangements, which are fragmented despite sharing strategic objectives. Challenges also remain in proactively managing the registry so that it is fit for purpose, and in the level of oversight of national activities that are shared between numerous entities.

D. Option to redesign sector to address key challenges

Option D builds on Option C, proposing that governance and service delivery management of the sector are overhauled, in addition to changing arrangements for recruitment, tissue typing, searching and matching, and donor coordination. This option envisages giving one entity full responsibility for directing and managing activities in line with a nationally agreed strategy.

1. Recruitment	2. Donor coordination	3. Initial tissue typing/verification typing	4. Searching and matching	5. Governance and service delivery management
1b – Target (to meet domestic need)	**2b – Centralise coordination**	**3b – NextGen central laboratory (batch samples)**	**4b – Centralise (national provision)**	**5b – Assign service delivery responsibility to one body**
		3c – NextGen demand hubs (east and west)	**4c – Demand hubs**	

Table 47 outlines the key benefits and risks associated with Option D.

Table 47: Option D key benefits and risks

Pros	Cons/risks
As per Option C, the likely benefits of improving tissue typing and recruitment arrangements include: • local clinicians making better use of the domestic registry • reducing the cost of typing • using a more consistent and coordinated approach to search initiation and matching, and donor coordination • improving the domestic registry, which would reduce reliance on international donors	As per Option C, the risks from improving tissue typing and recruitment arrangements include: • loss of expertise and relationships associated with tissue typing and search coordination • increased reliance on international supply • exposure to the increasing costs of internationally sourced HPCs • the registry operator would need to have the ability to manage donor coordination and provide analytics that inform the sector's strategic direction • aspects of coordination may be increasingly devolved to transplant centres • costs associated with new contractual and funding

Pros	Cons/risks
	arrangements to support changed functions
Shared and coordinated strategy, governance and management activities would improve the operation of the sector	Large-scale reshaping of coordination, and typing and searching functions, as well as establishing a central entity with new responsibilities, bring implementation and change risks
Improved policy and decision making from better and more comprehensive analysis of trends and information on the sector, and more detailed reporting	Challenges may arise due to changed responsibilities and reporting across the sector, including for service providers who have not traditionally reported to a registry operator
Improved connections and communication between service providers and funders within the sector	Greater operational expenditure is required to support a larger registry operator with more functions
Improved direction and control of activities	Changed arrangements under new service providers may lead to problems with staff retention and loss of expertise
	Inability to identify a provider willing to manage some activities within the sector due to inexperience or lack of capability, misalignment with their organisational objectives or lack of desire to adopt new responsibilities (for example, managing the NCBCN or the ABMTRR)

This option addresses the key challenges identified in this review, but redesigning the current arrangements introduces new risks.

E. Option to establish a domestic and internationally oriented registry

Option E proposes introducing a central model for all elements of service delivery, to address key challenges within the sector. Arrangements focus on central service delivery, including batching tissue typing (3b), and for searching and matching (4b), and recruiting to significantly expand the registry to meet domestic and international needs (1c). One body would manage all service delivery within the sector (5b).

1. Recruitment	2. Donor coordination	3. Initial tissue typing/verification typing	4. Searching and matching	5. Governance and service delivery management
1c – Target (to meet domestic and international needs)	**2b – Centralise coordination**	**3b – NextGen central laboratory (batch samples)**	**4b – Centralise (national provision)**	**5b –Assign service delivery responsibility to one body**

Table 48 summarises the key risks and benefits associated with this approach.

Table 48: Option E key benefits and risks

Pros	Cons/risks
As per Option D, the likely benefits of improving tissue typing, recruitment arrangements, coordination and central governance include: • local clinicians making better use of the domestic registry • reducing the cost of typing • using a more consistent and coordinated approach to search initiation and matching, and donor coordination • improving the domestic registry, which would reduce reliance on international donors • improving oversight and control of the sector, using a shared and coordinated strategy • better policy and decision making associated with having more complete information	As per Option D, there are likely risks from improved tissue typing and recruitment arrangements, coordination and central governance including: • Potential for loss of expertise and relationships associated with tissue typing, search coordination and within the registry manager • Potential for increased reliance on international supply • Exposure to increasing costs from internationally sourced HPCs • New capability requirements of the registry operator to manage donor coordination and to provide analytics which informs the sector's strategic direction • While undertaken centrally, or in a standardised way, there is a risk that coordination aspects, such as donor consent/travel arrangement/form lodgement, be increasingly devolved to transplant centres, placing burden on hospitals due to a desire to localise engagement (or a perceived efficiency from a central perspective in devolving this aspect of coordination) Risks and costs associated with new contractual and

Pros	Cons/risks
	funding arrangements to support changed functions • Governance challenges associated with changed roles and responsibilities and associated reporting not traditionally held by providers • Detrimental impact on the management of some activities will fall outside the capability/focus of one registry operator (for example, NCBCN etc..)
Increasing provision of HPCs to international donors, which would support financial sustainability and, potentially, self-sufficiency of the administering organisation	Damage to reputation or the public's trust by distributing more HPCs to international patients
Greater collaboration and engagement with the international community	Greater burden on hospitals through increased donor collections for international patients
Improved branding for the registry operator, which may provide greater financial control and also the ability to better support cost recovery and potentially undertake philanthropic activities	More resources will be needed to coordinate the increase in the number of donors
	Managing and administering a larger, more active registry will increase operating costs

This option seeks to address all key challenges identified in this review.

Forward strategy for the NCBCN

In 2016, a Review of the NCBCN (the Stage Two Review of the NCBCN) analysed the current and future needs of cord blood banking in Australia. In that review, a number of challenges and future requirements were identified against which nine potential scenarios were considered to assess how value-for-money could be driven across the Network. A summary of the key benefits and risks associated with those scenarios is provided below. Further details on each of these scenarios and the full risks and benefits identified can be found in the full report of the Stage Two Review of the NCBCN.

Scenario	Key benefits and risks
Scenario 1 – Status quo Maintaining the role of the three banks under current collection rates	• Maintain ability to enhance quality and diversity of inventory • High recurrent costs for operation • Leverage existing relationships and expertise
Scenario 2– 2 banks,~7 collections (storage redist.) Maintaining two banks, with storage onsite, and collections in the two states in which the banks are based	• Cost savings and leverage existing facilities, while reducing in-hospital costs • Acceptability risk in deciding which bank closes • Leverage existing relationships and expertise
Scenario 3 - 1 bank ,~4 collection centres (new site) Maintaining one bank, with collections in the state in which the bank is based, but with storage offsite	• Cost savings in reduced operations (processing and collection) • Potential legal liability risks associated with initial transfer of stored CBUs • Lesser ability to enhance quality of inventory through fewer collections- diversity of inventory may reduce over time
Scenario 4 – 1 bank (new site),~10 collection centres Establishing a new bank with storage, with 10 collection centres	• Maintain ability to enhance quality and diversity of inventory • Regulatory burden unable to be shared among banks • May result in some in-kind support being withdrawn
Scenario 5 – 1 bank (new site),~7 collection centres Establishing a new bank with storage, with 7 collection centres	• Cost savings in reduced operations (processing and collection) • Potential loss in collection and processing expertise who cannot transfer • Regulatory burden unable to be potentially shared with other banks
Scenario 6 – 1 bank (new site), 0 collections Establishing a new bank with storage, no collections	• Cost savings in reduced operations (processing and collection) • Potential loss in processing expertise who cannot transfer • If there is a change to future requirements there will be a need to scale back up which will be time and resource consuming
Scenario 7 – alternative storage provider, 0 collections Ceasing all banking, establishing an alternative storage solution for the inventory	• Cost savings in economies provided by an alternative provider • Large reliance on international cords for Australian patients • If there is a change to future requirements there will be a need to scale back up which will be time and resource consuming
Scenario 8 – alternative provision Establishing a banking and storage arrangement with an alternative provider whom would also have collection responsibilities	• Ability to leverage wide collection networks already in place • High initial costs associated with transport of stored CBUs • Potential loss of banking knowledge and efficiencies of existing licensing arrangements
Scenario 9 – 3 banks, 0 collections Maintaining the role of the three banks without collections	• Harness processing expertise and AusCord efficiencies • High recurrent costs for operation • Loss of collection knowledge and relationships with maternity units • If there is a change to future requirements there will be a need to scale back up which will be time and resource consuming • Inability to increase quality of inventory

That review identified that governments should (full descriptions can be found in the Stage Two Review of the NCBCN report):

- consider the most appropriate structure to deliver on future needs, including the streamlining of collection and processing centres as well as the supporting governance arrangements. There may be specific opportunities in rationalising the Network to maintain one or two of the banks and still deliver on future requirements.
- undertake a stocktake of the existing inventory, and taking steps to rationalise CBUs in storage which are non-compliant, or are unlikely to be used; and
- re-consider the need to support the ongoing operation of the NT Program; and,
- consider undertaking a review and developing a strategy for HPC provision from all sources of which the Network is a part of.

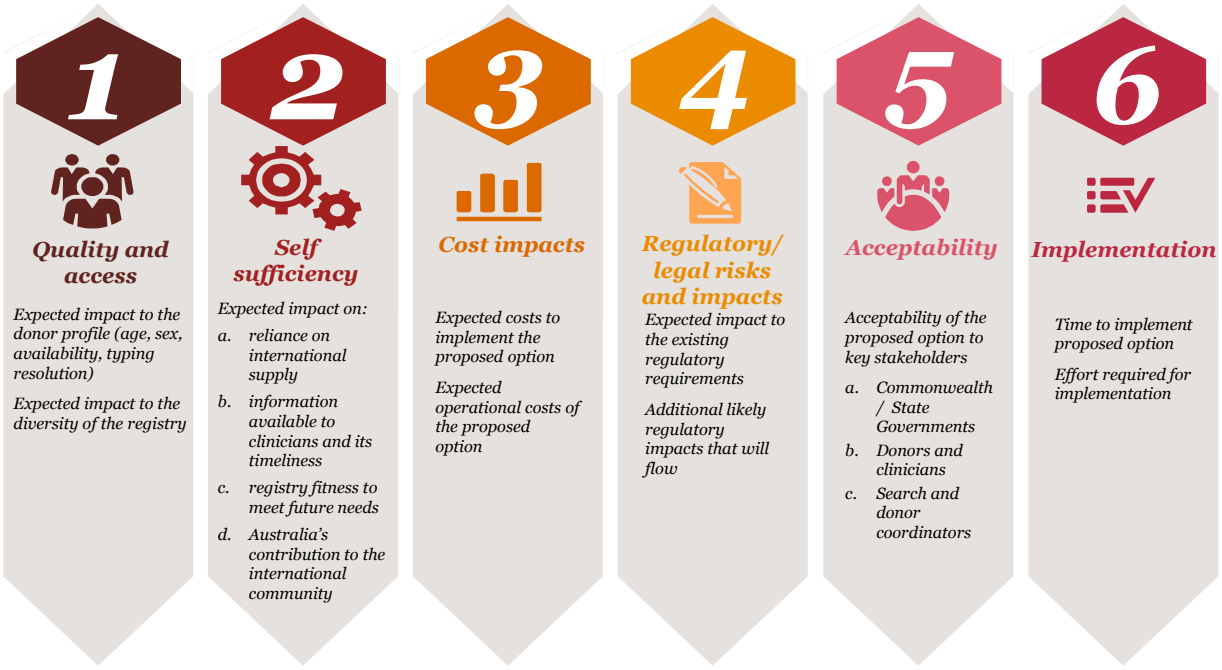
This review confirms the findings of the Stage Two Review of the NCBCN, including its key finding that Australia's current CBU inventory is likely appropriately sized to meet Australia's future needs. As part of government's consideration of the options of this review, the options provided in the NCBCN review should also be considered and affirmed in line with an overarching government position on the HPC sector.

9.2 Evaluation

To evaluate the relative impacts of each option, the following evaluation framework was adopted. It was built around criteria for the most important aspect of the sector – ensuring patients have access to HPCs – and includes the following:

- The way the registry recruits and maintains donors affects **quality and access** to HPCs.

- One of the tenets of Australia's registry is **self-sufficiency** to promote the ongoing enrolment of donors and, where possible, to facilitate the use of Australian HPCs over internationally supplied HPCs when clinicians have like-for-like choices.
- As with all government programs, the provision of HPCs to patients should be undertaken in a **cost-effective** manner. Both upfront spending (capital expenditure) and ongoing costs (operating expenses) are explored.
- The **regulatory and legal risks and impacts** should be balanced against the benefits of each option.
- The option selected should be **acceptable** to key stakeholders, including Commonwealth, and state and territory governments, donors, clinicians, Search Coordinators, Donor Coordinators and patients.
- It is important to consider the scale of **implementation** (both time and effort required) so that access to HPCs is not impeded and governments can make rational choices regarding resource allocation.



To provide a qualitative measure of the relative impact of adopting one option over others, the following scale has been used. The assessment reflects the benefits and risks outlined above for each option against these criteria, to provide a guide to their relative impact.

No/little negative impact *Minor negative impact* *Some negative impact* *Moderate negative impact* *Significant negative impact*

9.2.1 Quality and access

Quality and access relates to the expected impact on the availability and resolution of Australian HPCs, as well as the overall ethnic diversity of donors on the registry. Under status quo recruitment activities (options A and B), the number of donors and their diversity would not increase as there would no change to recruitment activities or tissue typing. With improved initial tissue typing (NextGen), under Option B, it is likely that clinicians see a relative improvement in the quality of information available upfront.

Options C and D adopt improved recruitment practices and NextGen initial tissue typing. Both actions would improve the quality of the registry and improve access to Australian donors, so they should be rated as having equal impact. However, Option E shifts focus to

international needs, meaning the ethnic diversity needs of the local population may not be addressed during recruitment, which is an indirect impact.

Criteria	*Option A – Status quo*	*Option B – Tissue typing*	*Option C – Recruitment and tissue typing*	*Option D – Address key challenges*	*Option E – Domestic and internationa lly oriented*
Quality and access					

9.2.2 *Self-sufficiency*

Self-sufficiency relates to the ability of Australia's registry to provide for domestic needs. It is exhibited when our reliance on international supply is limited, clinicians select Australian donors over international donors when they have a like-for-like choice, and when the registry is 'fit' to meet future needs. Additionally, Australia contributes to the international community supporting international patients where possible.

Under the status quo scenario, Australians' use of HPCs from international donors is not projected to change much, so Option A rates poorly compared to other options. Option B, in which new recruits to the registry would be better typed, may slightly reduce our reliance on international donors over time. It may also increase options for clinicians who would otherwise seek international HPCs, although this impact is likely to be nominal. In comparison, options C and D – featuring improved typing and greater ethnic diversity of new donors attracted under changed recruitment strategies – are likely to have a positive effect on our self-sufficiency. Option E risks that recruitment would be oriented to international needs, diminishing the domestic focus, which may reduce our self-sufficiency.

Criteria	*Option A – Status quo*	*Option B – Tissue typing*	*Option C – Recruitment and tissue typing*	*Option D – Address key challenges*	*Option E – Domestic and internationa lly oriented*
Self-sufficiency					

9.2.3 *Cost impacts*

The cost impacts of each option vary, both for the associated ongoing operational costs and the upfront investment required to implement new arrangements. A detailed analysis is required to properly consider the costs of each option. Such an analysis would identify the costs not captured in this review. It would also be able to assess the operational detail of each option, clarifying the specific costs of each activity.

In comparing the likely costs of each option, the following observations are made. Options B to E would lower the operating costs for tissue typing by producing economies of scale. However, these options may also drive proportional growth in the number of domestic collections needed to support Australian patients, which would increase the ongoing costs of coordinating and undertaking collections. This, of course, would be partly offset by the lower costs for international searches and collections, and potential cost recovery from increasing the number of HPCs provided internationally. Maintaining the status quo (Option A) risks escalating the costs associated with sourcing HPCs internationally. Additionally, it would mean continuing to have a fragmented funding model.

Each option would incur additional costs, particularly for upfront investment to implement the changes. Significant costs may be associated with establishing or procuring new arrangements with tissue typing providers, and setting up new central or demand hub offices and contractual arrangements for overseeing the whole sector (under options D and E).

In the absence of detailed costings, Option B is likely to cost less than other options, while Option C is likely to need greater upfront investment to rearrange service delivery activities. Option A clearly needs no upfront investment, but due to the increasing costs associated with relying on international HPCs, operational costs are likely to grow over time. Options D and E involve fundamentally rearranging the sector, which would need significant upfront expenditure. However, this option may lead to long-term gains associated with self-sufficiency and the ability to control and negotiate costs as alternative providers or options become available.[82]

Criteria	***Option A – Status quo***	***Option B – Tissue typing***	***Option C – Recruitment and tissue typing***	***Option D – Address key challenges***	***Option E – Domestic and internationa lly oriented***
Cost (upfront investment)					
Driven by:		New laboratory and tissue typing arrangements	New laboratory and tissue typing arrangements New central or demand hub offices Recruitment campaign costs Contractual rearrangement (service delivery)	New laboratory and tissue typing arrangements New central or demand hub offices Recruitment campaign costs Contractual negotiation and establishment costs	New laboratory and tissue typing arrangements New central or demand hub offices Recruitment campaign costs Contractual negotiation and establishment costs
Costs (ongoing expenditure)					
Driven by:	High reliance on international HPCs	Slightly reduced reliance on international HPCs Economies of scale for typing costs	Reduced reliance on international HPCs Increased donor engagement and recruitment costs Higher typing costs from increased	Reduced reliance on international HPCs Higher typing costs from increased volume Economies of scale for typing costs Greater	Reduced reliance on international HPCs Large increase in typing costs from increased volume Economies of scale for typing costs More

[82] Note: the costs of Transplant Coordinators, domestic collection and associated activities (donor work-up, education, testing, travel, courier costs and collection), and international searches and collection (including expenses, testing and collection) are not explored across options as these costs are expected to occur across all options. However, a detailed costing activity may provide further insight into the different cost drivers associated with clinical, coordinator and collection costs.

		volume Economies of scale for typing costs Increased volume of domestic collections	operational costs for central management and coordination Increased volume of domestic collections	resourcing to support registry operation Large increase in volume of domestic collections Increased cost recovery from providing HPCs internationally

9.2.4 *Regulatory/legal risks and impacts*

This criterion considers the expected impacts from existing regulatory requirements and additional impacts that might arise (such as the need to consider new regulatory arrangements or the legal implications of changes).

Any scenario that adopts an international laboratory to provide batch tissue typing (which could apply to options B to E) would probably be subject to TGA certification, which international providers currently don't have. Additionally, Option E, in which more HPCs are sourced internationally, could have moderate negative impacts (such as cost and effort) linked to sharing and transporting donor samples for testing. Options B to D also require renegotiation of service provider agreements, which may identify potential legal risks.

For different reasons, maintaining the current arrangements under Option A, with its heavy dependence on international supply, also brings risks with exposure to international regulatory regimes. Additionally, there may be risks in managing and using donor information if it was necessary to undertake retrospective typing or other use of samples that called for reconsidering the donor's original consent (explored in Appendix I). This would also apply to options B to E. Options D and E may expose the registry to some of the regulatory risks associated with changing tissue typing arrangements and negotiating with suppliers. However, using a centralised contractual management structure would avoid the risks associated with having multiple contracts with providers, as in option B and C.

Criteria	***Option A – Status quo***	***Option B – Tissue typing***	***Option C – Recruitment and tissue typing***	***Option D – Address key challenges***	***Option E – Domestic and internationally oriented***
Regulatory/ legal risks and impacts					

9.2.5 *Acceptability*

Each option is considered in terms of its likely acceptability to key stakeholders, including the Commonwealth, and state and territory governments, donors, clinicians, State Search Coordinators and Donor Coordinators.

Under current arrangements (Option A), some stakeholders are likely to be unhappy that some of the key challenges of the sector (such as recruitment and tissue typing) go unaddressed. This is especially so for governments and clinicians, who may be concerned that systemic issues are not addressed.

Government stakeholders are also less likely to accept options B and C, under which aspects of the sector such as tissue typing and recruitment are managed, but broader issues such as strategic risk (services will not be aligned to strategic direction) are not.

Stakeholders including clinicians, Donor Coordinators, Search Coordinators and the ABMDR are likely to welcome changes to tissue typing and recruitment (under options B and C) because it would aid their goal of finding better matches. However, providers delivering the services that would be most affected by changes to arrangements (for example, under options C to E) are less likely to accept the changes. It is likely that patients would welcome any changes that improve matching outcomes, especially outcomes under Option D.

The changed service delivery activities under options C and D are likely to be negatively perceived by some State Search Coordinators, Donor Coordinators and service providers who would be affected. If Option E was not managed carefully, donors and clinicians could react negatively to the changes, which would result in a significantly bolstered (and funded) registry from additional collections bound for international patients.

Criteria	*Option A – Status quo*	*Option B – Tissue typing*	*Option C – Recruitment and tissue typing*	*Option D – Address key challenges*	*Option E – Domestic and internationa lly oriented*
Acceptability					

9.2.6 *Implementation*

The level of effort required to implement the options varies. The following assesses the impacts in terms of relative costs (and resources), as well as time frames.

There is no impact under Option A because arrangements wouldn't change. Rearranging tissue typing and recruitment agreements (and potentially providers) would require procurement and engagement effort. However, it should be possible to remediate this between current and future agreements in 12–24 months.

Fundamentally rearranging the role of a national entity is a much larger task, compared to options B and C. In particular, it is likely a significant effort would be required to streamline funding arrangements from the current fragmented state. It would require ministerial, cross-jurisdictional, market and contractual engagement. It would also involve procurement activity, legal drafting and policy setting to agree a shared strategic objective(s). Additionally, it would probably take several years to implement. Options D and E would require similar effort and implementation time frames.

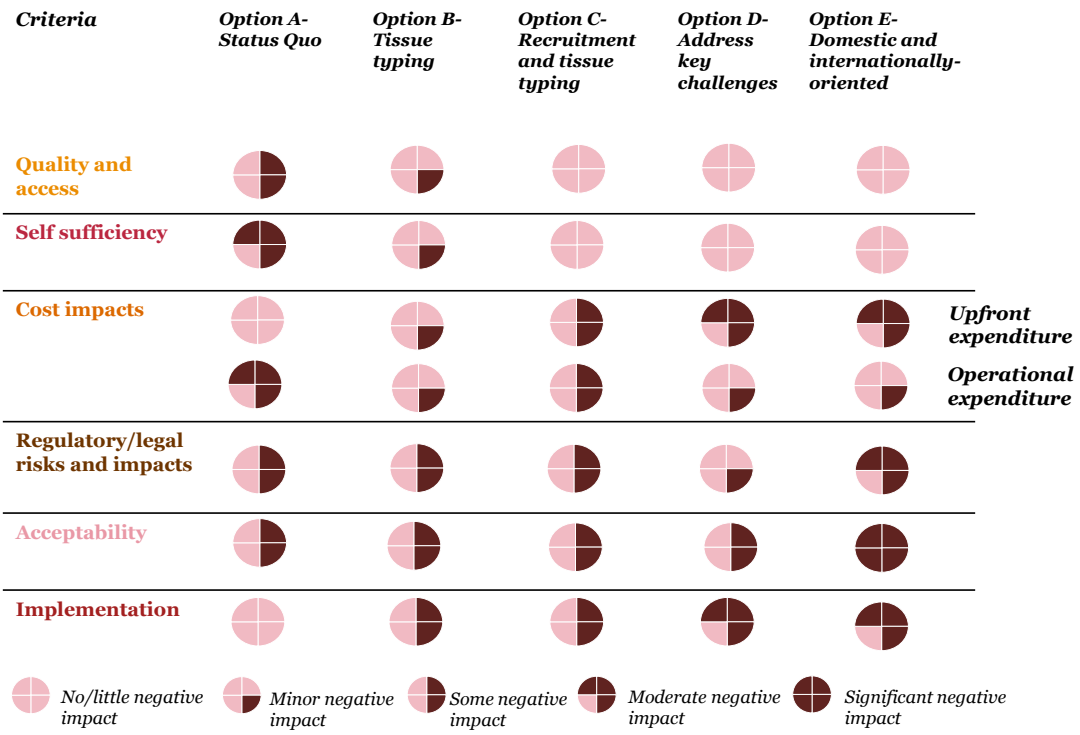
It is also worth noting that it would be some time before any of the new recruitment options changed the profile of the registry (the ABMDR estimates it could take 10 years to substantially change the donor characteristics to reflect target recruitment groups).

Criteria	*Option A – Status quo*	*Option B – Tissue typing*	*Option C – Recruitment and tissue typing*	*Option D – Address key challenges*	*Option E – Domestic and internationa lly oriented*
Acceptability					

9.3 Assessment

Figure 94 provides an overview of an assessment of the relative impacts of each of the options identified.

Figure 94: Assessment of options



The key sectoral challenges identified by this review included the need to improve the typing resolution of donors to provide better upfront information to clinicians and to recruit donors whose profile more closely aligns with clinicians' preferences. Additionally, governance, funding and reporting arrangements need to be addressed across the sector, which can be inefficient and fragmented. These challenges are addressed incrementally under options B to E. Options D and E best address key challenges, particularly with their proposal to empower one entity to oversee and manage service delivery activities. However, based on the criterion used in this evaluation, each option is likely to have risks and challenges.

Of all the options, options B and C, which address tissue typing and recruitment, have the fewest barriers. Option C also seeks to realign activities to a shared strategic direction across jurisdictions. Option D also envisages rearranging the operations of the sector, which will require greater upfront costs and effort to implement the new arrangements, compared to options B and C.

Option E is likely to rank more negatively across the criterion than other options, due to the overall change in direction and operation, and the likely risks associated with acceptance and implementation. This compares to Option A, which is likely to have greater ongoing costs due to increasingly expensive international donors.

In respect of acceptability – perhaps one of the most important criterion, given the reliance on volunteer goodwill and trust of patients and clinicians – there may be risks in adopting an option that is significantly oriented towards providing more donations internationally. While these risks might be overcome through careful messaging and communication, any perceptions of profit-making could unravel the foundations of the sector.

In view of the evaluation framework considered here, options B, C and D provide the greatest opportunity to address sectoral challenges, compared to other options. Maintaining the

status quo will not achieve the objectives of the registry, which are to meet future needs, without significantly rearranging recruitment and tissue typing activities. While complex, it's likely that Option D would provide the greatest longer-term gains by delivering a fit-for-purpose registry. It would also address issues such as governance and accountability, and set a strategic direction.

10

Implementation considerations

This chapter covers...

- *the need for a forward agenda for the haemopoietic progenitor cell (HPC) sector*
- *structure and contractual arrangements, including funding that should be considered*
- *some operational considerations for the organisation(s) that deliver services in the HPC sector.*

Key messages:

Governments should consider the findings of this review and work inter-jurisdictionally to determine the preferred option(s) to set the future strategy. The position and forward strategy should consider:

- *setting registry targets*
- *tissue typing requirements, including consideration of activities such as retrospective andpre-emptive high-resolution tissue typing of donors*
- *reporting requirements to assess whether the strategic direction is being met*
- *whether the National Cord Blood Collection Network (NCBCN) is meeting the sector's needs (including the proposed inventory and future collection needs)*
- *how to meet funding needs, including future needs and how they might be funded.*

A wide range of issues need to be considered when deciding on the preferred option, including funding, governance, reporting and the design of specific activities. These require government direction to support contractual arrangements.

Specific implementation considerations, such as how donors are recruited, tissue typing, technology and marketing will require consideration by the appointed service provider(s).

10 Implementation considerations

This review has identified challenges, needs and opportunities associated with the HPC sector. Chapter 9 presented future options, which considered how the activities of the sector could be rearranged. This chapter includes:

- matters governments should consider
- structure and contractual arrangements, including funding
- operational considerations for the organisation(s) that deliver services.

10.1 Developing an intergovernmental position

Governments should consider the findings of this review, and work inter-jurisdictionally to determine the preferred option(s) to set the future strategy. The position and forward strategy should:

- assist with achieving registry targets – including recruitment targets to meet Australia's future needs – and decide on the preferred approaches to recruitment, marketing and DNA sampling methods
- set tissue typing requirements for newly recruited donors, such as typing resolution standards
- focus on activities that meet Australia's needs, such as conducting retrospective or pre-emptive high-resolution tissue typing of donors, and major recruitment campaigns
- include reporting requirements to assist with the operation of the registry and inform decision making
- introduce service delivery approaches across parties, such as specifying the forward strategy to enable the NCBCN to meet the sector's needs (including its proposed inventory and future collection needs). If relevant, it should also change recruitment, coordination and tissue typing provisions, and time lines for achieving these changes
- examine funding needs and how to meet them. Because the majority of funding is from governments, there may be a need to explore ways to expand funding options and/or consider alternatives, such as philanthropic funding. How to achieve those funding streams, target funding levels and what those levels will finance, should all be examined.

Australia's international obligation to promote self-sufficiency underpins the strategy, and strategic directions should align with this obligation.[83]

The strategy should be developed in consultation with key stakeholders, including governments, health services, clinicians, donor and patient groups, and donor recruiters. This will assist with attaining buy-in and ensure relevant parties inform aspects of the strategy.

The language used in the strategy should be simple and accessible to the general public. For example, it should adopt consistent language around 'stem cells', reducing confusion about the difference between 'HPC transplant', 'bone marrow' and 'cord blood'. Inclusive language will also help convey the breadth of activities that support the sector, and is something that

[83] World Health Organization (2012) Expert Consensus Statement on achieving self-sufficiency in safe blood and blood products, based on voluntary non-remunerated blood donation (VNRBD).

international registries have sought to adopt (for examples, see Anthony Nolan and Canada's One Match network in Appendix E).

The strategy should provide a holistic picture of the sector and how it will meet Australia's future needs. Governments need to consider a number of critical aspects of the HPC sector, to address the key challenges found in this report. While the responsible agency(ies) will implement any changes, governments will set the strategic direction and embed it in contractual arrangements. These are explored below.

10.2 Structure and contractual arrangements

Governments should bear in mind their agreed strategic direction when they consider the structural and contractual arrangements of the organisations that deliver the services. This section seeks to explore these considerations.

10.2.1 Governance

A formalised governance group that builds on the role of the ad hoc Jurisdictional Haemopoietic Progenitor Cell Committee (ahJHPCC) should be established to provide oversight and policy direction to the sector. This committee will be a forum to discuss and review strategic direction to ensure it is in line with current government and patient needs.

The governance group should have formal terms of reference outlining its scope, frequency of meeting, reporting responsibilities and role as a forum for:

- sharing of information and measures of activity across jurisdictions
- monitoring contractual progress against funding or service agreement(s) and specified reporting measures, and ensuring accountability
- providing strategic direction and guidance to the sector, including on key decisions sought by the registry operator.

Lessons from the way in which the NCBCN is governed may be drawn to establish how the sector can be more effectively governed

In addition to these functions, the forum should periodically perform sector-wide reviews of progress, and where it deems necessary, strategic reviews of needs. The review function may incorporate a role for clinicians and health professionals, who are effectively customers, to provide direction on future needs.

Participants of the forum would include representatives of all governments, the registry operator and, potentially, a managing contractor of the sector's service providers (if, for example, this contract was held by an entity other than the registry operator). This would enable upward reporting to governments to inform policy making, but would not be a forum for service delivery management.

10.2.2 Service delivery responsibilities

At present, agencies such as the Australian Bone Marrow Donor Registry (ABMDR), the Australasian Bone Marrow Transplant Recipient Registry (ABMTRR) and the Australian Red Cross Blood Service (ARCBS) provide the different services within the HPC sector. While this structure meets the needs of Australian patients requiring transplants, it does not provide a national perspective on activities such as recruiting new donors to the registry, high-resolution tissue typing and outcomes reporting.

Therefore, in line with the strategic direction, governments should consider the appropriate structural arrangement for service delivery and whether it assigns responsibility for HPC services across Australia to one or more agencies. If it uses one agency, it would be responsible for meeting all the government's strategic objectives, and would procure or

contract with multiple other parties to deliver underlying services such as tissue typing, donor recruitment and coordination, and registry maintenance (as discussed in Chapter 9).

Furthermore, there is scope to consider whether there are additional roles for non-government organisations to support the sector, such as patient and donor groups or volunteers. This is explored further in Appendix H.

10.2.3 Contractual arrangements

After the strategic direction has been set and the organisation(s) appointed to deliver services, governments should enter into contractual arrangements with the organisation(s). The current contractual arrangements are aligned to the four programs (the Core Services funding, NCBCN, ISP and BMTP) and state-based government arrangements with the ARCBS, PathWest and Pathology Queensland. There may be opportunities to refine these contracts and make them more cost-efficient.

Table 49: Opportunities in existing program arrangements

Program	Current contractual arrangement	Funding
Core Services Funding	A specific funding mechanism for managing the registry should be developed to provide clarity about the activities and objectives of registry managers, set out key metrics and goals to be achieved, as well as reporting	The current funding for operating the registry is insufficient. Additional funding should be sought and the registry's operations should be reviewed to better understand expenditure and resource allocation needs
National Cord Blood Collection Network	This program merges the funding arrangements for the NCBCN and the ABMTRR, but it could instead be split for the individual activities. This would help clarify funding objectives. It would also assist with measuring performance, as well as direct governance and reporting lines for each activity	There are opportunities to review the level of funding to organisations delivering on the NCBCN and the ABMTRR, which should be in line with any proposed changes to the overall strategy
International Searches Program (ISP)	The ISP and Bone Marrow Transplant Program (BMTP) could be merged and managed through one responsible entity. Activities associated with the initiation, funding and support of international donors could be efficiently co-managed, and would provide transplant centres with one point of contact	Should these programs be managed by one entity, then funding could be linked to activities. The funding could be calculated by tracing applications to identify patterns where hospitals or types of patients lodge searches that result in an application to the BMTP. These activities could be managed to measure the effectiveness of the program and inform future funding

Bone Marrow Transplant Program	Mechanisms could be introduced to reduce the exposure of any managing entities to the risk of uncapped funding liability (including any cash flow needs) and to ensure that the program is patient-centred and simple to navigate.	allocations. This function is currently undertaken by the Commonwealth, using information provided by the ABMDR. Centralisation will reduce reporting and may enhance timing.
State-based contracts with ARCBS, PathWest and Pathology Queensland	These contracts could be formalised (where they don't exist) and separated from other laboratory services to promote transparency and enable clear tracking of metrics. The metrics should align with intergovernmental direction	There are opportunities to capitalise on high typing volumes and acquire higher-resolution typing methods by streamlining tissue typing contracts across the country

Clauses should be established in funding agreements and/or service agreements to enable contract managers (and/or funders) appropriate control to meet the required objectives. It would also enable the contract managers to make the necessary adjustments should these objectives change.

Building appropriate mechanisms into the contract would also enable performance management against defined key performance indicators (KPIs) that support the defined strategic objectives.

10.2.4 Reporting

The contractual arrangements should specify the type of reporting the organisation(s) undertaking activities in the sector must provide to the governance committee. This reporting should include KPIs to measure progress against the defined strategic objectives.

10.3 Operational considerations

The agency/agencies responsible for activities in the sector should consider the following points, with strategic direction provided by the governments.

10.3.1 Achieving registry targets

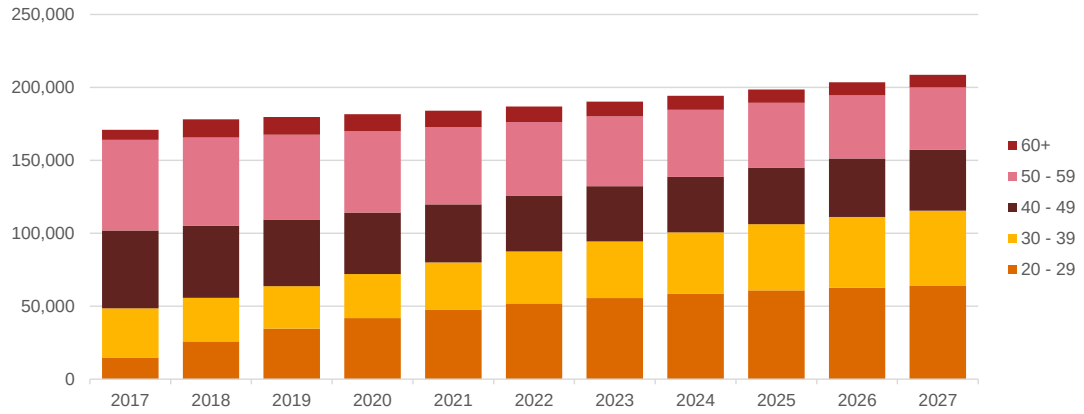
A strategy that outlines the registry's targets should be made available to the public – even in short form – as it will increase understanding of the need to register as a new donor.

The targets should be simple and easily measured. Clinicians prefer younger male donors, who should comprise a large proportion of new donors recruited, given that the current registry profile does not perfectly align with this preference. If, for example, it was decided to have a registry with around 200,000 donors (acknowledging that while the current registry of 160,000 appears to be sufficient, there may be merit in building a 'buffer' to account for low donor availability and those who 'drop out'), the profile of the registry could be changed by recruiting 98,000 donors aged 18–30 over the next 10 years. (To reach 200,000 donors by 2027, an additional 29,087 donors are required. However, nearly 69,000 of the current donors are aged 50 or older and will need to be replaced as they are retired at age 60.)

If all new donors recruited are aged below 30, approximately 14,000 donors should be recruited each year. This assumes that 20% of all donors within an age bracket will pass into

the next age bracket each year and that 100% of donors in the 60+ age bracket will be retired within a year of turning 60).

Figure 95: Projected donor age re-profiling under a target registry of 200,000 donors by 2027



Source: PwC analysis of ABMDR donor data

This review doesn't pass judgment on the upper age limit for recruitment, except to say that clinicians are less likely to select older donors, who yield a lower return on investment given their shorter length on the registry before they are retired. International registries are adopting younger thresholds, capping at age 30 or 35. However, in Australia this cap should be informed by the number of donors the recruitment provider considers is needed to achieve recruitment targets. Additionally, if a lower age limit (say, age 30) is adopted, consideration should be given to the way the registry is marketed to younger age brackets. Other aspects of engaging younger donors also need to be considered. These include better supporting their welfare (for example, the UK experience is that younger donors may be more anxious about the procedure) and understanding their financial circumstances. Many people aged 18–25 will have less secure employment compared to older donors, and may require more support from the registry to access leave for donation and to cover expenses not paid for under casual employment. They may also need greater flexibility in collection scheduling.[84]

The recruitment targets (age brackets, total number to be recruited and recruitment campaigns) should be embedded in service agreements with recruitment providers, to ensure alignment with the strategy. Consistent messaging that is easy to access and contains clear guidance about which donors are being targeted should also be communicated to potential donors.

Targets should be regularly reported on and publicly available. Further commentary on reporting is provided below.

10.3.2 Recruitment approach

When determining the most appropriate mechanism for recruiting the targeted donors, consideration should be given to the best method for capturing a DNA sample. Newer methods – such as a buccal swab or saliva tube – are significantly cheaper than Australia's traditional approach of taking a blood sample. These methods also avoid the need to use a phlebotomist and they comply with the (different) risk criteria of the ARCBS (under

Many international registries have moved to using buccal swabs or saliva tubes to enhance recruitment and reduce costs

84 Australian Parliamentary Library (2015) Casual Employment in Australia: a quick guide, accessed at: http://www.aph.gov.au/About_Parliament/Parliamentary_Departments/Parliamentary_Library/pubs/rp/rp1415/Quick_Guides/CasualEmploy

ARCBS criteria, a potential donor may be unable to register because of having a cold or other medical indication that could affect a blood donation, but not a HPC donation).

The following table shows the relative costs of three different methods used to collect a DNA sample. These figures are based on recruiting 5,561 new donors a year (2016 figures) and demonstrate the significantly higher cost of taking a blood sample compared to using a buccal swab. These figures do not include costs associated with logistics, batching, storing or shipping (which are likely to be around $60 per sample).

DNA sample type	Blood sample	Saliva tube	Buccal swab
Estimated cost per sample	$220	~$20	$15
Total annual cost	~$1.2 million	~$110,000	~$85,000

Source: PwC estimations, based on ABMDR consultations

Other factors for consideration when adopting an alternative approach to DNA sampling include ease of swabbing with a buccal swab or spitting into a saliva tube. These easier sampling methods – which can be done at home, are not invasive and don't require scheduling or travel to and from a donor centre to draw a blood sample – might increase the number of registrations. Additionally, samples can also be stored for longer than blood before becoming non-viable, thus better supporting batching of samples for testing. However, some stakeholders said the action of drawing blood helps reinforce a donor's commitment to donation if they are called up, and, if they are not anxious about needles, they are less likely to opt out of donating, which is medically invasive.

A full analysis of the different options for collecting DNA samples should be considered to inform the most appropriate approach in the Australian context.

10.3.3 Tissue typing

Currently, tissue typing arrangements are disparate and provide plenty of scope for cost-inefficiency because each state negotiates its own agreement, instead of there being a national agreement. Depending on the future option pursued, there are opportunities to streamline negotiated agreements to capitalise on higher typing volumes as well as require use of high-resolution typing methods. Laboratories could scale up to test greater volumes, which would be more efficient. For example, a number of international registries use providers that are able to undertake high-volume typing of samples to a consistent resolution (in streamlining typing, these laboratories do not undertake ad hoc requests for testing at different loci and at low volumes).

This review was advised that the ARCBS plans to roll out Next Generation (NextGen) tissue typing across its east coast laboratories in the new financial year (from July 2017). This may fundamentally change the arrangements it has with the states and territories.

The Queensland Cord Blood Bank recently signed an agreement with Pathology Queensland to run high-resolution typing on its collections. This capability may soon be available in all laboratories in Australia, but it is unclear whether they could handle the current volume of newly recruited donors and in what time frames typing could be achieved, even with these new capabilities.

Consideration should be given to requiring high-resolution typing at six loci for new donors where NextGen technology is used. Depending on the capability of alternative providers and the cost, there may also be scope to explore third-generation sequencing to gain even higher resolution information on new donors.

Just as recruitment methods vary, there are significant differences between providers of initial tissue typing. The differences are seen in estimated figures per sample attained. As

such, they are very high level and would need to be validated through market engagement. This demonstrates that tissue typing arrangements should be reviewed to assess whether high-resolution typing could be adopted and at what cost. Again, these estimates are based on comparisons for recruiting 5,561 new donors a year (2016 figures) and do not capture the costs of logistics, storage or other associated expenditure.

Initial typing	Domestic – low resolution	Domestic – high resolution	International – high resolution
Estimated cost per sample	~$480	~$180	~€30
Total annual cost	~$2.7 million	~$1 million	~$250,000

Source: PwC estimations. Currently, most tissue typing in Australia is undertaken to a low resolution and these costs have been extracted from sighted tissue typing agreements. High-resolution typing is only undertaken in Western Australia and these costs have been based on consultations with PathWest, while international high-resolution costs are derived from consultations with the ABMDR and the Anthony Nolan Registry.

A similar assessment could be made about whether to adopt retrospective typing as part of the strategy. This reflects that many committed, willing donors in the desired age range are already on the registry. It could be worth investing in re-typing the DNA samples of desirable donors currently stored in laboratories to a higher resolution. This could include registered male donors aged below 30.

10.3.4 Donor welfare

Looking after donor welfare could include producing 'how to' guides and educational material such as a short video showing what happens to a donor during the donation process. This material could be held in a central repository and be made available country-wide. It could include detailed information available online for potential donors seeking further information.

Additionally, the registry could consider working with service delivery entities to develop information for patients. Often, when a patient learns that they need to search for an unrelated donor, they will seek out information themselves. A clinician will always be the most important source of information for a patient, but if the registry were to provide consistent, consolidated information, it would strengthen the perception that it is also a leading source of material on the topic. This would also help to make the patient experience consistent across hospitals.

10.3.5 Marketing

This review has observed that there is limited donor engagement beyond the ARCBS blood donor centres, or when a donor is identified as a potential match. Many international registries have adopted modern approaches to engaging with donors to improve their education, awareness, retention, and, ultimately, commitment to donating if they are called up. Given the lower levels of donor availability and limited channels for engagement under current settings, the registry should rearrange the way it markets itself and engages with donors. As a complement to its strategy, the registry should:

- improve its engagement with potential donors by providing better education and outreach materials. This would enable recruited donors to reach out to their own communities on behalf of the registry, extending its reach
- use social media to promote its role and the importance of joining or becoming a supporter. This would also extend its reach and provide a better sense of connection between registered donors and the registry

- improve its messaging to potential and registered donors about the importance of their role, reinforcing their commitment. It would also increase awareness in the community and promote goodwill towards altruistic donors
- improve messaging about the role of different entities in the sector. Currently, potential and actual donors engage with different entities and do not have a clear understanding of how the sector is arranged and how the parties work together (for example, the steps in engagement of donors first register with the ARCBS, then ongoing engagement with the ABMDR who manage the registry, then in engaging with transplant centres if the donor is 'called up' or with cord blood banks for prospective parents). Consistent messaging that presents the registry as a unified organisation would assist donors to navigate the donation process – ideally through one point of contact – and build their confidence in the role of the registry.

10.3.6 Technology and infrastructure

A key area for improvement identified in this review was the need to improve business analytics and reporting to inform policy, and measure outcomes and progress. The information management systems of the registry and service delivery parties should be bolstered to support regular reporting to the governing body and to streamline data capture processes, which are currently spread among providers. Improved practices would provide more complete and accurate data for reporting, assist with timeliness, and reduce manual manipulation and extraction. Ultimately, this would eradicate duplicated data handling and reporting, address poor decision making and improve financial reporting procedures. This may require the introduction of new data reporting and capture processes, or potentially, the development of a simple database that is centrally held and managed. Where possible, opportunities for integration with key systems should be considered to reduce manual handling and potential for data errors.

The analytical and reporting functions should enable automated processes and data capture, and allow for query functionality to enable ad hoc extraction of data of interest. This would also support any progress reporting built into future funding agreements and alleviate some the administrative burden associated with reporting under current funding agreements. Analytics should exist for:

- new donors to the registry and include:
  - donor age
  - donor ethnicity
  - donor jurisdiction
  - donor's reason for joining and how they became aware of the ABMDR
- clinicians' requests, covering the characteristics of patients – both domestic and international – and include:
  - HPC type
  - time frames: date of request, transplant urgency, time between request and typing results (including which laboratory processed the sample to measure processing time differences), and time between donor consent and mobilisation
- clinical decisions, such as reasons for selecting one HPC over another, for:
  - donors who go on to work-up, as well as those who ultimately donate, and include:
    - time between request and work-up date
    - donor availability metrics and reasons for donor unavailability
    - costs of collections, including donor expenses.

Ideally, information would be linked to the outcomes registry to 'pre-populate' transplant information and make this reporting process less burdensome on transplant centres, as well as more complete from the registry's point of view.

Additionally, information on donor outcomes should be captured in the same system, removing all aspects of manual handling and data capture.

10.3.7 Reporting and performance management

Regular performance reporting and trend reporting should be incorporated into the activities of service providers. Ideally, reporting of the sector should be centralised and collated to present a unified view of trends, progress and activities. For example, service providers should provide relevant inputs to the registry operator for upward reporting.

There may be a role for clinicians and other parties with an interest in the activities and strategic objectives of the sector to contribute to reporting. A number of international registries allow professional groups to contribute to outcomes data collection and reporting; however, the Bone Marrow Transplant Outcomes Reporting Review touches on this aspect.

Reporting should be made available to key stakeholders, and consideration should be given to providing a publicly accessible version on websites and to stakeholders with an interest in the registry's performance.

Three aspects of reporting should feature in the registry's operation, and could be included in reporting obligations under any future funding agreements. These are:

- reporting on the composition of the registry itself, including key statistics, to inform decision making and track progress
- financial reporting, capturing income and expenditure, to meet reporting obligations under the funding agreement, measure efficiency and potentially report publicly on how money is expended (consistent with practices adopted internationally and by many other non-government activities)
- donor and patient outcome information, for internal monitoring of donors and reporting to decision makers. This data should be centrally captured to provide insight into trends, and to have complete coverage of outcomes.

Bone Marrow Transplant Outcomes Reporting Review 2017

In 2017, a review was undertaken of outcomes reporting by the Australasian Bone Marrow Transplant Recipient Registry to assess is current practice for reporting outcomes can meet current and future reporting demand. The review identified a number of issues which interrelate to this review and are outlined below:

- while stakeholders strongly support the registry function, there is limited awareness of the ABMTRR's role
- Governance and oversight relationships are complex, informal and are comprised of multiple parties
- The funding mechanism for the ABMTRR is inefficient due to its indirect nature
- There is opportunity for improvement in the completeness and timeliness of data collection and cleansing processes
- The core clinical reports produced by the ABMTRR are not used widely to inform clinical practice
- Current financial arrangements are unsustainable to support the roles of the registry

The review recommended that by mid-2018:

1. That Option 2 (Maintain the ABMTRR, but strengthen the current model) is the preferred operating model for future provision of priority functions
2. To undertake a project to establish a more robust governance structure to oversee the new operating model and deliver improved transparency and representation
3. Establish formal contact points and communication processes with Commonwealth and all State and Territory Departments of Health
4. Undertake a project to develop and implement standard benchmarking and peer comparison methods

And, within the next 24 months:

1. Review costs and resource requirements for Registry operations to ensure funding is sufficient to support a sustainable, efficient operating model into the future
2. Undertake a focused review of the range and definitions of data items and collection instruments, focusing on the utility for Australia and New Zealand reporting purposes and their consistency with international registries
3. Review the range of reporting products and the channels used for reporting in order to strengthen the utility and accessibility of the data
4. Review the data flows from transplant centres to the ABMTRR and international registries, with a focus on opportunities to streamline, eliminate double handling and reduce the effort required by transplant centres.

Donor outcome information should be captured on a central system. Information from each transplant centre's donor follow-up procedures should be integrated with outputs. This would provide a longitudinal view of donors beyond the adverse events that are captured in the World Marrow Donor Association's (WMDA's) Serious (Product) Events and Adverse Reactions (SPEAR) program. Possible integration with the Australasian Bone Marrow Transplant Recipient Registry's patient outcomes database might be considered as the systems and data capture procedures largely align with the needs of an outcomes database and is already familiar to transplant centres.

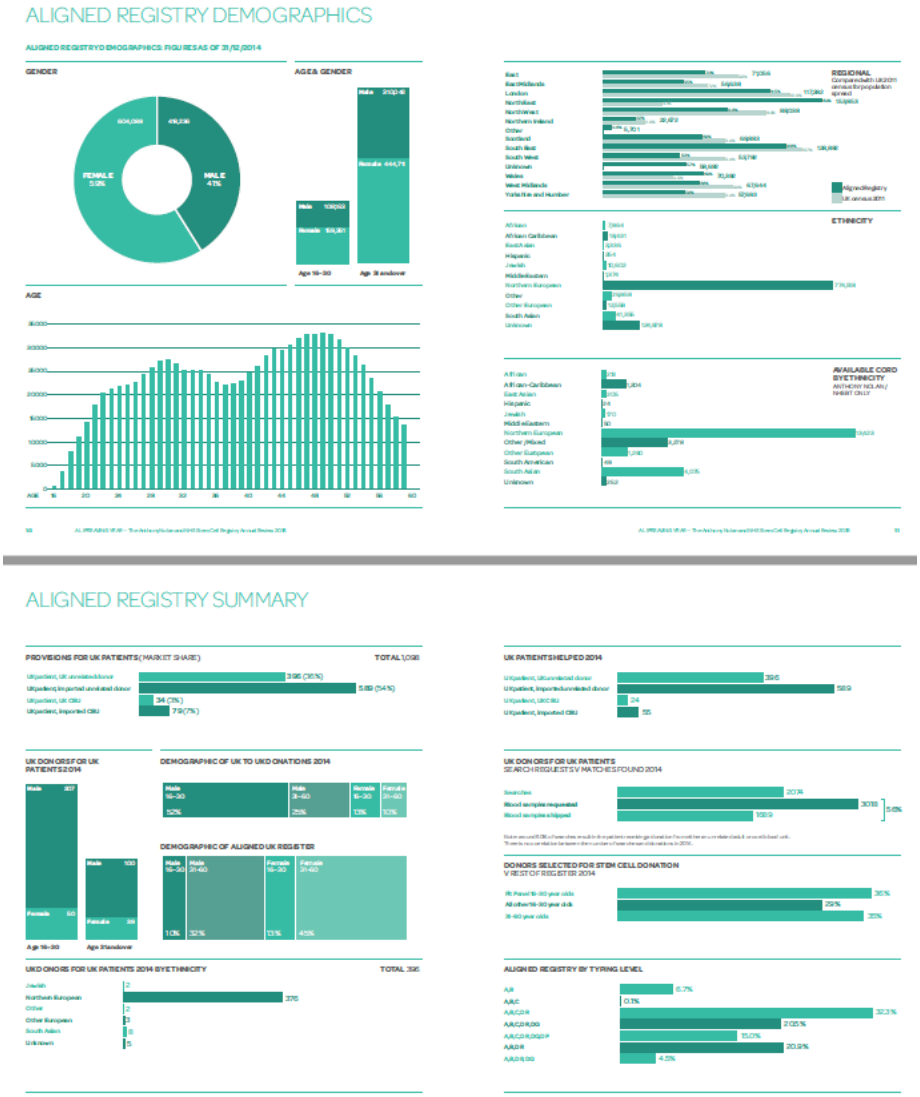
Like the UK's State of the Registry, key metrics that would guide decision making include:

- progress towards recruitment targets (number of new recruits and donor characteristics such as age, sex and ethnicity)
- percentage of the registry in specific ethnic groups
- percentage of the registry that is male

- donor availability metrics (percentage for the reporting period and change from previous reporting periods)
- retired recruits (over the reporting period)
- number of searches initiated over the reporting period
- percentage of international searches and donors
- number of patients matched over the reporting period (including which were matched to domestic or international donors and the reasons, as well as data on match requests where no match or an undesirable match was found)
- donor utilisation figures, possibly by utilisation
- donor age profile
- number of cord blood units (CBUs) collected (number banked and number released)
- number of internationally provided HPCs and key destinations.

Importantly, reporting should be made public to enhance awareness of how vital it is to donate and to build public trust in the role of the registry and how individuals are contributing to the bigger picture. Figure 96 shows an extract of Anthony Nolan's publicly available State of the Registry report. This type of reporting may also address, in part, the findings and recommendations of the Bone Marrow Transplant Outcomes Reporting Review (as shown above).

Figure 96: An extract of Anthony Nolan's State of the Registry report



Source: The Anthony Nolan and NHS Stem Cell Registry Annual Review 2015: A lifesaving year

10.3.8 Cost transparency

During consultations for this review, it became clear there was a need for improved transparency of costs and funding needs. A number of transplant centres communicated that without a guide on the true cost of undertaking extended typing, verification typing, book searches and international collection of HPCs, clinicians were often agnostic when deciding which option(s) to proceed with. While certainly not an indicator of whether a donor was the appropriate match to a patient, some centres reasoned that clinicians might be more price-sensitive in decision making if this information was available upfront.

Consideration should also be given to holding cost recoveries from providing HPCs to international patients in trust so that a governance committee could guide its disbursement, much like the Cord Blood Trust. At the very least, key reporting on this line item should be captured to promote transparency and inform decision making.

10.4 Implementation risks and considerations

In selecting the most appropriate option for the HPC sector, the Commonwealth and state and territory governments need to understand and address a number of key risk factors. The following sections outline these factors.

Legal questions and considerations

During consultations and evaluation of options, this review identified legal and ethical questions. Professor Emeritus Loane Skene[85] has considered a number of these to guide the assessment presented in this review. Her perspectives are shared at Appendix I.

The key risks are:

- A targeted recruitment approach may create perceptions of discrimination; however, as donating is voluntary, these perceptions are likely mitigated and are unlikely to raise any particular community concern, given the benefits of donating.
- Sharing DNA among laboratories and using volunteer donors and CBUs for purposes other than haemopoietic reconstitution may raise legal and ethical risks, depending on the extent of consent sought.
- Sharing donor and patient data among entities, including international entities, may raise legal and ethical risks, although these would probably be mitigated by complying with privacy legislation.

The perspectives provided do not constitute legal advice. Implementation planning would need to include development of the formal legal position.

An initial assessment of the key risks associated with implementation of the preferred option is presented in Appendix H.

Future state regulation

Regulatory requirements may change with any new arrangements and activities. The government should consult closely with the Therapeutic Goods Administration (TGA) when considering the appropriate option, to identify regulatory risks or considerations. Some regulatory considerations identified are explored below.

International transit

Any future option that includes transporting blood samples for international tissue typing would need to take into account the need for an export permit to transport a blood product with more than 50mL volume. This means that new donor samples of blood would be subject to permits and is a consideration when assessing the viability of pursuing international typing of samples from new Australian donors. In contrast, saliva samples may be exempt if each was less than 50mL[86], meaning that buccal swabs may have free passage for international typing.

Tissue typing

TGA approval may be required to use in-vitro diagnostic devices (IVDs) during tissue typing, which falls under the TGA's regulatory oversight domestically. The IVD kits have implicit approval under current regulatory requirements for Australian tissue typing laboratories, which are all accredited by the National Association of Testing Authorities (NATA). However, international laboratories that use IVD kits for tissue typing new Australian donors may need TGA certification for their test criteria, kits and the quality of the facility.

Induced Pluripotent Stem Cells/Ex Vivo expansion techniques

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[85] *Professor Skene is a Professor of Law in the Faculty of Law and an Adjunct Professor in the Faculty of Medicine Dentistry and Health Sciences at the University of Melbourne. She is a member of the National Health and Medical Research Council's Legislation Review Committee on Human Cloning and Embryo Research (the Heerey Committee) and the Australian Health Ethics Committee. Professor Skene is widely published in the field of medical law, and was engaged by PwC as an expert adviser to this review.*

[86] Under Schedule 6 of the Customs (Prohibited Exports) Regulations 1958, exporting of goods is prohibited if permission is not granted under regulation 8 Item 1.

Under current regulations, the TGA does not regulate HPCs when stem cells are destined for clinical use that requires haemopoietic reconstitution. This captures all HPC transplants currently undertaken in Australia for indications recognised as benefitting from their clinical application. However, recent technological advances hold promise for the future use of induced Pluripotent Stem Cells (iPSCs) and ex vivo expansion techniques, which manipulate stem cells for use in HPC transplants and in new transplant treatments. These techniques involve greater intermediary effort and manipulation than that specified in the Excluded Goods Order, which excludes HPCs for *direct donor-to-host* transplantation or HPCs *collected … and manufactured … under supervision of [the same] medical practitioner … for treatment*. As such, these techniques and products would probably need to meet TGA requirements.

Under such requirements, the organisation manipulating cells for use would be subject to the TGA's Biologicals Framework, unless otherwise excluded. The organisation would need to be able to demonstrate the clinical application (through clinical trials) to apply for approval to distribute the product for use in Australia. It would also need to demonstrate that it complies with the code of Good Manufacturing Practice (cGMP), to gain licensing approval to produce and include its product on the Australian Register of Therapeutic Goods (ARTG). Likewise, iPSCs of international origin would be subject to these requirements.

There are various mechanisms for accessing unapproved products, including the TGA's Special Access Scheme, clinical trials or by being an authorised prescriber. Clinicians can use one of these avenues to seek access to products not yet included on the ARTG or approved for use in Australia. Approval is granted on a case-by-case basis and, in this scenario, would likely fall under the clinical provisions.

Under the current regulatory framework, new products must demonstrate clinical efficacy, although the TGA may weigh access in special cases against the seriousness of the disease the product is being used to treat. Additionally, the NCBCN has Special Release Procedures to enable release of CBUs for clinical trials for purposes other than haemopoietic reconstitution.

10.5 Next steps

We recommend that governments consider these options to assess the appropriate next steps. Governments should take into account the strategic needs identified, focusing on reinvigorating the registry to improve the donor profile to better meet the needs of clinicians. This would better position Australia to meet its future needs and deliver on the government's continuing commitment to providing Australians with access to HPCs for transplantation.

To act on the findings of this review, governments should consider undertaking the activities outlined in Figure 97 and described below.

Figure 97: Proposed next steps following this review

The first step would be to understand the state and territory governments' preferred option(s) from the findings of this review, and draw up a shortlist of options. To support the development of an agreed intergovernmental position, detailed costings of the preferred option(s) should be undertaken to better understand the implementation and operating costs.

Governments should then agree on a strategy for the HPC sector for the next five to 10 years, to provide the direction needed to change arrangements. For example, the strategy may guide the desired registry size, target number of new donors, tissue typing resolution and sectoral arrangements that best suit governments (for example, whether funds should be consolidated for tissue typing or remain with the states). The strategy should remain a high-level document for communicating policy needs, objectives and desired outcomes. However, it should also specify key actions, responsibilities of governments to deliver the preferred option(s), and key inputs and outputs.

Governments should then establish revised governance arrangements, to provide an operating framework for the sector. This should include establishing a formal committee to

oversee the sector and the decisions made. Terms of reference should be developed and agreed with all relevant parties ahead of implementation. Additionally, high-level agreements should be established to reflect the desired future state of the sector. These agreements could include contracts – reflecting the revised sectoral arrangements – with organisation(s) delivering and/or managing services.

To ensure they are ready for implementation, the service provider(s) (engaged through the high-level agreement(s)) should then develop, and act on, implementation and business plans. These plans may be informed by market engagement activities to understand what providers and offerings are available to deliver services, particularly for donor recruitment and tissue typing activities. For example, an analysis of DNA sample methods (using blood samples, buccal swabs or saliva tubes) should be reviewed to inform future recruitment activities.

The business plan should specify the interrelationship of activities and responsible parties within the sector. It should outline the activities, operations and longer-term objectives. The plan should be developed in close consultation with governments, health services and providers to align with investment objectives and gain agreement with changed governance, reporting and operational arrangements. It should be regularly revised to reflect changes in operations and address challenges encountered.

The implementation plan may include activities such as developing or renegotiating funding agreements, data migration and/or integration, communicating and managing change (among patient and donor groups, health services, typing providers, international bodies and registries), appointing providers, procurement, office accommodation and fit-out, developing web material and social media portals, and managing the CBU inventory. In addition, it may include upfront activities (for example, preparatory activities for changing arrangements, such as re-engaging donors, conducting a stocktake of DNA samples and CBUs, and renewing donor education material).

The service provider(s) should then act on the implementation plan and preparatory activities. At this stage, the activities and revised operating framework for the sector would be phased in. When the new arrangements are in place, the registry operator(s) should undertake progress reporting and regular upward reporting to the committee.

The progress of implementation should be monitored through project reporting and governance activities, to ensure alignment with project planning and delivery of objectives. Where activities have diverged from the plan, decision makers should develop appropriate project controls to mitigate risks.

The strategic objectives and ongoing relevance of the HPC sector strategy should be reviewed periodically. Reviews should consult widely and draw in a variety of perspectives to ensure the sector still aligns with patient needs.

Careful project planning will be needed to engage stakeholders, ensure project considerations are taken into account and costs are measured. The input of clinical, operational design, information management, costing and implementation experts should be sought to inform any decisions made. As this is a relatively bespoke sector, much of this input will need to be sought from the sector itself. Implementation planning, in particular, will require specialist support to promote cost-effective delivery that meets agreed outcomes. For example, this might include expertise in areas such as information technology, change management, business continuity, contract negotiation, quality and safety guidance, and business support.

Consideration should also be given to taking advantage of the lessons of international registries that have undertaken similar exercises to re-orient their strategies. Examples may exist in the UK and Canada.

Appendices

Appendix A Acronyms and definitions

1 Acronyms

ABMDR	Australian Bone Marrow Donor Registry
ABMTRR	Australasian Bone Marrow Transplant Recipient Registry
ABS	Australian Bureau of Statistics
ahJHPCC	Ad hoc Jurisdictional Haemopoietic Progenitor Cell Committee
AHMAC	Australian Health Ministers' Advisory Council
AIHW	Australian Institute of Health and Welfare
APBMT	Asia-Pacific Blood and Marrow Transplantation Group
ARCBS	Australian Red Cross Blood Service
ASBMT	American Society for Bone and Marrow Transplantation
ASHI	American Society for Histocompatibility and Immunogenetics
AusCord	Australian network of CBB and collection centres
BM	Bone marrow
BMDC	Bone Marrow Donor Centre
BMDI CBB	Bone Marrow Donor Institute Cord Blood Bank (Melbourne)
BMDW	Bone Marrow Donors Worldwide
BMT	Bone marrow transplant
BMTP	Bone Marrow Transplant Program
CBB	Cord Blood Bank
CBNMC	Cord Blood National Management Committee
CBU	Cord Blood Unit
CIBMTR	Center for International Blood and Marrow Transplant Research
CMV	Cytomegalovirus
DRG	Diagnosis related group
EBMT	European Society for Blood and Marrow Transplantation
EMDIS	European Marrow Donor Information System
FACT	Foundation for the Accreditation of Cellular Therapy
FTE	Full-time equivalent
GvHD	Graft versus Host Disease
HLA	Human leukocyte antigen

HPC	Haemopoietic progenitor cells
HPCP	Haemopoietic Progenitor Cell Program
IHPA	Independent Hospitals Pricing Authority
iPSC	Induced Pluripotent Stem Cells
ISP	International Searches Program
JACIE	Joint Accreditation Committee – ISCT and EBMT
KPI	Key performance indicator
MSC	Mesenchymal stem cells
NCAU	Northern Caucasian
NCBCN	National Cord Blood Collection Network
NextGen	Next Generation DNA sequencing (used in tissue typing)
NMDP	National Marrow Donor Program (US)
NWCAU	North West Caucasian
NWE	North West European
PB	Peripheral blood
RIC	Reduced intensity conditioning
SCAU	Southern Caucasian
SCBB	Sydney Cord Blood Bank
TGA	Therapeutic Goods Administration
TMF	Technical Master File
TNC	Total nucleated cell
QALY	Quality-adjusted life year
QCBB	Queensland Cord Blood Bank
WHO	World Health Organization
WMDA	World Marrow Donor Association

2 Definitions

Allogeneic refers to donations to a person made by another person. In the case of HPC transplants, these are genetically matched for transplant.

Apheresis is a method for collecting stem cells from a donor. It is also referred to as a peripheral blood collection. It involves the use of G-CSF injections in the lead-up to collection to mobilise the stem cells into the donor's blood stream. Needles are then inserted into each of the donor's arms to collect and return blood from which the stem cells are collected in an apheresis machine.

Autologous donations are made by a person for personal use. In autologous transplants, a patient may have their stem cells collected before treatment, and then returned to them as a transplant following treatment.

Banking includes all activities relating to the acceptance, documentation and preliminary storage of a cord blood unit before testing. This includes handling activities of non-searchable and non-compliant cord blood units and well as activities as they relate to regulatory audits, licensing and compliance to operate as a bank.

Collection includes all activities associated with the physical collection of stem cells through either a peripheral blood collection, bone marrow harvest or collection of a cord blood unit from a maternity collection site.

Confirmatory typing is a term interchangeable with *verification typing*. It represents the full, high resolution testing of a donor at all loci. The sample used is collected from a donor following their matching to a patient. In this way, this test confirms that the donor has the tissue type as was originally identified on the registry or through extended typing.

Extended typing is tissue typing undertaken on a DNA sample provided by the donor at registration. On occasion – if, for example, the DNA sample is no longer viable – the donor may be called in to provide a new sample to conduct tissue typing on. Extended typing is undertaken to the extent requested by the clinician or identified by a search coordinator. It therefore may only type certain loci rather than the full HLA of the donor.

Haplotype is a description given to the series of HLA genes inherited by an individual that are located together. Haplotypes enable immunologists to identify potential donors to patients.

HLA match human leukocyte antigens (HLAs) are proteins on the surface of white blood cells, and like blood groups for red blood cells, are the mechanism for characterising white blood cells and matching a patient for HPC transplantation.

HPC Haematopoietic Progenitor Cells (HPCs) are stem cells found within bone marrow, and umbilical cord blood, which are responsible for forming blood and immune cells within the body. 'HPC' is interchangeable with the terms 'stem cells' or 'haemopoietic stem cells'. This report also uses the spelling 'haemopoietic', which holds the same definition as the American and European spelling 'hemapoietic' and 'haematopoietic'.

HPC transplant is a transplant involving the replacement of a patient's blood forming system using HPCs from either the patient themselves (autologous) or another person (allogeneic). HPC transplants are interchangeable with 'stem cells', 'bone marrow transplants' and 'stem cell transplants'.

Loci refers to the alleles at a given site at an individual's Chromosome 6. Together, these the characteristics of the loci form the individual's HLA type. Tissue typing is undertaken at different loci to determine is a donor is a match to a patient.

Next Generation typing refers to a high-resolution method for testing an individual's tissue typing. Low and intermediate resolution methods may not be able to distinguish between alleles at a given loci, whereas, Next Gen typing removes this ambiguity.

Non-searchable cord blood units: CBUs that have been banked/stored but are not yet registered – and are not searchable - for potential release for transplant due to testing or other reasons.

Non-compliant cord blood units: CBUs that do not meet TGA or banking requirements, and are deemed not suitable for transplant

Storage refers to activities that support the storage of searchable cord blood units. It includes the management of inventory, registration of newly tested, viable cord blood units and reporting.

Search activities include activities associated with initiating, undertaking and reporting on potential donors for a given patient. This includes searching of domestic and international registries, and the activities undertaken to make an assessment of a match.

Testing describes all testing and follow-up activities required to make a donor or collected cord blood unit searchable on the registry. This includes donor testing, medical questionnaires and other follow up. It also includes blood testing and tissue typing activities.

Verification typing is a term interchangeable with *confirmatory typing*, which is now the more common reference for the full, high resolution testing of a donor at all loci. The sample used is collected from a donor following their matching to a patient. In this way, this test confirms that the donor has the tissue type as was originally identified on the registry or through extended typing.

Appendix B Clinical applications of HPCs

1 Clinical evolution of HPC transplants

Bone marrow transplants – as they originated – first came to clinical practice in the early 1970s. They were pioneered by E Donnall Thomas in the late 1950s who conceived transplantation as a method for treatment for leukaemia. He was later awarded the Nobel Prize in 1990 for his work. The specific interest in HPC transplants arose from a need to treat patients who had been exposed to irradiation during the Second World War.[87] Its clinical value in the treatment of leukaemia was first recognised following animal trials. Approximately 200 transplants were undertaken in humans through the late 50s and 60s, although most of those patients succumbed to Graft versus Host Disease (GvHD) which tempered their widespread use. However, the primary factors that had led to poor results during this time were revolutionised in the late 1960s following the discovery of the human leukocyte antigen (HLA) system.

Throughout the 1970s, the first successful autologous and allogeneic transplants were undertaken.[88] Originally sought from bone marrow harvests themselves, peripheral blood mobilisation techniques came about in the mid-1980s, while cord blood was demonstrated as a HPC source in 1986. Their uses became more prominent in the late 1990s as clinical approaches in preparatory regimes and post-transplantation treatments advanced. Additionally, the use of HPC transplants in a broader range of clinical indications was recognised, and supported by the proliferation of unrelated donor registries which enabled clinicians to access HPCs from sources other than siblings. True international collaboration and integration of HPC registries that listed unrelated donors who volunteered to donate their stem cells was formalised in 1988 when the World Marrow Donor Association (WMDA) was established.[89] The functions and current approaches for collaboration have since been grounded in these origins.

2 Clinical indications for transplant

In 2015, the American Society for Bone and Marrow Transplantation (ASBMT) developed guidance on the indications for different transplant treatments and whether these are recognised as a standard of care (defined by evidence), a standard of care (but without the scale of clinical trials that would otherwise evidence it), a developmental treatment or not recommended for treatment.[90] It provides a guide as to clinical indications that clinicians may look to HPC transplants to treat. A reformatted version is provided below.

Note: the following legend applies:

Standard care (S)	Standard of care (clinical evidence/rare indication) – large clinical trials unavailable (C) or (R)	Developmental (D)	Not recommended (N)

87 The EBMT Handbook 'Haematopoietic Stem Cell Transplantation' 6th edition, European School of Haematology and the European Society for Blood and Marrow Transplantation, Chapter 1

88 EBMT 'Timeline', accessed at <https://www.ebmt.org/Contents/Quality-Management/AboutJACIE/Pages/About-JACIE.aspx>

89 The EBMT Handbook 'Haematopoietic Stem Cell Transplantation' 6th edition, European School of Haematology and the European Society for Blood and Marrow Transplantation, Chapter 1

90 Majhail NS et al (2015) 'Indication for Autologous and Allogeneic Hematopoietic Cell Transplantation: Guidelines from the American Society for Blood and Marrow Transplantation' *Biology of Blood and Marrow Transplantation* 21 1863-1869

Table 50: Clinical guidance, HPC transplants and clinical indications for which they are recognised as treatments, ASBMT 2015, reformatted.

	Paediatric		Adult	
Indication and Disease Status	**Allogeneic HCT**	**Autologous HCT**	**Allogeneic HCT**	**Autologous HCT**
Acute myeloid leukemia				
CR1, low risk	N	N	N	C
CR1, intermediate risk	C	N	S	C
CR1, high risk	S	N	S	C
CR2[b]	S	N	S	C
CR3+			C	C
Not in remission	C	N	C	N
Acute promyelocytic leukemia, relapse	R	R		
CR1			N	N
CR2, molecular remission			C	S
CR2, not in molecular remission			S	N
CR3+			C	N
Not in remission			C	N
Relapse after autologous transplant			C	N
Acute lymphoblastic leukemia				
CR1, standard risk	N	N	S	C
CR1, high risk	S	N	S	N
CR2	S	N	S	C
CR3[b]	C	N	C	N
Not in remission	C	N	C	N
Chronic myeloid leukemia				
Chronic phase	C	N		
Chronic phase 1, TKI intolerant			C	N
Chronic phase 1, TKI refractory			C	N
Chronic phase 2+			S	N
Accelerated phase	C	N	S	N
Blast phase	C	N	S	N
Myelodysplastic syndromes				
Low risk	C	N		
Low/intermediate-1 risk			C	N
Intermediate-2/high risk			S	N
High risk	S	N		
Juvenile myelomonocytic leukemia	S	N		
Therapy related	S	N		
Therapy-related AML/MDS				
CR1			S	N
Myelofibrosis and myeloproliferative diseases				
Primary, low risk			C	N
Primary, intermediate/high risk			C	N
Secondary			C	N
Hypereosinophilic syndromes, refractory			R	N
Plasma cell disorders				
Myeloma, initial response			D	S
Myeloma, sensitive relapse			C	S
Myeloma, refractory			C	C
Plasma cell leukemia			C	C
Primary amyloidosis			N	C
POEMS syndrome			N	R
Relapse after autologous transplant			C	C
Mantle cell lymphoma				
CR1/PR1			C	S
Primary refractory, sensitive			S	S
Primary refractory, resistant			C	N
First relapse, sensitive			S	S
First relapse, resistant			C	N
Second or greater relapse			C	S
Relapse after autologous transplant			C	N
T cell lymphoma				
CR1			C	C
Primary refractory, sensitive			C	S
Primary refractory, resistant			C	N
First relapse, sensitive			C	S
First relapse, resistant			C	N
Second or greater relapse			C	C

	Paediatric		Adult	
Relapse after autologous transplant			C	N
Lymphoblastic lymphoma CR1			N	N
Primary refractory, sensitive			N	C
Primary refractory, resistant			R	N
First or greater relapse, sensitive			R	C
First or greater relapse, resistant			R	N
Relapse after autologous transplant			C	N
T cell non-Hodgkin lymphoma CR1, standard risk	N	N		
CR1, high risk	S	N		
CR2	S	N		
CR3[b]	C	N		
Not in remission	C	N		
Lymphoblastic B cell non-Hodgkin lymphoma (non-Burkitt) CR1, standard risk	N	N		
CR1, high risk	S	N		
CR2	S	N		
CR3[b]	C	N		
Not in remission	C	N		
Burkitt's lymphoma First remission	C	C	C	C
First or greater relapse, sensitive	C	C	C	C
First or greater relapse, resistant	C	N	C	N
Relapse after autologous transplant			C	N
Hodgkin lymphoma CR1	N	N		
CR1 (PET negative)			N	N
CR1 (PET positive)			N	C
Primary refractory, sensitive	C	C	C	S
Primary refractory, resistant	C	N	C	N
First relapse, sensitive	C	C	S	S
First relapse, resistant	C	N	C	N
Second or greater relapse	C	C	C	S
Relapse after autologous transplant			C	N
Anaplastic large cell lymphoma CR1	N	N		
Primary refractory, sensitive	C	C		
Primary refractory, resistant	C	N		
First relapse, sensitive	C	C		
First relapse, resistant	C	N		
Second or greater relapse	C	C		
Diffuse large B cell lymphoma CR1 (PET negative)			N	N
CR1 (PET positive)			N	C
Primary refractory, sensitive			C	S
Primary refractory, resistant			C	N
First relapse, sensitive			C	S
First relapse, resistant			C	N
Second or greater relapse			C	S
Relapse after autologous transplant			C	N
Follicular lymphoma CR1			N	C
Primary refractory, sensitive			S	S
Primary refractory, resistant			S	N
First relapse, sensitive			S	S
First relapse, resistant			S	N
Second or greater relapse			S	S
Transformation to high grade lymphoma			C	S
Relapse after autologous transplant			C	N
Cutaneous T cell lymphoma Relapse			C	C
Relapse after autologous transplant			C	N
Plasmablastic lymphoma CR1			R	R
Relapse			R	R
Chronic lymphocytic leukemia High risk, first or greater remission			C	N
T cell prolymphocytic leukemia			R	R
B cell, prolymphocytic leukemia			R	R

	Paediatric		Adult	
Transformation to high grade lymphoma			C	C
Solid tumours **Germ cell tumour, relapse**	D	C	N	C
Germ cell tumour, refractory	D	C	N	C
Ewing's sarcoma, high risk or relapse	D	S	N	C
Breast cancer, adjuvant high risk			N	D
Breast cancer, metastatic			D	D
Renal cancer, metastatic			D	N
Soft tissue sarcoma, high risk or relapse	D	D		
Neuroblastoma, high risk or relapse	D	S		
Wilms' tumour, relapse	N	C		
Osteosarcoma, high risk	N	C		
Medulloblastoma, high risk	N	C		
Other malignant brain tumours	N	C		
Non-malignant diseases **Severe aplastic anaemia, new diagnosis**	S	N	S	N
Severe aplastic anaemia, relapse/refractory	S	N	S	N
Fanconi's anaemia	R	N	R	N
Dyskeratosis congenita	R	N	R	N
Blackfan-Diamond anaemia	R	N		
Sickle cell disease	C	N	C	N
Thalassemia	S	N	D	N
Congenital amegakaryocytic thrombocytopenia	R	N		
Severe combined immunodeficiency	R	N		
T cell immunodeficiency, SCID variants	R	N		
Wiskott-Aldrich syndrome	R	N	R	N
Hemophagocytic disorders	R	N		
Hemophagocytic syndromes, refractory			R	N
Mast cell diseases			R	N
Common variable immunodeficiency			R	N
Lymphoproliferative disorders	R	N		
Severe congenital neutropenia	R	N		
Chronic granulomatous disease	R	N	R	N
Other phagocytic cell disorders	R	N		
IPEX syndrome	R	N		
Juvenile rheumatoid arthritis	D	R		
Systemic sclerosis	D	R	N	D
Other autoimmune and immune dysregulation disorders	R	N		
Mucopolysaccharoidoses (MPS-I and MPS-VI)	R	N		
Other metabolic diseases	R	N		
Osteopetrosis	R	N		
Globoid cell leukodystrophy (Krabbe)	R	N		
Metachromatic leukodystrophy	R	N		
Cerebral X-linked adrenoleukodystrophy	R	N		
Multiple sclerosis			N	D
Rheumatoid arthritis			N	D
Systemic lupus erythematosus			N	D
Crohn's disease			N	D
Polymyositis-dermatomyositis			N	D

Source: Majhail NS et al (2015) 'Indication for Autologous and Allogeneic Hematopoietic Cell Transplantation: Guidelines from the American Society for Blood and Marrow Transplantation' Biology of Blood and Marrow Transplantation 21 1863-1869

Changing needs

As was explored in the NCBCN Review, there are a range of cancers which, together, account for the primary clinical indications for allogeneic transplant. To explore how these

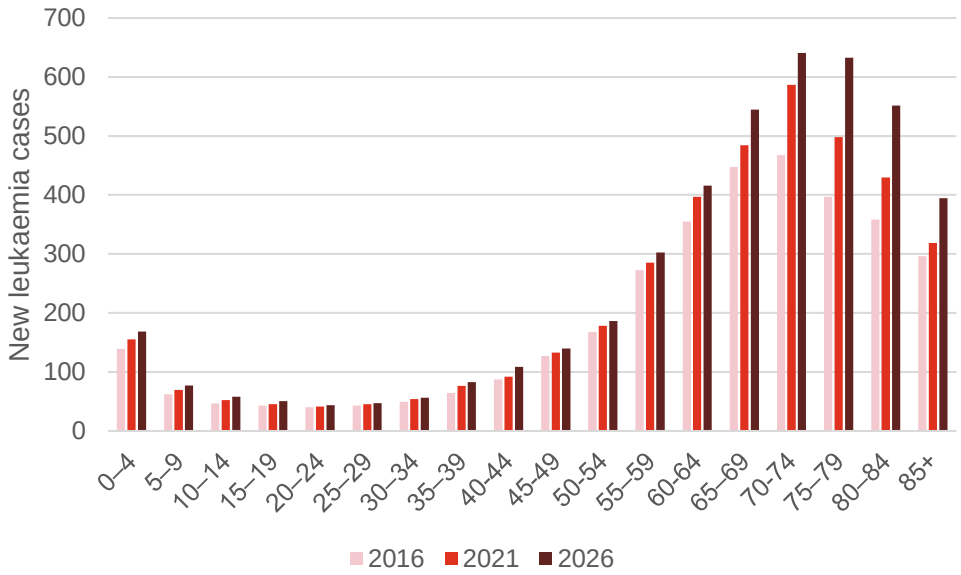
indications have historically changed over time, the number of patients diagnosed has been captured to consider their annual growth rate.

Clinical indication	2014	2015	2016	Average forecast growth (pa)
Myeloma (C90)	1,680	1,730	1,780	2.90%
Chronic lymphocytic leukaemia (C91.1)	1,300	1,330	1,360	2.30%
Acute myeloid leukaemia (C92-94)	1,020	1,050	1,070	2.40%
Hodgkin lymphoma (C81)	605	615	630	2.00%
Non-Hodgkin lymphoma (C82-C85)	4,940	5,070	5,200	2.60%
Acute lymphoblastic leukaemia (C91.0)*	361	368	374	1%

Source: Australian Institute of Health and Welfare, Cancer in Australia: an overview 2014, Australasian Association of Cancer Registries, Note: (*) for Acute lymphoblastic leukaemia figures are drawn from incidence data for 2010, 2011, 2012 and 2013. No figures are available for ALL incidence over 2014-2016 from the AIHW[91]

Using AIHW 2016 projected incidence figures, the number of new cases of leukaemia is projected to grow across all age brackets and particularly among older age brackets.

Figure 98: Projected new cases of leukaemia, 2016 data, projections 2016-2026



Source: AIHW Leukaemia incidence rates, accessed at http://www.aihw.gov.au/cancer/leukaemia/ and ABS, http://www.abs.gov.au/AUSSTATS/abs@.nsf/DetailsPage/3222.02012%20(base)%20to%202101?OpenDocument, Time Series spreadsheets, TABLE A9. Population projections, By age and sex, Australia - Series A

Among other clinical indications, clinical incidence rates for indications for transplant are much more prominent among older age groups. For examples, higher rates of incidence is projected for lymphoma (including Hodgkin's disease, non-Hodgkin's lymphoma and T-cell lymphoma) in older populations (107.5 new cases per 100,000 population for 75-79 year olds

[91] AIHW (2017) Australian Cancer Incidence and Mortality (ACIM) books: Acute lymphoblastic leukaemia (ALL) Canberra, accessed at <www.aihw.gov.au/acim-books>

as compared to 60.6 per 100,000 population for leukaemia).[92] Similar trends are identified for Multiple Myeloma of which there are 0 incidence rates for people under the age of 15, but which grows with age to an incidence of 45.3 cases per 100,000 population for those aged 80-84.[93]

Additionally, diagnostic advancements has assisted the early identification of immunological disorders. Many of these present in younger patients. As a result of earlier identification, HPC transplant is becoming a more viable option for many of these patients. Without identification, patients may regress to a point where transplant is not an option. As a result, more paediatric patients with immunological disorders are expected to drive demand for HPCs.

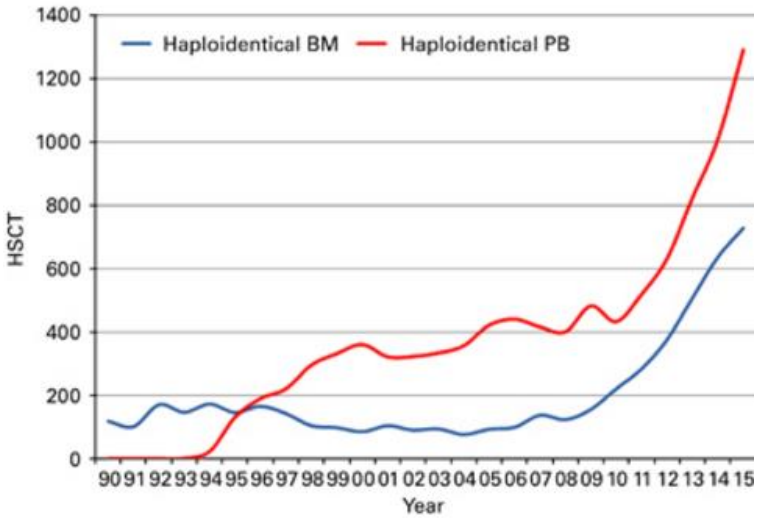
Demand is compounded by trends which are leading to smaller family sizes, meaning fewer patients have matched siblings suited to donate. This is likely to drive reliance on the Australian and international registries to identify suitable donors.

Haploidentical transplants

The growth in clinical indications for allogeneic transplants is partly offset by the growing use of haploidentical transplants. Haploidentical transplant provide a treatment option to many patients, and is preferred by some transplant centres in cases where a perfectly matched donor is otherwise unable to be found. It was first developed as a treatment for Chinese patients who, as a result of the Chinese Government's one-child policy, did not have siblings who might be able to act as a donor. While it is difficult to quantify the extent to which these will reduce reliance on unrelated donors for transplants, there is a clear trend towards their use.

In internationally published information, haploidentical transplant rates continues to grow. For example, in Europe, their use has increased by 291% since 2005 across all clinical indications. This growth is shown in Figure 99 below.

Figure 99: Haploidentical transplants in Europe over time



Source: Passweg JR, Baldomero P et al (2017) Use of haploidentical stem cells transplantation continues to increase: the 2015 European Society for Blood and Marrow Transplant activity survey report Bone Marrow Transplantation advance online publication (13 March 2017)

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92 Australian Institute of Health and Welfare (AIHW) Lymphoma in Australia, accessed at <http://www.aihw.gov.au/cancer/lymphoma/>

93 Australian Institute of Health and Welfare (AIHW) 2017. Australian Cancer Incidence and Mortality (ACIM) books Multiple myeloma (ICD-10 code 90.0) <http://www.aihw.gov.au/acim-books>

Emerging applications

Directed donations and private banking

In hope of the potential returns of stem cell research, there is growing demand for private banking facilities to store one's own (autologous) or another source of stem cells (for example, cord blood stored by parents in a private facility). In these cases, individuals pay for the secure storage of stem cells for their later use. Stem cells might be directed (for example, use of cord blood of one birth for use in the treatment of a sibling to that child). In Australia, stem cells that haven't been stored in a TGA-accredited facility cannot be used in HPC transplants.

Induced Pluripotent Stem Cells

There are a number of areas of clinical application interested in stem cells. This includes the use of embryonic stem cells for application in tissue replacement therapies. Their use is mired in ethical concerns regarding the use of embryos and rights associated with embryos [94]

Another specific area of interest is in the use of induced pluripotent stem cells (iPSCs). iPSCs are cells that have been reprogrammed to their pluripotent state (thus circumventing embryonic stem cells by 'recreating' these from tissue-specific stem cells (including HPCs)). The technology provides opportunities to researchers to advance regenerative applications and if proven, may enable autologous cell replacement for patients who might benefit from their use. [95]

A recent advancement is observed in Japan who has recent given regulatory approval for iPSC use in retinas. In March 2017, the first ever iPSC retina transplant was undertaken on a patient with macular degeneration using the cells from an unrelated donor.[96] The technology was pioneered by Shinya Yamanaka who won a Nobel Prize for his work. In Japan, there are moves afoot to develop an iPSC bank to support their widespread use.

T cell depletion

T cell depletion is a method used to prevent or minimise the impacts of GvHD. Donor T cells activate the production of lymphocytes which recognise the host tissue as foreign. Through cascade, cells then activate in response to damage host cells creating inflammation. T cell depletion seeks to block this receptor cycle to reduce the induction of GvHD, alongside of immunosuppressive treatments.[97] It has been used for some time in clinical practice, but techniques for its use has improved over time.

Advancements in T cell depletion offer clinicians flexibility to manage mismatched donors, such as haploidentical donors, as well as to provide better transplantation outcomes to all patients who might otherwise be at risk of GvHD. For example, approximately 30 to 50% of patients with a HLA-identical sibling used in transplant will experience chronic GvHD.[98] This brings with it the potential to reduce the reliance on unrelated donors, or where a patient is currently difficult to match to a donor, bring forward options for their treatment.

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94 The EBMT Handbook 'Haematopoietic Stem Cell Transplantation' 6th edition, European School of Haematology and the European Society for Blood and Marrow Transplantation, Chapter 4

95 The EBMT Handbook 'Haematopoietic Stem Cell Transplantation' 6th edition, European School of Haematology and the European Society for Blood and Marrow Transplantation, Chapter 4

96 Cyranoski D (28 March 2017) 'Japanese man is first to receive 'reprogrammed' stem cells from another person' Nature, accessed at < http://www.nature.com/news/japanese-man-is-first-to-receive-reprogrammed-stem-cells-from-another-person-1.21730>

97 Ho V T and Soiffer RJ (2001) The history and future of T-cell depletion as graft-versus-host disease prophylaxis for allogeneic hematopoietic stem cell transplantation *Blood* 98 3192-3204

98 Ho V T and Soiffer RJ (2001) The history and future of T-cell depletion as graft-versus-host disease prophylaxis for allogeneic hematopoietic stem cell transplantation *Blood* 98 3192-3204

Testing

Many new tests are under develop that assist in the identification of disease to inform clinical decision making, including for use of a HPC transplant for certain clinical indications. For example, the Murdoch Children's Research Institute has developed the Organ Health BMT test which identifies the engraftment outcomes post-transplant sooner than other available methods. Its use enables clinicians to make decisions post-transplant sooner to improve transplant outcomes.[99]

[99] Murdoch Children's Research Institute 'New test to monitor the success of bone marrow transplants', accessed at <https://www.mcri.edu.au/news/new-test-monitor-success-bone-marrow-transplants>

Appendix C Clinical aspects of HPC transplants

1 Autologous transplants

Autologous transplants are used for some clinical indications that are also treated with allogeneic transplants (for example, some blood cancers), but are also used for other cancers such as solid tumours (for example, Breast cancer, testicular cancers, osteosarcoma).[100]

For certain diseases, such as acute myeloid leukaemia, use of autologous transplants are typically avoided to reduce the likelihood of cancer relapse (as a patient's own HPCs will likely contain cancer-forming cells). These are not usually preferred due to a lack of proven efficacy over intensive chemotherapy. For indications that can be treated with autologous transplants, there is a much lower risk of infection and improved patient outcomes as compared to allogeneic transplants, which use the stem cells of someone other than the patient (i.e. a relative or unrelated donor).

Single autologous transplants

Single autologous transplants involve the collection of a patient's own stem cells, which are transplanted back to the patient after treatment. Collected stem cells are frozen and stored on-site at the hospital in which they are collected. These patients, like with allogeneic transplants, undergo conditioning (which varies depending on the clinical indication as well as the transplant type), are then transplanted, and recover in hospital. However, autologous transplant patient typically have a speedier recovery time as they are transplanted with their own cells, meaning there is a lower risk of infections as compared to allogeneic transplant patients.

Autologous transplants are used as part of treatments for multiple myeloma, relapsed lymphoma and (a very much smaller group of) germ-cell tumour patients.

For multiple myeloma patients, autologous transplants are pursued as a component of initial treatment.[101] Their treatment with an autologous transplant prolongs response, but won't cure their disease. For multiple myeloma patients, transplants are now used in those patients up to 70 years old. The process is undertaken over a four month period. In this time, the patient's cells are collected after initial disease control, then about one month later will undergo chemotherapy (conditioning). Around 24-48 hours later, the patient is then transplanted with their cells following which they go through recovery over a 2-3 month period.

Autologous transplants are used in lymphoma patients as a treatment option for those who have relapsed. Unlike multiple myeloma, transplants for relapsed lymphoma patients are expected to be a curative treatment.

Staged autologous transplants

Staged autologous transplants also use a patient's own cells, but is conducted over two transplants and are also known as 'double' or 'tandem' transplants. In these types of transplants, the initial collection of stem cells typically collects for both transplants (they draw double the amount via apheresis), which are both frozen and stored on-site.

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[100] Leukaemia Foundation Autologous (Self) Transplants, accessed at: http://www.leukaemia.org.au/treatments/stem-cell-transplants/autologous-self-transplants, 7 February 2017

[101] There are discrete instances of multiple myeloma patients who undergo allogeneic transplant as the first stage of treatment, however, autologous transplants is the primary treatment for this indication.

Staged transplants may be used for multiple myeloma patients, and while previously used by many clinicians for these patients, they are less frequently adopted as a treatment pathway now due to advancements in myeloma treatments which provide excellent outcomes for patients.

Patients undergoing staged transplants undergo intensive conditioning treatment, which is a very strong dose of chemotherapy after which their stem cells are transplanted followed by recovery. Approximately 4-6 months later, the patient will undergo a second transplant procedure using their remaining stem cells.

2 Allogeneic transplants

Allogeneic transplants follow the same procedure as autologous transplants, but differ in:

- The clinical indications for which it is a treatment
- The process and identification of stem cells, which will either come from a relative, unrelated donor or cord blood unit
- The conditioning treatment used to prepare the patient for transplant. In 2015, 51% of patients were prepared using reduced intensity conditioning, with the remaining receiving myeloablative conditioning treatment.[102] The agents used as part of the conditioning regime vary widely and are dependent on a physician's decision regarding the approach to be taken given the patient's disease status and indication.
- The recovery period of the patient (which may take 6-12 months)
- The patient outcomes, where allogeneic transplant patients have a much higher risk of infection, GvHD and mortality rates

Patients who undergo autologous transplant and later are treated with allogeneic transplants

For a small number of patients, an autologous, followed by an allogeneic transplant might be decided upon as the appropriate treatment plan. The only indication for which this is currently pursed is myeloma. For myeloma patients, with high risk disease patients may first be transplanted with autologous stem cells and later transplanted using allogeneic cells.

Some lymphoma patients may relapse after autologous transplant and for these patients, an allogeneic transplant may be pursued. These patients will undergo 'salvage' chemotherapy to achieve a disease status ready for transplant (i.e. the disease is under good control). Cells are then collected (from the donor) and the patient undergoes conditioning chemotherapy after which they are transplanted. For young patients with relapsed lymphoma, their recovery period is approximately 3-6 months. As it is difficult to know which patient may undergo this course of treatment, it is difficult to project how many autologous to allogeneic transplant patients there may be. While current outcomes reporting does capture transplant episodes of each type, it doesn't distinguish in data summaries the number of patients that first receive autologous, and later, allogeneic transplants.[103]

3 Identifying a donor

Donor registries, including Australia's own ABMDR, list the genetic profile of individuals who have volunteered to donate stem cells in the case that they are a match to a patient. State Search Coordinators, who are part of the ARCBS (or PathWest in WA or Pathology

[102] ABMTRR (2015) Annual Data Summary report

[103] ABMTRR reporting does of course include information regarding relapse and transplant number for patients.

Queensland in QLD), undertake searching and matching of these donors to identify which donors might be a suitable match to a patient. State Search Coordinators engage closely with clinicians to determine which donors may be further tested (tested in Australian laboratories) to obtain all the information needed to make a decision to determine which donor should be selected. Clinicians review these search reports and select a donor (which may be domestic or international). Donor coordinators, who are also from the ARCBS, will then engage with the identified donor and seek to coordinate their work-up and collection to coincide with the clinician's preferred schedule to transplant. Through careful coordination, donations are then made at a transplant centre other than the patient's and couriered to the requesting transplant centre in time for the patient to undergo transplant.

It is commonly accepted that for most patients who would benefit from a HPC transplant, they will be able to find a suitable donor source.[104] However, there are exceptions among patients with some clinical indications as to the HLA-match and the HPC source that a clinician might use in their treatment.[105]

Increasingly, HPC transplants are being used to treat more and more patients. In particular, this is driven by an increasing ability to treat older patients. This reflects that chronological age itself doesn't restrict transplantation treatments provided a patient's fitness for transplant is met.

Additionally, survival outcomes between a matched sibling and a matched unrelated donor is comparable, including if the HPC source is a cord blood unit.[106]

Chromosome 6

To characterise a patient, clinicians look to a patient's sixth chromosome at which their genetic code is located (the major histocompatibility complex). The genes located at chromosome 6 at responsible for coding antigens and are split into two regions:

- Class I which contains HLA-A, -B and –C genes
- Class II which contains HLA-DR, - DP and –DQ genes

Alleles (gene variants) are expressed at each loci, inherited from biological parents and define a patient's HLA. If two different alleles are inherited from each parent, both will be expressed at the locus.[107] With many different alleles recognised within the human population and high level of polymorphism (grouping/different expressions), there are many, many different HLA types worldwide. This makes the task of finding the right match for a HPC transplant complex and potentially, wide-ranging.[108]

Haplotypes are known as the series of HLA genes which are inherited; one from each biological parent. The combined haplotypes of a patient is known as a phenotype. Among siblings, there is a 1 in 4 chance that two siblings will have inherited the same two haplotypes, meaning that they are a perfect match to one another. Additionally, of every four siblings, on probability, two will have inherited one haplotype of the same inherited by a patient. These siblings are *haploidentical*. By the same logic, a patient's biological parents, or

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[104] Majhail NS et al (2015) 'Indication for Autologous and Allogeneic Hematopoietic Cell Transplantation: Guidelines from the American Society for Blood and Marrow Transplantation' *Biology of Blood and Marrow Transplantation* 21 1863-1869

[105] Ibid

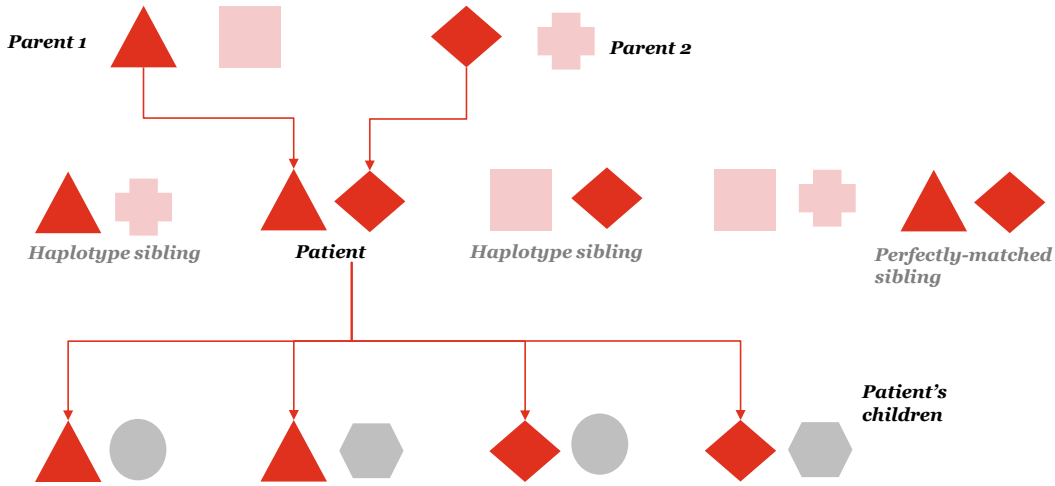
[106] Ibid

[107] Sonnenberg F et al (1989) Bone Marrow Donor Registries: The Relation Between Registry Size and Probability of Finding Complete and Partial Matches *Blood* 74 (7) 2569-2578

[108] The EBMT Handbook 'Haematopoietic Stem Cell Transplantation' 6th edition, European School of Haematology and the European Society for Blood and Marrow Transplantation, Chapter 4

biological children will also be *haploidentical* as they will carry one of a patient's gene set (see for example, Figure 100).

Figure 100: Stylised HLA type



Source: Based on BMT Network NSW – Allogeneic Bone Marrow Transplant: A patient's guide

Some haplotypes are common among some ethnic groups. A haplotype is a grouping of alleles (not necessarily at all loci) and are a genetic expression of evolutionary advantage; the genes 'stick together'. The occurrence of certain alleles together at greater frequencies than others is called *linkage disequilibrium*.[109] For this reason, a patient might find a match among extended family, or more likely, among populations with a similar ethnicity to the patient. Immunogeneticists use these clues to begin their search for a match for a patient needing a HPC transplant.

Linkage disequilibrium methods enables scientists, in some cases, to predict what alleles a patient might have. The EBMT give the example that for more than 95% of Caucasian patients with HLA-B*07.02, they will carry HLA-C*07.02. [110] Additionally, there are alleles that are likely paired with a range of other alleles (for example, B18*01 with either C*07.01, C*12.03 or C*05:01).[111] This enables a donor's haplotype to be 'predicted' through a set of known rules.

A number of registries are now using predictive search technology which leverages algorithms to match patients with potential matches. These include HapLogic (NMDP) and OptiMatch (ZKRD) which use medium resolution HLA typing to search for matches. The Anthony Nolan and NHS Stem Cell Registry is developing a predictive search technology (based on 20,000 HLA types) to match UK's major ethnic groups.[112]

Extent of matching for transplant

When looking for a HLA-match, there are different clinical needs as to the level of match that might be required for different patients. Differences also exist in the changes in clinical

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[109] The EBMT Handbook 'Haematopoietic Stem Cell Transplantation' 6th edition, European School of Haematology and the European Society for Blood and Marrow Transplantation, Chapter 5

[110] The EBMT Handbook 'Haematopoietic Stem Cell Transplantation' 6th edition, European School of Haematology and the European Society for Blood and Marrow Transplantation, Chapter 5

[111] The EBMT Handbook 'Haematopoietic Stem Cell Transplantation' 6th edition, European School of Haematology and the European Society for Blood and Marrow Transplantation, Chapter 5

[112] UK NHS (2014) 'Unrelated Donor Stem Cell Transplantations in the UK', accessed at <http://www.nhsbt.nhs.uk/download/unrelated_donor_stem_cell_transplantation_in_the_uk.pdf> p23

practice over time. What was once known about HLA types is now better understood with advancements in genetic testing, which has enabled clinicians to consider matching at more genes than was previously possible.

The standard commonly accepted globally is an 8/8 match which maximise post-transplantation outcomes.[113] That is, that HLA-A, -B, -C and –DRB1 are identical between patient and donor.[114] A 6/6 match means that the alleles at loci -A, -B and –DRB1 are identical. Matches at the DQB1 and DPB1 loci are also considered by clinicians, which confers benefits in reducing the risk of GvHD and may provide benefits depending on the level of match at other loci. Table 51 specifies what is typically meant in referring to different matches.

Table 51: HLA loci that are relevant to different matching levels

Class	HLA-loci	6/6 match	8/8 match	10/10 match	12/12 match
I	A	✓	✓	✓	✓
	B	✓	✓	✓	✓
	C		✓	✓	✓
II	DRB1	✓	✓	✓	✓
	DQB1			✓	✓
	DPB1				✓

A mismatch is represented by reducing the total match out of the total loci being matched. For example, a 7/8 match indicates that one of HLA-A, -B, -C or -DRB1 isn't a match between patient and donor.

There are some 'permissive' mismatches that may result in similar clinical outcomes as a perfectly matched transplant, which is determinate upon the patient's disease status, the graft-versus-leukaemia effect desired and transplant options compared to other treatments available to the patient.[115] For example, a mismatch at -DQB1 is tolerated more than others, while some exceptions for a mismatch at HLA-C, -DPB1 or DQB1 may be made.[116] High resolution matching at loci HLA-A, -B, -C and –DRB1 has demonstrated the best post-transplantation survival outcomes.[117] These are clinical decisions made at the time of searching what donors might be available.

Increasingly, international registries are high resolution typing at all six loci (n/12 match)

[113] Spellman et al (2017) 'A perspective on the selection of unrelated donors and cord blood units for transplantation' *Blood Journal* 120(2)

[114] Howard et al (2015) 'Recommendations for Donor HLA Assessment and Matching for Allogeneic Stem Cell Transplantation: Consensus Opinion of the Blood and Marrow Transplant Clinical Trials Network (BMT CTN)' *Biology Blood Marrow Transplant* 21(1) 4-7

[115] Nowak J (2008) 'Role of HLA in hematopoietic SCT' *Bone Marrow Transplantation* 42 S71-S76

[116] Tiercy JM (2016) 'How to select the best available related or unrelated donor of hematopoietic stem cells?' *Haematologica* 101(6) 680-687

[117] Spellman et al (2017) 'A perspective on the selection of unrelated donors and cord blood units for transplantation' *Blood Journal* 120(2)

Under current policy, the ABMDR does not allow donors for transplants if two or more mismatches exist at HLA-A, -B, -C and –DRB1. [118] For each mismatch avoided there is up to a 10% reduction in risk among patients with low-risk diseases.[119]

Genetic matching

Matching HLA alleles is a complex scientific field. There is significant variation within the human population meaning that the probability of finding a donor can be very difficult for some patients with unusual or rare haplotypes.

At present the total number of known alleles exceeds 16,000.[120] The number of alleles identified is increasingly helped by scientific methods of identification, but also as populations are better understood. For example, in 1999, approximately 1,000 alleles had been identified and named, by 2010, this number had grown to over 4,500, with over 15,000 recognised by 2016.[121]

Of the loci of most interest to clinicians, the number of alleles whose official sequences are named by the World Health Organization (WHO) Nomenclature Committee for Factors of the HLA System are shown in Table 52 below.

Table 52: Number of named alleles for each HLA gene[122]

Number of HLA alleles			
Class I	**A**	**B**	**C**
	3,830	4,647	3,382
Class II	**DRB**	**DQB1**	**DPB1**
	2,252	1,054	740

Note: there are null alleles, genes, proteins and pseudogenes not represented in this table. Please refer to the EBI website for full published information.

With this number of alleles, scientists leverage predictive algorithms to analyse the haplotypes of volunteer donors to provide search reports to clinicians to identify the likelihood of a patient finding a perfect, or mismatched donor. An earlier study identifying the possible match probabilities for the (then-known) 6,336 phenotypes corresponded to a possible 20,075,616 possible genotypes. This is now a figure well exceeded through current scientific understanding of the number of alleles.[123]

Typing resolution

The task of identifying a suitable donor is further complicated by the tissue typing resolution that has been employed to characterise a donor's HLA. When bone marrow registries were first established, serological testing was the most advanced testing available to analyse a donor's genetic profile. This means that for many donors that have been on the registry for some time, their profile contains limited information that can only be confirmed through

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118 ABMDR (2011) chapter 5 – Tissue Typing Standards Document ABMDR-GL-OP-005-08

119 Spellman et al (2017) 'A perspective on the selection of unrelated donors and cord blood units for transplantation' *Blood Journal* 120(2)

120 The European Bioinformatics Institute 'International Immunogenetics Information Systems project IPD-IMGT/HLA Database', accessed at <http://www.ebi.ac.uk/ipd/imgt/hla/stats.html>

121 Anthony Nolan Research Institute 'Nomenclature for Factors of the HLA System', accessed at <http://hla.alleles.org/nomenclature/index.html>

122 The European Bioinformatics Institute 'International Immunogenetics Information Systems project IPD-IMGT/HLA Database', accessed at <http://www.ebi.ac.uk/ipd/imgt/hla/stats.html>

123 Allele frequency net 2015 update: new features for HLA epitopes, KIR and disease and HLA adverse drug reaction associations. Gonzalez-Galarza FF, Takeshita LY, Santos EJ, Kempson F, Maia MH, Silva AL, Silva AL, Ghattaoraya GS, Alfirevic A, Jones AR and Middleton D *Nucleic Acid Research 2015, 28, D784-8*

further testing. This compares to newer registrants whose genetic profile may have been tested using DNA-based method. Additionally, some loci may be tested to different resolutions. As a result, clinicians may be presented with a range of donors for whom information may be limited.

However, in some cases, lower-resolution information may be sufficient to guide decision making. For example, certain serotypes recognise cells of other serotypes (due to small variations). This means that for the purposes of matching some alleles can be ambiguous (for example, a patient with serotype DRB1*12:01/06/10 could be matched to a donor with either DRB1*12:01 or DRB1*12:06 or DRB1*12:10. Another example is DRB1*14:01/54, in which the donor could have either DRB1*14:01 or DRB1*14:54 and be considered a match. In these cases, a clinician won't require additional typing to determine which specific allele is present).[124] Another example exists in biological siblings, where low-resolution typing may be adequate to match a patient, as the allele will have been inherited by both siblings (and so, there isn't a need to decode ambiguity). As such, due to family genetics, typing normally only require Class I (HLA-A and -B) from serology and Class II (HLA-DR) using high-resolution typing to inform assessment of suitability for transplant.

However, for the most part in an unrelated donor search, the better the information available, the easier (and quicker) the ability to assess potential matches to a patient. There are specific code and nomenclature rules which guide immunogeneticists. These are summarised in Table 53 below.

Table 53: Tissue typing resolution categories

Common descriptor	Example	Description
Serological	A1	Allele group
Low resolution	A*01	Allele group DNA based typing (denoted by an asterisk)
Medium resolution (also intermediate resolution)	A*01:01 or A*01:02	Allele subtypes Often a 'string' of possible alleles
High resolution	B*44:65 May be denoted by a letter at end of sequence (expression) e.g. A*01:01P (specifies protein sequence for peptide binding region of a molecule)	Specific allele (no ambiguity) This method is also referred to as 'Next Generation' typing which is genetic sequencing to remove ambiguity in which alleles are present.

Source: The EBMT Handbook 'Haematopoietic Stem Cell Transplantation' 6th edition, European School of Haematology and the European Society for Blood and Marrow Transplantation, Chapter 5

[124] ABMDR (2011) chapter 5 – Tissue Typing Standards Document ABMDR-GL-OP-005-08

Tissue typing standards

The current levels of typing associated with Australian donors on the ABMDR registry are[125]:

- Molecular typing for HLA-A, -B and –DRB1 at enrolment (where DRB1*01 – DRB1*16 is performed using DNA methods)
- Allelic-level confirmation typing at HLA-A, -B and –DRB1 loci at preliminary search request
- Extended typing not identified in a preliminary search request includes HLA-C, -DQB1 and –DPB1
- Verification/confirmatory typing is undertaken using a fresh sample of a donor and is carried out at the level requested by the transplant centre
- At a minimum, typing must be conducted to HLA-A, -B, -C and –DRB1 at the four digit allelic level and –DQB1 at the generic/allelic level. [126]

Tissue typing laboratories are located in the ARCBS's Melbourne, Sydney and Adelaide locations, as well as PathWest in Perth and Pathology Queensland in Brisbane. Laboratories are responsible for updating typing libraries every six months of newly identified alleles. [127]

The current funding rules require that coordinators identify whether or not a suitable donor exists in Australia before pursuing an international option. This carries a risk of increasing the time taken to find a match because extended HLA typing of potential Australian donors may need to be undertaken.[128]

Cord blood unit characterisation

The TNC is a measure of cell concentration in the CBU, while the CD34+ indicates cell viability. These are carefully measured when the CBU is banked and stored and re-measured when the CBU is identified as a potential match to a patient.

CBUs can be easier to match to paediatric patients who are typically lower weight than adult patients as clinicians are able to achieve the cell counts they need for a successful transplant. They are additionally assisted in the fact that HPCs in CBUs are immunologically naive and so transplant can be managed with more mismatches than HPCs from bone marrow or peripheral blood. This is why clinicians often only look to an n/6 match (at least 4/6); the HLA-C loci may not play as great a role in successful engraftment as it might with use of HPCs from adult donors. However, clinicians must still achieve the right cell dose to support a transplant. For adults, this can mean that two CBUs are needed. These are known as double-cord transplants and present further difficulties in searching as two CBUs must be found to be a match rather than just the one. The high-level rules of thumb in identifying a CBU for a patient are shown in Table 54 below.

Table 54: Guidelines to CBU characteristics used in patients

Patient's condition	HLA match	TNC count	CD34+ count

[125] ABMDR (2011) chapter 5 – Tissue Typing Standards Document ABMDR-GL-OP-005-08

[126] ABMDR (2011) chapter 5 – Tissue Typing Standards Document ABMDR-GL-OP-005-08

[127] ABMDR (2011) Chapter 5 – Tissue Typing Standards Document ABMDR-GL-OP-005-08

[128] ABMDR *Unrelated HPC sourcing strategy* (Version 1.2, 10 May 2016), provided by the ABMDR

Patient's condition	HLA match	TNC count	CD34+ count
Malignant	0-2 HLA mismatches	>2.5x10^7 TNC/kg	*or* >2x10^5 CD34+/kg
Non-malignant	0-1 HLA mismatches	>3.5x10^7 TNC/kg *Or* Two CBUs to equate to >3x10^7 TNC/kg	

Source: EuroCord requirements

Due to the growing need for high cell dose CBUs, CBBs around the world are increasing the thresholds of CBUs that they bank. Currently, in Australia, these thresholds are:

- TNC counts of 120x10^7 for European donors and 70x10^7 for non- European donors (including Indigenous donors)
- Volumetric thresholds of 60mL[129]

4 Finding a donor for a patient

The search, typing, contact and activities associated with family (matched and haploidentical) donors is managed within transplant centres and is independent of the ABMDR and the Commonwealth Government's HPC program. Immediate and extended family searches may be assisted by tissue typing laboratories (and thus, State Search Coordinators). Although extended family searches (and testing) are only pursued for patients with a haplotype frequency which is commonly represented (defined as >60/10,000 haplotypes) in the general population.

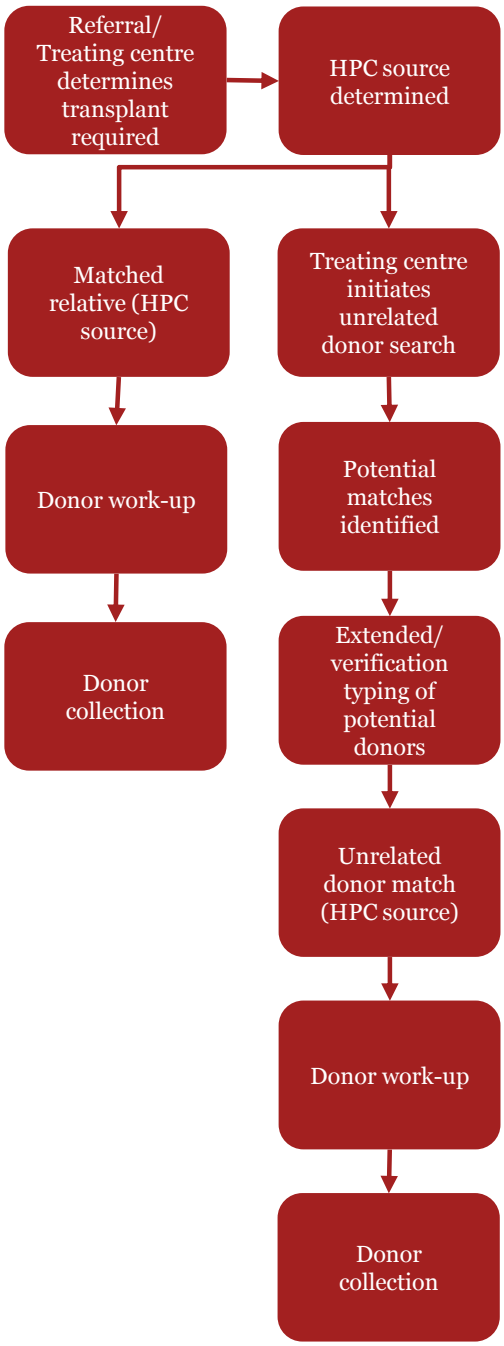
To find an unrelated HPC donor, the treating transplant centre:[130]

1. Initiates an unrelated donor search by filling out an ABMDR Preliminary Search Form ('110 form') and emails this to their State Search Coordinator, while confirmatory typing of the patient (as tested at the relevant state tissue typing laboratory) is shared as part of the search
2. The State Search Coordinator(s) will then load the patient's details onto MatchPoint (the Australian registry database) to identify potential Australian donors
3. The State Search Coordinator(s) may also look to international registries to identify potential matches. For non-urgent cases, international searches follow the identification of potential donors from the Australian registry. For some of these registries, information can be accessed through the BMDW and the European Marrow Donor Information System (EMDIS)

[129] AusCord, May 2017

[130] ABMDR (2011) Chapter 7 – Search process for Identification of a Haemopoietic Progenitor Cell (HPC) Donor, ABMDR-GL-OP-007-08

Figure 101: Allogeneic HPC donation pathway



4. State Search Coordinators prepare preliminary search results outlining potential matches and their degree of match based on available information on the typing of the donor. This is sent to the transplant centre for decision making on potential donors

5. For both domestic and international donors, the transplant centre will fill out a *patient funding application* which specifies a patient's Medicare eligibility. Non-Medicare eligible patients must either self-fund their treatment, may be supported philanthropically by a treating hospital, or may be referred on to a private centre (or international centre, as these patients are typically non-residents of Australia).

6. Potential domestic donors are requested by the transplant centre for extended typing (to test other loci, or at a higher resolution) and then sought for verification typing (a confirmation that they're a match). The latter is initiated by submitting a *Final recipient HLA typing* form which is submitted to the ABMDR.

7. For potential international matches, the transplant centre fills out an *application for initial funding* (either international family donor search or international unrelated donor search), which activates funding approval from the International Searches Program (ISP). The ISP funds typing, blood samples, testing, sample freight, search activation fees (if not reciprocal), CBU testing and freight.[131]

8. Upon receipt of the request forms, the ABMDR's Donor Coordinators will get in touch with the requested donor to seek their preliminary consent, and to arrange for a blood sample to be taken. The Donor Coordinator manages all engagement with the donor from this point onward. If the donor is international, the ABMDR will engage with their equivalent registry to similarly seek a blood sample to be sent and tested in Australia. And if suitable, that registry will also manage arrangements for their donation at an international donor centre.[132]

[131] ABMDR (2015) Patient funding access policy, ABMDR-POL-OP-PAT-01

[132] *Note: For patients with relatives living internationally who are potential matches, the treating transplant centre will work with the patient to get in touch directly with the relative and seek their tissue type. For these donors, there is no requirement to have their blood sample tested by the ARCBS (although they still may), and so they may seek testing at a local tissue typing laboratory, or in very rare instances, use a buckle swab and send it to Australia to be tested.*

9. The State Search Coordinator will provide details of the potential donor's verification typing back to the transplant centre as it becomes available. If the transplant centre then decides on a suitable donor, the Centre will then takes steps to *mobilise* the donor for collection.

5 Mobilising a donor

As per identifying a donor, there are three types of unrelated donors supported by the HPC program. These are:

- Unrelated domestic donor
- Unrelated international match
- International matched relative

Each has a different pathway for mobilization, which are outlined in the following figures.

Domestic related and autologous donations are managed directly by the treating transplant centre and common only in the work-up and collection activities that are represented here for unrelated HPCs.

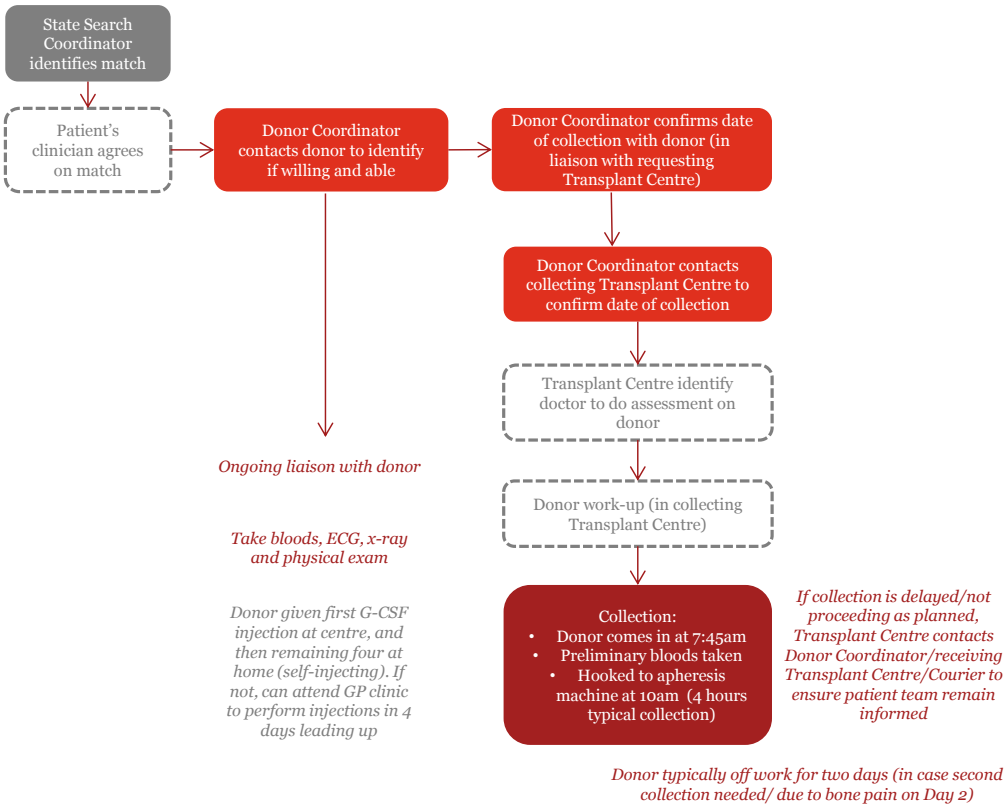
It is important to manage the coordination between donor and patient carefully as there is a limited window between preparing the patient for treatment, and collecting the cells so that they arrive viable for transplant. To manage this, transplant centres work closely with the ABMDR and the ARCBS to ensure collections are made in line with a patient's transplant plan. The mobilisation steps comprise three common steps:

- Prescription of HPC collection, which is filled by the patient's physician at the requesting transplant centre. It specifies the cell content required and HPC type (peripheral blood or bone marrow). This is provided to the Donor Coordinator who then works with the donor collection centre (another transplant centre, if the donor is Australian) to schedule 'filling' the prescription
- Donor work-up, which involves the Transplant Coordinator making contact with and scheduling the donor to come into the transplant centre for 'work-up'. This includes collection of a blood sample, an ECG, chest x-ray and physical exam. Upon work-up, the work-up physician will declare if a donor is 'fit and able' to donate, and if they're not, advise the donor on seeking further medical advice. If the donor is able and willing, they are provided with education regarding the procedure and their formal consent is sought. Once consent is gained, the transplant centre treating the patient will begin patient conditioning in readiness for transplant.
- Donor collection, at which point the physical donation is undertaken. Once collected, the cells are couriered to the patient's transplant centre for infusion. Couriers are arranged for by the patient's transplant centre, and if it is an international collection, are escorted by a volunteer on commercial flight routes.

Domestic donors

The key steps in mobilising a domestic donor is conceptualised in Figure 102. It illustrates the key roles across the three coordinators in bringing a donor through to collection. In doing so, the needs of the requesting clinician are carefully balanced against those of the donor in scheduling their work-up and then, collection. Collection is undertaken in a transplant centre other than the one treating a patient. In states with only one adult transplant centre, the donor will be assigned a different clinician to undertake their work-up and suitability for donation to ensure privacy and interests are maintained. The same pathway is followed for a bone marrow harvest, except that the donor will typically be kept overnight to recover from the anaesthesia. All donors remain nearby to the transplant centre on the day following their collection in case a second collection is needed. Costs associated with the collection are worn by the transplant centre, while donor expenses are reimbursed (or provided upfront by, for example, cab vouchers) by ARCBS Donor Coordinators.

Figure 102: Unrelated domestic donor pathway

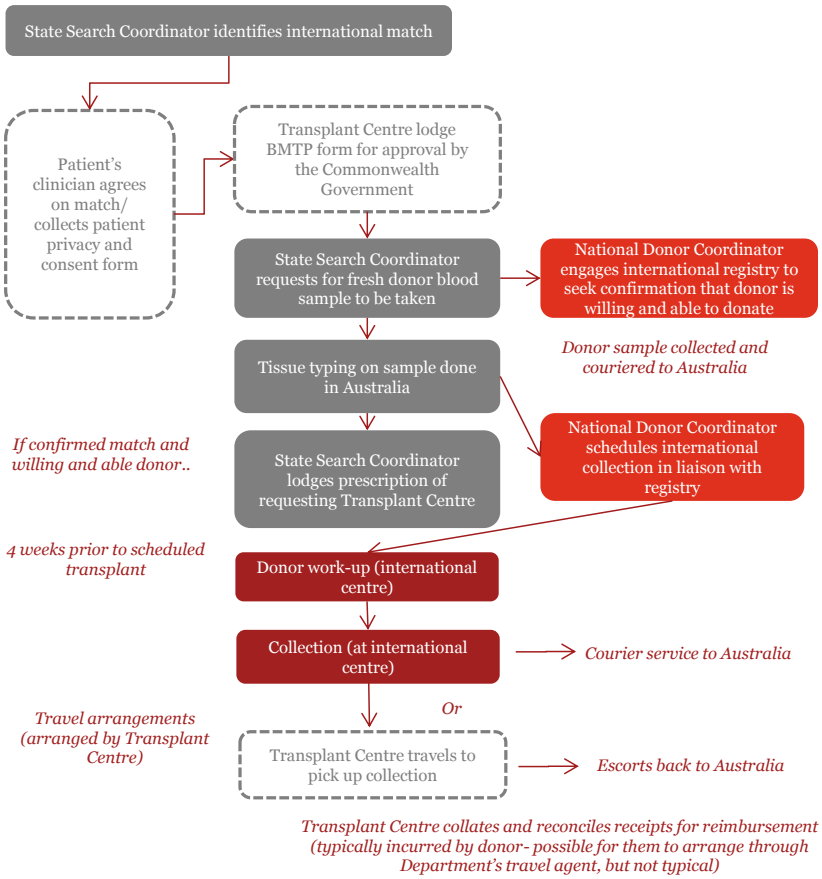


International donors

Similarly, the pathway for mobilising an unrelated international donor is carefully managed across coordinators, this time involving the National Donor Coordinator. The key difference in identifying an international donor is that a fresh sample is sought for testing in Australia and due to the potential for transport delay, requires very active logistical management. While in most cases, collected HPCs are transported back to Australia (using a commerical accredited courier), in some cases, a staff member of the requesting Australian transplant centre may travel to escort the donation back to Australia.

Funding approval is first sought by transplant centres from the BMTP program before mobilising an international donor. These expenses are expended upfront and later reimbursed by the Commonwealth upon provision of invoices incurred by the donor and courier.

Figure 103: Unrelated international donor pathway



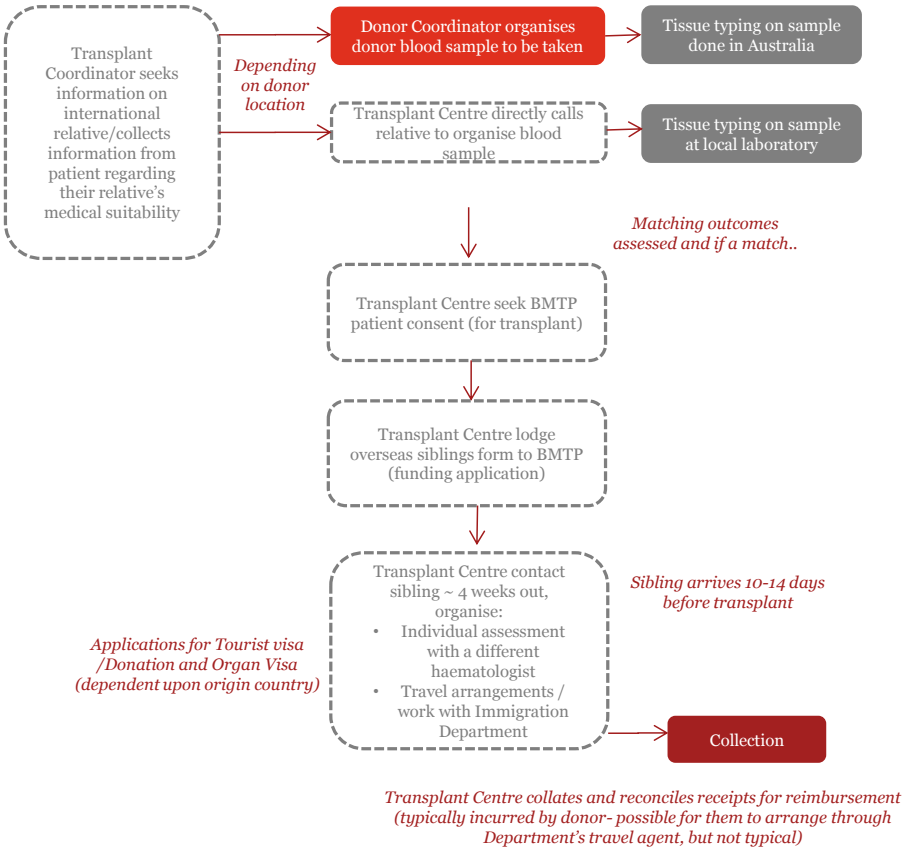
International related donor

Unlike unrelated donors, related donors located internationally draw much closer involvement of the Transplant Coordinator treating a patient. State Search Coordinators can play a role in undertaking extended family searches, and can facilitate for donor blood to be sampled and tested. However, in many cases, Transplant Coordinators will often work in concert with patient families to get directly in touch with relatives to seek testing. Often this is undertaken outside of the formal pathway, with relatives seeking out (with the assistance of the Transplant Coordinator) local laboratories that can undertake serological and/or genetic testing.

This review heard of some cases in which Transplant Coordinators would be actively involved in searching for an appropriate local testing facility, and even sending 'test packs' which contained buccal swabs to encourage relatives to send back samples for testing in Australia if their country didn't have adequate facilities. These anecdotes were typical of South East Asian countries which did not have a registry or appropriate laboratory present.

Like with international donors, collections from related international donors are supported by the BMTP program to which the transplant centre will seek funding before mobilisation. Expenses are then reimbursed following collection, meaning the relative donor can often incur significant upfront costs to facilitate the collection (for example, for flights and accommodation).

Figure 104: Related international donor pathway



6 Preparation and conduct of HPC transplants

Patients undergoing HPC transplants are prepared (conditioned) to receive the stem cells, and once transplanted, they are supported through engraftment and recovery. This includes:[133]

- Insertion of a central line (known also as a central venous catheter or Hickman catheter) which runs into the vein near to a patient's heart. This is used for delivery of the stem cells, samples, medication and fluid delivery for the duration of the pre- and post- transplant period

- Conditioning treatment, involving chemotherapy and/or radiotherapy:

    - Myeloablative transplants are strong doses that completely kill off a patient's blood forming system
    - Reduced intensity conditioning (RIC) which involves lower doses of conditioning treatment. RIC is typically employed among older patients, or where a clinician is seeking to optimize the graft-versus-leukaemia effect (associated with Graft versus Host Disease (GvHD) in the transplant.[134] (Note that each transplant will be an individual case)

[133] Bone Marrow Transplant Network NSW (undated) Allogeneic Bone Marrow Transplant – A Patient's Guide

[134] Sengsayadeth S (2015) Reduced Intensity Conditioning Allogeneic Hematopoietic Cell Transplantation for Adult Acute Myeloid Leukaemia in Complete Remissions – A review from the Acute Leukaemia Working Party of the EBMT, *Haematologica* 100

- The transplant, which involves delivery of the healthy stem cells through a patient's central line (over a 30–60 minute period)
- Engraftment period, which may include antibiotics to prevent and manage potential infections, blood and platelet transfusions to manage haemoglobin levels and bleeding, and medications to prevent GvHD (in allogeneic transplants only). The in-hospital engraftment period takes approximately 4-6 weeks.
- Follow-up patient care, which includes ongoing outpatient care provided in-hospital. Rehabilitation and recovery can take up to 12 months for an allogeneic transplant, and additionally, there is ongoing patient care arising from potential of long term effects of HPC transplant conditioning.

Bone marrow or peripheral blood?

While, the selection of bone marrow or peripheral blood is a decision made by a clinician in determining how many cells are required by the patient and what will provide the most favourable outcome. Bone marrow may be favoured by paediatric haematologists as it has demonstrated better post-transplantation outcomes as compared to peripheral blood in younger patients.[135]

Clinical preferences

The ABMDR undertook engagement in late 2015 with transplant physicians across all transplant centres in Australia to better understand clinical preferences in decision making. It found that cord blood units were still in use among transplant centres, but that some maintained a clinical philosophy which preferenced haploidentical transplants over cord blood transplants. These are summarised below.

Table 55: Clinical approach to cord blood use

Transplant centre	Approach
Adult centres	
The Alfred (Vic)	Maintains CBU program
Fiona Stanley (WA)	Maintains CBU program
Royal Adelaide (SA)	Maintains CBU program
Royal Brisbane & Women's Hospital (QLD)	Does not use CBUs
Royal Melbourne (Vic)	Maintains CBU program
Royal North Shore (NSW)	Haploidentical preferred over CBUs
Royal Prince Alfred (NSW)	Haploidentical preferred over CBUs
St Vincent's (NSW)	Haploidentical preferred over CBUs
Westmead (NSW)	Does not use CBUs
Paediatric centres	
Lady Cilentro Children's (QLD)	Haploidentical preferred over CBUs
Princess Margaret (WA)	Maintains CBU program
Royal Children's (Vic)	Haploidentical preferred over CBUs
Sydney Children's (NSW)	Maintains CBU program
Children's Hospital at Westmead (NSW)	Haploidentical preferred over CBUs

Source: ABMDR Unrelated HPC sourcing strategy (Version 1.2, 10 May 2016)

[135] Alwasaidi T and Bredeson C (2014) Peripheral blood stem cells or bone marrow as the graft for allogeneic hematopoietic cell transplantation? *Journal of Taibah University Medical Sciences* 9(2) 91-99

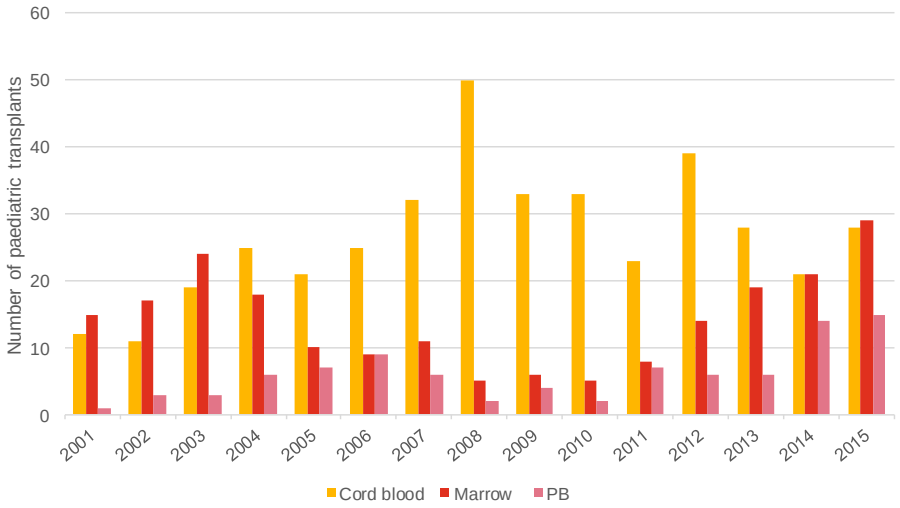
Clinicians are also treating older patients who had not previously been offered HPC transplant as a treatment option. This reflects advancements, particularly in reduced intensity conditioning. Currently there is no 'chronological' threshold for transplant, with overall 'fitness' and co-morbidities being the measure by which clinicians assess patient suitability for transplant.

7 Transplant trends in Australia

Paediatric patients

Paediatric patients are defined as those below the age of 16. Consistent with adult patient trends, the demand for HPC transplants among paediatric patients has increased over the last five years. 2015 saw a 90% increase in the number of allogeneic paediatric transplants since 2011. In addition to the total number of transplants performed, there has been a shift in the type of HPCs requested for paediatric patients. In 2008, 88% of paediatric transplants used cord blood, while in 2015, this figure has reduced to 39%, although in absolute terms, the number of CBUs used has slightly risen between 2001 and 2015. In 2015, 29 transplants requested bone marrow as the HPC source, representing 41% of total transplants and a growth of over 200% since 2011.

Figure 105: Paediatric transplants, by HPC type

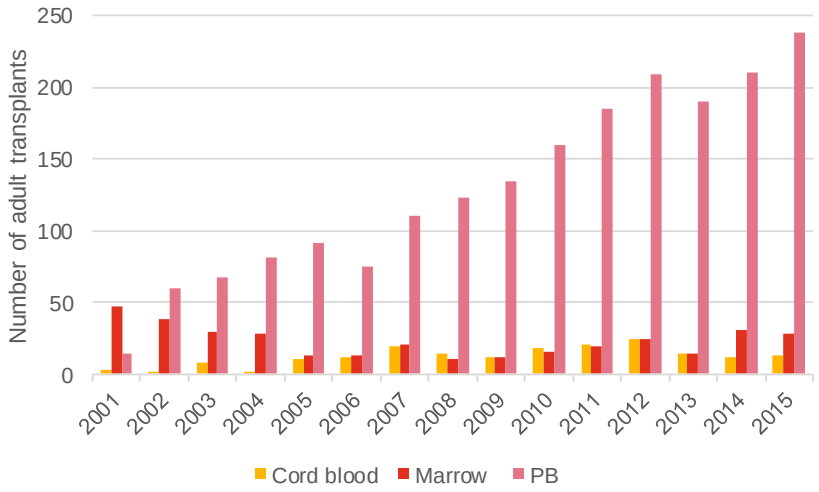


Source: ABMTRR Unrelated HPC donor report 2015

Adult patients

Amongst patients aged 16 and older, the most common form of HPC requested is peripheral blood. Used in over 80% of adult cases, there were 238 peripheral blood transplants in 2015. For patients with unique haplotypes, clinicians may opt to use cord blood transplants; 13 HPC transplants sourced cells from CBUs in 2015. Bone marrow was used for 10% of adult HPC transplants in 2015. The global growth in young, well-typed donors has provided patients with a greater chance of identifying a matched unrelated donor and is considered a primary driver of the growth in HPC transplants using peripheral blood.

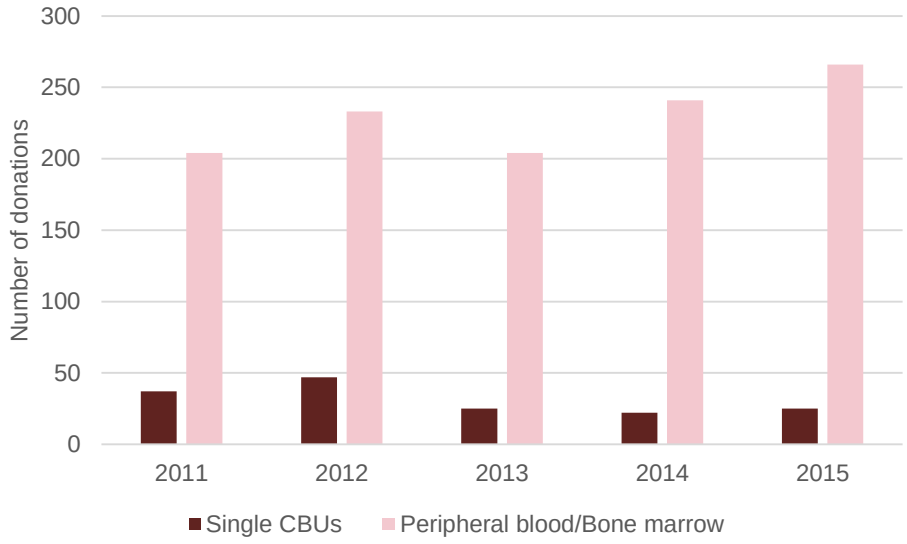
Figure 106: Adult transplants, by HPC type



Source: ABMTRR Unrelated HPC donor report 2015

This trend is reflected in the HPC sources sought from Australian donors. Between 2011 and 2015, the number of CBUs used in transplant declined from 37 individual CBUs to 25, while bone marrow and peripheral blood donations grew.

Figure 107: Number of HPC donations used in adult patients, 2011-2015

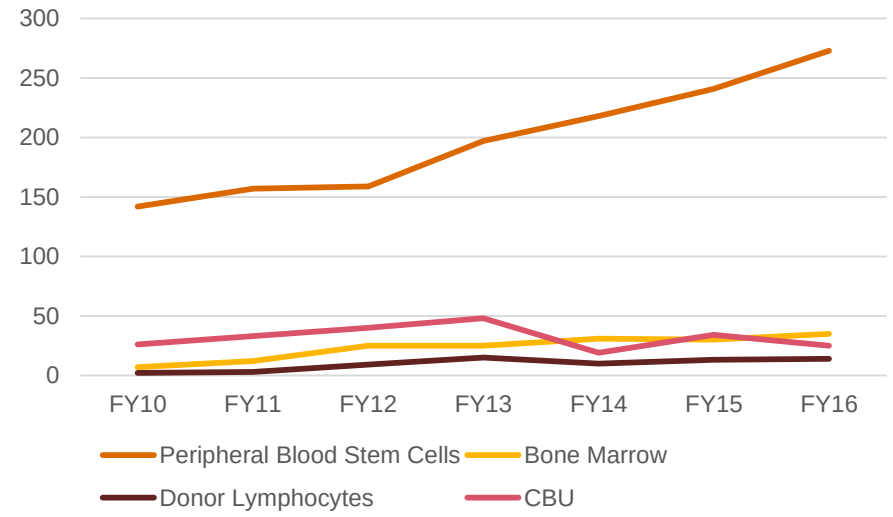


Source: ABMTRR Unrelated donor haemopoietic stem cell transplants in Australia 2015. Note: Cord Blood units refer to the number of single CBUs used in transplant (i.e. two in the case of a double cord transplant)

Transplants supported by international donors

Figure 108 represents trends in HPC types requested from overseas donors, with demand for peripheral blood continuing to grow.

Figure 108: HPC sources, international donors (adult and paediatric patients)

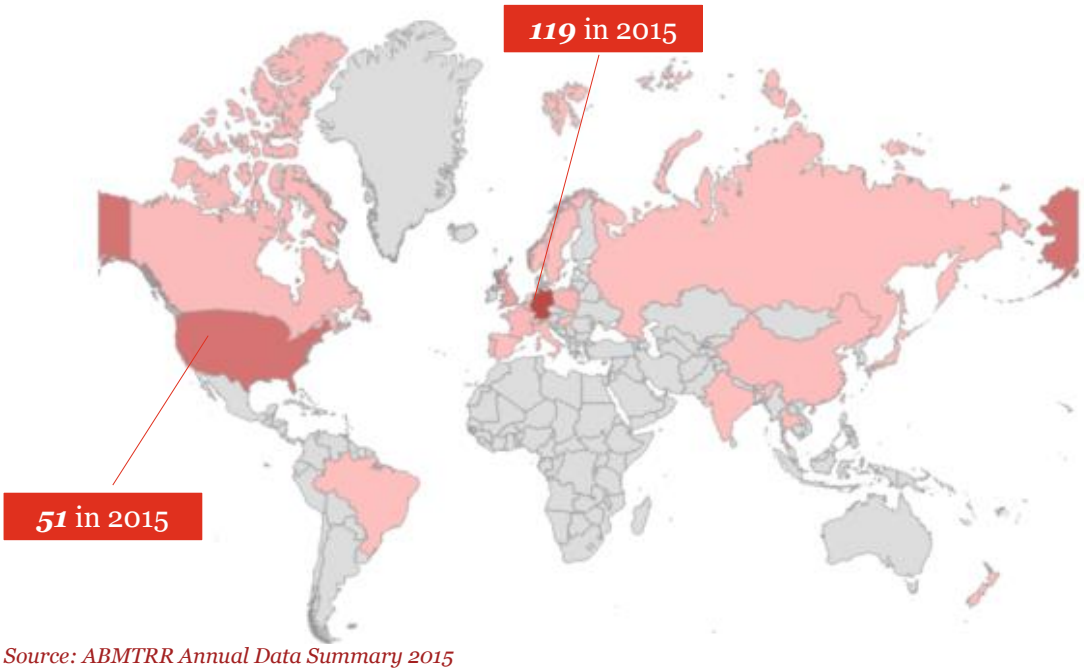


Source: HPC programs – October 2016 brief (BMTP data)

Consistent with previous years key reasons for selecting an international CBU over an Australian CBU were recorded in 2016 as, in order: 1. A better match if available internationally; 2. The international CBU is a better size and match; or, 3. The international CBU is a better size.[136]

In 2015, 54% of peripheral blood and bone marrow HPCs funded by the BMTP program were sourced from Germany.

Figure 109: International donors by country - 2015



Source: ABMTRR Annual Data Summary 2015

[136] ABMDR 2015-16 End of Financial Year Report- National Cord Blood Collection Network

The BMTP supports the collection of HPCs from a broad number of countries, but Germany is disproportionately represented among the reported transplants in Australia using international HPCs over the past three calendar years. The US and the UK are also valuable sources of volunteer donors to Australian patients.

Table 56: Top five international donor countries

HPC source		2013	2014	2015
Germany	Bone marrow or peripheral blood	86	87	119
	Cord Blood Unit	1	3	2
US	Bone marrow or peripheral blood	33	47	51
	Cord Blood Unit	16	13	27
United Kingdom	Bone marrow or peripheral blood	-	-	22
	Cord Blood Unit	-	-	4
France	Bone marrow or peripheral blood	3	6	1
	Cord Blood Unit	2	4	5
Poland	Bone marrow or peripheral blood	4	5	9

Source: ABMTRR Annual Data Summary 2015

Appendix D Background to the ABMDR

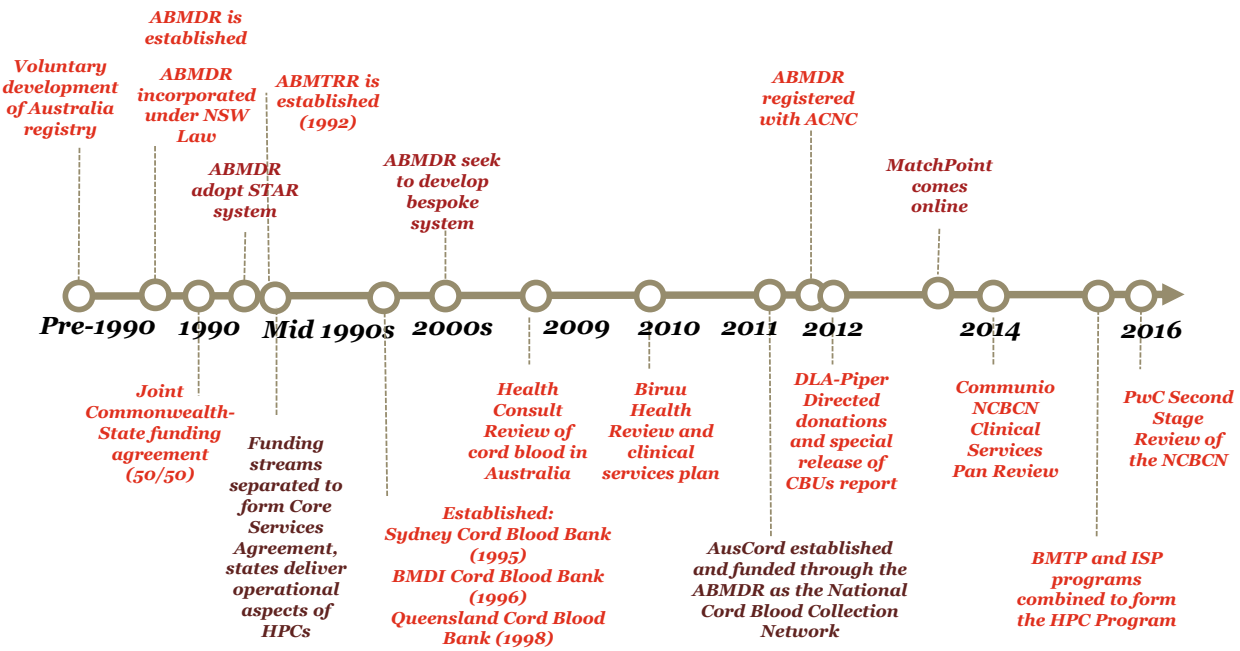
1 Evolution of the Australian Bone Marrow Donor Registry

The Australian Bone Marrow Donor Registry (ABMDR) was established in 1990, following a number of philanthropic efforts and one-off funding drives to create an Australian registry for stem cell donors. Its establishment followed approval by the National Health and Medical Research Council that transplant outcome data demonstrated the clinical efficacy of transplants. The ABMDR began its operation at around the time other registries were emerging internationally, however, most served domestic needs, with international cooperation following much later in the process.

At the time of its establishment, the registry was a small enterprise, developed at first from a $100,000 charitable donation from IBM together with approximately $500,000 in information technology (IT) support to build a fit-for-purpose registry system. It was supported by one ARCBS employee. It encouraged the registration of volunteer donors, primarily recruited through regular blood donors, as well as later supporting CBBs which stored Cord Blood Units (CBUs) for HPC transplants which had until 2001 operated independently.

The ABMDR was established as a not-for-profit organisation in NSW and was incorporated under the Corporations Act. It was centrally funded for its operations, receiving 50% of its funding from the Commonwealth Government, and the other 50% from state and territory governments. These arrangements continued for the first ten years of operation of the ABMDR.

Figure 110: Overarching chronology of the ABMDR



As more Australians registered as voluntary donors with the ABMDR, the original IBMAS400 system that supported the initial 10,000 donors to the registry needed to be

upgraded to support the greater number of searches being undertaken. Globally, registries were addressing the need to develop complex information technology (IT) infrastructure to support donors, but most importantly, searches which required algorithmic matching mechanism as clinicians sought more, and better information on potential matches to their patients.

At this time, the US had led the development of a custom-built system – STAR (Search, Tracking and Registry system) - that supported the registration and matching of donors, initially out of a need to support US Navy marines who had been exposed to radiation and needed stem cells. Australia, in close collaboration with the UK, Germany, France, and the US agreed on a series of international protocols to support sharing of donor information for matching in the early 2000s to give effect to their shared objectives.

Acknowledging a need to upgrade its technology, Australia, through the Department of Foreign Affairs and Trade, sought to establish a bi-national agreement that facilitated Australia's adoption of the US STAR system. A truly complex IT platform – initially taking 27 man years of 'Accenture time' to develop – the STAR system was the first of its kind. The agreement brokered in the late-1990s supported IT technicians to travel to Australia to implement the solution and 'Australianise' the IT to fit the ABMDR's needs.

However, the needs of registries continued to evolve and in the mid-2000s, the US redesigned their system to adopt a new customised Commercial-off-the-Shelf solution. Recognising that the legacy arrangements would not serve Australia well into the future, the ABMDR set about developing its own bespoke system that would support the ever-increasing numbers of donors and HPC transplant patients, as well as the growing international protocols that supported international searching and transport of HPCs. The ABMDR secured $2.2 million from governments to develop a bespoke system to meet these needs. The system, MatchPoint, came online in 2013 following a number of years of development and continues to support the functions of the ABMDR today.

Funding arrangements equally evolved over this time. Following the 50/50 funding arrangements originally established by governments, funding was streamlined among governments in the mid-late 1990s which had the effect of relegating operational funding responsibilities back to the states (as per Medicare Agreements), while the Commonwealth maintained core service funding. Later again, a requirement to fund the National Cord Blood Collection Network (NCBCN) required the ABMDR to register with the Australian Charities and Not-for-profits Commission in 2012. Funding for the NCBCN is supported by a head contract between the Commonwealth and the ABMDR, but is funded 50%by states and territories. These arrangements, and legacy changes has led to the current state and many of the processes in place today. These are explored further in this section.

From its humble beginnings, the ABMDR now manages over 170,000 volunteer donors, of which almost 1,000 are requested each year for typing and facilitates the transplant of over 350 Australian patients using HPCs from either an unrelated donor or cord blood unit.

This review follows a long list of reviews of the cord blood banking aspects of the sector:

- 2016 PwC Stage 2 Review of the NCBCN
- 2014 Communio NCBCN 2011-14 clinical services plan review;
- 2012 DLA Piper Directed donation and special release of cord blood units – Report on policy considerations;
- 2010 Biruu Health Review and clinical services plan; and
- 2009 HealthConsult Review of demand for, and supply and use of, cord blood in Australia

Despite this, a comprehensive review of the sector, including its current state, challenges, opportunities and future needs has not been conducted in the entire time of operation of the ABMDR.

2 State and territory activity

In NSW:

- The Bone Marrow Transplant Network manages NSW transplant centres, and enables one Standard Operating Procedure for all transplant centres as part of quality management requirements. The BMT Network undertakes accreditation statewide, provides education services, professional development opportunities and clinical guidance.

- Westmead (adult) transplant centre undertake bone marrow harvests for all collections undertaken in the state.

- The other three adult centres, Royal North Shore, Royal Prince Alfred and St Vincent's, undertake peripheral blood collections and will be allocated donors by State Search Coordinators, depending on the location of the donor and the spread of allocations among centres.

- Liverpool Hospital undertake matched sibling transplants (that may fall under the BMTP program), but refers on unrelated donor patients to Westmead, and occasionally, RPA and St Vincent's.

In Victoria:

- The Austin Transplant Centre is newly established, being only one year old. It falls under the purview of The Royal Melbourne Hospital who oversee clinical treatment of allogeneic-unrelated patients. The RMH undertakes all collections for the Austin, who do not currently undertake collection (except for related peripheral blood collections)

- Both the RMH and the Alfred undertake bone marrow collections, however, because the Alfred is a designated trauma centre, they don't have a dedicated morning theatre spot which typically means that bone marrow collections are diverted to RMH

- The Alfred and St Vincent's undertake peripheral blood collections, and the Alfred also maintains a CBU program for treatment of its patients

- All unrelated transplants in Victoria are referred on to the major centres who manage the patient through treatment

In South Australia:

- All allogeneic transplants (related and unrelated) are undertaken at the Royal Adelaide Hospital. RAH transplant physicians also maintain a role in oversighting allogeneic transplant candidates from the NT.

- Paediatric patients are referred on and treated interstate

In Western Australia:

- The Fiona Stanley Hospital has only been operating for 2.5 years, formally transferring from Royal Perth (where it had operated for some time). It treats all allogeneic adult patients. It also undertakes all ABMDR donor collections in Western Australia

- The Princess Margaret Children's Hospital treat allogeneic paediatric patients

In Queensland:

- All unrelated transplants are performed at Royal Brisbane & Women's Hospital, who also conduct all matching activities. The RB&WH also undertake unrelated paediatric transplants referred on from the Lady Cilentro Children's Hospital who don't hold accreditation to undertake unrelated transplants

- While all centres in Queensland refer on to the RB&WH if a patient is a candidate for an allogeneic-unrelated transplant, Townsville Hospital will perform unrelated allogeneic transplants as a secondary centre in the next 5-10 years

In Tasmania:

- All patients for an allogeneic-unrelated transplant are referred on to Victorian centres. However, the Royal Hobart Hospital undertakes collections on behalf of the ABMDR.

In addition to Australia's public CBBs, there is one private cord bank that stores (for a fee) umbilical cord blood for potential future use. These are not considered part of Australia's HPC sector as these constitute directed donations and are not available for release to unrelated patients. The ARCBS has established, in partnership with Rotary, a new CBB in Perth. It is currently finalising TGA accreditation and expects to be operational by the end of FY2016-17. The bank will seek FACT accreditation (once it has banked 500 CBUs) to enable it to list CBUs on the ABMDR registry for use by unrelated patients. The bank is not part of the NCBCN at present, and is considering a public-private model that could support research activities.

3 Patient referrals and management

Patient pathways are defined in each state, however, there are a number of notable exceptional cases:

- A number of transplant centres support Caledonian patients under government arrangements with the New Caledonian Government (CAPHAT)

- Medicare-eligibility is a tenet of the current operating arrangements for HPC transplants and access to international and domestic unrelated donors. However, this review heard of many cases in which non-Australian residents had presented to transplant centres to seek treatment. These patients are either referred on and can access transplants as a private patient (and so would be referred to a small number of private centres). Previously, there had been case-by-case philanthropic treatments approved and funded by hospitals but this has since been ceased across all transplant centres.

The referrals pathways for patients are explored further in Chapter 0 of this report.

There is no standardised care pathway in relation to allogeneic or autologous transplant patients and many of the examples given through consultation of referrals were based on either the relationships among clinicians, or were related to the typical practices carried out in that centre (for example, where clinicians had trained and were familiar with the procedure of transplant of a centre and so preferenced it in their practice or in the referral pathway they adopt).

4 International search streamlining project

Under current arrangements, Transplant Coordinators must lodge preliminary search forms to their State Search Coordinator to initiate an unrelated donor search for a patient. If a clinician wishes to search internationally, the Transplant Coordinator must also complete Medicare-eligibility forms, and an ISP application form, all of which capture similar information, duplicating the effort of transplant centres. In an effort to streamline this activity, the ABMDR is currently developing a workflow extension on their MatchPoint

software to automate Medicate-eligibility checks and ISP applications using one web page form.

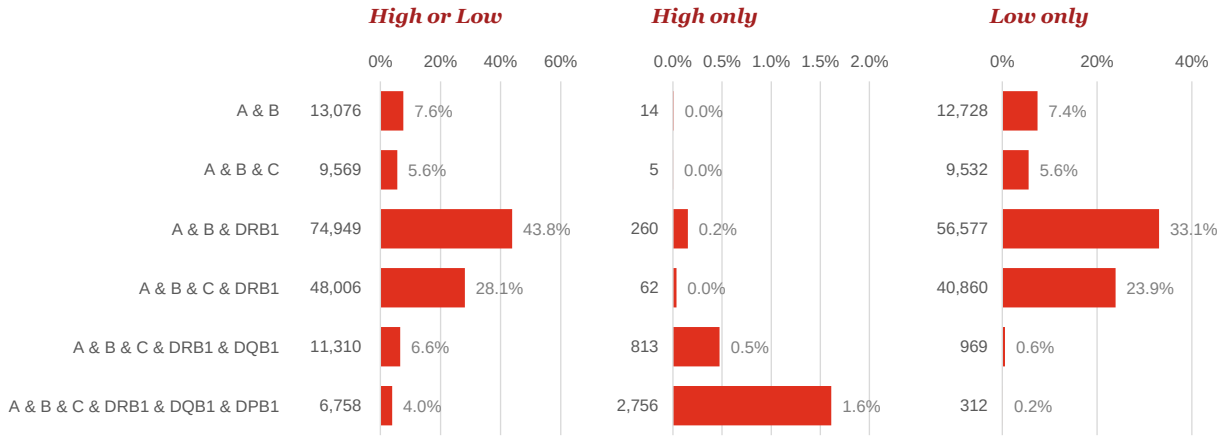
5 Cord Blood Bank Operational Alignment Project

A 2016 review of the NCBCN identified that the CBBs were undertaking a standardisation activity of processes and procedures to enable submission of a single Technical Master File to the TGA. The Operational Alignment Project aims to standardise banking activities including labelling, processing, cryopreservation, testing and storage of CBUs.[137] The Project has been underway over the past three years and at end of September 2017 is mostly completed.

6 The Australian registry

When clinicians are seeking information on donors, they look to multiple loci to identify a match. Subsequently, even though a donor may be well-typed at one loci, does not mean that they are typed as well at other loci. As a result, there is often a need to request extended typing to understand how close a match a donor is. Figure 111 outlines the typing combinations across Australian donors for different HLA loci.

Figure 111: Typing resolution of donors



Source: ABMDR Data 'Question_1a_to_1g – COMPLETE REGISTRY.xlsx'. Note: Figures do not add to 100% due to missing information on some donors. Available and Temporarily Unavailable donors represented only.

Of the information analysed, retired donors have more HLA-A and -B- and HLA-A and -B and -C-only low-resolution tissue-typed (23.1% and 17.5%, respectively). This reflects the impact of higher resolution tissue typing techniques which has improved typing over time. Notably, at high resolution, a handful (1.6%) are now typed at all six loci. This compares to the 33% of donors typed at low resolution for HLA-A, -B and –DRB1.

Verification requests

Since 2012, NSW has received the highest volume of verification requests across all states. This is likely driven by its high population and large donor registry. WA recorded 209 requests compared to VIC's 227 and NSW's 284. Requests are commonly made to multiple donors, both locally and internationally simultaneously to optimise a patient's chance of finding a donor, however, this inflates the figures for 'true' demand for HPCs. The trend over time in verification requests is consistent with earlier discussions of increasing demand.

[137] ABMDR (2015) Annual Report 2014-15

Table 57: Number of verification requests over time by state

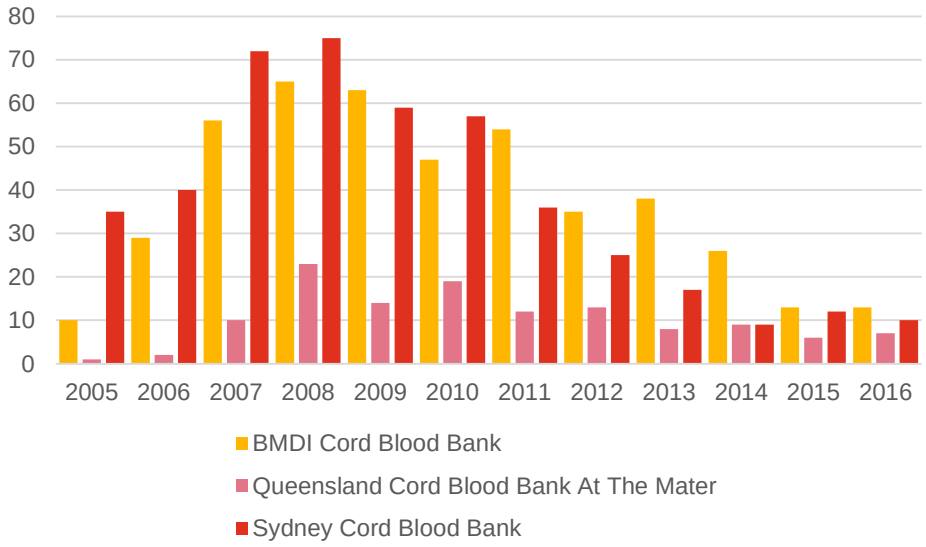
Year	ACT	NSW	NT	QLD	SA	TAS	VIC	WA
1995		42		6	10		46	17
1996		99		35	48	6	122	77
1997		135		38	33	2	155	110
1998	2	155	1	68	44	2	155	99
1999	2	149		44	39	3	157	100
2000	1	164	1	55	35	5	169	84
2001	7	186	1	76	58	2	185	118
2002	3	150		68	32	2	208	107
2003	2	199		66	41	2	215	84
2004	1	185		72	48	2	187	91
2005	1	222		82	52	3	191	112
2006	5	201		77	37	2	202	118
2007	3	252		99	53		200	132
2008	3	234		110	53	5	211	130
2009	2	224		127	70	2	244	180
2010	3	226		128	62	5	226	151
2011	4	169		107	55	6	234	152
2012	3	215		111	50	6	195	152
2013	3	232		198	41	3	196	182
2014		303		173	63		253	180
2015		290		203	65		259	185
2016	1	284		189	52		227	209*

*Source: ABMDR Question 2.xlsx. *Note: PathWest information suggests that datasets may differ (in 2016, PathWest undertook 337 verification typing requests)*

Cord blood inventory

Over the last five years, the Melbourne CBB (BMDI) has shipped the highest volume of CBUs, releasing 13 units in 2015. Consistent with the other banks however, the number of CBUs shipped has slowly declined, with a total reduction of over 300% since 2011. A number of factors influence this trend, including the wider availability of international CBUs and international donors, clinical preferences and haploidentical transplants.

Figure 112: Total CBUs shipped, by Cord Blood Bank

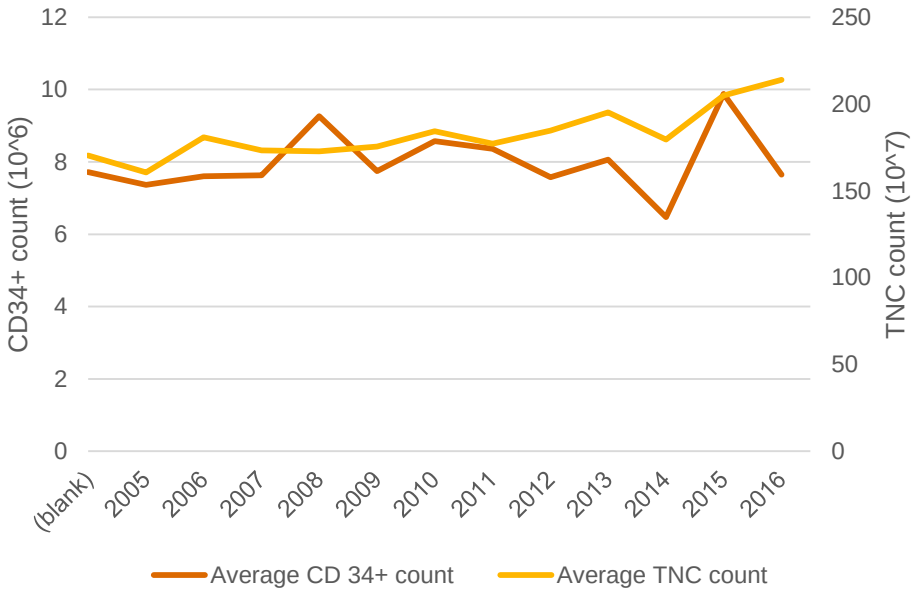


Source: CBUData-PWC-2016-02-29.xlsx, and ABMDR Question 2.xlsx

CBUs of high Total Nucleated Cell (TNC) count are typically in greater demand. Proportionately, Melbourne and Sydney store higher TNC count inventories. Figure 112 demonstrates the average TNC count for shipped units across banks. The average TNC count for cords collected in 2016 was 127.6 x 10^7 at BMDI CBB. Since 2001, the average TNC count of shipped units has slowly increased, before a fall in 2013 to an average count of 122.7 x 10^7. CBUs with TNC counts between 150 – 175 (x 10^7) are in greatest demand.

Figure 113 demonstrates the growth in both CD34+ count and TNC count in the CBUs shipped over time. Exploring ABMDR data from 2001, the greatest volume of total searchable units fall under a CD34+ count of 2.5 x 10^6. However, CBUs with higher CD34+ counts (of between 2.5 and 5 x 10^6), are increasingly in demand.

Figure 113: Characteristics of shipped CBUs (by year of release)

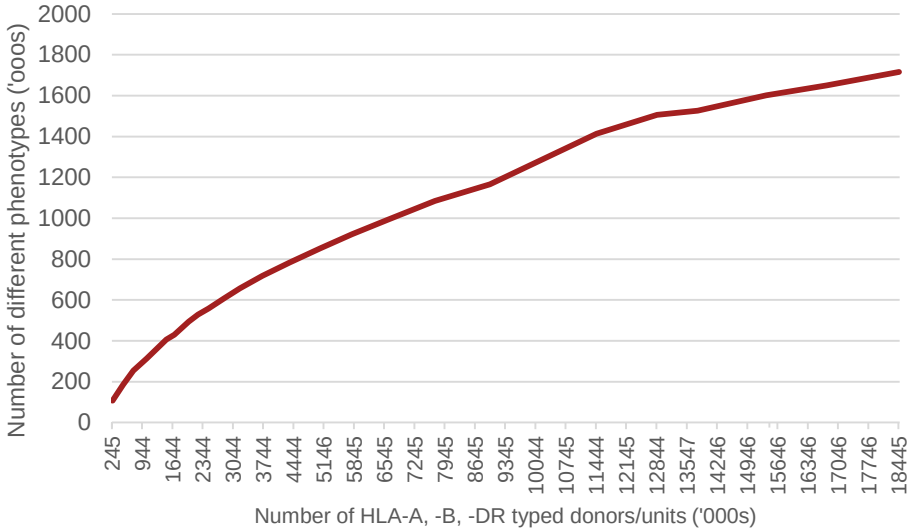


Source: CBUData-PWC-2016-02-29.xlsx, and ABMDR Question 2.xlsx

7 International registries

As per BMDW data (Figure 114), the number of newly added phenotypes added to global registries plateaus as more donors are registered.

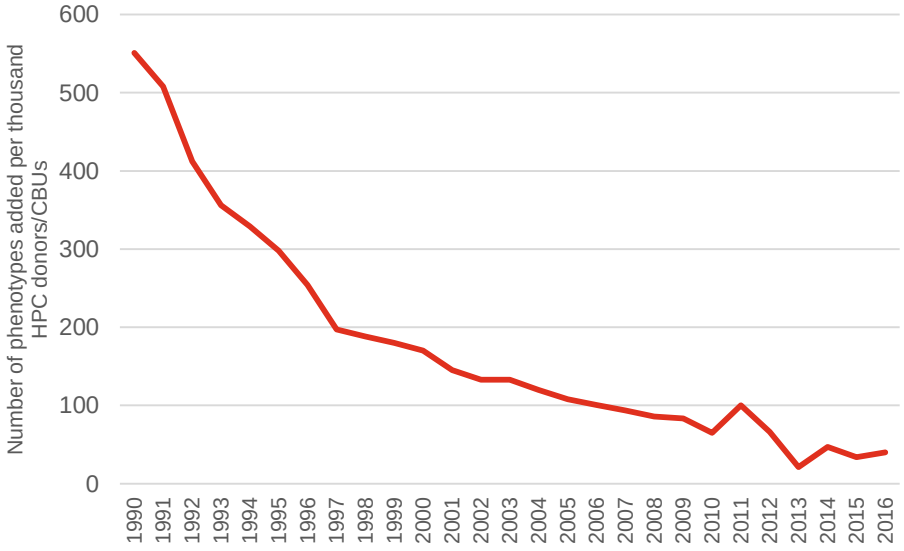
Figure 114: Number of different phenotypes added to the BMDW database



Source: WMDA additional information, slide pack 2016

This decline in the additional representation of diverse phenotypes is shown in the additions to the global database over time for both volunteer donors and stored CBUs.

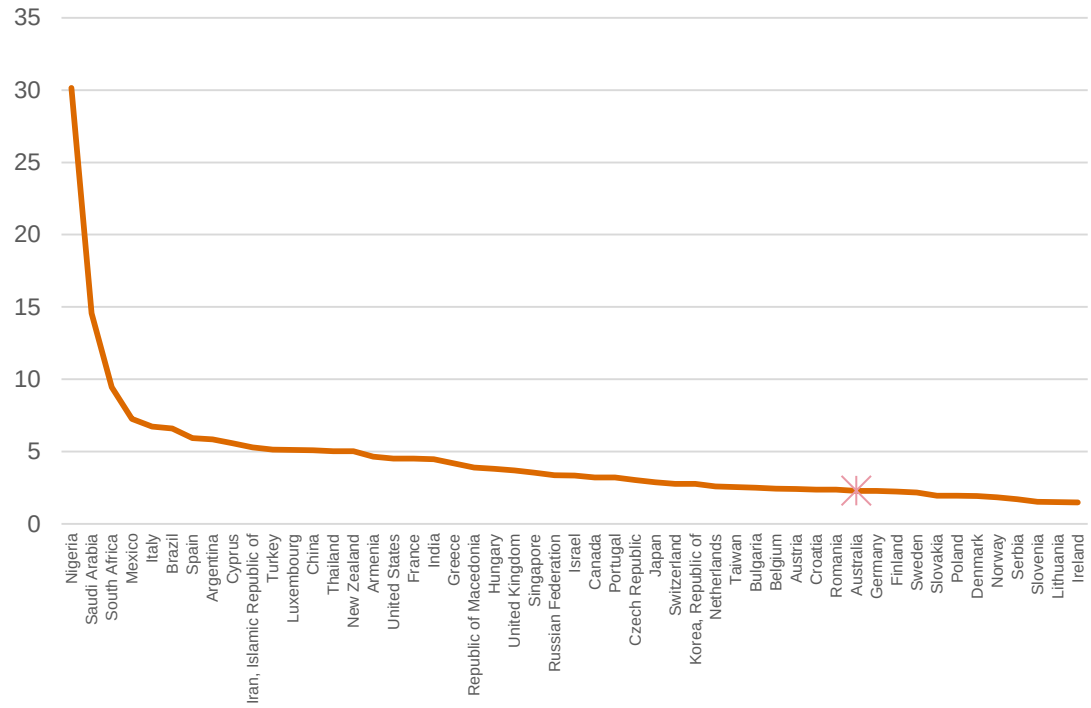
Figure 115: Number of different phenotypes added to the BMDW database per thousand new stem cell donors and CBUs



Source: WMDA additional information, slide pack 2016

The addition of new phenotypes not represented on the global database reflects the success and large representation of long-established registries as well as their relatively lower levels of genetic diversity within their populations. As such, greater HLA diversity is shown in countries such as Nigeria and Saudi Arabia (see Figure 116 below). In comparison, Australia contributes approximately 2.3% of unique phenotypes to the global database. This is comparable to countries such as Germany (2.3%), Finland (2.2%) and Romania (2.4%).

Figure 116: Relative percentage of unique phenotypes (HLA-A, -B and –DRB1) on the BMDW database, by country



Source: WMDA additional information, slide pack 2016. Note: Australia denoted with marker

The rate of registration of new donors and of newly collected CBUs continues to steadily rise globally. In 2015, a very large pool of newly registered donors and CBUs were added to the BMDW database. Table 58 lists the top 5 registries, by number of new donors, in 2015. In comparison, Australia registered 5,599 new volunteer donors in 2015.

Table 58: Newly added donors, by registry, 2015

Registry	Number of new donors
ZKRD Germany	775,174
NMDP US	515,890
REDOME Brazil	342,330
CMDP China	166,182
DKMS Polska	139,578

Source: WMDA Annual Report slide pack 2015

Proportionally, South Asia has the most HPC donors to CBUs registered (57:1), while the Americas and Europe maintain large donor and CBU registries (proportionally 47:1 and 43:1, respectively). This compares to the Western Pacific region (including Australia) which maintains roughly 19:1 donors to CBUs.

In 2015, 2,585 CBUs were dispatched for use by clinicians in the countries in which they were banked. In the same year, 827 were provided by international CBBs to patients in another country. Asia (and especially, Japan) was the greatest distributor of CBUs in 2015, surpassing North American who had been the largest provider of CBUs between 2006 and 2012. Table 59 outlines the number of CBUs of certain TNC counts for those dispatched in 2015. For adult patients, the high number of CBUs with TNC counts above $250x10^7$. This compares to Australia's average CBU which has a TNC of $120x10^7$.

Table 59: Key characteristics of internationally provided CBUs (global), 2015

TNC Count (single)	<125	125-149	150-199	200-249	>250
Paediatric	180	120	193	95	65
Adult	41	28	110	78	116

Source: WMDA Annual Report slide pack 2015

Table 60 lists the top five registries, by number of CBUs added in 2015, where Australia banked the second most CBUs behind the US.

Table 60: Top 5 registries by number of newly added CBUs, 2015

Registry	Number of new CBUs
NMDP US	12,965
ABMDR	3,079
REDMO Spain	2,538
JMDP Japan	2,357
Jeevan India	1,692

Source: WMDA Annual Report slide pack 2015

Appendix E International supply analyses

1 International supply analysis

This section provides an overview of the HPC profiles of key countries, including UK, Canada, US, Spain, France and Germany.

United Kingdom

HPC profile

The UK's stem cell supply is supported by two bone marrow registries: British Bone Marrow Registry (as part of the National Health Service Blood and Transplant) and the Anthony Nolan Trust registry (operated as a not-for-profit organisation).[138]

The British Bone Marrow Registry (BBMR) has approximately 300,000 volunteer donors,[139] while the Anthony Nolan registry has over 600,000 volunteer donors. The Anthony Nolan maintains a growing recruitment target of 80,000 new donors this year, with a target of 100,000 donors in 2018. This strategy is bolstered by a strong engagement strategy which engages closely with registered donors and supports retention.

The BBMR recognises the need to enhance representation among Black, Asian, Minority Ethnic (BAME) and mixed heritage groups who have a less than a 40% chance of finding a match.[140] Over the ten years 2005-2015, the National Health Service Blood and Transplant (NHSBT) facilitated the donation of 1,763 HPCs through the British Bone Marrow Registry.[141] Under current registry arrangements, approximately 80% of Caucasian patients will find a perfect match among UK donors.

In 2014, the NHS identified that there is underrepresentation among donors of the following ethnicities: [142]

- African
- African-Caribbean
- South Asian
- Chinese
- Jewish people of European descent
- Eastern European

[138] UK NHS 'Bone Marrow Donation', accessed at <http://www.nhs.uk/conditions/bone-marrow-donation/Pages/Introduction.aspx> 20 March 2017

[139] UK NHSBT 'Bone marrow', accessed at <http://www.nhsbt.nhs.uk/what-we-do/british-bone-marrow-registry/>

[140] NHSBT 'Join the British Bone Marrow Registry' leaflet, accessed at <http://www.nhsbt.nhs.uk/download/bbmr_recruitment_leaflet.pdf>

[141] UK NHSBT 'Strategic plan 2015-2020', accessed at <http://www.nhsbt.nhs.uk/download/strategic_plan_2015_20.pdf>

[142] UK NHS 'Bone Marrow Donation', accessed at <http://www.nhs.uk/conditions/bone-marrow-donation/Pages/Introduction.aspx> 20 March 2017

United Kingdom

- Southern European

The British Bone Marrow Registry is undertaking high-resolution tissue typing of 10,000 adult donors to improve the availability of information to clinicians.[143] Additionally, the NHSBT has targets to recruit an additional 12,000 donors to the fit panel in FY2017-18, increasing to an additional 16,000 recruits in FY2019-20.[144] The Anthony Nolan registry undertakes third generation typing at six genes for initial tissue typing and maintains a registry represented by approximately 40% males and 20% from BAME backgrounds.

The UK's strategy to develop a 'fit panel' of 75,000 donors emanates from its establishment of a UK Stem Cell Strategic Forum in 2010.[145] The Forum explored how unrelated donor stem cells and their use could be improved, of which they delivered a series of recommendations in 2010. Prominently, it set about changes to streamline the UK's three registries to improve how transplant centres seek and secure stem cells for their patients. It also refocused recruitment and cord blood collection towards ethnically diverse individuals. Since these changes, the UK has been able to increase the number of patients who can identify a donor by 30%. In 2014, the Oversight Committee endorsed the continuation of recruitment to the 'fit panel' so as to grow it to a target of 150,000 donors. There are approximately 2,000 UK patients searching for a match every year.

To test if third generation sequencing affects the donor selected for a patient, the Anthony Nolan is undertaking a retrospective study of donor HLA and patient HLA to assess where differences exist. These types of activities are hoped to inform future activities and investments of the registry.

The UK is looking to better understand future needs, particularly of BAME and mixed ethnicity patients, as well as to understand the impact of haploidentical transplants on the need for building out the cord blood inventory.

Additionally, consideration is being given to how donor welfare is provided across donors. In particular, for sibling donors who are not currently supported by any registry- this is an ongoing area of interest of the WMDA.

Governance

The UK's bone marrow donation program is overseen by the National Health Service (NHS) in collaboration with the Anthony Nolan charity.

Additionally, DKMS UK was established in 2013 as an extension of the German Registry. DKMS hold partnerships with a number of charities and companies to recruit new donors.[146] DKMS donors are registered to the one

143 UK NHSBT 'Bone marrow', accessed at <http://www.nhsbt.nhs.uk/what-we-do/british-bone-marrow-registry/>

144 UK NHSBT 'Strategic plan 2015-2020', accessed at <http://www.nhsbt.nhs.uk/download/strategic_plan_2015_20.pdf>

145 UK NHSBT (2014) Unrelated Donor Stem Cell Transplantation in the UK: A report from the UK Stem Cell Strategy Oversight Committee November 2014

146 DKMS UK, accessed at <https://www.dkms.org.uk/en/content/about-dkms> 20 March 2017

United Kingdom

registry managed by Anthony Nolan and the NHS covering all English, Scottish, Northern Wales and Northern Ireland donors.[147] The amalgamation of donors to one searchable registry was aligned in 2011.

The NHS manages a CBB which collects CBUs from specialist hospitals, made available through the registry to patients who need them. Stem cells therapies are also supported by the NHSBT among researchers. The Anthony Nolan also stores cord blood at its Cell Therapy Centre, which have a dual purpose for transplantation, but also release of CBUs for research.[148]

The Anthony Nolan has also established its own research institute to *make bone marrow transplants more successful*.

The NHS Blood and Transplant (NHSBT) was established in 2005 as a Special Health Authority to undertake functions associated with the collection, process and provision of blood and blood products, as well as organs and tissues. It merged the functions of the National Blood Service and UK Transplant.

The British Bone Marrow Registry falls under the Blood and Components services division under the NHSBT[149]. Outcomes reporting is captured by the British Society of Bone Marrow Transplantation, run by physicians. The BSBMT and government work in collaboration to inform policy setting and report to NHS Commissioners who sit within the Department of Health. Commissioners are interested to know more about outcomes, patients and conditions that are supported by HPC transplants, which is broken down by hospital – although this level of benchmarking is difficult to achieve in practice (only about 30% of transplant centres provide data and it is not always complete).

The Anthony Nolan, on behalf of the BBDR and DKMS UK produce a *State of the Registry* annual report which outlines achievements of the collective network over the year prior, as well as statistics regarding who is on the registry (for example, ethnicities).[150] Additionally, the Anthony Nolan captures donor outcomes.

Operational structure

The British Registry enrols donors between 17 and 40 years of age, while the Anthony Nolan accepts volunteer donors between 16 and 30 years of age. The British Registry also restricts enrolment to male blood donors, although females are accepted if they are of Black, Asian, minority or mixed ethnicity.[151] Donors on both registries are retired at age 60.

Donors to the British Registry is done via blood donor centres, much like

147 NHS Bone Marrow Division <http://www.nhsbt.nhs.uk/bonemarrow/qa/index.asp#howdo>

148 Anthony Nolan Registry, accessed at <https://www.anthonynolan.org/clinicians-and-researchers/anthony-nolan-cord-blood-bank-and-cell-therapy-centre>

149 Department of Health (UK) NHS Blood and Transplant Commercial Review (October 2011) Procurement, Investment and Commercial Division <https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/215390/dh_130563.pdf>

150 Anthony Nolan 'State of the Registry 2015', accessed at <https://www.anthonynolan.org/sites/default/files/State%20of%20the%20Register%20Report.pdf>

151 NHS Bone Marrow Division <http://www.nhsbt.nhs.uk/bonemarrow/qa/index.asp#whatis>

United Kingdom

Australia. However, Anthony Nolan and DKMS UK provide online registration options that send and return buccal swabs from new donors.

The Anthony Nolan primarily registers donors online, sending them a spit kit to provide a saliva sample.[152] The Anthony Nolan provides direct education to its donors, and has a wide range of material available to potential donors. For example, there are short videos explaining the process of joining the register, the process of potentially being potentially matched and what happens next. The Anthony Nolan also provides educational material for stem cell transplant patients.[153]

Their coordinators engage proactively with donors throughout their journey, including through mailed hard copy material. Volunteers support recruitment through drives and the national office functions, and additionally man social media channels to reach out to potential and actual donors. These volunteers are supported by an international learning and development program and buddy scheme.[154]

Blood samples (for verification) are taken at a local GP, and if matched, the Anthony Nolan coordinates their donors to travel to London for work-up. Collections are undertaken at one of three centres, including a London or Sheffield specialist collection centre.[155] BBMR or DKMS UK donors are managed by their registries through identification to collection and follow up.

Donors undergoing peripheral blood donation have a nurse visit the donor in the four days of injections in the lead-up. The Anthony Nolan Donor Coordinators visit donors in hospital during collection and provides a 'goody bag' to the donor. They also follow-up directly with the donor when they've returned home, and an opportunity for the donor to 'tweet' about their experience on Twitter. The Anthony Nolan has observed that donor welfare is an important part of its activities, particularly given its relatively younger donor base (including 17, 18 and 19 year olds). In making sure each donor is visited, there is a feeling of connection established.

Anthony Nolan has its own tissue typing laboratories, and provides services in graft identification, Additionally, it provides private testing services as well as testing for solid organs and other blood testing.

The Anthony Nolan and NHS are responsible for initiating and managing searches. Identified donors – on either registry- are contacted by the Anthony Nolan who coordinate their verification and collection. Donor work-up and peripheral blood collection is undertaken at Anthony Nolan's collection centres. Bone marrow harvests are undertaken at one of three hospitals that are under MoU arrangements (one of which is a private hospital that provides the 'best rate' for collection). Allocation is based on the capacity of the hospital to collect from the donor, as well as the donor's

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152 Anthony Nolan Registry, accessed at < https://www.anthonynolan.org/8-ways-you-could-save-life/donate-your-stem-cells>

153 Anthony Nolan, accessed at <https://www.anthonynolan.org/patients-and-families/having-stem-cell-or-bone-marrow-transplant>

154 Anthony Nolan Registry, accessed at <https://www.anthonynolan.org/8-ways-you-could-save-life/volunteer-us/learning-and-development>

155 Anthony Nolan Registry, accessed at < https://www.anthonynolan.org/8-ways-you-could-save-life/donate-your-stem-cells>

United Kingdom

location. Collections are paid for by the Anthony Nolan and later reimbursed by NHS.

The Anthony Nolan is supported by a team of approximately 300 people which are split between its: research and tissue typing laboratory; policy/public affairs and campaigning (approximately 75 people); registry support and arrangement; operations department (approximately 60 people, including donor liaison, search and selection roles and donor welfare, as well as one dedicated FTE to travel booking); information technology (IT) department; and, finance department.

A significant component of the Anthony Nolan's operations are its volunteer base. Volunteers provide substantial resources to run recruitment events, including recruitment at universities (approximately ¼ of new donors come through this channel), the 'Register to be a lifesaver' campaigns (aimed at 15-17 year olds in schools). Older volunteers (including those retired from the registry) may be trained to act as 'carriers' to transport HPC cells after they are collected.

Some methods for promoting recruitment include allowing for 2 days of reflection and a teabag (to prompt students to talk to their parents) in its 'Register to be a lifesaver' before revisiting schools to offer to enrol new donors, enrolling volunteers from 16 years of age and promoting enrolment among organ and blood donors. Other avenues include patient appeals (although these are less of a focus due to high attrition rates), recruitment among military and police members, recruitment through partnerships (corporate entities). Military engagement can be one of the most valuable streams of recruitment due to a high level of donor commitment, and support by the UK Military's Joint Chiefs who support the organisation. Approximately 45% of all recruitment is achieved online and is supported by seven paid FTE.

Costs/ funding

DKMS UK is a charity, and receives cost recovery funding for extended typing and donation activities. It also accepts volunteers to work at its office. [156]

The NHS BT's expenditure in FY2015–16 was £68 million, which includes the operational income and expenditure associated with blood, blood products, organs and stem cells.[157] Stem Cell Donation and Transplantation, and Cellular and Molecular Therapies are budgeted for £21.1 million in FY2016-17 and £24.2 million in FY2019-20.[158]

The Anthony Nolan operates on a revenue base comprised of £13 million from fundraising, £1 million from government (issued as a grant to support cord blood collection) and £30 million from stem cell supply (to both domestic and international patients). Expenditure covers activities including recruitment, registry management as well as coordination and expenses reimbursed to donors for travel etc. The UK government also provide ad hoc funding to support recruitment typing to fill BAME gaps.

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156 DKMS UK, accessed at <https://www.dkms.org.uk/en/content/about-dkms> 20 March 2017

157 UK NHSBT, accessed at <http://www.nhsbt.nhs.uk/news-and-media/review-accounts/>

158 UK NHSBT 'Strategic plan 2015-2020', accessed at <http://www.nhsbt.nhs.uk/download/strategic_plan_2015_20.pdf>

United Kingdom	
	The Anthony Nolan identified cost of £60 to register a donor. Having switched from blood samples about eight years ago, buccal swabs are much cheaper (~20 pence per swab) and provides good quality DNA. To achieve scale in tissue typing, while their own laboratories have capacity to undertake high-resolution typing, new recruits are typed by Histogenetics to undertake 6-gene typing).
Accreditation/ international associations	Laboratories of the NHS are accredited by JACIE (the Joint Accreditation Committee – ISCT and EBMT) and the UK's Medicines and Health Care Regulatory Agency Clinicians and scientists collaborate through the British Society of Blood and Marrow Transplantation and the British Society for Histocompatibility and Immunogenetics, who produce guidance and support discussion regarding clinical practice.

Canada	
HPC profile	OneMatch, Canada's bone marrow donor registry, enrols donors between 17 and 35 years old, primarily targeting male donors.[159] It maintains a target of recruiting 35,000 new recruits each year. This figure was based on an analysis undertaken in 2014 considering the haplotypes on the registry and within its general population to determine what the probability would be of identifying a match for a given patient. An assessment was then undertaken to assess the marginal value of growing the registry as compared to investment. The Canadian Blood Service is attempting to "replicate the face of Canada" when recruiting new donors to the registry. Canada's Cord Blood Bank was launched in mid-2015. At 2014–15, 8,800 CBUs had been collected, with 1,200 of these banked ready for release. OneMatch upfront types its new male donors under 35 at high resolution for 5 loci, while female donors are typed at intermediate resolution. CBS is considering providing Next Generation typing as part of its service portfolio, although its investment is not yet underway. An ongoing challenge in achieving its targets is in the ability to recruit enough under 35 year old males. Currently the 'shortfall' is met by female donors. Additionally, there are specific ethnic groups underrepresented on the registry, including First Nations peoples.
Governance	The Canadian Blood Service operates the OneMatch Stem Cell and Marrow Network as well as Canada's Cord Blood Bank, in addition to its role in providing blood and blood products for Canadians and organ and tissue responsibilities. The Canadian Bone Marrow Registry – OneMatch - was only recently reorganised to come under the purview of the Canadian Blood

[159] Canadian Blood Services 'OneMatch Information', accessed at < https://blood.ca/en/stem-cell/onematch-information-new-registrants>

	Service. The CBS is a not-for-profit organisation, funded via various avenues, including provincial governments. It reports to a working table through which provincial government's oversight the CBS's activities including its blood, transplantation and stem cell responsibilities. It is represented by Ministry Officials from all of Canada's provinces.
Operational structure	The donor recruitment stream of CBS's work recruits for all lines of its business (blood, organ donors and stem cell donors) and was established as a standalone support service in 2013. This enables specialist expertise to be leveraged, as well as to build on the donor management systems of the CBS as a whole. Recruitment campaigns are targeted at younger donors, including through universities. The donor relations team also works with larger groups to promote recruitment, including of underrepresented ethnic groups. Donors enrol online through creating a personal profile, after first completing a *knowledge test* which tests potential donors on the basics of stem cell donations. Donors are then sent a buccal swab kit to send back to the CBS which is then typed and details registered against the donor. Buccal swabs have been used since 2008/09 for both recruitment events and online registration channels. The OneMatch registry runs targeted campaigns to enrol desirable donors – currently the *Give Life* movement, which promotes young men to register as donors.[160] Many of these events are assisted by volunteers who are trained in collecting optimal DNA samples. The CBS maintains its own three tissue typing laboratories, which also supports its other activities. But for most of its initial typing, samples are batched and sent internationally for typing (a few hundred at a time, procured through a bidding process). Searching and matching activities are undertaken in the one location under CBS. To initiate a search, the preliminary steps are largely automated, and transplant centres are responsible for entering their own records and develop their own search reports through an inbuilt software tool (which produces both CBS and BMDW donor reports). Three search analysts, who are specialists in immunology, are available to provide analysis or advance search support, although many transplant centres rely on their own expertise to undertake analysis. OneMatch will reach out to transplant centres if many workflows are being raised in the system for the one patient, although it is at the discretion of the transplant centre whether they ultimately seek this support. All additional testing and donor contact is managed by OneMatch. A Donor Coordinator team within OneMatch then supports the activities associated with mobilising a donor. The team is split by administrative staff (who organise the collection of blood, arrange for the donor to go to the collection centre), a team of case managers (who take donors through preliminary health screening and do donor follow-up, all based in Ottawa). However, once a donor is selected, that donor is assigned the one contact who supports the donor through work-up to donation (whether a domestic

[160] Canadian Blood Services 'Men Give Life', accessed at <https://blood.ca/en/mengivelife>

	and international donor). Blood samples for verification typing are all sent to CBS for testing. Donors are collected from at eight centres with whom the CBS has MoUs. These hospitals are funded to undertake collections and are allocated to depending on the location of the donor. CBS also undertake donor follow-up surveys at 30 days, 60 days and 1 year post-procedure, While the information is captured by OneMatch, it is not forwarded on to any groups unless it is an adverse event, in which case it is assessed by the Medical Director and reported to WMDA. An ongoing challenge to OneMatch is in maintaining donor availability; among younger donors there is an increasing rate of decline in those proceeding to verification typing when identified, as well as a general inability to contact these donors in the first instance. This has meant processing time has grown and consent may not be able to be achieved. CBS finds that donors with a stable job typically are easier to contact and those in their late 20s and early 30s are more committed than younger donors. OneMatch's CBB was funded by governments in 2011 and established in 2013 with the support of a large fundraising campaign. Collections are made in Vancouver, Ottawa, Edmonton and Toronto and are support by two manufacturing facilities (east and west) which bank the CBUs. Donor testing, HLA typing and marketing associated with the CBB all leverage the in-house services of the CBS.
Costs/ funding	Canadian Blood Services is funded by provincial and territory governments to undertake its activities and operates as a not-for-profit entity. In addition to this, CBS receives philanthropic funding, much of which is tagged to programs or links services to specific provinces. Of the $2.8 million in voluntary donations to CBS in 2014–15, 1% was committed to the OneMatch Network, with a further 41% allocated to the establishment of Canada's CBB.[161] Recruitment is provided with an operating budget to which activities are designed (effectively capped). Some additional funding was accrued to enable investment in the CBB as it grows its inventory. Donors are reimbursed for expenses by OneMatch, channelled through the donor coordination team.
Accreditation/ international associations	The Canadian Blood and Marrow Transplant Group is a member-led group who advocate for patient care, research and education in HPC transplants. They oversight a series of committees that deliver streams of work against this role. The CBB is accredited by the AAC.

United States

[161] Canadian Blood Services (2015) 2014-2015 Report to financial donors

HPC profile	The US is comprised of a number of not-for-profit registries which support volunteer donors to be matched to patients. Among its most prominent is the NMDP Network and its now-called Be The Match Registry. The NMDP lists affiliations with 20 US Cord Blood Banks which store CBUs for use in HPC transplants.[162] Be The Match was initially established through federal government contributions, including from the US Department of Defense stemming from its interest in treating servicemen who had been exposed to radiation while on deployment. The other prominent registry is the Gift of Life Registry which was initially established 25 years ago to seek a match for its Jewish founder. The Registry now has 262,514 registered donors and operates on a not-for-profit basis.[163] The NMDP maintain one of the world's most prominent bioinformatics services which support the analysis of, and inform the strategic direction of the registry's needs to support American patients. Among these is an identified need to enhance the diversity and representation of ethnically diverse groups on the registry, as well as to address donor availability. However, with over 8 million donors registered, and an approximate half a million new donors registered every year, the NMDP maintains the world's largest volunteer donor registry. The NMDP reports that 47% of transplants it facilitates use an international donor or donate to an international patient. In 2016, 6,200 patients underwent a HPC transplant.
Governance	As independent, not-for-profit organisations, the NMDP and Gift of Life operate under different governance protocols. The NMDP is led by an Executive Committee and Board which is supported by a wide range of advisory and working groups which inform it. Through its various funding avenues, the NMDP report to government and other funding organisations for progress and delivery against project funding. Each registry is closely linked with the American Society of Bone Marrow Transplantation (ASBMT) which is run by clinicians and provides guidance, training and professional development to those working in the sector. The NMDP partnered with the Medical College of Wisconsin in 2004 to create the CIBMTR to support research and outcomes data capture. The CIBMTR and ASBMT run a joint-conference, often attended by international clinicians, that supports information sharing and collaboration. It is through these forums, and others, that the NMDP will collaborate with partners and input into the international community, of which it is a very active member.
Operational structure	NMDP-affiliated transplant centers undertake formal searches of the NMDP's registry and initiates additional testing for potential matches.[164] In all, Be The Match works with 175 transplant centres.[165]

[162] Be The Match 'Global Transplant Network', accessed at <https://bethematch.org/about-us/global-transplant-network/cord-blood-banks/>

[163] Gift of Life 'About us', accessed at < https://www.giftoflife.org/page/content/aboutus>

[164] NMDP (2006) An introduction to marrow and cord blood transplants, accessed at < https://www.ebmt.org/Contents/Resources/Library/Patientanddonorpublications/Documents/12.%20NMDPIntroBooklet.pdf>

[165] Be The Match 'Transplant Centers', accessed at <https://bethematch.org/about-us/global-transplant-network/transplant-centers/>

	The NMDP has an Office for Patient Advocacy which provides educational material and patient support (including a phone line which provides interpreter services). [166] The NMDP also produces standards which specify criteria for participation in its network, donation, collection, storage and reporting requirements for HPC transplants.[167] Gift of Life pioneered the widespread use of buccal swabs to enrol donors. It is supported by a significant donor drive effort, which includes 'SpeedSwabbing' and 'Be my marrow' campaigns that target younger potential donors to enrol. It works with 11 transplant centres and 8 collection centres (cancer centres in hospitals/medical centres). [168] Information regarding HLA-typed donors on the NMDP and Gift of Life are available to international registries through EMDIS and the BMDW database.[169] Additionally, the NMDP retains the world's largest tissue sample storage facility, which is used in medical research.
Costs/ funding	The NMDP's income for FY2015–16 was USD$393.6 million which is primarily comprised of search and procurement fees (USD$339.1 million) and government contracts, cooperative agreements and contributions (USD$54.0 million).[170] In FY2015–16, 59% of NMDP's expenditure was allocated to medical services, 12% to recruitment, 9% to research, 4% to public awareness and 16% to management and fundraising.[171] The Gift of Life Registry operates on a much lower operating budget. In FY2013–14, a total of USD$7.2 million in revenue, of which USD$2.7 million came from contributions and grants and USD$4.5 million in service revenue. It expends almost all its revenue, with USD$6.4 million directed to programs, USD$0.4 million to development and USD$0.4 million to administrative functions.[172] Search costs, including additional testing, is charged to the patient's treatment and, depending on their insurance coverage, may be an expense to the patient. [173] To support this, a range of organisations, including Be The Match, run philanthropic financial assistance programs to support patients in need.

166 NMDP (2006) An introduction to marrow and cord blood transplants, accessed at < https://www.ebmt.org/Contents/Resources/Library/Patientanddonorpublications/Documents/12.%20NMDPIntroBooklet.pdf>

167 NMDP/Be The Match 23rd Edition Standards and Glossary, January 1 2016, P00008 rev.4 NMDP Standards (1 January 2016)

168 Gift of Life 'About us', accessed at < https://www.giftoflife.org/page/content/aboutus>

169 Gift of Life 'About us', accessed at < https://www.giftoflife.org/page/content/aboutus>

170 Be The Match 2016 Report to the Community, accessed at <https://bethematch.org/workarea/downloadasset.aspx?id=8755>

171 Be The Match 2016 Report to the Community, accessed at <https://bethematch.org/workarea/downloadasset.aspx?id=8755>

172 Gift of Life 2014 Report to the Community, accessed at < http://www.giftoflife.org/flyers/2014_Report_to_the_Community2.pdf>

173 NMDP (2006) An introduction to marrow and cord blood transplants, accessed at < https://www.ebmt.org/Contents/Resources/Library/Patientanddonorpublications/Documents/12.%20NMDPIntroBooklet.pdf>

Accreditation/ international associations	NMDP and Gift of Life is accredited by WMDA. Cord Blood Banks are accredited by the Foundation for the Accreditation of Cellular Therapy (FACT) and the American Association of Blood Banks (AABB).

Spain

HPC profile	In 2016, the Spanish registry announced it had surpassed the 250,000 donor mark as well as having banked 60,000 CBUs in its public CBBs. Its registry, the Spanish Register of Bone Marrow Donors (REDMO), was established in 1991.[174] The National Transplant Organisation specifies an 18-55 year old age range for new donors which are engaged online and via donor centres. It is seeking to better support self-sufficiency, currently relying on a large portion of donations from international donors.
Governance	The current bone marrow registry is guided by the National Bone Marrow Plan which was developed in 2013 by the National Transplant Organisation. It specified a target of 200,000 donors by the end of 2016 to support patients. The Plan was renewed in 2015, specifying a revised target of 400,000 donors by 2020 to work towards self-sufficiency.[175] The National Transplant Organisation is an organ of the Spanish Ministry of Health, established 25 years ago, to coordinate organ donation, tissues, cells and bone marrow transplants.[176] REDMO holds a general agreement with the Ministry of Health, first signed in 1994, and then a second agreement in 2009. The second agreement specifies objectives of the partnership with the Ministry as well as procedures of the registry. REDMO works through the auspices of the Josep Carreras Leukaemia Foundation who maintain responsibility for the recruitment, search, coordination and registry management activities associated with bone marrow donation.
Operational structure	REDMO works with over 100 hospitals across Spain that undertake allogeneic-unrelated transplants.[177] It manages, through the Josep Carreras Leukaemia Foundation, the process of initiating a search application, the search coordination itself (employees of REDMO) of domestic and international donors, assessment of search outcomes, search activation (donor samples if not high-resolution typed), donor coordination (including scheduling and arranging medical consultations for Spanish donors) and patient follow-up.[178] Its website lists 51 bone

[174] Government of Spain 'Media Release 16 September 2016' , accessed at <http://www.lamoncloa.gob.es/lang/en/gobierno/news/Paginas/2016/20160916-marrow-donation.aspx>

[175] Government of Spain 'Media Release 16 September 2016' , accessed at <http://www.lamoncloa.gob.es/lang/en/gobierno/news/Paginas/2016/20160916-marrow-donation.aspx>

[176] See generally, http://www.ont.es/Paginas/Home.aspx

[177] Josep Carerras Leukaemia Foundation 'Spanish Bone Marrow Donors Registry (REDMO)', accessed at <http://www.fcarreras.org/en/redmo>

[178] Josep Carerras Leukaemia Foundation 'The search for a compatible donor', accessed at < http://www.fcarreras.org/en/the-search-for-a-compatible-donor_1999>

	marrow donor centres at which potential donors can enrol to join the registry. Evaluation of potential donors is guided by official regulations. DKMS Foundation (emanating from Germany) maintains a presence in Spain to promote the registration of Spanish donors to its registry.[179] It was formally established in 2011 and was authorised to undertake promotion activities in 2014. Formal recruitment and typing activities still require permission of Spain's Autonomous Communities before they can be undertaken.
Costs/ funding	The Jose Carreras Foundation lists revenue from a variety of sources including, in FY2014–15, €4.9 million from international searches of the REDMO registry, €6.7 million in member donations and €13.1 million in searches for Spanish patients. In respect of expenditure, in the same year, €1.4 million was committed to awareness raising, €2.2 million to administration and fundraising, €2.6 million to capital expenses, €4.5 million to searching REDMO for international patients and €12.4 million to undertake searches for Spanish patients.[180] In support of its National Bone Marrow Plan, Spain's Minister of Health has co-funded recruitment and typing activities. Federal funding of €830,000 per annum has been provided over four years to give effect to the development of the registry.
Accreditation/ international associations	REDMO is WMDA accredited.

France	
HPC profile	The France Greffe De Moelle Registry was created in 1986 to register French donors for patients searching for a match. It currently has approximately 180,000 people registered and supports a cord blood inventory of 9,000.[181] An approximate 2,000 French patients need a HPC transplant each year. To better support this need, the France Greffe De Moelle Registry is seeking to recruit more donors to grow its registry numbers.
Governance	The Registry is managed by the Agence de la biomedicine, which is part of the French health ministry. It was established in 1986, and came under the purview of the Agence de la biomedicine in 2006. The Agence is responsible for policy setting and the strategic direction of the registry.
Operational structure	Operationally, the registry supports activities from enrolment through to donor coordination. The Agence undertakes donor searches and coordinates donor collections and their transplant. Typing is conducted at

179 DKMS 'Media release 28 January 2015', accessed at <https://www.dkms.es/en/spain-permission>

180 Josep Carerras Leukaemia Foundation, accessed at <http://www.fcarreras.org/en/where-our-funds-come-from-and-how-we-distribute-them_856>

181 Agence de la biomedicine 'France Greffe De Moelle Registry;, accessed at <http://www.dondemoelleosseuse.fr/france-greffe-moelle-registry>

	the French Blood Agence's laboratories as well as through a number of identified teaching hospitals which support typing activities. Donors can enrol online, via post or via a call centre provided they are between the ages of 18 to 50. At recruitment events, saliva tubes are used to collect a DNA sample from which donors can be typed. For all other donors, they are required to complete a health questionnaire and provide a blood sample. Their website lists a very large number of volunteer donor centres and affiliated centres.[182]
Costs/ funding	The France Greffe De Moelle Registry, including the cord blood program is funded by the French Government through the Ministry of Health, although specific funding allocations are unknown.
Accreditation/ international associations	France Greffe De Moelle Registry has been a member of the WMDA since 2004, and an accredited member since 2009.

Germany	
HPC profile	The German stem cell donor base is supported by two primary registries; the DKMS registry and the ZKRD registry. The ZKRD registry is the world's second largest registry, with over 7.3 million donors. 35% of the DKMS registry is typed at high resolution for six loci. A further 21% is typed at high resolution for five loci. [183] To improve donor quality, the registry has prospectively typed many of its donors. ZKRD donors must be between 18 and 55 years old and are Next Generation typed at five loci at registration.[184] The DKMS also has a CBB, which it established in 1997. It is partnered with over 90 hospitals to collect CBUs and at 2014, had approximately 8,305 CBUs in inventory. The ZKRD maintain the registry of CBUs held in five CBBs (including DKMS's).
Governance	The DKMS is a not-for-profit organisation, established in 1991. Under its parent organisation, DKMS is established in Germany as well as the US, Poland, Spain and the UK. The ZKRD registry was established at a similar time – in 1992 – under funding provided by the Ministry of Health to maintains a central registry. It holds primary responsibility to manage the central registry of German donors and does so with information provided on available donors to it, and from DKMS and CBBs established throughout Germany.

[182] Agence de la biomedicine 'France Greffe De Moelle Registry, accessed at <http://www.dondemoelleosseuse.fr/se-renseigner-pres-moi>

[183] DKMS Annual Report 2014, accessed at: https://www.dkms.de/en/about-dkms

[184] ZKRD Annual Report 2015 accessed at: https://www.zkrd.de/_pdf/ZKRD_Jahresbericht_2015.pdf

Operational structure	Germany (ZKRD/DKMS) runs a lean registry in which is doesn't do research, cord blood or donor care. This enables it to focus on recruitment and mobilisation of identified donors. Among the key characteristics of German registries are the following: • Germany recruits and educates its donors well. • Military conscription means that German registries work closely with the German army and are able to capture young men early. These donors also typically stay on the registry for life. • The DKMS also runs donor drives at schools and universities to capture younger donors • ZKRD also use celebrities to reach out to younger donors to encourage their registration and promote the cause The ZKRD maintains a register of collection centres to whom identified donors are worked up and can make their donation. To ensure it has the most up-to-date information, the DKMS mails (and emails) registered donors to verify held contact information. In addition, as Germany also has a requirement upon its citizens to keep individual identification updated, DKMS at times, also pays a fees to the Residents' Registration Offices to access updated addresses (this forms part of the initial consent process). Capturing this information greatly assists it in its ability to quickly find and contact potential donors. Donors can therefore be quickly mobilised, and when one is identified, is often available for donation. DKMS primarily recruit new donors online via swab kits sent by mail (~60%). The vast majority of other donors recruited come from public donor drives (35%) and to a smaller extent, company donor drives (~5%). They undertake significant marketing campaigns and are supported by a dedicated team who administer social media profiles to engage with actual and potential donors. This effort is reflected in evidence where 47% of Germans know about DKMS's work.[185] In all, the DKMS is supported by a staff of approximately 260. [186] The ZKRD registry uses an OptiMatch system which enables algorithmic matching to identify potential donors. Paired with high resolution information, donors are quickly identified and mobilised. This had also led to Germany being a large distributer of HPCs to support international patients. Clinicians to this review remarked that German donors are often identified in preliminary searches and are considered to be reliable donors if requested to proceed to confirmatory typing. Donors are also well supported through the collection process. For example, DKMS support identified donors in working with their employer to seek sick leave. They also provide a certificate to support the granting of

[185] DKMS Financial Information 2013/14 report, accessed at: https://www.dkms.de/en/about-dkms

[186] DKMS Annual Report 2014, accessed at: https://www.dkms.de/en/about-dkms

	this leave, and due to its culture, DKMS report that it is rare that leave for donation isn't granted.[187]
Costs/ funding	ZKRD is funded by philanthropic funds of its founding member as well as through reimbursements through the health system. Philanthropic funds in particular, have enabled it to scale quickly and expand its activities. The scale of the two registries can mean that there is some competition between registries to maintain revenue streams necessary to their operation. DKMS is funded through voluntary donations as well as reimbursements for collections.[188] Approximately €14.5 million is from philanthropic donations. Due to its high representation in supporting international as well as domestic transplants, DKMS was supported by approximately €80.3 million in cost reimbursements for stem cell collections in 2014 (of which approximately €63.7 million was inflow from international jurisdictions). DKMS expenditure in 2014 exceeded €93 million. DKMS registration costs exceed €24 million, which in 2014 supported the recruitment of 604,548 new donors (about €40 per new donor). Typing costs are approximately €19 per donor, while logistics and communications account for another €13. [189] DKMS database maintenance and uplift activities cost approximately €8.3 million in 2014, while data administration accounted for approximately €140,000 and marketing an approximately €3.4 million. Search and collection activities account for approximately €35.8 million of all expenditure.
Accreditation/ international associations	Both the DKMS and ZKRD are accredited by the WMDA and are active contributors to the international community.

2 Background to the World Marrow Donor Association

The WMDA is the umbrella organisation to international collaboration on hematopoietic stem cell donor registries, CBBs, donor centres and transplant centres. It was established in 1988 as a mechanism to promote global collaboration and engagement on hematopoietic stem cells. It is supported by voluntary membership, comprising stem cell donor registries, CBBs and other entities with an interest in HPC transplants. Its membership is near-universal, comprising 93 hematopoietic stem cell donor registries and 158 affiliated CBBs, as well as donor, transplant and collection centres across its 52 member countries. Continued engagement and a shared commitment to international collaboration and promotion of safety in hematopoietic stem cell donation is reflected by the membership, but also by the widespread transit of HPC products between borders; indeed, approximately 50% of all unrelated HPC products used in unrelated transplantation are sourced from a country other than that in which the patient is treated.

[187] DKMS Frequently Asked Questions, accessed at: https://www.dkms.de/en/faq

[188] DKMS Annual Report 2014, accessed at: https://www.dkms.de/en/about-dkms

[189] DKMS Annual Report 2014, accessed at: https://www.dkms.de/en/about-dkms

Since 1 January 2017, the WMDA took over three functions, formerly filled by separate organisations, which are:

- BMDW which is the global database of volunteer donors and cord blood products
- NetCord which is an education organisation associated with cord blood banking
- EMDIS which is a community protocol for information sharing and ordering process.

Alongside these, the WMDA is a forum to a multitude of committees and working groups which develop new standards and guidelines to which the international community contributes. As the field is evolving WMDA members meet twice a year in their working groups and committees. Every other year the International Donor Registry Conference takes place which is the official WMDA congress.

Important for setting up guidelines and standards is the Serious (Product) Events and Adverse Reactions (S(P)EAR) database. The S(P)EAR reporting system is a mandatory reporting system which used by the Australian Bone Marrow Donor Registry to report its adverse reactions. Reported events are reviewed by clinicians.[190]

Among activities regularly engaged upon and continuously improved among members are registry aspects in relation to cord blood banking, information technology, medical practice, quality and regulation and registry operation. Alongside of standard and guideline development, the WMDA runs a series of education programs that support training and professional development of those working within the sector, including, for example, search coordination certification programs. In all, the WMDA is supported by a staff of 8 FTE and volunteers from organisations around the world.

3 Accreditation bodies

WMDA

The WMDA also provide accreditation services, which is a role that originally emanated from a need to foster international exchange of high quality hematopoietic stem cell donations. Some European countries have implemented the WMDA accreditation in their legislation in order to be able to control the import of hematopoietic stem cell products to their country.

Since its conception in 2003, WMDA accreditation has become the global standard for quality standards, with now 85% of global donors on the BMDW database associated with a WMDA-accredited registry.

To become an accredited WMDA registry, newly established registries will get in touch with the WMDA after setting up their initial donor file which specifies the specifics of volunteer donors enlisted to their registry. The WMDA assists in establishing standards to which accreditation requires, including protocols regarding exchange of information regarding donors and international donor databases as well as transit of HPCs to other countries. This allows for searching of other registries, as well as other registries searching it, for potential donors. Donors from registries which don't hold WMDA accreditation are flagged on the BMDW database, allowing physicians to identify these donors from others. Once standards are established, the registry may apply for WMDA membership. Membership enables participation on WMDA working groups and use of knowledge and education materials prepared by its members. Additionally, members can access key performance indicators that enables registries to compare to other registries. There are a small handful of registries not affiliated with the WMDA, however, the WMDA is truly viewed as the first point of access and so this is primarily limited to registries just starting out.

[190] See for further detail: https://www.wmda.info/wmda-eduction?id=61

Following accreditation, the WMDA conducts audits of members approximately every four years and captures annual reporting from each of its members which the ABMDR adheres to as a member. This enables it to have a truly global view of the sector, as well as to inform clinical and quality developments among members.

JACIE

In Europe, the Joint Accreditation Committee – ISCT and EBMT (JACIE) is responsible for international accreditation activities and quality management standards. It was established by the EBMT and ISCT to establish standards for medical and laboratory practice associated with HPC transplants. It operates as a not-for-profit and has done so since 1998.[191] JACIE is adopted and used by 17 European countries to meet its regulatory obligations. [192] However, it is not adopted by any aspects of the Australian HPC sector. Some stakeholders argue its adoption would drive consistency with international standards, attractiveness of Australian HPCs and streamline accreditation requirements across the sector.

[191] EBMT 'About JACIE' , accessed at <https://www.ebmt.org/Contents/Quality-Manatrgement/AboutJACIE/Pages/About-JACIE.aspx>

[192] The EBMT Handbook 'Haematopoietic Stem Cell Transplantation' 6th edition, European School of Haematology and the European Society for Blood and Marrow Transplantation, Chapter 2

Appendix F Donation cost outline

1 Domestic collection costs

A broad assessment of the costs associated with the work-up and collection of peripheral blood from a donor includes the following activities. These costs have been established with the inputs of the Tasmanian Department of Health and Human Services, transplant centres, The Royal Melbourne Hospital, Pharmaceutical Benefits Scheme listed price and hourly rate assumptions using award wage listings.

Activity	Effort/cost input
Donor work-up	
Transplant Coordinator scheduling and meeting of donor with haematologist/donor education (2-7.5 hours)	$1,248 (full day estimate)
Donor work-up with haematologist	$78
Donor blood testing: Nucleic Acid Testing Viral Serology Red Cell Thickening Test Blood Group	$280
Donor travel	*Unknown*
Donor collection	
Pre-donation consult with Haematologist (15 minutes)	$39
Blood test	$35
Apheresis collection Registered nurse (6 hours, including set up/pack up) Apheresis kit	$352 (level 2 nurse) $350 (kit)
Pathology repacking and labelling (90 minutes)	$142
Additional pathology tests post-collection	$169
Post-donation consult with Haematologist (30 minutes)	$78
Donor travel	*Unknown*
3 month follow-up with Haematologist	$78
Sub-total costs (health service)	***$2,849***
Pharmaceuticals (G-CSF costs) (Commonwealth) PBS filgrastim (10 x 0.5ml syringes)	$1,206
Total estimated cost	***$4,055***

Source: Figures kindly provided by the Tasmanian Department of Health and Human Services and PwC internal pharmaceuticals team

A bone marrow harvest comprises the following activities:

Activity	Effort/cost input
Donor work-up	
Transplant Coordinator scheduling and meeting of donor with haematologist/donor education (2-7.5 hours)	$1,248 (full day estimate)
Donor work-up with haematologist	$78
Donor blood testing: Nucleic Acid Testing Viral Serology Red Cell Thickening Test Blood Group	$280
Donor travel	*Unknown*
Bone marrow harvest	
Transplant Coordinator time (4 hours)	$224
Registrar (2 hours)	$100
Anaesthetist (3 hours)	$396
Theatre cost (1.5 hours)	$4,500
Consumables	$300
Pathology repacking and labelling (90 minutes)	$142
Additional pathology tests post-collection	$169
Post-donation consult with Haematologist (30 minutes)	$78
Donor travel	*Unknown*
3 month follow-up with Haematologist	$78
Total estimated cost	***$7,594***

Source: Figures kindly provided through consultation with transplant centres, The Royal Melbourne Hospital and using first year hourly rate assumptions for registrar and specialists as per http://www.westernhealth.org.au/Careers/Documents/Salary%20Rates/Circ-633%20Doctors%20in%20training%20and%20specialists.pdf

2 Projected BMTP expenditure (international donors)

The slight reduction in BMTP expenditure between FY2015–16 and FY2018-19 is due to a higher per average cost for BMTP and ISP applications in FY2015–16 ($33,395 and $2,322, respectively). This simple analysis also does not take into account patient-based demand (the number of transplants undertaken in Australia over time).

Table 61: Projected volumes and costs for internationally sourced HPCs

Financial Year	ISP applications	BMTP applications	ISP costs ($ million)	BMTP costs ($ million)	HPCP program cost ($ million)
2009	**436**	**169**	**-**	**-**	**-**
2010	**439**	**177**	**-**	**-**	**-**
2011	**514**	**205**	**$0.98**	**$4.04**	**$5.02**

Financial Year	ISP applications	BMTP applications	ISP costs ($ million)	BMTP costs ($ million)	HPCP program cost ($ million)
2012	**644**	**233**	**$1.17**	**$5.40**	**$6.57**
2013	**667**	**285**	**$1.32**	**$6.83**	**$8.14**
2014	**661**	**278**	**$1.47**	**$6.30**	**$7.77**
2015	**798**	**320**	**$1.50**	**$8.25**	**$9.75**
2016	**734**	**347**	**$1.70**	**$11.59**	**$13.29**
2017	*844*	*371*	*$1.65*	*$9.20*	*$10.85*
2018	*896*	*398*	*$1.75*	*$9.86*	*$11.61*
2019	*948*	*424*	*$1.85*	*$10.52*	*$12.37*
2020	*1,000*	*451*	*$1.95*	*$11.18*	*$13.13*
2021	*1,051*	*478*	*$2.06*	*$11.83*	*$13.89*
2022	*1,103*	*504*	*$2.16*	*$12.49*	*$14.65*
2023	*1,155*	*531*	*$2.26*	*$13.15*	*$15.41*
2024	*1,206*	*557*	*$2.36*	*$13.81*	*$16.17*
2025	*1,258*	*584*	*$2.46*	*$14.47*	*$16.93*
2026	*1,310*	*610*	*$2.56*	*$15.13*	*$17.69*
2027	*1,362*	*637*	*$2.66*	*$15.78*	*$18.45*
2028	*1,413*	*664*	*$2.76*	*$16.44*	*$19.21*
2029	*1,465*	*690*	*$2.86*	*$17.10*	*$19.97*
2030	*1,517*	*717*	*$2.97*	*$17.76*	*$20.72*

Source: HPCP – Annual report 2015-2016. Note: average cost per BMTP application calculated for actual years and then multiplied by projected volume numbers for 2017 +. Bold = actual, other = projected.

Appendix G Optimum supply approaches

Determining an optimal size and composition of a donor registry is dependent on the haplotype frequencies within populations, to then assess these against 'all possible pairings between a donor and a recipient'.[193] However, without all known possible frequencies and pairing probabilities, this activity is not able to be conducted. In place of this, cost-effectiveness approaches are typically used to assess what registry size will meet matching needs given the probability of achieving a match within the donor and recipient populations.

Against this, optimum supply must also take account of key aspects of managing a registry, which are:[194]

- Age and gender of donors
- Donor availability and eligibility
- Composition, size and diversity of registry.

To identify studies that have analysed optimum supply, Google Scholar and academic databases were searched for the terms "optimum HPC/HSC", "stem cell optimum", "supply bone marrow", "peripheral blood donors", "optimum donor pool HPC/HSC". These identified a number of studies which have been drawn upon below to assess approaches to optimising supply.

This section provides an overview of theoretical and actual approaches to establishing an optimum HPC supply profile.

United Kingdom

Summary:

In their seminal 2014 study, the UK's Stem Cell Strategy Oversight Committee used a cost-effectiveness analysis to determine the optimum supply profile for the UK. The approach used:

- QALY metrics to assess the case for additional donors (in both assessing Cord Blood Units and additional donors to the UK's 'fit panel')
- This was based on 9/10 and 10/10 match rates analysed for North West European and non-NWE patients through a retrospective study: Lown,et al. (2013) and match rates for a 5/6 and 6/6 match for cord blood units established by Querol et al (2009)
- An analysis of unmet demand was also undertaken to identify supply gaps
- The differences in meeting this gap and additional lives saved were used to quantify

[193] Sonnenberg F et al (1989) Bone Marrow Donor Registries: The Relation Between Registry Size and Probability of Finding Complete and Partial Matches *Blood* 74 (7) 2569-2578

[194] http://ec.europa.eu/health//sites/health/files/blood_tissues_organs/docs/economiclandscapes_humantissuescells_en.pdf p123

United Kingdom

QALYs and estimate the number of donors to a "fit panel" and in the cord blood inventory to improve domestic matching rates

Patient matching:

The NHS method used groupings of North West European and non-NWE to establish where supply gaps might exist in the current inventory. The probability of matching as a NWE or non-NWE was based on an academic study which analysed 332 patients through their search and treatment outcomes in UK transplant centres. This allowed the study to illustrate the likelihood of finding a match (at 9/10 or 10/10 match level) or if haploidentical or cord blood units were pursued as a treatment pathway. Each was used as a measure of unmet demand for NWE and non-NWE patients (accounting for patient factors) in the analysis of future supply needs.

Supply mix:

Analysis of transplant type, and mismatches of those transplant recipients to identify unmet demand.

Unmet demand was scaled with estimations of patients who would get a match/1 mismatch match from inventory calculations (Querol 2009 study)

Mix was identified using QALY costs of each type (BM v CB v imported) and Monte Carlo simulations

Method:

- First, estimates of unmet demand for cord blood units in the UK were developed. This is based on selection criteria among patients and those with sub-optimal adult donor matches.
- The additional lives saved was then calculated where the cord blood inventory is assumed to comprise 30,000 donations which assumes that:
    - CBU inventory is expanded
    - utilization of domestic CBUS increases
    - donations are only accepted for those which contain over $14x10^8$ TNC.
- Then, the net QALY gain was calculated for unrelated HPC transplant for both adult and paediatric patients (whom receive additional CBUs under the expanded inventory scenario)
- The authors then estimated the net cost of performing a cord blood transplant as compared to other treatments otherwise provided.
- Then, the estimated cost of providing stem cells from a cord blood inventory of 30,000 donations was calculated to estimate the cost per QALY
- This was then subjected to sensitivity analysis to test assumptions.

Key data inputs needed:

- HLA information (patient searches, match outcome and transplant option selected)
- Probability of match information (academic studies)
- Cost of each donor/donation pathway
- Patient outcome information
- Inventory utilisation rates (cord blood and donor list)

United Kingdom

- Ethnic profile of inventory (cord blood and donor list)

Source:

NHS Blood and Transplant *Unrelated Donor Stem Cell Transplantation in the UK*, A report from the UK Stem Cell Strategy Oversight Committee, November 2014

United States

Summary:

A series of population genetics models have been used to identify likelihoods of funding HLA matches for different ethnic groups across the US. Cost-effectiveness was then assessed against different projection scenarios to determine an optimum supply model.

Patient matching:

Against 5 race/ethnicity groupings (Black, American Indian/Alaska Native, Asian/Pacific Islander, White and Hispanic), patient searches between July and December 2001 was analysed to identify the percentage of searches which identified at least one potential HLA-A, -B, -DR match. The number of patients for whom a search was conducted, but no potential match was identified was also assessed.

Supply mix:

Donor availability was assessed to determine which of the volunteers, and from which race/ethnicity, were available to donate. This took account of those whom were available to provide confirmatory typing,

Optimal size or composition of the registry was not defined due to the competing trade-off between the diminishing return on additional donors to the registry to enhancing match probabilities and the cost of recruitment and maintenance of a larger registry.

Method:

- To estimate demand, Kollman et al used an expectation maximisation algorithm to generate HLA haplotype frequencies across the general US population (based on phenotypes in the NMDP registry). Groupings were determined only for those for whom there were at least 100,000 HLA-typed donors.
- Race/ethnic specific predictions were then developed to estimate the probability of finding a donor for different registry sizes and compositions.
- Measures of availability were estimated drawing on patient request information to temper the projected probability of a match to represent actual availability.
- Supply (donor availability for each grouping) was assessed against worst-case and best-case demand scenarios to analyse the percentage of a search proceeding through to a transplant for each race/ethnic grouping (assuming 70% of transplants would source an unrelated donor).
- Costs for recruitment and HLA typing for a matched donor were then assessed and discounted at 3% annually over 5 years. Cost-effectiveness assessed total effectiveness of the addition of a new donor by multiplying the increase in the transplant rate by the average time that a volunteer is present on the registry (for the NMDP, 25 years).
- This was estimated to be between $14,200 and $54,500 for each additional

United States

transplant facilitated (not including donor search, harvesting or transplant costs).

- Marginal increases in the probability of finding a matched donor were also estimated for every new 10,000 donors added to the registry. This measured the additional transplants against race/ethnic groupings for different registry sizes as compared to the current state.

Key data inputs needed:

- Patient search information (ethnicity, no of searches, no of potential matches, no of those matches for which a donor is available, HLA-typing level, donor match ethnicities)
- Probability matching for each ethnic grouping against donor pool size
- Ethnic data on general population
- Transplant information, by ethnic group
- Costs of recruitment and HLA typing

Source:

Kollman et al (2004) Assessment of Optimal Size and Composition of the US National Registry of Hematopoietic Stem Cell Donors Transplantation 78 89-95

Beatty P, Mori M, Milford E. Impact of racial genetic polymorphism upon the probability of finding an HLA-matched donor. Transplantation 1995; 60: 778.

Canada

Canada doesn't have publicly available information on modelling or information on optimum registry size, however, a number of studies have looked at the probabilities of finding a match among its common ethnic groups. In particular, Canada maintains a unique profile in that only 20-30% of its patients seeking an unrelated stem cell donor finds one within the Canadian Registry OneMatch.[195] In one study, scenarios were modelled to establish the benefits of focusing recruitment of donors among ethnically diverse people over self-sufficiency. It took a computational approach to estimating the matches within the current supply (128,000 young, available donors) against a 1 million donor registry to establish the efficiency profile. It identified efficiencies in recruiting additional Native Americans, while Caucasian populations were well served among a 27.6% registry representation. African American donors were calculated to be poorly covered.[196] However, recruitment rates to support a 1 million donor registry would imply that 32% of all Canada's First Nations population register; indicating that self-sufficiency is difficult to achieve in practice. The analysis found that there remains a need to build the cord blood inventory to support supply for hard-to-match populations.

[195] Blake et al (2016) Modeling the optimal ethnic composition of an adult stem cell registry *European Journal of Operational Research* 1-10

[196] Blake et al (2016) Modeling the optimal ethnic composition of an adult stem cell registry *European Journal of Operational Research* 1-10

A review by the Canadian Blood Services in 2014 considered all adult and cord blood stem cell programs against other registries in terms of size and composition.

Blake, J., McTaggart, K., & Killeen, D. (2014). Determining recruiting strategies for an adult stem cell registry. Ottawa, ON: Canadian Blood Services. Overview accessed at: http://www.nature.com/bmt/journal/v41/n1/full/1705866a.html

France

Summary:

A welfare model was analysed against the French HSC registry to assess the efficiency of additional donors to the registry. Modelling found that efficiency gains are slow to be realised, but that the French Government's recruitment target of an additional 100,000 new donors (over ten years) was justified. The analysis found that improvements could be made in making donor information available early in search and that typing costs should be reduced to support recruitment.

The same authors produced a mathematical model for establishing bone marrow and CBB registries using economic parameters. That study identified that of the 130,000 donors on the French Registry in 2010, fewer than 10% of patients find a perfectly matched donor.

Modelling showed that increasing the registry had little impact, except where very much larger sizes are considered. A CBB of at least six times the size considered was suggested to achieve optimal efficiency.

Patient matching:

It does not consider potential supply of HPCs from international registries nor patients of very rare haplotypes. Wide estimations relating to the number of present French haplotypes are assumed to theoretically assess probabilities within the registry, and no analysis of ethnicity/haplotypes are explicitly considered.

Supply mix:

Costs and matching (assuming perfect matches for bone marrow and up to one mismatch for cord blood) are simulated in this theoretical analysis. In doing so, the relative efficiency benefits of investing in bone marrow donor recruits, or in expanding CBBs is explored. However, specific outputs are not covered to determine allocation between investments.

Method:

This method introduces a mathematical solution to estimating the efficiency of additional donors to the registry:

- It first assumes an initial registry of donor types (130,000 donors)
- It then adds new donors, where the donors are of a type (of frequency within a sample) (10,000 new donors per year against then known 66,000 haplotypes recorded in the registry, assuming 500,000 total genotypes within the French population)
- Probability functions are assumed and derived to test the availability of a donor of a given type within the registry
- An optimal size mechanism has also been defined mathematically against which the two functions are simulated
- A simulation is also undertaken where 1 mismatch is accepted to expand the analysis to cord blood banking

France

- This method acknowledges difficulties in application using real data

Key data inputs needed:

- Registry details including haplotypes and tissue typing resolution within the registry
- Population haplotype frequencies, characteristics and overall numbers

Source:

Feve F, Cambon-Thomsen A, Eliaoi JF, Gourraud PA, Raffoux C and Florens JP (2007) Economic evaluation of the organisation of a registry of haematopoietic stem cell donors *Rev Epidemiol Sante Publique* 55(4) 275-84 [abstract translated into English]

Feve F and Florens JP (2010) A Mathematical Model for Bone Marrow Donors' Registries and Cord Blood Banks *Toulouse School of Economics Working Paper* 10-177

Germany

Summary:

The German registry, DKMS, has undertaken a wide range of studies considering the availability of donors for different ethnic groups. While details specific to identifying the optimal size of the German registry (and modelling supporting this) is not publicly available, many publications emanating from DKMS authors identifies approaches used which typically analyse haplotype frequencies among donors and then probability of different patient groups in being able to identify a suitable match, adjusting for different donor base sizes.

In part, this broader analysis reflects the overrepresentation of German donors is supporting international patients, and in the high participation rate of Germans in their own registries (optimality is considered through the lens of global needs, rather than the bounds of Germany itself).

One study of 8,862 German donors identified that with high-resolution typing of donors, a registry of 1,000,000 donors yields a probability of being matched of 67.8%. If the registry is 7,000,000 donors in size, this increases to 85.9%. Under a low-resolution scenario a 1,000,000-sized registry provides a probability match of 86.3%.

Another analysis of broader increases in match probability establish that an additional 500,000 donors from either Bosnia-Herzegovina, Greek or Romanian populations yielded increases in probability of 25%, 21% and 20%, respectively. Much smaller increases in probability if the same additions were made for European Americans, German or Hispanic Americans. When considering global optimums, an additional 5,000,000 donors was calculated, which largely accounts for some 3,900,000 Chinese donors required to make up for match probabilities within current registries which don't necessarily support the global Chinese population. The analysis concludes that same-population recruitment is required to enhance matching probabilities and in particular, for national registries that haven't grown registries in support of their own population size.

Patient matching:

Each approach analyses haplotype frequencies within specific populations using stem cell donor data.

Calculations are based on HLA-A, -B, -C and –DRB1 frequencies within populations, against

Germany

which fixed numbers of donors, optimal composition of new registrants and minimum numbers of donors are analysed to achieve defined matching probabilities.

Supply mix:

No consideration of the optimum mix between stem cell types is considered, except that only and n/8 match resolution was considered.

Analysis of donors considers also whether donors are high or low resolution tissue typed (this informs both cost, but also probability of matching within the donor base if HLA-A, -B, -C and –DR is considered as compared to HLA-A, -B and –DR matching).

The broader optimal analysis analysed additional probabilities added to each of the 21 populations given intra- and inter-country recruitment, identifying that smaller countries benefitted more in matching for their patients when larger registries added more donors.

Method:

- Like Kollman et al (US), the German registry has developed and uses an expectation maximisation algorithm to estimate haplotype frequencies within a population. For its assessment of global optimum inventory:
- Matching probabilities are estimated for patient populations (and in this study, for 21 populations) using mathematical probability functions, which are adapted to account for combined patient populations (based on given samples of populations available from stem cell donor registries)
- The matching probabilities for each population are then calculated under a fixed number of additional donors (assuming, they too have the haplotype frequency of the given population)
- Additionally, defined matching probabilities were then reverse-analysed to establish the number of minimum additional donors (of the haplotype frequency of the given population) from each of the 21 populations to achieve those probabilities
- Both approaches use algorithmic methods using world population statistics from the CIA World Factbook
- The authors identify, that as the first attempt to establish global optimum supply, there are inherent limitations which arise from the data available (predominantly based on German minority donors) and sample sizes used. Additionally, no factors regarding accessibility nor disease incidence among particular populations are incorporated.

Key data inputs needed:

- Haplotype frequencies of given populations and within registries (from which a sample can be sought), ideally, population-specific
- Established expectation maximisation algorithm (used by registries)
- Country populations and accurate demographics

Source:

Schmidt AH, Baier D, Solloch UV, Stahr A, Cereb N, Wassmuth R, Ehninger G and Rutt C (2009) Estimation of high-resolution HLA-A, -B, -C, -DRB1 allele and haplotype frequencies based on 8862 German stem cell donors and implications for strategic donor registry planning *Human Immunology* 70(11)

Schmidt AH, Sauter J, Pingel J and Ehninger G (2014) Toward an Optimal Global Stem Cell

Germany

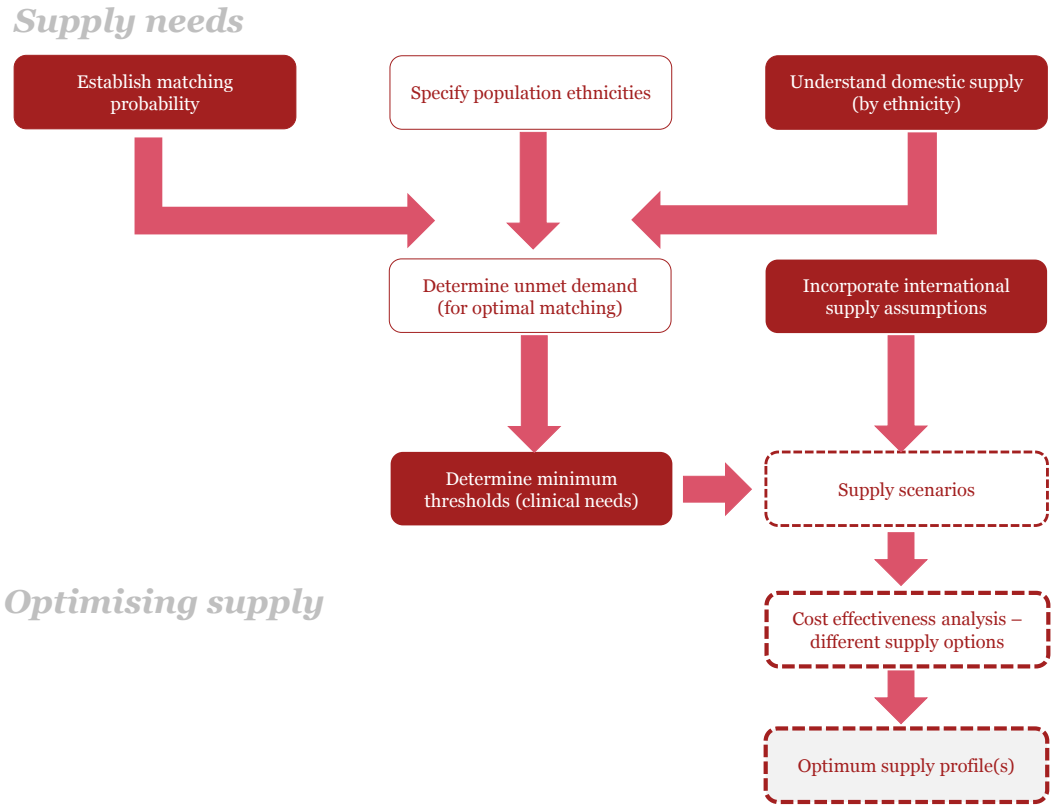
Donor Recruitment Strategy *PLoS ONE* 9(1)

1 Determining an optimum supply approach

This review has sought to leverage the approaches adopted internationally to inform how supply options are considered in the Australian context.

In practice, each option presented above shares commonalities in that they establish the likelihood of a patient being matched in the domestic setting (often by their ethnic grouping), considering what unmet demand might exist (either by unfulfilled unrelated searches, or in 'diverted' demand among patients who received a haploidentical transplants or double CBU). The 'optimum' supply is then determined through establishing minimum matching thresholds (options) against the cost-effectiveness of providing the equivalent number of donors. Our analysis has adopted the same high-level approach as shown schematically below.

Figure 117: Schematic of approach to determining optimum supply profiles



Establishing matching probabilities

With information known regarding the current Australian registry (as provided by the ABMDR), the main complexity associated with the analysis in this review is in determining the matching probability among Australian patients. This review originally set out to determine the matching rates of patients by assessing initiated search outcomes by ethnicity group. We had, like the UK's method, hoped to identify specific patient groups that might have hidden or unmet demand in that searches were going unfulfilled or were identifying less than desirable matches. However, when PwC issued information requests to transplant centres and to the ABMDR for search outcome information, we were unable to secure it. As such, the approach for considering matching probability was reassessed. The options available to assess matching probability are outlined in Table 62 below.

Table 62: Matching probability approaches

Option	Approach	Use	Benefits/limitations
A – Patient based analysis	Involves provision of patient search history among transplant centres to analyse search outputs of potential matches (match n/10, haploidentical, CBU by ethnicity) Analyse to determine likelihood of identifying a perfect match (by patient ethnicity) to form the basis of where unmet needs might exist	United Kingdom	*Data limitations in sample size and significant request of transplant centres (limited availability due to current data capture processes)*
B- Literature based projections	Infer matching probability using published academic literature (domestic (limited) and international) Develop matching probability by ethnicity (based on other registry information) to develop 'best' dataset Assumes ethnic grouping can be aligned with published studies	N/A	*Significant limitations in assumptions and in identifying information that can be 'localised' to Australian context. Very hypothetical exercise*
C- ABMDR analysis/ projections	Use Australian-based registry estimates of matching probability developed using algorithmic analysis performed by bioinformatics service.	Germany, United States	*Allows analysis based on Australian data. Relies upon ABMDR-based analysis.*
D- Utilisation rates	Establish utilisation rates based on different searches conducted in Australia, broken down by ethnicity Develop probability of getting a match (by ethnicity) Unmet demand would need to be inferred – those who don't find a match can't be identified (would have to be assumed from number of haploidentical/CBU use), and requires assumption of 'perfect' match (i.e. 9/10 is less than optimal)	N/A	*Requires information relating to 'successful' and 'unsuccessful' searches which is not readily available from the ABMDR*

2 Optimum supply analysis

In consultation with the ABMDR, this review identified that the NMDP Bioinformatics Service had in fact undertaken an analysis of the Australian registry, and the probabilities of being matched among the ten top ethnic groupings on the registry were assessed. In their analysis, the NMDP undertook modelling on a wide range of registry sizes. Their assessment considered volunteer donors and didn't take into account the probability of being matched to a CBU.

We have leveraged this work to establish what the probability of finding a match is across a number of modelled registry sizes.

The NMDP's analysis considered ten ethnicities which had adequate representation on the current Australian registry to enable analysis of their probability of finding a match (being a 7/8, 8/8, 9/10 and 10/10 match). We have drawn on these probabilities to assess relative transplant outcomes across different registry sizes for these ethnicities, being:

- NCAU (Northern Caucasian)
- NWCAU (North West Caucasian)
- Jewish
- NCAU-SCAU (Northern-Southern Caucasian)
- Sri Lankan
- Aboriginal
- Chinese
- Indian
- Middle Eastern
- Southern Caucasian (SCAU)

The NMDP considered the ABMDR's donors to better understand its haplotype frequencies and the projected match rates of patients with those haplotypes to identify a match on registries of different sizes. To first establish what donors exist, donors with reported ethnicities were mapped against major ethnic groups to improve minority sample sizes, based on the NMDP's expertise in genetics. Samples were considered where 500 samples of HLA-A, -B and –DRB1 typed donors existed. The NMDP's analysis is based on haplotype frequency analysis of 59,767 adults against which an Expectation Maximisation algorithm was applied to resolve differences in the resolution of typing of those donors.

The matching probabilities used draw on the highest possible match rate for each ethnic group. That is, while someone of a particular matching group has a chance of finding a match outside of their ethnic group, their best chance lies within their own ethnic group. We've therefore taken the probability of finding a match within their ethnic group to estimate their match probability in a given registry size. However, the NMDP had considered:

- The match rates of ethnic groups within and against other ethnic groups
- The match rates with donor availability of 100% and 75% availability
- The match rates considering the US Be the Match registry in addition to Australian donors.

The matching probability, generated by the NMDP, across a select number of registry sizes is shown in Table 63.

Table 63: Modelled match probabilities on the Australian registry (NMDP Modelling)

		CURRENT SIZE	PROPOSED REGISTRY SIZE					
Ethnicity	**HLA match type**	**160,000**	**240,000**	**400,000**	**720,000**	**1,040,000**	**1,520,000**	**2,000,000**
NCAU	10/10	49%	54%	59%	65%	69%	72%	75%

		CURRENT SIZE	PROPOSED REGISTRY SIZE					
Ethnicity	**HLA match type**	**160,000**	**240,000**	**400,000**	**720,000**	**1,040,000**	**1,520,000**	**2,000,000**
NWCAU	10/10	44%	48%	53%	58%	61%	65%	67%
Jewish	10/10	28%	32%	38%	45%	50%	54%	58%
NCAU-SCAU	10/10	30%	33%	36%	41%	44%	47%	49%
Sri Lankan	10/10	13%	16%	20%	26%	30%	35%	39%
Aboriginal	10/10	19%	21%	25%	29%	33%	36%	39%
Chinese	10/10	8%	10%	14%	19%	23%	28%	31%
Indian	10/10	7%	9%	12%	16%	20%	24%	27%
Middle Eastern	10/10	6%	8%	11%	15%	18%	22%	25%
SCAU	10/10	26%	29%	34%	39%	43%	47%	49%
NCAU	9/10	80%	83%	87%	90%	92%	94%	95%
NWCAU	9/10	75%	79%	82%	86%	88%	90%	91%
Jewish	9/10	57%	62%	69%	76%	80%	83%	86%
NCAU-SCAU	9/10	61%	65%	69%	74%	77%	80%	82%
Sri Lankan	9/10	35%	41%	49%	58%	64%	69%	73%
Aboriginal	9/10	41%	45%	51%	57%	61%	65%	68%
Chinese	9/10	22%	27%	35%	43%	49%	55%	59%
Indian	9/10	28%	34%	41%	49%	55%	60%	64%
Middle Eastern	9/10	27%	32%	39%	46%	52%	57%	60%
SCAU	9/10	56%	61%	66%	73%	76%	79%	81%
NCAU	8/8	52%	56%	62%	68%	71%	75%	77%
NWCAU	8/8	48%	51%	56%	61%	65%	68%	70%
Jewish	8/8	29%	34%	40%	47%	52%	57%	60%
NCAU-SCAU	8/8	36%	39%	43%	48%	51%	55%	57%
Sri Lankan	8/8	14%	17%	22%	28%	33%	38%	42%
Aboriginal	8/8	22%	24%	29%	34%	38%	42%	45%
Chinese	8/8	8%	11%	15%	20%	25%	30%	34%
Indian	8/8	8%	10%	14%	19%	23%	27%	30%
Middle Eastern	8/8	7%	9%	12%	17%	20%	24%	27%
SCAU	8/8	28%	31%	36%	42%	46%	50%	53%
NCAU	7/8	88%	91%	93%	95%	96%	97%	98%
NWCAU	7/8	86%	88%	90%	92%	94%	95%	95%
Jewish	7/8	69%	74%	80%	85%	88%	91%	92%
NCAU-SCAU	7/8	75%	78%	82%	85%	87%	89%	91%
Sri Lankan	7/8	51%	58%	66%	74%	79%	83%	86%
Aboriginal	7/8	60%	64%	70%	76%	79%	83%	85%
Chinese	7/8	37%	44%	52%	61%	67%	72%	75%
Indian	7/8	43%	49%	57%	66%	71%	76%	79%
Middle Eastern	7/8	38%	44%	51%	60%	65%	70%	73%
SCAU	7/8	68%	72%	77%	82%	85%	87%	89%

Source: ABMDR NMDP Models Report

The registry supply approach

Our approach uses the NMDP information, against the current registry characteristics to develop a number of options against which to assess different approaches to meet future needs. Importantly, in this analysis, there are a number of baseline assumptions adopted:

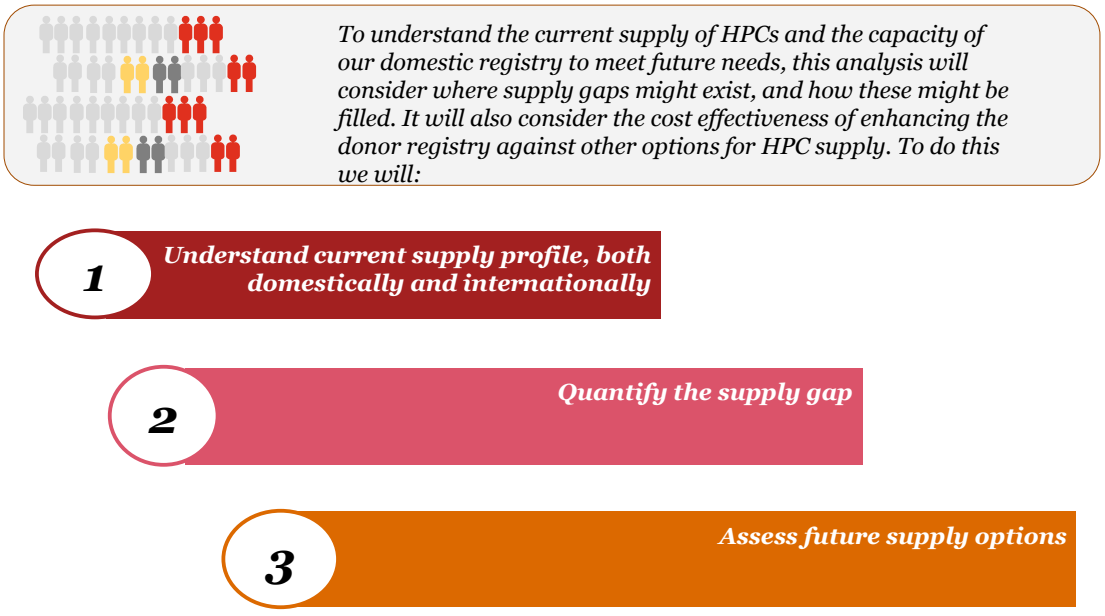
1. Ethnicity is used as a proxy to define the likelihood of finding a suitably matched donor within a registry of a given size. Within each ethnicity, populations will have different haplotype frequencies which changes the probability of finding a donor. This analysis is intended as a representative analysis, and shouldn't be relied upon deterministically.

2. Additionally, the concept of ethnicity is highly subjective, and in the case of patients and registry donors, is self-reported. This brings about limitations and as observed by the NMDP, can mean that while a particular ethnicity might be reported by a donor, their genetics might display a strong haplotype representative among other ethnic groups.

3. We define the optimal size as being that at which the return from adding a donor no longer matches the costs of doing so (Kollman et al 2004). The proposed approach for assessing future supply options leverages the work of the ABMDR, and draws on that undertaken in the UK and US, but has been adapted as data and its limitations was better understood through analysis.

To assess the supply options, we apply the approach to the Australian registry, as per Figure 118 below.

Figure 118: Supply analysis steps



This analysis leverages the work of the UK in estimating the additional transplants facilitated by analysing how many transplants are currently supported by the Australian registry, assessing how many HLA-identical and HLA-mismatch transplants proceed under changed match probabilities of registries of different sizes and analysing the differences between outcomes.

1 Understand current supply distribution

To understand where gains might be made across the ten ethnicities applied the number of HPC matches for each ethnic group under the current settings has been assessed.

Patients with identified ethnicities who have been matched to a HPC between 2013 and 2016 (using ABMDR-provided data) have been assessed to determine the percent of transplants which have gone to each ethnicity. Of the 1,051 transplants that proceeded with Australian volunteer donors in that time, 829 (79%) did not list an ethnicity. Of the remaining 222, we identify the relative percentages for each ethnicity (in many cases, drawing on the patient's ethnicity to allocate it to the NMDP's ethnic groupings. For example, the ABMDR's 'Other Middle Eastern' group has been allocated to NMDP's 'Middle Eastern').

Table 64: Distribution of domestic HPCs across NMDP ethnic groups (2013-2016)

	NCAU	NWCAU	Jewish	NCAU-SCAU	Sri Lankan	Aboriginal	Chinese	Indian	Middle Eastern	SCAU	Other
Percent	10.4%	76.1%	3.6%	1.8%	0.0%	2.7%	1.4%	0.0%	0.9%	1.8%	1.4%

Source: PwC analysis of ABMDR data

Of the 475 transplants for Australian patients facilitated using international HPCs during 2013 to 2016, we have undertaken a similar exercise. Of these, 134 (28%) did not list a patient ethnicity. For the remaining 341, we have again analysed the percent across each NMDP ethnic group.

Table 65: Distribution of international HPCs across NMDP ethnic groups (2013-2016)

	NCAU	NWCAU	Jewish	NCAU-SCAU	Sri Lankan	Aboriginal	Chinese	Indian	Middle Eastern	SCAU	Other
Percent	5.3%	68.9%	3.2%	6.7%	1.5%	0.0%	2.3%	1.5%	2.6%	2.9%	5.0%

Source: PwC analysis of ABMDR data

To then assess the current state of how transplants of different are distributed across ethnic groups, we have then drawn on ABMTRR data to analyse the number of reported transplants that went ahead in 2015. This assumes:

Table 66: Key assumptions and inputs, ABMTRR data 2015

HPC type	Number	Source
International donor transplants	219	ABMTRR Matched unrelated HPC report *Assume distributed as per ABMDR distribution of transplants across ethnicities*
CBU donor transplants	41	ABMTRR Matched unrelated HPC report 2015, Adult + Paediatric, single + double cords *Assume equally distributed across all ethnicities*
Aus donor transplants	91	ABMTRR Matched unrelated HPC report, 2015 *Assume distributed as per ABMDR distribution of transplants across ethnicities*
Percent Identical	0.88	ABMTRR Annual Data Summary, 2014 and 2015 *Assume each ethnicity has this ratio of HLA-identical transplants (from domestic donors)*
Percent Mismatch (of any kind)	0.12	ABMTRR Annual Data Summary, 2014 and 2015 *Assume each ethnicity has this ratio of*

		HLA-mismatch transplants (from domestic donors)

Applying these ratios against 2015 figures, we assume a current state distribution of HPC transplants for each ethnic group as represented below.

Table 67: Current state distribution of HPCs across ethnic groups (2015)

HPC source	NCAU	NWCAU	Jewish	NCAU-SCAU	Sri Lankan	Aboriginal	Chinese	Indian	Middle Eastern	SCAU	Total
CBU	3	3	3	3	3	3	3	3	3	3	28
International	12	151	7	15	3	0	5	3	6	6	208
Domestic: identical	8	61	3	1	0	2	1	0	1	1	79
Domestic: mismatch	1	8	0	0	0	0	0	0	0	0	11
Total	24	223	13	19	6	5	9	6	9	11	326

Source: PwC analysis of ABMDR and ABMTRR data

Please note:

- That ethnicities not captured in this analysis have not been analysed. This is due to a lack of information, and considerations regarding their ability to find a matching donor are important to decision making
- This approach provides a representative outline of how many transplants are currently facilitated but cannot be relied upon due to limitations in the data on which it is based. This includes a lack of patient ethnicity, which means that some ethnic groups do not 'show up' in the transplants facilitated.
- For simplicity, we have also considered all transplants rather than those for adult patients and those for paediatric patients. While the decision making, and preferences of clinicians vary between treatments for adults and paediatric patients, this approach is intended to represent potential outcomes, rather than specify between patient types.

2 Assess supply gap

Each ethnic group has then been assessed to determine how many additional transplants are facilitated under the registry sizes: 160,000 (~current size), 240,000, 400,000, 720,000, 1,040,000, 1,520,000 and 2,000,000.

a. Adjust total demand

Using the figures in Table 67, we assume that there are a percentage of patients who seek a match, but never identify one and so don't go on to transplant. In the absence of information on unmet demand, we assume a supply gap factor of 2% for all ethnicities.

b. *Assess number of theoretical domestic HLA-identical matches*

Taking the total demand for each ethnic group (the sum of CBUs, international, domestic identical, domestic mismatched and supply gap), we then assess how many of those patients should theoretically receive an identical match (8/8) using the match probabilities in Table 63.

c. Assess the number of theoretical identical international matches

Acknowledging that a clinician is likely to consider international donors if an identical donor cannot be found in Australia, we assume 65% of patients who did not find an identical domestic donor will identify an identical international donor. This reflects the findings in this review that many clinicians opt for international donors.

d. Assess number of theoretical domestic HLA mismatches

Of the patients who didn't receive a theoretical HLA-identical match, we then assess the number who should theoretical receive a mismatch (7/8) again using the match probabilities in Table 63.

e. Donor unavailability

However, we know that for each match identified, not all donors will be available to donate due to their health, pregnancy or personal circumstances. We assume 25% of identified donors do not proceed to donation.

f. HPC substitution

Of the patients remaining who do not identify a HLA-identical or HLA-mismatch domestic donor, many of these will be matched to a CBU or an international HPC. We assume 30% of these patients are matched to a CBU and the other 70% are matched to an international donor.

% of non-matched patients	Assumed proportion
CBU	30%
International	70%

g. Unwell patients

Additionally, a number of patients who identify a match for transplant will be unable to proceed to transplant due to their disease progressing/that they are not well to proceed to transplant. We assume 2.5% of patients go not go ahead to transplant.

h. Assess additional transplants facilitated/improved matching outcomes

We then analyse the hypothetical domestic matches, CBUs and international transplants for each ethnic group, as well as the overall number of transplants under each registry size to determine how many additional transplants go ahead, and the number of patients who have improved matching outcomes as compared to the base case (current settings).

We run the same analysis for each registry size to compare the relative outputs.

3 Assess future supply options

Overall additional transplants

Out of 8 matches

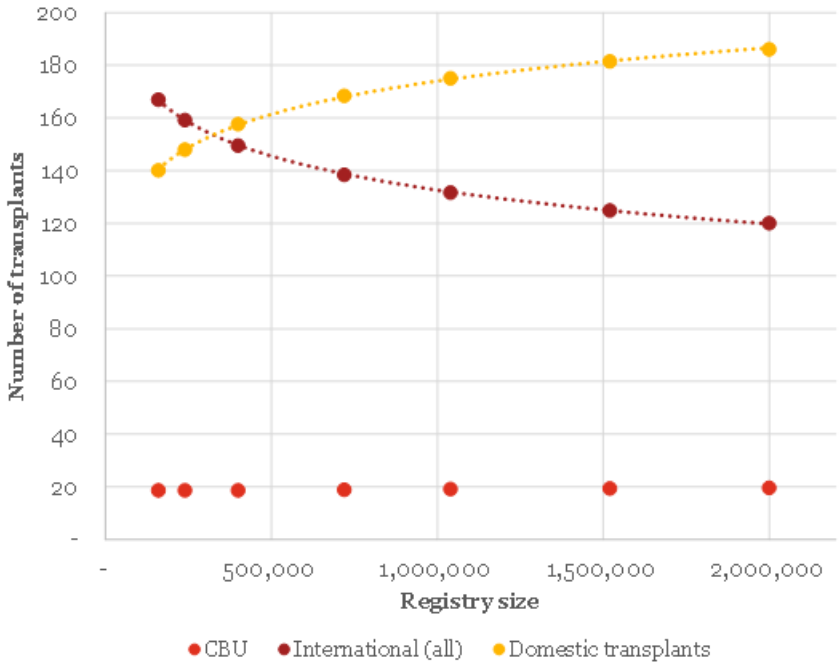
Against the approach, the transplants and transplant types facilitated for 7/8 and 8/8 matches across all registry size scenarios are shown in Table 68 and Figure 119 below.

Table 68: Transplant outcomes, out of 8 matching

Scenario	Registry size	Identical	Mismatch	CBU	International	Total
Base	160,000	79	11	28	208	326

Base - potential	160,000	102	38	19	167	326
Scenario 1	240,000	111	37	19	159	326
Scenario 2	400,000	122	35	19	150	326
Scenario 3	720,000	136	33	19	138	326
Scenario 4	1,040,000	144	31	19	132	326
Scenario 5	1,520,000	153	29	19	125	326
Scenario 6	2,000,000	159	27	20	120	326

Figure 119: Total transplants for different registry sizes (7/8 and 8/8 matching rates)



In our analysis, we identify that 50 additional domestic transplants would occur, including 23 HLA-identical transplants which use domestic donors. Under these theoretical match rates, this identifies that either large gains could be achieved by just making the current donor base better typed (and so information that would present potential matches is available to clinicians upfront) or that we have adopted overly generous assumptions in calculating the transplant rates.

Donor availability

Running these scenarios again, but with a changed donor availability rate, the total number of domestic transplants that proceed changes quite substantially across all registry supply sizes.

Table 69: Total number of domestic transplants (identical and mismatched) that proceed under different donor unavailability rates

Scenario	Registry size	75%	50%	25%	15%	10%
Base- current state	160,000	90	90	90	90	90
Base - potential	160,000	72	106	140	154	161
Scenario 1	240,000	74	111	148	163	170
Scenario 2	400,000	76	117	158	174	182

Scenario 3	720,000	78	123	168	187	196
Scenario 4	1,040,000	79	127	175	194	204
Scenario 5	1,520,000	80	131	182	202	212
Scenario 6	2,000,000	80	133	186	207	218

Registry representativeness

The feasibility of registry sizes analysed is reliant upon participation of voluntary donors in the population. To guide the selection of registry sizes considered here, the extent that the registry's ethnic groups were proportionally represented against the wider population (as defined by census responses) was first considered.

To consider this, we have assessed how the registry compares against Australia's current demographic profile. We have drawn on ABS data to establish how many persons in Australia fall within each of the ethnicities assessed by the NMDP. While this is a crude analysis, it does provide a sense of which ethnicities are represented within our community.

Table 70 shows how we have allocated the ABS census population grouping to the NMDP ethnic groups.

Table 70: Ethnicity grouping, ABS to NMDP groups

ABS grouping	NMDP ethnicity allocated
Australian	NCAU
Australian Aboriginal	Aboriginal
Chinese	Chinese
Croatian	SCAU
Dutch	NCAU
English	NCAU
Filipino	Other
French	NCAU-SCAU
German	NCAU
Greek	SCAU
Hungarian	NCAU
Indian	Indian
Irish	NWCAU
Italian	NCAU-SCAU
Korean	Other
Lebanese	Middle Eastern
Macedonian	SCAU
Maltese	SCAU
Maori	Other
New Zealander	NCAU-SCAU
Polish	NCAU
Russian	NCAU
Scottish	NWCAU
Serbian	SCAU
Sinhalese	Sri Lankan
South African	Jewish
Spanish	SCAU

ABS grouping	NMDP ethnicity allocated
Turkish	Middle Eastern
Vietnamese	Other
Welsh	NWCAU
Other(d)	Other
Ancestry not stated	Other

Source: ABS 2011 Census of population and housing basic community profile, including individuals who identify as an ethic group with: both parents born overseas, father or mother only born overseas, both parents born in Australia or Birthplace not stated.

With these groupings, we developed a profile of the Australian population against the NMDP ethnic groups. This is shown in Table 71 below.

Table 71: Australian population spread among NMDP ethnic groups

Ethnicity	Population
NCAU	15,885,002
NWCAU	4,005,975
Jewish	108,956
NCAU-SCAU	1,213,721
Sri Lankan	22,938
Aboriginal	127,667
Chinese	866,205
Indian	390,894
Middle Eastern	270,057
SCAU	924,596
Other	4,085,751
Total	27,901,762

Source: ABS 2011 Census of population and housing basic community profile. Note: 27,901,762 persons indicates the number of responses to the ABS census, which may include individuals who have responded as having multiple ethnicities.

Against the broader population and the ethnic groups represented on the Australian registry, we looked at how each ethnic group is represented, excluding all 'other' ethnicities. These proportions are shown in Table 72.

Table 72: Proportional representation of the NMDP's ten ethnic groups on the registry, and in the wider population (as indicated by ABS census response)

Ethnicity	ABS population %	Registry population %
NCAU	56.9%	73.9%
NWCAU	14.4%	4.8%
Jewish	0.4%	4.2%
NCAU-SCAU	4.3%	5.1%
Sri Lankan	0.1%	1.4%
Aboriginal	0.5%	2.1%
Chinese	3.1%	1.7%
Indian	1.4%	2.4%
Middle Eastern	1.0%	1.4%
SCAU	3.3%	0.2%

Source: PwC analysis

The (absolute) number of registered donors for each of the ten ethnic groups was scaled against a number of registry sizes. In doing so, it was sought to establish how many people within the community, from each ethnic group, would need to enrol to support a larger registry (to reflect NMDP's modelled probabilities). In line with the NMDP's analysis, this assumes the same proportional representation across ethnic groups as is currently registered.

Table 73 and Table 74 shows the percentage of each group's population within the Australian community required to register as a donor if the registry size were increased and match probabilities calculated by the NMDP were held (i.e. are not adjusted to reflect the proportional representation in the broader community). It shows that for some ethnicities – prominently, Jewish, Sri Lankan and Aboriginal – a very large number of those communities would need to be enrolled to support larger registry sizes. The highlighted red shading shows where more than 20% of the broader community's ethnic group would need to enrol to support a larger registry size.

Table 73: Number of persons of each NMDP ethnic group required for larger registry sizes

Ethnicity	240,000	400,000	720,000	1,040,000	1,520,000	2,000,000
NCAU	177,433	295,721	532,299	768,876	1,123,741	1,478,607
NWCAU	11,526	19,211	34,579	49,948	73,000	96,053
Jewish	10,048	16,746	30,143	43,539	63,634	83,730
NCAU-SCAU	12,315	20,526	36,946	53,366	77,997	102,628
Sri Lankan	3,352	5,587	10,056	14,526	21,230	27,934
Aboriginal	4,925	8,208	14,774	21,340	31,190	41,039
Chinese	4,168	6,946	12,503	18,060	26,395	34,730
Indian	5,698	9,496	17,093	24,690	36,086	47,481
Middle Eastern	3,294	5,490	9,881	14,273	20,860	27,448
SCAU	531	884	1,592	2,300	3,361	4,422

Source: PwC analysis of ABMDR and ABS data

Table 74: Proportion of Australian population required for different registry sizes, by NMDP ethnic group

Ethnicity	240,000	400,000	720,000	1,040,000	1,520,000	2,000,000
NCAU	1.1%	1.9%	3.4%	4.8%	7.1%	9.3%
NWCAU	0.3%	0.5%	0.9%	1.2%	1.8%	2.4%
Jewish	9.2%	15.4%	27.7%	40.0%	58.4%	76.8%
NCAU-SCAU	1.0%	1.7%	3.0%	4.4%	6.4%	8.5%
Sri Lankan	14.6%	24.4%	43.8%	63.3%	92.6%	121.8%
Aboriginal	3.9%	6.4%	11.6%	16.7%	24.4%	32.1%
Chinese	0.5%	0.8%	1.4%	2.1%	3.0%	4.0%
Indian	1.5%	2.4%	4.4%	6.3%	9.2%	12.1%
Middle Eastern	1.2%	2.0%	3.7%	5.3%	7.7%	10.2%
SCAU	0.1%	0.1%	0.2%	0.2%	0.4%	0.5%

Source: PwC analysis of ABMDR and ABS data

While NMDP's modelling considered a number of registry sizes between 40,000 to 2,160,000, it is clear from this analysis, that a registry with proportional representation across ethnic groups within the community is infeasible for some sizes. Setting out to establish a large registry, say, above 720,000, would require close community engagement to seek new donor enrolment. For some communities, a greater proportion of their overall community will need to be enrolled to support registry growth. Additionally, consideration of the impact on the mix of the registry should be considered as it's likely this would change

with larger registry sizes, and so, some of the matching probabilities established by the NMDP may not hold with changed registry proportions. As part of recruitment, there will be a need to continue to enhance the representation of ethnic groups currently underrepresented.

Given this, registry sizes above 2,000,000 (approximately 7% of Australia's total population) are likely to be less achievable, particularly in considering a large number of the wider community are too old, too young or unfit to donate. This also reflects that for a 2,000,000 size registry, Australia would need approximately 7,160 donors for every 100,000 population (from the current 699 enrolled per 100,000 population). This compares to the currently enrolled 2,567 donors per 100,000 population for the NMDP, 987 for Anthony Nolan and 1,150 donors for every 100,000 population in Canada. Australia's achievement of a registry of 2,000,000 would mean that Australia would be leading many registries worldwide on a per capita basis.

This analysis is therefore not definitive, as not all ethnicities are modelled by the NMDP and the match probabilities modelled assumes the same registry proportion as now (it doesn't take account of a 'resetting' of the registry to reflect the wider demographic of Australia). Care should therefore be taken in how the results of this analysis are interpreted.

Appendix H Additional implementation considerations

This appendix highlights additional considerations in implementing a preferred option to supplement that provided in the body of this report.

Additional roles for non-government organisations

In addition to the non-government roles which already exist in the sector, in particular of the ABMDR and ARCBS, there could be consideration of other organisations to consider additional roles in supporting service delivery. These organisations might include patient and donor groups such as the Leukaemia Foundation and UR the Cure which play an active role in advocating and supporting patients receiving HPC transplants. For example, there could be a role – perhaps a joint delivery role – for patient groups with an interest in promoting recruitment. Examples also found that internationally, there is use of volunteers in undertaking certain functions of the registry. Key activities which should be considered for a role among non-government entities and individuals include:

- Recruitment campaigns
- Donor engagement (for example, Social media, mailouts, email and donor reconnection campaigns)
- HPC couriering
- Donor welfare and potentially, early components of education
- Volunteer coordination and training
- Donor follow-up (post-collection)

Key discussions could be held with prominent organisations, such as the Leukaemia Foundation, to determine if there is an interest among those parties to participate in the sector in this way, and if so, what capacity might be appropriate.

Procurement

There are multiple approaches that can be employed to engage with potential providers and scope available services. The following approaches might be employed:

- Request for information/Market scan. In which potential providers are researched and specific questions sought. This type of preliminary assessment provides guidance to which procurement approach might be employed, as well as to assist in detailed costing activities.
- Expression of interest, which may be employed to engage with potential suppliers. This type of activity would promote the scope of services sought and seek market responses to those questions. It is a non-binding activity that provides better detail than a market scan and could initiate vendor-specific discussions of services. It also gives a clue as to which suppliers are available, their capacity and a rough price point.
- Direct engagement, which enables consultation with a supplier and teases out the specifics of their capability, costs and requirements. This also pre-empts a direct

appointment, depending on procurement rules of the contracting party, to better develop any agreements or contractual arrangements.

- Open/closed tender, a method employed as per government procurement rules to ensure value for money capture as well as to encourage a wide response from suppliers to better assess capabilities.

A market scan is needed to identify potential tissue typing suppliers. This should be assessed against a set of minimum requirements in respect of volume, capability, resolution, turnaround time and reporting/past performance to ensure vendors are aligned with Australia's needs.

Implementation and operational risks

With any large change in organisational arrangement or delivery approach, there are risks in both implementation and ongoing operation. Some of these are new risks, while others are already exposed within the sector and may become amplified with change. Each risk requires a risk mitigation and monitoring plan to ensure potential costs and implications are understood and managed. For the purposes of identifying these key risks, the risk matrix in Figure 120 has been adopted to assess those identified in consultation and in evaluation of potential options.

Figure 120: Risk assessment matrix

The key risks and proposed mitigation activities are outlined in Table 75 below. A thorough risk mitigation plan should be developed in detailing any detailed option analysis and implementation planning.

Table 75: Risk assessment

Risk	Description	Likelihood / Impact	Mitigation
Loss of key staff	Any changes in delivery and sectoral arrangements will likely impact the current structure and operation of delivery parties. This could include the potential for a change in individual role definition, redeployment and/or changes in the activities and direction of an organisation. There is a risk that key staff		Decision makers and parties should engage closely through consideration of potential future options and development of a preferred implementation option. Likely challenges in retention should be identified early, and mechanisms put in place to ensure timely and comprehensive knowledge transfer and a staged approach that doesn't risk operational functions.

Risk	Description	Likelihood / Impact	Mitigation
	currently involved in delivery discontinue their roles.		
Loss of in-kind support	A change in sectoral arrangements will likely draw the attention of, and potential retraction of in-kind support of parties, such as the ARCBS, St Vincent's and hosting hospitals.		Close and ongoing stakeholder engagement will facilitate information sharing, as well as to bring to bear potential risks of a retraction of support. Appropriate mechanisms to continue support or to make alternative arrangements can then be planned for.
Upfront investment more than originally projected	A large implementation of any kind presents complexity and potentially, unexpected costs.		Careful project planning, supported by detailed costing will guide the identification of investment risk and enable early action to remedy the potential for costs not accounted for.
Low levels of recruitment	There is a risk that even with a changed approach to recruitment that the number of new recruits to the registry doesn't increase much above current levels and falls short of recruitment targets.		Regular and informative business analytics on the number of new donors, their jurisdiction and demographic should regularly be shared with decision makers to identify any emerging challenges in recruitment. Appropriate strategies, whether this be a changed marketing approach or direct engagement with donors, could then be developed to address any key issues to continually improve the approach employed.
The use of HPCs grows beyond forecasted values	With improved clinical treatments and a wider range of clinical indications for which HPCs might be able to be used, there is a risk that HPC use escalates far beyond that projected.		Regular and informative business analytics on the nature and number of request for HPCs should regularly be shared with decision makers to identify any emerging trends. Greater use of HPCs may bring with it commensurate growth in operational expenditure, which could be managed through regular review of funding arrangements, informed by reporting.
Demand for donor HPCs for new clinical indications	With new research emerging, it is likely that there will be interest in using the donor registry as a source of HPCs for new clinical indications, and perhaps even in trials.		Regular and informative business analytics on the nature and number of request for HPCs should regularly be shared with decision makers to identify any emerging trends. If this risk emerges, a government response/position should be developed to guide the registry operator and clinicians so that expectations are set and understood. Additionally, there would be a need to re-engage with donors to ensure consent is aligned to any applications which are different to those they originally consented to.
The number of international HPCs continues to grow despite investment	There is a risk that despite investment in changed arrangements, the number of international HPCs used in Australian transplants continues to grow. This may be due to preferences, availability or upfront information.		The operator of the registry should be charged with a responsibility to develop insightful, measurable and regular analytics that identifies changes in trends. This information should be shared with appropriate decision-makers to influence the drivers for international HPC demand; domestically recruited donors, level of typing on the registry, clinician education/engagement, donor engagement and costs.

Risk	Description	Likelihood / Impact	Mitigation
Loss in public confidence	This risk might emerge if there are any changes in key delivery parties and/or if there arise public concern regarding costs or activities of the registry (such as international provision of HPCs or a lack of a coordinated recruitment strategy)		The registry operator should retain close relationships with its key stakeholders to communicate any planned changes and how the registry will manage any change.
Ongoing investment more than originally projected	With changed arrangements for the registry's operation, and ongoing expenditure associated with typing, recruitment, coordination and collections, there is a risk that incurred costs exceed those projected.		Careful project planning, supported by detailed costing will guide the identification of investment risk and enable early action to remedy the potential for costs not accounted for. Additionally, contractual negotiations must take account of potential for the way in which costs are accounted for and acquitted. Contracts must enable contract managers to have control over incurred costs and to provide appropriate mechanisms for changed arrangements.

Appendix I Ethical and legal analysis

This review, through consultation with key stakeholders, has identified a series of legal, and especially ethical questions regarding current challenges and the application of international approaches if they were adopted in Australia. Among these are questions regarding the implications associated with different approaches to recruitment, including targeted campaigns, the management of DNA and of donor information, issues associated with donor availability and new and different uses of HPCs.

To assist with understanding some of the considerations with these questions, Emeritus Professor Loane Skene has developed a paper to support this review, which is provided below.

Prepared by Emeritus Professor Loane Skene, May 2017

NOTE: This paper should not be considered to constitute detailed legal advice. A formal legal position will need to be developed to support any actions undertaken in this area.

1 Recruitment of donors

Opt out schemes

The first Australian legislation on tissue donation was based on recommendations of the Australian Law Reform Commission (ALRC) in 1977.[197] Its report included draft legislation that was subsequently enacted in all states and territories – a rare achievement in achieving consistent provisions on health issues that usually fall within state jurisdiction.

Later amendments have led to differences in the legislation of the various jurisdictions but much of the language and the underlying principles have not changed. A fundamental principle is that the authority to remove human tissue for use in transplantation, and for other therapeutic purposes, or for medical or scientific purposes, is the consent of the donor, or a person authorised on their behalf to consent. In the case of donation by a deceased person, the authority may come from a donor during their lifetime, or from the donor's 'senior available next of kin', as defined in the legislation, after the patient has died; see, for example, Human Tissue Act 1982 (Victoria) section 26(1), (c),(d). This is 'opt in' consent and it is widely accepted. Although the possibility has been considered from time to time that more tissue could be available for transplant with an 'opt out' system (as has occurred in a number of other countries), that scheme has been rejected in Australia. Donation rates are relatively high in this country, and have been increasing, without an opt-out system.[198]

It may be noted, however, that the Australian legislation has, in fact, allowed a limited form of 'opt out'. The Victorian Act, for example, states that tissue may be removed for transplantation from a deceased person without consent from the person or their representative, if the person is not known to have objected before death and the next of kin cannot be found: Human Tissue Act 1982 (Victoria) section 26(1)(e).[199]

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[197] *Human Tissue Transplants* [1977] Australian Law Reform Commission, page 7 http://www.austlii.edu.au/au/other/lawreform/ALRC/1977/7.html

[198] See *Australian Donation and Transplantation Activity Report* 2016; especially in DonateLife Week, 2016 – increase of 68% on previous year: page 6; increase of 17% on previous year for tissue transplants: page 8: http://www.donatelife.gov.au/national-performance-data

[199] The *National Statement on Ethical Conduct in Human Research* 2007 (updated 2015) (later called, '*National Statement*'), also provides for a waiver of consent to use human biospecimens that were collected for clinical purposes if there is no known reason to believe the donor would not have consented if asked, and the use is approved by a Human Research Ethics Committee – para 3.4.12 (b).

Where tissue comes from a living person, it is difficult to imagine an opt-out situation when the tissue is to be used in treatment, rather than in research. The 'donor' (or their representative, if the donor is not competent to consent) would generally be asked to consent in advance to have the tissue removed for transplant and it would then be removed and transplanted.

It is possible that a person's tissue might have been removed for later use by the 'donor' and then stored; or transferred to a tissue repository for later use by someone else. It could then be used for research, even without consent, as envisaged in the National Statement,[200] and possibly also for treatment, for example, if the initial consent form did not mention later uses of the tissue. However, that seems unlikely, given that protocols and good practice clearly require that informed consent should be obtained from a donor before using their tissue in treatment. Also, clinicians are keen to preserve the reputation of the transplant scheme; they will not want to attract adverse publicity.

In summary, whether tissue is to be used from a living donor, or after the donor's death, a proposal to move to an 'opt-out' scheme is unlikely to be favoured in Australia. This country has a long history of voluntary participation in medical research; and donor consent is fundamental. One indication of the Australian community's concern to maintain confidence in organ donation procedures is the refusal by medical personnel to undertake organ removal from a deceased person who had expressed a wish to become a donor, if any relatives object after the person's death. The consent of the potential donor is sufficient legal authority to remove the organs, but the relatives' wishes are allowed to prevail.

Targeted recruitment

Specific ethnic groups

I do not see any objection to ethnic groups advertising to members of that group in order to attract potential donors, on the basis that more donors are needed from their ethnic group to benefit other members of that group. A similar argument might be made to justify approaches to members of ethnic groups by government agencies. However, it might be different if the tissue from these groups was collected for the benefit of the wider community. The ethnic group might then regard the process as exploitation by a powerful majority.

Advertising to specific ethnic groups is not unlawful discrimination. That involves treating a person less favourably than the 'discriminator' would treat another person in circumstances that are not materially different; see, for example, Disability Discrimination Act 1992 (Commonwealth) section 5 (definition of 'direct discrimination', in that case relating to discrimination on the grounds of a disability). There is no suggestion that members of ethnic groups will be 'treated less favourably' than anyone else who is encouraged to donate.

Another strategy to attract donors from different ethnic groups might be to improve communication to them as a group well before the time they are approached to become donors. In a Sydney survey investigating attitudes to cord blood donation in 2009-2012, participants noted that information about cord blood banking on the internet is available only in English; and the information is not always clear and uniform.[201]

Young males

It may be appealing to advertise specifically for young male donors, as their bodily material is likely to lead to better outcomes in transplantation. However, approaching young males is different from approaching an ethnic group. The intention is that the removed tissue would be used to benefit anyone. The benefits would not be directed to other young males. In other words, they would not be asked to participate in an activity that could directly benefit them or their group. This might be argued to be discriminatory, from an ethical perspective; that

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[200] See n 198 above.

[201] Dr Maree Porter, *Workshop on Umbilical Cord Blood*, Sydney, 25 Feb 2011.

is, it is unethical or 'unfair' to treat people not solely for their own means, but to benefit someone else. However, that seems a flimsy argument when the young males are merely being encouraged to make an altruistic donation, which they can easily refuse. Also, even if one accepted the ethical argument, such as it is, there would not be any unlawful discrimination, because the legislation prevents discrimination only in certain activities, such as the provision of health services.

In any event, there is no reason why young males should not be approached as part of general advertising for donors, with emphasis perhaps on the need for more young male donors, to benefit members of that group as well as the wider community – see below, *General Comments*.

Targeting of Military/emergency service/immigrating individuals

The arguments regarding these groups are similar to those regarding young males. They would be asked to donate for the benefit of a wider class of people than themselves, or their group. One could, perhaps, add family members of people who have received donated tissue, or indeed those people themselves. They, too, would be asked to donate in circumstances where the potential benefits would not be limited to them. However, this does not make the advertising to them unlawful discrimination, or even unethical. – see below, *General Comments*.

General comments

It is ethically justifiable to seek donations from people to benefit a wider group than the one to which they belong; and this may be an effective means of increasing the number of potential donors. A broad notion of reciprocity may be invoked. A recent UK survey 'found that making small changes to a government website encouraging people to donate led to significantly increased registrations for the NHS Organ Donor Register'. The most effective wording involved a suggestion of 'reciprocity': 'If you needed an organ transplant would you have one? If so please help others'.[202] As the report observed, '[this wording] seeks to draw on people's inherent desire for fairness and to reciprocate—in other words, to give back when they receive something'.[203]

The NHMRC's *Ethical guidelines for organ transplantation from deceased donors 2016* also list reciprocity in the list of ethical values to guide decision making when allocating donated organs. 'Reciprocity' is defined as '[a] relationship between parties characterised by corresponding mutual action in return for contributions given'. The Guidelines note that 'In the context of healthcare, this generally refers to broad reciprocal socio-political obligations rather than to specific obligations owed to individuals (such as monetary payment or access to a particular organ at a particular time) directly in "return" for their decisions or actions'. Solidarity, 'the concept of "standing together" as a group, community or nation, which reflects a collective commitment to share "costs" (financial, social, emotional or otherwise) to assist others'; and Altruism, 'Acts that are not based on any form of understanding that something will be returned', are also listed, in addition to the more traditional values of respect, autonomy, justice, equity, transparency, effectiveness and efficiency.[204]

It has been noted in Australia that relatives are more likely to consent to donation if the donor has registered and/or they know the donor's decision.[205]

2 Donation management

Sample management

[202] https://www.gov.uk/government/publications/organ-donor-registrations-trialling-different-approaches

[203] Ibid.

[204] Compare NHMRC, *National Statement on Ethical Conduct in Human Research* 2007 (updated 2015), Section 1, Values and Principles of Ethical Conduct: Research merit and integrity; justice; beneficence; and respect: https://www.nhmrc.gov.au/book/section-1-values-and-principles-ethical-conduct

[205] *Australian Donation and Transplantation Activity Report* 2016, page 6.

Retaining DNA

The legal authority for a laboratory that has lawfully removed human tissue[206] to retain and use it, derives from the voluntary, informed consent of the donor, or a person authorised on their behalf to consent, under human tissue legislation. To constitute an informed consent, the donor would need to be given 'material' information, for example, the possible uses of their bodily material, clinically or in research; for how long it will be stored; any rights that they may have to find out what use has been made of it, or to use it themselves if the need arises; and any limitations on any of those rights.[207] These principles are based on the common law and the ethical principles of autonomy and self-determination.[208]

The information can be provided well in advance. For example, in the context of cord blood removed after a baby is delivered, information could be provided during pregnancy and not in the delivery room. It could cover the availability of public and private CBBs and their purpose; the reasons for collecting and storing cord blood, with a realistic description of the potential benefits without exaggeration; potential uses of stored cord blood – either by the baby, family members or the wider community, and the success rates to date of various uses of stored blood; how cord blood is collected, when it is collected and by whom; any risks associated with the collection of the blood, for example, if collecting cord blood may deprive the new born baby of blood the baby may need after birth, or distract the nursing staff from attending to the mother and her new-born baby as the placenta is delivered, or in other ways; the cost of collecting and storing cord blood if it is stored in a private CBB, noting the costs to be paid by the parents; and the cost of retrieving it, if it is later needed for treatment of the baby or a sibling; and the parents' opportunity to ask questions.

The consent to remove and use the material may take effect at once, or after the donor has died. Human tissue legislation specifically refers to the effect of the person's consent in terms of an 'authority'. The Human Tissue Act 1982 (Victoria), for example, refers to the consent being 'sufficient authority for a registered medical practitioner …to remove the … tissue specified in the consent for the purpose or the use, as the case may be, specified in the consent': sections 7,8,16, emphasis added. This wording avoids the issue of whether the removed bodily material is, or is not, legally, 'property', which can be 'owned'; made subject to consumer protection provisions; and perhaps 'sold'.

However, the legal nature of human bodily material is an increasingly contentious issue in legal commentary and case law. If there is a valid informed consent, it is clear that removed bodily material can be used, under the legislation, in transplantation, and for other therapeutic purposes, or for medical or scientific purposes, as authorised in the consent. The right to retain the tissue, and to transfer it to someone else for similar purposes, seems inherent in the right to use it (as explained below), though that is not spelt out in the legislation. Note that this right to retain and use the tissue is a right that falls short of full ownership, because there are conditions attached to the use that may be made of it; and other people, such as the donor, may have limited rights in it. The tissue must be used in accordance with the donor's consent, for 'proper purposes'. The laboratory could transfer the material to a hospital or research institution for treatment or research, but it could not lawfully use it in an artwork. If such an 'improper' use were proposed, the donor might have a legal right to prevent that happening (though there is no direct legal authority on this point – see below). Overall, however, the laboratory's right to retain and use the tissue is a greater right than anyone else has in relation to the tissue, and if it is properly used, the donors (and their relatives) have no continuing rights in it.

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[206] I use this term to describe cellular material such as blood and stem cells, as well as solid organs

[207] *Rogers v Whitaker* [1992] High Court of Australia [Reports] page 58 at para [16] duty to warn of 'material risk'.

[208] Ibid. See also, NHMRC, *National Statement*, Chapter 2.2 General requirements for consent; information for 'genetic' research – 3.5.12; 'Family involvement' and 'Community involvement' for genetic research: paras 3.5.8; 3.5.11.

In short, a donor who has given an informed consent is assumed to have no ongoing rights in respect of the removed bodily material.[209] Whether that applies in all circumstances has recently been cast into doubt. There have been a number of legal cases in which men have stored their semen for later use and they or their spouses have been held to be entitled to have the semen transferred to them on request, as if they had property rights in it.210 Some commentators have suggested that this may be a precedent for other people whose tissue is 'stored' also to have it returned to them on request. However, that is not likely as a general principle, in my view, on the basis of the reasoning of the judges in the stored semen cases. In particular, it was intended from the outset in those cases that the semen would be stored for the men, not for the use of other people. An argument might perhaps be made regarding blood or bone marrow deposited in a tissue bank specifically for the later use of that person or a nominee; but not where the stored bodily material is intended to treat others, or for medical or scientific purposes.

As noted earlier, removed bodily material is not legally 'property'. However, a laboratory that has lawfully removed, and is storing, the material, has rights in it that are essentially property rights. In law, those rights derive from the 'work or skill' the laboratory personnel have undertaken in removing and preserving the material for later use, or the fact that the material has acquired 'different attributes'.[211]

In summary, the laboratory that first removed the material, with the informed consent of the donor, 'owns' the removed material, and it is entitled to use it, transfer it to someone else and recoup its costs,[212] and dispose of it. However, this is a right short of complete ownership, because the laboratory must deal with the material in good faith, taking account of the purposes for which consent was given. If the donor suspected that the material was to be used improperly, they could obtain a court order to prevent that happening, based on their continuing equitable rights in the material. [213]

When the laboratory transfers the material, or information derived from it, to someone else, then that person 'owns' the material, subject to the same obligation to use it in accordance with the donor's consent. It can use the material, or transfer it to another person, or dispose of it.

Sharing among laboratories (domestic)

Transfers of stored bodily material can lawfully be made from one jurisdiction to another as the human tissue legislation is similar throughout Australia. Also, appropriate payments can be arranged to cover the costs associated with the transfer. Although the human tissue legislation prohibits trade in human tissue for valuable consideration, there are exceptions for reimbursement of costs associated with the preparation, storage and transfer of biological products.[214]

When the transfer is made, it is presumed that there is an implied limitation that the material must be used in accordance with the donor's authority. However, the law is not clear on this point, and it is preferable for this obligation to be spelt out in the agreement to transfer the material. Once the material has been removed with the donor's voluntary and

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[209] A comparison may be made with stored Guthrie cards. The person whose blood spots are on the card has no legal right to take them away, restrict their use, or to have them destroyed.

[210] See, for example, *Re Edwards* (2011) 4 Australian Succession and Trusts Law Reports page 473; [2011] NSW Supreme Court [Reports] page 478 at para [88].

[211] *Doodeward v Spence* [1908] High Court of Australia [Reports] page 45.

[212] See, for example, Human Tissue Act 1982 (Vic) Pt 8; s 39 A tissue bank may recover 'the reasonable costs associated with the removal, evaluation, storage, processing at the tissue bank and distribution from the tissue bank of tissue …'.

[213] This assumes that the donor has an equitable right to prevent their removed bodily material being used 'unlawfully' or in a way that is inconsistent with a medically directed purpose. However, there is no direct legal authority on this point.

[214] Note 212 above.

informed consent, the donor's right to control the use of it is problematic.[215] On legal principles, the consent or directions of the donor are legally relevant only when the bodily material is first collected, under the law of trespass, in ensuring that there is proper consent to the removal of the tissue. If it is not used at that time, or it is transferred to someone else, any restrictions in the initial consent do not apply to later uses of the material (subject to a contract or other legal arrangement to the contrary; or a possible legal action by the donor if it is to be used improperly).

The ethical position is slightly different. The ethical principles of respect, or custodianship, set out in the National Statement, would suggest that removed bodily material should continue to be handled in accordance with the directions of the donor, if the donor cannot be contacted to seek further consent regarding the material, and the proposed use of it is different from the use that was initially envisaged. Ethical issues may arise where appropriate informed consent was obtained at the time of the donation, but there have later been significant changes in scientific knowledge and experience since the material was collected. In such circumstances, it may be ethically advisable to contact the donor and ensure that their consent still applies.

Transportation and analysis of samples in international laboratories

An Australian laboratory is legally entitled to transfer removed bodily material to a laboratory in another country, on the basis of its right to possess and use the material, deriving from the donor's informed consent and the 'work and skill' it has undertaken in collecting and preserving the material. There may be ethical limits on the transfer of the material. First, it should be used in accordance with the donor's consent (as noted above); and secondly, the transferring laboratory should be satisfied that the international laboratory has similar principles for ethical standards as those in Australia, under the National Statement.[216]

3 Use of stored cord blood units for the production of Induced Pluripotent Stem (IPS) Cells

Legally, stored cord blood units could be used to produce IPS cells without specific consent from the people concerned; but there is ethical sensitivity about using bodily material that has been acquired for one purpose for another purpose, without specific consent.[217]

The law

As explained earlier, if stored bodily material, such as cord blood, has been lawfully obtained (e.g. with voluntary, informed consent), it can be used without further consent for a later purpose that might be regarded as 'proper' in the circumstances. If the person concerned initially consented to their bodily material being used in research, for example, a proper related purpose would presumably include producing IPS cells for use in research. These cells could possibly also be used for treatment but that would be more contentious, as it is more difficult to argue that the initial consent to donate bodily material for research also extended to its use to make a 'product' to be used in treatment. This is discussed more fully in section 4 below.

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[215] *Persons, Parts and Property. How Should We Regulate Human Tissue in the 21st Century?* Goold, Imogen; Greasley, Kate; Herring, Jonathan; Skene, Loane. Hart Publishing 2014.

[216] *National Statement*, para 3.4.15 – 'Human biospecimens' obtained for research in Australia may be sent overseas if ethical approval of an appropriate review body for importation; or consistent with the original consent and approved by an HREC for use in research. These paragraphs concern *research* but a similar ethical approach might be taken to the clinical uses of transported tissue, as the sensitivity of the tissue and the information it denotes are the same.

[217] NHMRC, *Ethics and the Exchange and Commercialisation of Products Derived from Human Tissue* Oct 2011, https://www.nhmrc.gov.au/_files_nhmrc/publications/attachments/e103_ecpd_humantissue_111019.pdf

The legal entitlement to use the stored material for a different purpose is based on the principles of property law described above, which enable the person who removed the cord blood initially (or their institution or other representative), to acquire a property right in it, provided the material was obtained with the informed consent of the person concerned. The property right is a right to possession and that right covers the use of the material and its conversion into something else. If the person from whom the material was removed gave informed consent to the removal of their material for use in research or treatment and the proposed new use is 'proper', they have no right to prevent that use (or to benefit financially from any 'commercialisation' of their material).

The requirement that the new use of the stored material must be 'proper', or of the type that might have been anticipated when the material was first removed, such as a medical or scientific purpose, derives from the right of the person concerned to prevent particular uses of their removed material. Although there is no legal authority on this point, it is likely that the person concerned would be entitled to obtain a court order (an injunction) to prevent an 'illegitimate' use of their bodily material, or to be compensated if that has already occurred. As suggested earlier, the stored material could lawfully be used in medical research, and possibly treatment; but not in an artwork.

When the IPS cells are produced, the person or institution that produced them is the legal 'owner' of the cells, provided that the stored material from which they were produced was legally obtained. This 'ownership', or proprietary right, arises from the 'work and skill' they have applied in producing the IPS cells.[218] They are then entitled to transfer the cells to other researchers (and arguably clinicians) for use in research (and possibly treatment), and to recover their costs.

Ethics

However, the ethical position is more problematic on whether stored bodily material can be used for a different purpose from the one for which consent was initially given; and one should not assume that this is acceptable in all circumstances.

The use of stored cord blood units for a purpose that was not anticipated when the blood was first acquired is a 'secondary usage', a term used in Chapter 3.4 of the National Statement, which has been recently revised.[219] This chapter, now called Human biospecimens in laboratory based research 'provides guidance for institutions and those involved in research using human biospecimens (including human cell lines) with respect to consent, secondary usage and import/export' (emphasis added; note the reference to 'cell lines').[220]

The term 'human biospecimens' includes 'any biological material obtained from a person including tissue, blood, urine, sputum and any derivative from these including cell lines'. The biospecimens may be donated or taken for clinical purposes and 'are commonly collected, stored and distributed by researchers, biobanks, clinical pathology services, health care providers, research institutes and commercial entities, such as pharmaceutical and biotechnology companies'.

Paragraph 3.4.11 deals with the use of human biospecimens collected for clinical purposes.[221] These biospecimens 'may be used for research[222] purposes if:

a. the identity of the donor is not necessary for the activity (see paragraph 3.4.9); or

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[218] *Doodeward v Spence*, note 211 above.

[219] Note 204 above.

[220] NHMRC, Summary of the Contents of the National Statement, https://www.nhmrc.gov.au/research/responsible-conduct-research/summary-national-statement-content

[221] This extends to the use of stored biospecimens acquired 'without specific consent for their use in research' as well as those acquired for clinical purposes: para 3.4.12.

[222] The *National Statement* deals with *research* but the same argument might be made regarding the use of the material in *treatment*, if 'the identity of the donor is not necessary for the activity'.

b. where the identity of the donor is required for the purposes of the research, a waiver of consent (see paragraph 3.4.12) has been obtained'.

Paragraph 3.4.12 deals with waiver of consent:

> 3.4.12 Where it is contemplated that proposed research will involve the use of human biospecimens that have been obtained without specific consent for their use in research (e.g. where biospecimens were collected for clinical investigation), or where the proposed research is not consistent with the scope of the original consent, the biospecimens may be used only if an HREC [Human Research Ethics Committee] is satisfied that the conditions for waiver of consent are met (see Chapter 2.3: Qualifying or waiving conditions for consent).
>
> Particular consideration should be given to:
>
> a. whether there is a pathway to identify and recontact the donor(s) in order to seek their informed consent to the use of their biospecimens in research; and
> b. whether there is a known or likely reason for thinking that the donor(s) would not have consented if they had been asked.

Summary

Legally, stored cord blood units can be used to produce IPS cells for use in research, and arguably in treatment, if that is consistent with the informed consent of the person concerned when the blood was removed. The person or institution that produces the IPS cells 'owns' them and can transfer them to others to use in research, and possibly treatment. The person whose blood was used to create the IPS cells has no rights regarding the cells, except perhaps an equitable right to prevent an 'improper' use of them by obtaining a court order (injunction).

Ethically, the position is similar, provided the proposed secondary use (producing IPS cells) is research; and 'the identity of the donor is not necessary for the activity'. An argument might be made for use in treatment but that is more problematic. If the donor's identity is needed, the stored blood may be used to produce IPS cells for research if a waiver of consent is obtained from an HREC, taking account of whether it is possible to gain the donor's consent and the proposed use of the stored material. An argument might be made to justify the use of the IPS cells in treatment but that is not covered by the *National Statement*.

4 Future use of bone marrow donors (seeking their voluntary donation) to support new clinical uses (currently, this is restricted to haemopoietic reconstitution)

It can be seen from the discussion above that emphasis is placed, both in law and in ethics, on the consent of tissue donors to the use of their bodily material in research. There are some circumstances when material that has been removed from a person and stored for one purpose (such as later treatment of that person), may be used for another purpose without the person's consent (such as research not anticipated when the material was first removed). However, there are limitations, especially from an ethical perspective. Consent is always desirable where it is possible to obtain it, especially if the stored material is to be used for a significantly different purpose from the one for which it was removed. This is especially pertinent when bodily material has been removed for research with consent, and then used to produce IPS cells, which are later proposed to be used in *treatment* of another person.

This would arguably be lawful on the basis that the person who removed the material with the informed consent of the person concerned 'owned' them and could then use them for any 'proper' purpose, as outlined earlier. However, one could question whether treatment of another person is within the 'ambit' of the initial informed consent, or indeed a 'proper' use of the removed material. This is even more the case from an ethical perspective, where great emphasis is placed on information and consent. People may be concerned about their bodily material being used to create a cell line for use in treatment, rather than used in research. Cell lines reproduce indefinitely and the cells have the DNA of the donor; this may have implications for the donor and their blood relatives. A cell line may be widely disseminated

and there is potential for wrongful use. A fully informed consent would require discussion of these aspects of 'genetic' research.

It follows from these factors that a new consent should be obtained from bone marrow donors if their bodily material is to be used for clinical procedures. Although I have suggested that an argument might be made, by analogy with research uses of stored material (see above), that the law is not clear regarding the need for additional consent, it is certainly preferable to recontact the initial donors if possible and obtain their consent to the proposed later use, especially for clinical purposes.

A 'second-best' option is perhaps to have a broader consent form when the bodily material is first collected. This could mention the possibility that the removed material might later be used to develop a cell line that could be used in treatment, as well as in research. However, that would make the consent form much broader and 'blanket' consent forms are open to question, both ethically and legally. As I have suggested, there are significant differences between donating one's bodily material for use in research, and donating it to develop a cell line for treatment. The consent process would more complex if all those matters had to be included for consent whenever tissue is removed for research; and it is preferable for consent to be as specific as possible.

5 Data management

Data ownership among entities

The management of data is governed by privacy legislation. This means the Privacy Act 1988 (Commonwealth), which applies to federal and privately owned institutions; and State and Territory privacy legislation which applies to state-owned institutions. The management of data includes collecting, using, disclosing and disposing of information about patients, such as the information that is collected about a donor on registration.

The Privacy Act 1988 (Commonwealth) has recently been substantially amended in relation to health information and genetic information (section 6, definition of 'sensitive information', section 6FA 'health information', which specifically includes 'personal information collected in connection with the donation, or intended donation, by an individual of his or her body parts, organs or body substances' (section 6FA(c)). In brief, health information should generally be used only for the purpose for which it was collected, and not for a secondary purpose (Privacy Act 1988 (Commonwealth), Schedule 1, Australian Privacy Principles, Principle 6). However, health information may be collected, used or disclosed in a 'permitted health situation'. This includes circumstances where collection, use or disclosure is necessary to provide a health service to an individual, or for research relevant to health and public safety (section 16B). 'Health information' (as defined above) may be collected or used without the consent of the person concerned, where that is necessary for research relevant to public health of safety (section 16B(3)); or 'to lessen or prevent a serious threat to the life, health or safety of a genetic relative' (section 16B(4)).

These provisions protect institutions that are covered by the federal Privacy Act from allegations of unlawful breach of privacy or confidentiality when they collect, use and disclose health information; and preserve and test human bodily material; and transfer information to other people, in the prescribed circumstances.

The State and Territory laws also have some protection, but their provisions are less specific and are not considered here.

> The same principles apply to information captured and used in donor registration, patient information used in search activities and donor information, as well as when it is handled and/or shared domestically or internationally.

Collection of data on donor ethnicity

Data concerning donor ethnicity may appear ethically sensitive but such collection is not unlawful discrimination. As noted earlier, unlawful discrimination involves treating a person less favourably than the 'discriminator' would treat another person in circumstances that are not materially different; see, for example, Disability Discrimination Act 1992

(Commonwealth) section 5 (definition of 'direct discrimination', in that case relating to discrimination on the grounds of a disability). If similar data is collected about all donors, there is no breach of this Act. Also, the Privacy Act 1988 (Commonwealth) permits the collection of 'information or an opinion about an individual's … racial or ethnic origin'.

6 Donor availability

Donors who enrol as part of donor drives but are ultimately unavailable for donation to unrelated patients

If donors enrol after a donor drive (or in any other circumstances that stimulate an enrolment that would not have otherwise been made), the most important factor is to maintain community support for the donor program. This means that the highest principles of ethics must be maintained and the ethical principle of autonomy or self-determination is paramount in medical law. The donor cannot be compelled, or shamed, to honour the earlier commitment, even if someone else will suffer if an organ is not available. To make such an attempt would pose a reputational threat to the whole program.

The issue might perhaps be averted by taking steps to encourage donors to maintain their willingness to donate; for example, sending a 'thankyou' letter, periodic information about the program and recipients' stories, etc

Worked-up donors who choose not to proceed to collection: Is there a claim for the patient/patient's family for whom the stem cells were destined?

The same argument might be made where a potential donor has been 'worked up' but decides not to proceed, and the recipient has had preparatory treatment for a transplant, and is now in a life-threatening position if it does not occur. One might say that the donor's autonomy is paramount. However, this situation is different from the one in the paragraph above. Here, the recipient has an immediate risk of severe harm, which has been caused or exacerbated by the earlier willingness of the other person to be a donor.

This case is perhaps similar to a semen donor changing his mind about donating his semen after it has been used to fertilise a woman's egg, but before the fertilised egg has been implanted. Should the law allow him to withdraw his consent at any time before the egg is implanted, even if the woman's precious egg is 'wasted'? Or should the man be allowed to withdraw consent only up to the point of fertilisation? (The first approach now appears to be the legislative position in Victoria, although this is not clear.[223]) In other words, the maintenance of donors' autonomy and ongoing consent is obviously important but it should not trump such an important interest of the potential recipient of the newly formed embryo.

In the case of a transplant recipient, the need to consider their interests as well as the donor's autonomy is stronger, because they may die without the planned transplant. The principle could perhaps be that a donor is not entitled to withdraw consent for donation after the potential recipient has been prepared for the transplant; and the donor should be reminded of this agreement at the final stage of the consent procedure. However, this argument (the analogy with the semen donation) could be made only where the donor's bodily material has already been removed, and the donor later reneges on its use. It would not be practicable to insist that a reluctant donor must undergo an invasive medical procedure to obtain bodily material for transplant.

If a transplant does not take place because the potential donor withdraws consent after the potential recipient has been prepared for the procedure, the patient or a relative would have no legal claim. Organ donation is an altruistic process. It is not a contract. Although it seems unfair for the donor to agree to donate and then to withdraw the consent, causing real harm

[223] Assisted Reproductive Treatment Act 2008 (Vic) section 20(1): 'A person who gives a consent [to a treatment procedure]… may withdraw it at any time before the action or [treatment] procedure is carried out'. A 'treatment procedure' includes 'assisted reproductive treatment', which in turn includes 'in vitro fertilisation' - section 3, definitions. However, 'in vitro fertilisation' is not defined. It could mean fertilisation of the egg, in which case consent could not be withdrawn after the egg has been fertilised; or it could mean implanting the fertilised egg into the woman's body.

to the potential recipient, or even death, there is no legal remedy against the donor, who has done nothing unlawful.

There are also no grounds for a legal claim against the hospital, or others involved in the aborted transplant. The patient or a relative might allege negligence in the consent process. However, that is unlikely to be established if there has been a proper discussion of the process and risks of the transplant (including the possibility that the donor might not proceed), and the patient then gave a voluntary and informed consent.

Appendix J Stakeholders consulted

Through this review, PwC consulted with a wide range of stakeholders to understand the processes, activities and perspectives of different organisations in their different roles in supporting the HPC sector. Stakeholders consulted are outlined below.

Organisation	Contact	Status
Bone Marrow transplant centre		
The Royal Children's Hospital Melbourne	Maria Scoyne	14 March 2017
The Royal Melbourne Hospital	Elizabeth O'Flaherty	27 January 2017
The Alfred Hospital Melbourne	Maureen O'Brien	25 January 2017
Royal Adelaide Hospital	Terry Ventrice Kendall Egglestone Caroline Stokes	13 February 2017
Fiona Stanley Hospital	Susan Buffery	2 March 2017
Royal Brisbane & Women's Hospital	Judy Cummings Annette Barnes Angela McLean Laura Skirrow	24 January 2017
Westmead Hospital Sydney	Stephanie Deren	20 January 2017
Sydney Children's Hospital	Laura Chapman	Written response received
Royal Prince Alfred Hospital Sydney	Louise Kerr	18 January 2017
Royal North Shore Hospital Sydney	Cassandra Reid	20 January 2017
St Vincent's Hospital Sydney	Annabel Horne	3 February 2017
Princess Margaret Hospital for Children Perth	Fiona Kerr Dr Shanti Ramachandran	1 March 2017
Townsville Hospital	Jodie Marsh	Written response received
Austin Health	James Hicks	15 February 2017
Liverpool Hospital	Gai Fairnham	24 January 2017
ABMDR		
Australian Bone Marrow Donor Registry Board	Professor Jeremy Chapman	19 January 2017 4 April 2017
	Leonie Walsh, President and Chairman, Fight Cancer Foundation	11 April 2017

Organisation	Contact	Status
Australian Bone Marrow Donor Registry	Anthony Montague Executive Officer Garth Healey Operations Manager	19 January 2017 27 and 28 February 2017
	Sasha Wright Project Manager- Enhancements Program/Transplant Outcomes Review	20 January 2017
Other		
ARCBS – National Affiliated Services	Suiyin Cheah National Business Manager - Affiliated Services	15 March 2017
ARCBS- Tissue typing laboratories	Rhonda Holdsworth, National Manager- Laboratories	15 March 2017
ARCBS - Donor coordinators	Paul Berghofer, National Operations Manager, Blood Marrow Donor Centres	27 March 2017
ARCBS- Search coordinator	Cathie Hart, Deputy Manager, Victorian Transplantation and Immunogenetics Service	22 March 2017
ABMTRR	Leonie Wilcox, Manager	28 February 2017
Therapeutic Goods Administration	Glenn Smith, Director, Biological Science Section	12 April 2017
Pathology Queensland	Dr Alycia Thornton, Principal Scientist, Tissue Typing Laboratory	10 April 2017
PathWest	Dr Dianne De Santis, Marrow Match Manager/Transplant Immunology Dr Lloyd D'Orsogna, Head of Transplantation (FHS Immunology)	15 March 2017
WMDA	Lydia Foeken, CEO	13 April 2017
Anthony Nolan, UK	Richard Davidson, Director of Engagement	5 April 2017
Canadian Blood Service	Kimberly Young – Director, Donation and Transplantation Dena Mercer – Associate Director, OneMatch Heidi Elmoazzen – Director, Cord Blood Bank & SC Manufacturing Dr. David Allan – Medical Director, OneMatch Stem Cell and Marrow Network Sherry Haun – Senior Program Manager, Policy	9 May 2017
ahJHPCC		
Tasmania	Joy Mendel	16 March 2017
Northern Territory	Maureen Brittin	18 April 2017

Organisation	Contact	Status
Queensland	Ellen Hawes Kaye Hewson	12 March 2017
NSW	Rada Kusic Janet Tyler	28 February 2017
South Australia	Sue Ireland	9 March 2017
Western Australia	David Forbes	22 March 2017
ACT	Carolyn Duck	13 February 2017
Victoria	Karen Botting	8 March 2017

Appendix K Key datasets analysed

To capture information to inform this review, PwC issued a number of information requests to key stakeholders. Table 76 below outlines the key datasets provided and the data points contained within them that have supported the review. This information was supplemented through consultations and specific data requests which provided many of the qualitative aspects explored.

Table 76: Key datasets provided to this review

File name	Description	Provided by	Date Range	Columns	Number of rows
Question_1a_to_1g.xlsx	Donor registry	ABMDR	1900 - 2016	Donor Status Year of consent Year of birth Sex Ethnicity (6 levels) CMV status Resolution (6 levels: high or low)	246,121
Question 1h.xlsx	Donor requests	ABMDR	11/08/1995 - 8/02/2017	VT Request date	14607
Question 2.xlsx	Cord blood	ABMDR	24/06/2003 - 16/06/2016	CBU location Collection date (date range) TNC content CD 34 count Date available Ethnicity (6 levels)	3655
4a-.xlsx	Transplant data: Australian patients, Australian donors	ABMDR	25/02/2000 - 7/12/2016	Patient Country Patient transplant centre Product request date Patient YOB Patient ethnicity (6 levels) HPC type Collection date Donor country YOB donor Sex of donor Donor ethnicity (6 levels)	1051

4b-.xlsx	Transplant data: Australian patients, International donors	ABMDR	28/11/2013–14/11/2016	Patient Country Patient transplant centre Product request date Patient YOB Patient ethnicity (6 levels) HPC type Collection date Donor country YOB donor Sex of donor Donor ethnicity (6 levels)	475
4c-.xlsx	Transplant data: International patients, Australian donors	ABMDR	20/10/1999 – 16/11/2016	Patient Country Patient transplant centre Product request date Patient YOB Patient ethnicity (6 levels) HPC type Collection date Donor country YOB donor Sex of donor Donor ethnicity (6 levels)	363
Shipped Cord Units 2014 - 2016.xlsx	Shipped Cord data	ABMDR	07/01/2014-20/12/2016	Cord bank Shipped date TNC CD34+ Shipped to country Ethnicity (2 levels)	108
Transplant activity by year and hospital.xlsx	Yearly transplants by state and hospital codes	ABMTRR	1992-2017	Year State Hospital code Number of transplants	690

Policies and standards provided to this review:

- 'ABMDR-GL-OP-001-08 ABMDR ORGANISATION AND QUALITY.pdf'
- 'ABMDR-GL-OP-002-07 Accreditation.pdf'
- 'ABMDR-GL-OP-004-12 Donor enrolment, extended HLA typing and verification typing.pdf'
- 'ABMDR-GL-OP-005-08 Tissue typing standards.pdf'
- 'ABMDR-GL-OP-007-08 SEARCH PROCESS.pdf'
- 'ABMDR-GL-OP-009-06 Workup coll and processing of HPC.pdf'
- 'ABMDR-GL-OP-010-07 ABMDR National Tissue Repository.pdf'
- 'ABMDR-GL-OP-013-08 Subsequent donation.pdf'
- 'ABMDR-GL-OP-015-12 Donor deferral adverse events follow u....pdf'
- 'ABMDR-GL-OP-016-009 DONOR EXPENSES, REIMBURSEMENT AND INSURANCE.pdf'
- 'ABMDR-GL-OP-018-11 Ethics Committee operations.pdf'
- 'ABMDR-GL-OP-021-02 Cord blood unit search process.pdf'

- ‘ABMDR-GL-OP-022-03 ABMDR operations with international registries.pdf’
- ‘ABMDR-POL-EXEC-002-001 Gift fund policy.pdf’
- ‘ABMDR-POL-EXEC-003-01 Research governance policy.pdf’
- ‘ABMDR-POL-EXEC-004-001 Ethics advice and use of external ethics committee.pdf’
- ‘ABMDR-POL-EXEC-005-001 Conflict of interest policy.pdf’
- ‘ABMDR-POL-FIN-010-04 Management of payables.pdf’
- ‘ABMDR-POL-OP-017-11 Privacy and confidentiality.pdf’
- ‘ABMDR-POL-OP-PAT-01 Patient funding access policy.pdf’
- ‘ABMDR-STD-OP-006-11 Donor health assess and infectious disease testing.pdf’
- ‘ABMDR-STD-OP-014-01 Standards and procedures for transporting fresh HPC.pdf’

Please note that while efforts have been made to present data in a consistent manner, available datasets capture data across different time periods. As a result, this report presents data in both calendar and financial years. Where data relates to a calendar year, that year has been used to present the data (for example, 2015). For financial years, the fiscal year is used with the prefix ‘FY’ to distinguish the year (for example, FY2015–16).

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