NHS
Blood and Transplant

Unrelated Donor Stem Cell Transplantation in the UK

Effective Affordable Sustainable

A Report from the UK Stem Cell Strategy Oversight Committee
November 2014

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Introduction

Haemopoietic stem cell transplantation is an increasingly important curative therapy for patients with leukaemia and other bone marrow disorders. It is a testament to the power and potential of regenerative medicine. Most patients lack a matched sibling donor and three decades ago the UK pioneered the use of stem cells harvested from unrelated donors as a strategy to extend the curative potential of transplantation. The number of patients benefiting from an unrelated donor stem cell transplant has risen threefold over the last decade, and this trend is set to continue. Survival rates continue to improve year on year[1] driven by advances in post-transplant care and improvements in donor matching and provision. Despite these advances, many patients in the UK, especially black, Asian and minority ethnic patients, cannot benefit from this potentially life-saving treatment because they lack a suitably matched donor – a clearly unacceptable situation.

In 2010, a UK Stem Cell Strategic Forum was set up at the request of the Minister of State for Public Health. Comprising more than 40 experts from the four countries of the UK, the Strategic Forum's remit was to bring forward recommendations to improve the provision and clinical application of stem cells from unrelated adult volunteer donors and cord blood in order to save the lives of patients with blood cancers and other haematological diseases.

The Strategic Forum's report[2] set out a strategy to save an additional 200 lives each year. It made 20 recommendations to improve the provision of adult donor stem cells, to increase the UK's cord blood inventory, to advance clinical practice, and to standardise commissioning processes. Key to achieving these aims would be the alignment of the UK's three stem cell registries in order to streamline provision for UK transplant centres. Recognising that neither UK patients nor the Life Sciences sector economy were benefiting sufficiently from rapid advances in stem cell science, the Forum proposed the establishment of a clinical trials network. The Forum also recommended that complex alternative donor transplants should be provided by regional centres of excellence. The Forum's recommendations were explicitly endorsed by the Minister of State in 2011, and the UK Stem Cell Strategy Oversight Committee was established to co-ordinate and monitor implementation of the recommendations across the four countries of the UK.

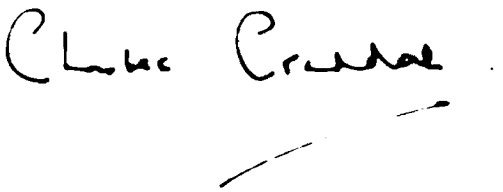
In this report the Oversight Committee revisits the 2010 recommendations. We report the alignment of the three UK stem cell registries, the creation of a 'fit panel' of young adult donors typed to high resolution, and an increased UK inventory of high quality cord blood donations. We show how these measures have increased and accelerated the provision of UK-sourced stem cells for UK patients, saving more lives, reducing costs, and improving equity of access to matched donors for black, Asian and minority ethnic patients. We recognise that the achievements of the last four years have occurred due largely to the collaborative approach between the Health Departments and service providers across the UK. In particular, the Department of Health has made a £4m *per annum* commitment to support the implementation of some of the Strategic Forum's recommendations.

1. Current Uses and Outcomes of Haematopoietic Stem Cell Transplantation, CIBMTR (2013).
2. The Future of Unrelated Donor Transplantation in the UK. A Report from the UK Stem Cell Strategic Forum (2010).

The striking progress which has been made as a result of implementing the Strategic Forum's recommendations, coupled with a robust reappraisal of national and international trends in stem cell provision, endorses the effectiveness of the UK's two complementary approaches towards improving stem cell provision. We confirm that increasing the number of young male adult donors typed to a high resolution remains a cost-effective way of providing stem cells for most patients; the provision of a high quality cord blood inventory remains the optimal approach towards achieving equity of access to stem cell transplantation for black, Asian and minority ethnic patients. Both strategies are supported by a refreshed health economic assessment of patient benefit. Specifically we confirm that a cord blood inventory of 50,000 donations best meets the requirements of UK patients. To that end, we recommend continued investment over a three year period to achieve an inventory of 30,000 donations in the first instance. We estimate that such an inventory will be financially sustainable, generating the income required to fund ongoing inventory growth beyond 2018 to 50,000 donations. Our health economic analysis shows that a cord blood inventory of 50,000 donations achieves a cost per additional quality-adjusted life year (QALY) in the region of £9,400. This is significantly below the £15,000 threshold used by DH to evaluate the effectiveness of NHS spending decisions, and a significant improvement on the Strategic Forum's 2010 cost per QALY estimate of £27,000, reflecting ongoing improvements in patient outcomes and the streamlining of the UK's stem cell supply chain.

Herein, we report on recent technological and medical advances which are driving substantial improvements in transplant outcomes. Nevertheless, patient outcomes are not keeping pace with scientific progress; 50% of patients still succumb to transplant complications and disease relapse. We therefore continue to highlight the absolute importance of driving forward initiatives which will improve patient outcomes. There remains an urgent need to establish a clinical trials network to attract inward investment and so that UK patients may benefit from scientific discovery; little progress has been made since this was recommended in 2010. We highlight the importance of establishing 'centres of excellence' for unrelated donor transplantation and the need to include the long-term care of patients in the commissioning of stem cell transplantation.

We have noted with interest the report from the House of Lords Science and Technology Committee on regenerative medicine, and we look forward to the report from Sir Michael Rawlins on how the government's ambition may be delivered. Stem cell transplantation is the most effective and widely practised form of regenerative medicine to date, and our recommendations are intended to support the delivery of regenerative medicine therapies into the clinic.



Ian Trenholm
Chief Executive
NHS Blood and Transplant

Professor Charles Craddock
Chairman
UK Stem Cell Strategic Oversight Committee

Executive Summary

Achievements

Key achievements since the Strategic Forum's 2010 report include:

- ***More UK patients are receiving a potentially curative stem cell transplant than ever before.*** 258 additional patients received a stem cell transplant from an unrelated donor in 2013/14 compared to 2010/11. This translates to an additional 130 lives saved each year.
- ***Over 60% of black, Asian and minority ethnic (BAME) patients are now able to find a well matched donor.*** This represents a significant improvement on the 40% figure cited by the Strategic Forum in 2010 but there is clearly much still to be done to ensure equity of patient access regardless of ethnic group.
- ***The process for stem cell provision has been streamlined.*** Anthony Nolan, the British Bone Marrow Registry, and the Welsh Bone Marrow Donor Registry have aligned activities to create the Anthony Nolan and NHS Stem Cell Registry, providing a turnkey solution for transplant centres in the UK.
- ***60,000 young donors have been HLA[3] typed to a high resolution.*** These 'fit panel' volunteers are eight times more likely to have donated stem cells compared to other registry volunteers.
- ***UK-sourced cord blood is increasingly meeting the needs of UK patients.*** This year over 25% of cord blood transplants will use donations from UK donors; this compares with just 10% in 2010.
- ***The time taken to provide stem cells from adult donors has been reduced.*** Samples for confirmatory HLA typing are provided from over 80% of donors within 15 days of request, compared to only 35% of donors in 2010, accelerating access to transplant – a critical advance given the brief window many patients with blood cancer have to access a curative transplant.
- ***More donors than ever are available to donat***e. For example, in 2013/14, 62% of UK donors provided confirmatory typing samples when requested. This compares to an average of around 40% for overseas donors .
- ***The use of UK-sourced stem cells saves the NHS money.*** UK-sourced adult and cord blood donations are priced at £13,950 and £14,500 respectively. Imported adult donations are typically around £25,000[4] and cord blood donations around £30,000.
- ***Commissioning is underpinned by expert opinion and an improved evidence-base.*** The Oversight Committee is supporting the work of the Clinical Reference Group for Blood and Marrow Transplantation (CRG BMT) through the provision of expert advice. A key component of the BMT CRG's service specification for adult transplantation has incorporated a central recommendation of the 2010 report by mandating that "centres which undertake umbilical cord transplants must be part of a provider network with a combined catchment population of at least 4 million people".

3. HLA refers to a genetically diverse system of 'human leukocyte antigens' which need to be typed and matched between donors and patients for successful transplant outcomes.
4. Donor availability and the price of stem cell provision varies considerably between registries. The Strategic Forum's 2010 recommendations were informed in part by the success of the German national stem cell registry, ZKRD. In 2014, although ZKRD's performance and price competitiveness remain among the best worldwide, the UK registry's performance is now comparable.

Offering curative therapy to more patients

Part One of this report focuses on the significant progress made towards the Strategic Forum's ultimate goal of saving an additional 200 lives each year through unrelated donor stem cell transplantation.

In 2010/11, 802 UK patients were transplanted;

In 2011/12, 905 UK patients were transplanted;

In 2012/13, 934 UK patients were transplanted;

In 2013/14, 1060 UK patient were transplanted.

258 additional patients are now receiving an unrelated donor stem cell transplant each year (111 by UK-sourced stem cells), compared to 2010/11. This means that around 130 additional lives are saved each year. Below, we describe how the Strategic Forum's recommendations have been delivered to achieve this outcome.

Streamlining stem cell provision

In 2010, the UK had three stem cell donor registries – Anthony Nolan, the British Bone Marrow Registry (BBMR) and the Welsh Bone Marrow Donor Registry (WBMDR) – with a combined panel of more than 770,000 adult donors. In order to maximise efficiencies and continue to deliver improvements in stem cell provision, Anthony Nolan and the BBMR began operating as a single registry in January 2012. In September 2013, the WBMDR became part of the Anthony Nolan and NHS Stem Cell Registry. This alignment of UK registries created a streamlined service for NHS transplant centres which now search only once before receiving a consolidated listing of all donors potentially matched to individual patients[5].

The progression of a patient's blood cancer whilst they are awaiting the identification of a suitable donor remains an important and preventable cause of treatment failure and death. The Strategic Forum pointed out that patients' outcomes would be improved through measures to increase donor reliability, and to decrease the time taken to select and test registry volunteers before donation. The Strategic Forum recommended that this be brought about through the creation of a 'fit panel' of 75,000 young and committed adult donors, HLA typed at high resolution to provide the best matching information possible.

At the time writing, over 60,000 donors have been added to the 'fit panel'. The strategy has exceeded expectations; 'fit panel' donors are eight times more likely to be selected compared to other registry volunteers.

5. In February 2013, the German stem cell donor centre (Die Deutsche Knochenmarkspenderdatei; DKMS) started recruiting UK donors. These are listed on the Anthony Nolan and NHS Stem Cell Registry in addition to ZKRD.

Given the urgency of proceeding as rapidly as possible to transplant in patients with blood cancers who often have only brief remissions, speed of access is increasingly recognised as critical in optimising patient outcome. Through a range of interventions to improve engagement with donors, registry turnaround times and donor reliability have also improved. In 2014, 80% of samples for confirmatory typing are provided within 15 days of request; this compares with 35% in 2010. In 2014 62% of requests for confirmatory typing samples from UK donors were fulfilled. This conversion rate takes into account many factors including cancellations due to patient reasons. In 2014 only 22% of confirmatory typing requests did not progress due to donor-related factors.

Improving equity of access to stem cells for black, Asian and minority ethnic patients

Patients from ethnic minorities have historically been disadvantaged in terms of unrelated donor stem cell transplantation. In 2010, the Strategic Forum reported that around 90% of white northern European patients would typically find a match, whereas the matching rates for black, Asian and minority ethnic (BAME) patients were estimated to be around 40% or lower, especially for patients of mixed ethnic heritage. HLA types are related to ethnicity, and donors from ethnic minorities are under-represented on adult registries. The Strategic Forum recommended that increasing the UK's cord blood inventory to 50,000 donations offered a cost-effective means to address this inequity.

It is possible to maximise the genetic diversity of a cord blood inventory by focusing collection at maternity units that serve ethnically diverse populations. Moreover, cord blood transplants do not require the same precision of HLA match as do transplants using stem cells from adult donors. Hence, they can be used with greater flexibility for patients with rare HLA types. Since 2011/12, cord blood banking rates have tripled in the UK, expanding collections to 24/7 operations at 14 NHS hospitals. Collections at nine of these hospitals are funded, or part-funded, via an ongoing allocation from the Department of Health.

Herein we report that the chances of BAME patients receiving a stem cell transplant have substantially improved since adoption of the Stem Cell Forum's recommendations in 2010, with more than 60% of BAME patients able to find a well-matched donor. Most of this improvement is due to improved access to UK-sourced cord blood donations. In one large prospective study[6] of patients with haematological malignancies, 21.3% of BAME patients received a cord blood transplant compared to 3.8% of white northern European patients. In 2011, UK-sourced cord blood donations accounted for less than 10% of the cord blood transplants in the UK; the rest were imported. In 2014, over 25% of UK cord blood demand is met from the UK inventory[7].

6. RN Lown (2013) Presentation to the American Society for Haematology.
7. Data from Anthony Nolan.

Reducing the cost of importing stem cells

UK-sourced adult stem cell donations are priced at £13,950 in contrast to imported adult donations which typically cost around £25,000[8]. Similarly UK cord blood units cost national transplant centres £14,500 whilst imported cord blood donations are typically priced around £30,000. Thus the growth in UK-to-UK provision of unrelated donor stem cells serves to contain costs at a time of increased transplant activity.

Opportunities and challenges

Although good progress has been made towards improving access to stem cells from adult donors and cord blood, significant challenges and opportunities remain. In some areas, changes recommended by the UK Stem Cell Strategic Forum in 2010 have not been implemented due to lack of funding. We herein reflect on recent medical and technological advances, and report a thorough refresh of our health economic analysis in order to derive the twelve recommendations which are set out at the end of this summary.

Part Two of this report reflects on the likely impact of recent medical and technological advances including:

- The vital importance of improving patient outcomes following stem cell transplantation;
- Emerging evidence on the efficacy of haploidentical[9] stem cell transplants;
- Next generation sequencing technology for cost-effective, allelic-level HLA typing;
- The advent of affordable whole genome sequencing;
- The emergence of regenerative medicine as a focus for new therapies and inward investment by the global pharmaceutical sector.

In particular, we have noted the emergence of haploidentical transplants as a potential treatment option in selected patients without a well-matched adult donor or suitable cord blood donation. There is however insufficient long-term follow-up on outcome, and concern exists about an increased risk of disease relapse using this strategy. The results of recently commenced prospective trials will be important in order to understand which, if any, patients derive long-term benefit from this currently experimental approach. At the same time it is important to note that outcomes following cord blood transplantation are significantly better than envisaged in 2010, increasing the importance of this stem cell source beyond that anticipated in the Strategic Forum report. For example, five-year survival for children is now around 70%[10] compared to estimates of 40% to 50% in 2010.

8. This varies between registries. Some, including ZKRD's registry, are considerably less expensive.
9. Donor and recipient share one of the two sets of HLA-genes they inherited from their parents. Rather than being a perfect match for each other, they are a half-match. Siblings have a 50% chance of being a half-match for each other. Biological parents and offspring have a 100% chance of being a half-match with the patient.
10. BSBMT 5th Report to Specialist Commissioners (2014).

The UK's dual approach to improve equity of access and to save the most lives

In Part Three we revisit opportunities to further improve the provision of unrelated donor stem cells for UK patients. We have reflected on the ongoing effectiveness of the UK's interlocking approaches for adult donor provision and cord blood banking. Thus whilst the provision of stem cells from unrelated adult donors remains the most effective way of meeting the needs of the majority of UK patients, the continued development of a genetically diverse UK inventory of cord blood remains the best way of addressing the needs of BAME patients.

Since 2010 the number of patients in the UK able to proceed to a potentially life-saving unrelated donor transplant has increased by over 30%. Against the growing number of UK patients now eligible for a life-saving transplant, we have re-assessed the unmet need for well-matched stem cells, and estimate that around 355 patients[11] each year are still unable to find a well-matched donor in a timely way; a persistent problem in patients from BAME communities.

The strategy outlined in Part Three for improving the provision of donor stem cells remains one of 'quality rather than quantity'. For adult donors, this involves expanding the UK's 'fit panel' of young, donors to 150,000, ensuring each donor is HLA typed to the highest resolution. For cord blood banking, this involves the establishment of a 50,000 donation inventory, banking only those donations with a 1% likelihood (or better) of being issued each year. Evidence presented to us demonstrates that these complementary approaches, originally proposed by the Strategic Forum, continue to strike the best balance between the need to achieve financial sustainability, and the need to improve patient outcomes.

Health economics and commissioning

At a time of constrained resource, the cost-effective provision of unrelated adult donor and cord blood stem cells remains key to the delivery of a sustainable national policy. We have therefore paid great attention to a reappraisal of the health economic implications of our proposals (Part Three of this report).

We confirm that a cord blood inventory of 50,000 donations best meets the needs of UK patients.[12] We find that this delivers a cost per additional quality-adjusted life year (QALY) in the region of £9,400, significantly better than the £15,000 threshold used by the Department of Health (DH) to evaluate the effectiveness of NHS spending decisions. Moreover, this represents a significant improvement on the Strategic Forum's 2010 cost per QALY estimate of £27,000, reflecting ongoing improvements in patient outcomes and the UK's stem cell supply chain. We recommend the expansion of the cord blood inventory should be achieved in two phases. In phase one, continued investment over a three year period should be used to achieve an inventory of 30,000 donations by 2018. We estimate that such an inventory will deliver a cost per QALY in the region of £10,400. In phase two, beyond 2018, we estimate that the inventory will be financially sustainable, generating the income required to fund ongoing inventory growth to 50,000 donations.

11. In 2010, the Strategic Forum estimated unmet need to be around 440 patients *per annum*.
12. We estimate that a 50,000 donation inventory will meet around 83% of unmet demand for optimally-matched stem cells in the UK.

We have also carried out an indicative cost effectiveness analysis of expanding the UK's 'fit panel' to 150,000. This analysis suggests that the cost per additional QALY is in the order of £8,500,[13] again significantly better than threshold used to evaluate the effectiveness of NHS spending decisions.

Long-term post-transplant complications can be debilitating, and can severely impact a patient's quality of life. We continue to highlight the fragmented nature of commissioning processes for patient care after stem cell transplantation. Herein we recommend the creation of a single commissioning process spanning a national patient pathway and encompassing the multi-disciplinary specialities required for stem cell transplantation and long-term post-transplant care.

Translating scientific discovery into patient outcomes

Stem cell transplantation remains a complex procedure and despite advances in supportive care many patients still die of treatment complications or resistant disease. In the past two decades an extensive portfolio of new drugs and cellular treatments with capacity to substantially improve the outcome of transplant patients has been developed. Before such therapeutic advances can be embedded into routine clinical practice their safety and efficacy must be assessed. This can only be done in the context of a well developed clinical trial network of sufficient size to ensure rapid recruitment. In 2010 the Strategic Forum therefore recommended the establishment of such a clinical trials network.

To date, it has not been possible to secure funding for this recommendation. As a result UK patients are denied rapid access to new, potentially life-saving therapies. At the same time the UK is failing to exploit the economic opportunity presented by its unique access to world class science and a large and coherent transplant population. It is missing the opportunity to attract inward investment by the global pharmaceutical sector into a high quality early phase trials programme. We therefore reiterate the urgent need to identify funding for the creation of a UK transplant trials network (UKTTN) within the governance structure of the NIHR.

New opportunities have presented themselves since the 2010 report. Next generation DNA sequencing now offers the opportunity to cost-effectively HLA type stem cell donors to the highest resolution. Improvements in IT interoperability offer enhanced functionality to support donor search and provision. We recommend continued development and deployment of both these technologies to drive better patient outcomes and reduce costs. Importantly, the UK's ambition to exploit the healthcare and economic benefits of regenerative medicine is now clear. Haemopoietic stem cell transplantation is the only established regenerative cell therapy. In that regard, our recommendations will contribute significantly to the human and capital infrastructure required to establish the clinical efficacy of innovative regenerative cell therapies.

13. Based on costs provided by NHSBT.

Recommendations

The Oversight Committee has carried out a review of progress made since 2010, and in response to recent and forthcoming medical, scientific and operational developments, has refreshed the UK strategy for unrelated donor stem cell transplantation accordingly. The recommendations set out below are the consensus view of the Oversight Committee. They pursue the original aims of the Strategic Forum namely:

1. To continue improving outcomes for all patients, regardless of ethnicity;
2. To continue reducing the overall cost of stem cell transplantation.

Given the ongoing financial constraints facing the NHS, the Oversight Committee believes it is essential to continue to increase the number of UK-to-UK donor transplants through an augmented adult unrelated donor panel and a financially sustainable cord blood banking operation. Both of these will ensure patients achieve the best possible match for their stem cell transplant whilst ensuring that the NHS benefits financially.

The Oversight Committee recommends that:

1. The Anthony Nolan and NHS Stem Cell Registry should continue to expand the UK's 'fit panel' to 150,000 donors. There should be a continued emphasis on recruiting young, male, ethnically-diverse donors predominantly aged between 16 and 30. Donors should be typed at high or allelic-level resolution.
2. The Anthony Nolan and NHS Stem Cell Registry should continue to develop evidence-based strategies to further improve donor availability when approached for donation. Stem cell supply organisations should undertake or commission research to better understand donor behaviours in relation to stem cell donation.
3. The Anthony Nolan and NHS Cord Blood Bank should establish an inventory of 30,000 cord blood donations by 2018. Beyond 2018, inventory growth to 50,000 donations should be funded via income generated through donation provision. Inventory utilisation should be maximised by banking only those donations likely to contain a clinically useful dose of stem cells, equivalent to 14×10^8 total nucleated cells before processing; 30% – 50% of donations should include BAME parentage.
4. Anthony Nolan and NHSBT should work with midwives and community groups with direct access to families, especially those from ethnic minorities, in order to raise awareness of the medical benefits of unrelated donor stem cell transplantation.

The Oversight Committee recommends that: *continued*

5. UK stem cell supply organisations should continue to implement next-generation DNA sequencing platforms for unambiguous HLA typing of selected adult donors and cord blood donations. The combined strengths of UK partners in the genomics of histocompatibility with particular reference to transplantation should be exploited to advance the UK Government's Life Sciences strategy.

6. Anthony Nolan, NHSBT, WBMDR, BSBMT and BSHI should collaborate to improve the selection and provision of adult donor and cord blood stem cells by gathering and sharing performance data, providing expert guidance, and supporting education.

7. Funding should be identified to support and improve the collection and analysis of patient outcome data. A more complete outcomes database should be established and interrogated by consolidating the patient and donor-related data held by BSBMT and organisations of the Anthony Nolan and NHS Stem Cell Registry.

8. The Anthony Nolan and NHS Stem Cell Registry should continue to develop and implement IT platforms to facilitate the rapid import and export of stem cell donations.

9. A national stem cell transplantation trials network should be established to facilitate and promote high quality prospective, randomised and controlled early phase clinical trials of new molecular and cellular therapies for patients with haematological malignancies.

10. Basic science laboratories should be encouraged to participate in relevant clinical trials to derive novel information on predictive biomarkers, in this way developing a stratified and personalised approach to stem cell transplantation.

11. Commissioning processes should encourage the development of regional centres of excellence for recipients of alternative donor transplants which reflect geographic constraints and are consistent with broader national policies including the delivery of early phase trials in regenerative medicine. There should be a consistent national approach for commissioning patient care after 100 days post-transplant.

12. The well established human and capital infrastructure currently supporting regenerative cell therapies for patients with bone marrow disorders should be fully exploited in delivering innovative regenerative cell therapies for other disorders.

The UK Stem Cell Strategy Oversight Committee

Prof Charles Craddock (Chair)
Professor of Haemato-oncology and Consultant Transplant Physician, University of Birmingham and Queen Elizabeth Hospital, Birmingham

Lynda Hamlyn (sponsor until July 2014)
Chief Executive, NHSBT

Dr Huw Williams (sponsor from August 2014)
Executive Director, Diagnostics and Therapeutic Services, NHSBT.

Prof Antonio Pagliuca
Chair, Blood and Marrow Transplantation Clinical Reference Group, NHS England.

Dr Andrew Hadley (Working Group Chair – Stem Cell Supply)
General Manager Specialist Services, NHSBT.

Ms Henny Braund
Chief Executive Officer, Anthony Nolan.

Prof Gordon Cook
President, British Society for Blood and Marrow Transplantation.

Prof Vanderson Rocha
Medical Director NHS Cord Blood bank and British Bone Marrow Registry, NHSBT and Professor of Clinical Haematology, Churchill Hospital, University of Oxford.

Prof David Marks
Consultant Transplant Physician, University Hospitals Bristol NHS Foundation Trust.

Dr Jackie Cornish OBE
Consultant Transplant Physician, University Hospitals Bristol NHS Foundation Trust; President of BSHI and Childhood Cancer and Leukaemia Group.

Dr Chloe Anthias
Interim Medical Director, Anthony Nolan.

Mr Colin Pavelin
Health Science and Bioethics, Department of Health.

Dr Rachael Hough
Consultant Transplant Physician, University College Hospital London, and Chair, BSBMT Cord Blood Working Group

Ms Janet Fyle
Policy Advisor, Royal College of Midwives

Claire Foreman
Accountable Commissioner, Blood and Marrow Transplantation Clinical Reference Group

Professor Paresh Vyas
Professor of Haematology, Weatherall Institute of Molecular Medicine, University of Oxford.

Mr Orin Lewis OBE
Chief Executive, African Caribbean Leukaemia Trust.

Mary Morgan
Director, Scottish National Blood Transfusion Service

Prof Marc Turner
Medical Director, Scottish National Blood Transfusion Service

Dr Tracey Rees
Head, Welsh Transplantation and Immunogenetics Laboratory, Welsh Blood Service.

Dr Kieran Morris
Chief Executive, NI Blood Transfusion Service.

Dr Geoffrey Carroll
Medical Director, Welsh Health Specialised Services Committee.

Mr Jackie Johnston
Director of Secondary Care, Department of Health, Northern Ireland.

Robert Girvan
Healthcare Strategy and Policy Directorate, Scottish Government.

Dr Paul Veys
Consultant Transplant Physician, Great Ormond Street Hospital.

Dr Jenny Byrne
Consultant Haematologist, Nottingham University Hospitals.

Dr Keith Wilson
Senior Clinical Lecturer in Haematology, Cardiff University School of Medicine; Consultant Haematologist, University Hospital of Wales.

Dr Anne Parker
Consultant Haematologist, NHS Greater Glasgow and Clyde.

Acknowledgements

Andrew Parker
Principal Operational Research Analyst, Department of Health

Stephen Dobra
Analytical Programme Manager, Department of Health

Maren Daraktchiev
Senior Operational Research Analyst, Department of Health

Guy Parkes
Head of Stem Cell Donation & Transplantation, NHSBT

Nicola Alderson
Director of Operations, Anthony Nolan

Christian MacNamara
Account Management Officer, Anthony Nolan

Dr Colin Brown
Head of Histocompatibility and Immunogenetics, Colindale Laboratory, NHSBT

Binal Anandji
Programme Co-ordinator, UK Stem Cell Strategy Oversight Committee

Peter Zarko-Flynn
Report writer

Part One: Progress Against 2010 Recommendations

Summary

In Part One we report on progress made towards implementing the stem cell supply chain improvements recommended by the Strategic Forum in 2010. Significant progress had been made streamlining and improving the supply of stem cells from unrelated adult donors and cord blood. The three UK registries have been aligned to create a seamless service for NHS transplant centres. The reliability and speed of providing adult stem cells have improved through a programme to HLA type young male donors at high resolution. We report that the chances of BAME patients receiving a stem cell transplant are now substantially improved, with more than 60% of BAME patients able to find a well-matched donor compared to around 40% in 2010; most of this improvement is due to improved access to UK-sourced cord blood donations. Overall, in 2014, 258 additional patients are now receiving an unrelated stem cell transplant each year compared to 2010/11.

Background

Haemopoietic stem cell transplantation (HSCT) is a life-saving therapy for a range of malignant and non-malignant diseases.

Stem cells are characterised by their dual ability to self-replicate and differentiate into multiple tissue types and cell lineages; they offer great potential for regenerative medicine. Haemopoietic progenitor cells are multipotent stem cells found in bone marrow and blood (including cord blood) with the ability to differentiate into red cells, platelets and cells of the immune system. This ability is exploited in HSCT.

HSCT can be performed using either an allogeneic or autologous donor:

- Allogeneic stem cell transplantation is performed with bone marrow, peripheral blood or umbilical cord blood stem cells that are collected from a related or unrelated donor;
- Autologous stem cell transplantation is performed with stem cells that are collected from the patient before treatment and are later re-infused.

Although autologous stem cell transplantation remains a valuable treatment in myeloma and high risk or relapsed lymphoma, there has been no significant increase in clinical activity in either the UK or internationally over the last five years. In contrast, allogeneic stem cell transplantation is an increasingly important treatment strategy in a wide range of malignant and non-malignant bone marrow disorders. In approximately one third of patients who require an allogeneic transplant it is possible to identify an HLA matched sibling but access to a suitably matched adult unrelated donor or cord blood unit is required for the majority of all patients with blood cancer.

Allogeneic stem cell transplantation was initially developed using bone marrow cells harvested from HLA matched siblings. Recognizing that approximately 70% of patients lack a suitably matched brother or sister, studies performed three decades ago established that suitably matched volunteer unrelated donors could provide stem cells for patients who lacked an HLA identical sibling. The pioneering work of Anthony Nolan, one of the world's first unrelated donor registries, led to the establishment of adult unrelated donor registries across the developed world which together list more than 24 million potential donors. As a consequence there is now a greater than 80% chance of identifying a suitably matched adult unrelated donor for Caucasian patients but, because of greater genetic diversity and under-representation on donor panels, the likelihood of finding a donor for a BAME patient is much lower (around 40%) and can be less than 20%.

In recognition of the lack of suitable adult donors for many patients, and because cord blood is rich in haemopoietic stem cells, subsequent studies were performed which demonstrated that cryopreserved cord blood may be used as an alternative source of stem cells. Moreover, cord blood stem cells and immune system cells are relatively biologically naive which permits tolerance of a greater degree of HLA mismatch between donor and recipient. As a result, the use of cord blood substantially increases the number of potential donors for patients from BAME communities who are currently under-represented on adult unrelated donor registries.

Stem cells for allogeneic HSCT may be harvested either from bone marrow, peripheral blood, or cord blood.

- Bone marrow – collected from the pelvic bones using a needle and syringe. The procedure lasts around half an hour and is performed under general anaesthetic. The donor is usually recommended to allow a few days rest to recuperate.
- Peripheral blood stem cells – collection is less invasive than for bone marrow. The donor receives four or five daily injections of GCSF (granulocyte colony stimulating factor), which causes stem cells to migrate from the bone marrow to the circulating blood stream. These injections are usually administered in the donor's home by a visiting nurse. Collecting the stem cells from peripheral blood is an outpatient procedure. The donor's blood is removed and, in a continuous process using an apheresis device, the stem cells are isolated and the remaining blood is returned to the donor. This process lasts 3 to 4 hours and a second session on the next day may be needed. The donor may suffer mild flu-like symptoms as well as minor discomfort during the collection process.
- Umbilical cord blood – donation takes place in hospital maternity departments after birth. There is no evidence of risk to mother or child providing the collection of cord blood takes place within the normal medical protocols surrounding birth. Historically, cord blood has been used predominantly for transplantation in children due to concerns that the low cell 'dose' might make it less suitable for patients with a larger body mass. In the adult setting, it has now become clear that by selecting cord blood units containing high doses of stem cells and through the use of two donations, known as a double cord blood transplant, good outcomes can also be obtained in patients with a higher body mass.

Stem cell transplantation in the UK

Recognising that a significant number of patients lacked access to a potentially curative unrelated donor transplant, the recommendations of the Strategic Forum aimed to increase and improve stem cell supply. Since the report's publication there has been a 32% increase in the number of unrelated donor transplants performed in the UK each year[14]. Despite this, many patients, especially those of non-white northern European ethnicity, cannot benefit from this potentially life-saving treatment because they lack a suitable unrelated stem cell donor.

Domestically sourced donors and cord blood donations reflect the unique genetic diversity of the UK population in a way that registries in other countries cannot. This is particularly important in light of the growing mixed race population in the UK. In addition, by achieving greater control over its own supply, the UK would strengthen the logistical links between its providers and transplant centres and have greater protection against disruptions in the global supply chain. In 2010 the closure of international flights in many parts of Northern Europe, due to an Icelandic volcanic ash cloud, highlighted the relative fragility of the global supply chain. A well-developed supply of donor stem cells would position the UK to fully exploit its position as world leader in cell-based therapies.

To address these issues a UK Stem Cell Strategic Forum was set up in 2010 at the request of the Minister of State for Public Health. Comprising more than 40 experts and representatives from the four countries of the UK, the Strategic Forum's remit was to advise on future options for the provision and use of stem cells from unrelated adult volunteer donors and cord blood.

The Strategic Forum's report[15] set out a strategy to save an additional 200 lives each year and provided 20 recommendations. The recommendations were grouped into three broad areas:

1. Improve the provision of unrelated adult donor stem cells;
2. Improve the provision of cord blood stem cells;
3. Drive quality and efficiency.

In 2011, following Ministerial support for the Strategic Forum's recommendations, the UK Stem Cell Strategy Oversight Committee was established to co-ordinate and monitor implementation of the recommendations across the four countries of the UK.

In 2014 the Oversight Committee revisited the 2010 recommendations and looked at progress against the original objectives. The full list of the Strategic Forum's 20 recommendations and the progress made against each one is detailed in Appendix One.

14. Data from Anthony Nolan - derived from unrelated donor transplants provided for UK patients.
15. The Future of Unrelated Donor Transplantation in the UK. A Report from the UK Stem Cell Strategic Forum (2010).

Improving the provision of adult donor stem cells

Creation of the Anthony Nolan and NHS Stem Cell Registry

In 2010 the UK had three stem cell donor registries with a combined panel of more than 770,000 adult donors; Anthony Nolan with 405,000 donors, the British Bone Marrow Registry (BBMR) with 310,000 donors, and the Welsh Bone Marrow Registry (WBMDR) with 60,000 donors. Following the Strategic Forum's 2010 report, it became clear that many of the recommendations could only be achieved through increased collaboration between the three registries. An alignment of registry activities offered the greatest opportunity for streamlining support for transplant centres, sharing best practice, developing a joint approach to performance management, and removing duplication. The alignment of the registries, including the development of supporting IT infrastructure, was a significant undertaking. In January 2012 Anthony Nolan and the BBMR began operating as an aligned registry, creating the Anthony Nolan and NHS Stem Cell Registry. In September 2013 the WBMDR became part of this registry, offering a fully aligned service for UK transplant centres.

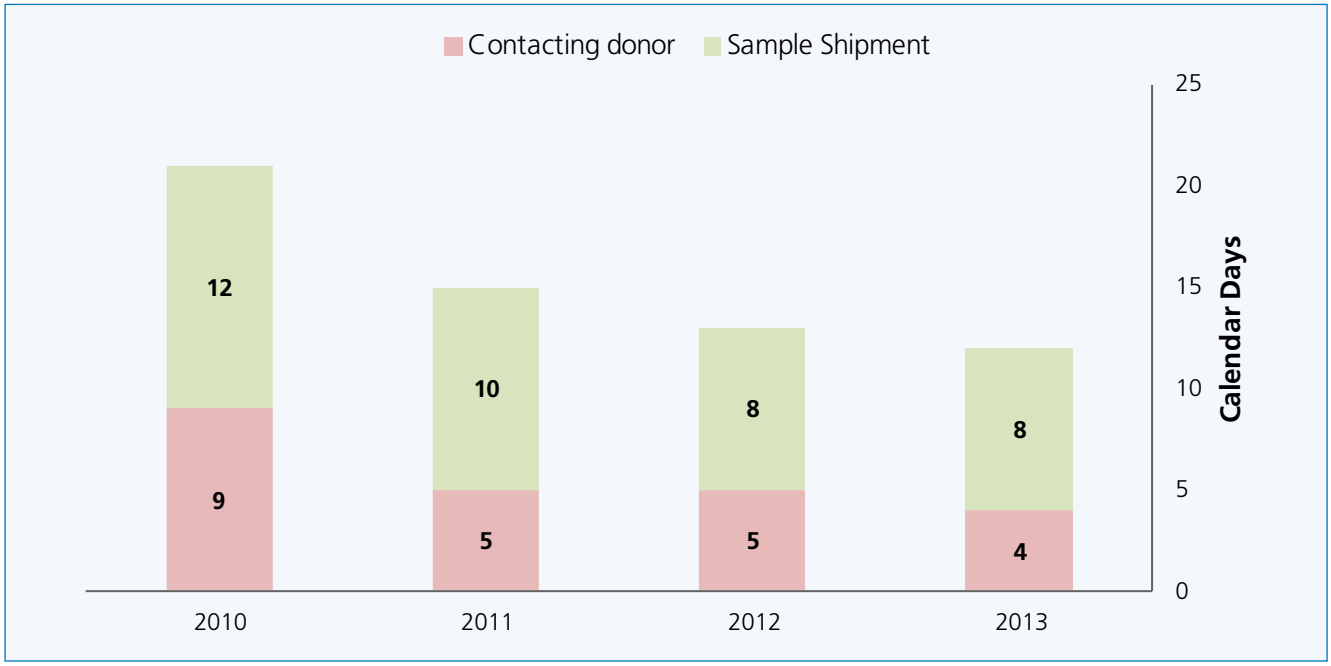
The Anthony Nolan and NHS Stem Cell Registry provides a single point of access for UK transplant centres searching for adult unrelated donors and cord blood units. Before the registries were aligned, transplant centres would submit search requests to each registry individually, and then receive three separate reports. Now, transplant centres only need to search once before receiving a single report listing all suitable donors for a given patient.

Minimising the turnaround time from donor search to transplantation is key to achieving the long-term goal of saving an additional 200 lives each year. The progression of a patient's disease prior to transplantation is an important contributing cause of treatment failure and death. A study of 3857 transplants between 1988 and 2003 found that, compared to patients transplanted at an early stage of their disease, the mortality risk for intermediate-stage patients was 38% higher. For advanced-stage patients, the risk was roughly double[16].

The efficiencies gained through the alignment of the UK registries, together with a raft of initiatives to improve engagement with volunteer donors, has led to a significant improvement in turnaround times. In 2010 only 35% of requests resulted in sample provision for confirmatory typing within 15 days. In 2014 over 80% of requests are fulfilled within 15 days. This compares to an international average of around 71%[17]. Figure 1 shows how the median time for sample shipment has been reduced from 21 days to 12 days.

16. Lee J *et al.* (2007) High-resolution donor-recipient HLA matching contributes to the success of unrelated donor marrow transplantation. Blood 110:457-683.
17. In the same period, international registries averaged 71%, ZKRD 77% and NMDP 70% of samples shipped within 14 days; data from Anthony Nolan.

Figure 1: Median time for sample provision for confirmatory typing



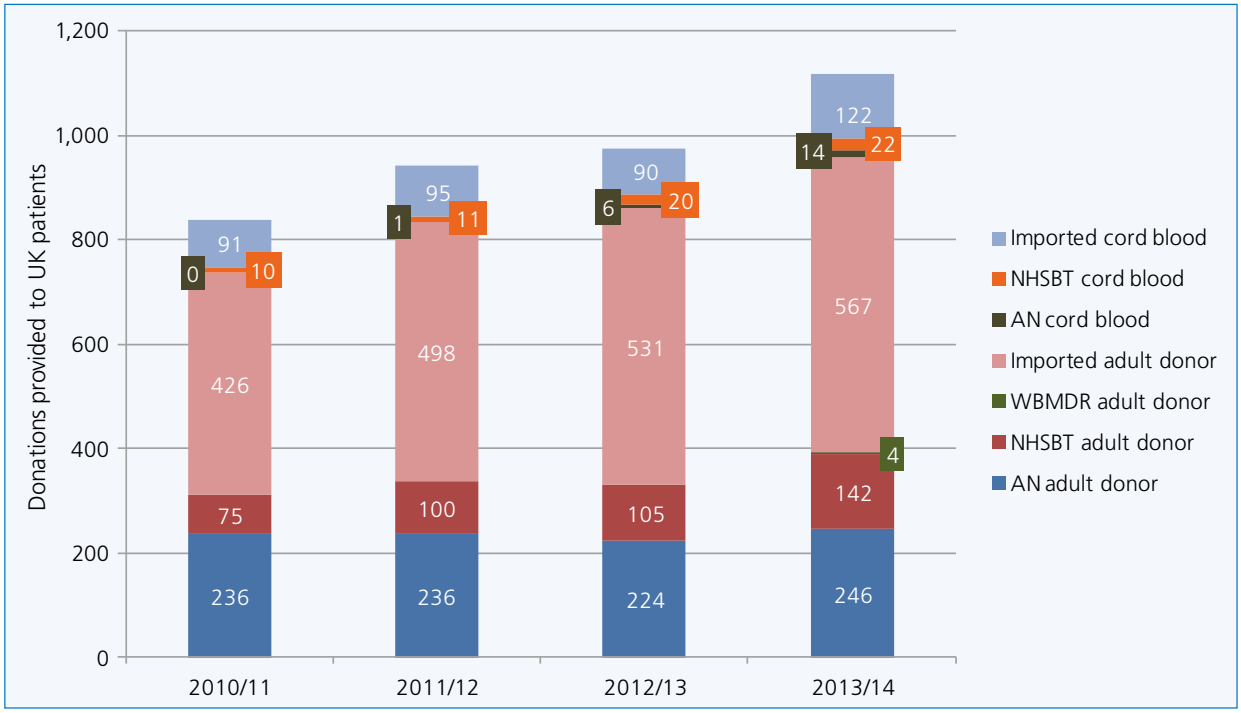
Therefore in 2014 UK donor blood samples are consistently provided more quickly more often than imported donor samples.

The quality of advice provided by histocompatibility and immunogenetics laboratories on donor selection and provision is equally important, and evidence suggests that practice across the UK is variable. The graft information advisory service (GIAS) provided by Anthony Nolan aims to expedite rapid donor selection tailored to the preferences of individual transplant centres. A study conducted through 2012 demonstrated the total time from search to transplant for centres using GIAS was shorter by an average of 32 days compared to some centres not using the service.

Curing more patients

In the last four years significant progress has been made towards the Strategic Forum's initial goal of saving an additional 200 lives each year through unrelated donor stem cell transplantation. Figure 2 shows the number of adult donor and cord blood stem cell donations (including imported donations) provided for UK patients since 2010/11.

Figure 2: Unrelated donor stem cell provision for UK[18]



The following trends in unrelated donor stem cell provision can be identified over the period:

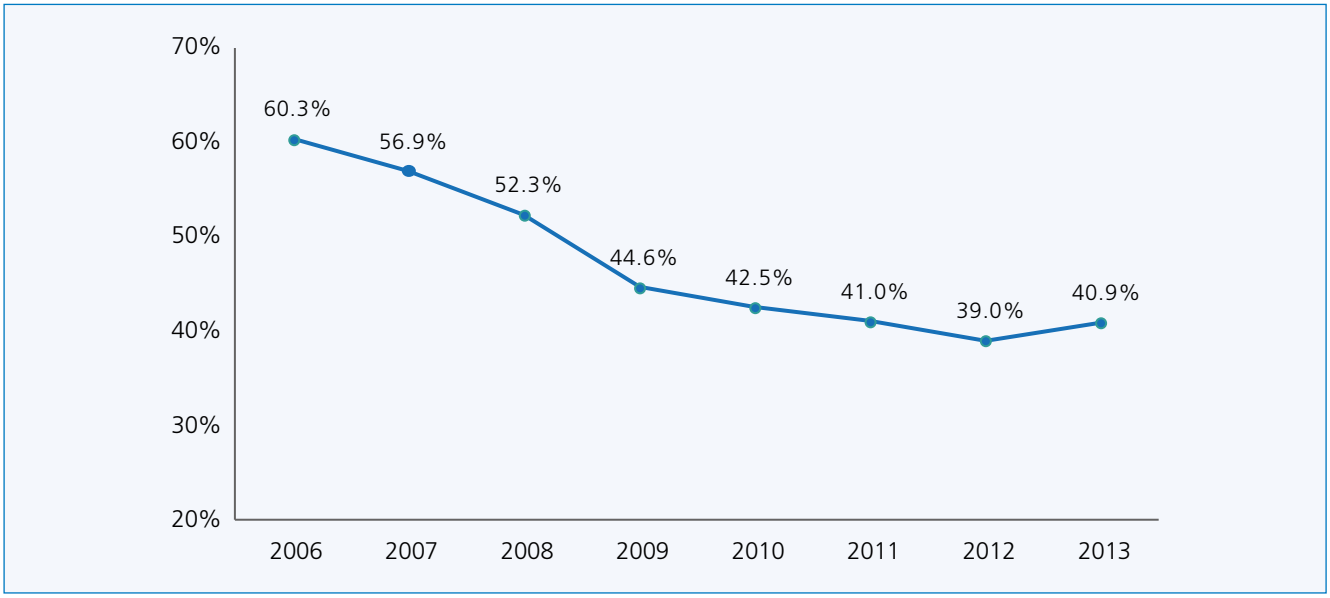
1. Around 88% of donations used for UK transplants come from an adult stem cell donor.
2. There was a 33% increase in the number of stem cell donations (adult donations and cord blood) provided by the Anthony Nolan and NHS Stem Cell Registry.
3. The percentage of imported stem cell donations (adult and cord blood) has remained relatively stable at 62% since 2010 following a period when imported donations were increasing year on year (see Figure 3).
4. The number of adult donations provided by NHSBT has increased, suggesting that transplant centres are offered better visibility of these donors via the consolidated registry reports.
5. There was a 30% increase in the number of cord blood donations provided, and a more than three-fold increase in the provision of UK-sourced cord blood.

The total number of UK patients given a potentially curative transplant option was as follows:[19]

- In 2010/11, 802 UK patient were transplanted;
- In 2011/12, 905 UK patients were transplanted;
- In 2012/13, 934 UK patients were transplanted;
- In 2013/14, 1060 UK patients were transplanted.

18. Data from Anthony Nolan showing the number of donations used in UK transplants. Note that most cord blood transplants require two donations. WBMDR figures excluded until 2013/14.
19. Extrapolated from donation provision data. Assumes that a patient was transplanted for every adult donation provided, and that the majority of cord blood donations were provided for double cord blood transplants.

Figure 3: Percentage of imported adult donations



As the figures for 2013/14 demonstrate, 258 additional patients are now receiving a stem cell transplant each year (of these 111 patients are receiving a UK-sourced donation), compared to 2010/11. Assuming a 50% cure rate, this translates to an additional 129 lives saved in 2013/14 compared to 2010/11. Further data on patient outcomes are presented in Appendix Two.

In 2010 the Strategic Forum recognised that patient outcomes would improve through measures to decrease the time taken to provide adult donor stem cells. They recommended that this be brought about through the creation of a 'fit panel' of young, motivated and medically fit adult donors who should be HLA typed at high resolution to provide transplant teams with the best matching information at the donor short listing stage. The recommendation was to reach a total of 75,000 'fit panel' volunteers. The intention was to:

- reduce the level of uncertainty at the donor-selection stage;
- reduce the time taken for donor provision;
- increase donor reliability;
- increase the probability of donors being selected for transplantation.

At the time of writing, 60,000 young (up to 30 years old) volunteers have been typed to a high resolution:

- Fit panel donors are eight times more likely to be selected for donation[20]; at least 40 lives were saved via fit panel donors in the last year alone;
- 33% of all UK-to-UK provisions are now supplied by 'fit panel' donors.[21]

Information technology

In 2010 the Strategic Forum recognised that high resolution typing of donors by DNA sequencing was costly and labour intensive.[22] Registries such as the NMDP and ZKRD had, therefore, developed computer programmes (HapLogic and OptiMatch) capable of predicting precise HLA matches from medium resolution typing data.

Since the creation of the Anthony Nolan and NHS Stem Cell Registry, work has been undertaken to build predictive search technologies into the registry's database. This work is almost complete. The necessary algorithms have been developed and are currently in final testing with good results. The predictive search technology, which is based on 20,000 HLA types representing the predominant UK ethnic groups, is planned to go live in 2015.

Improving the provision of cord blood stem cells

Growing the UK cord blood inventory

To achieve long-term financial sustainability, it is essential to direct investment towards the banking of cord blood donations which have a relatively high likelihood of being issued. Clinical teams in the UK and around the word preferentially select cord blood donations containing the highest available dose of stem cells in order to optimise engraftment rates in adult patients. This important trend was recognised by the Strategic Forum in 2010 who recommended that donations containing less than 9×10^8 total nucleated cells (TNC[23]) should no longer be added to the inventory.[24] A reappraisal of inventory utilisation rate by the Oversight Committee in 2012 led to a recommendation to increase quality even further by banking only donations containing over than 14×10^8 TNC. This remains current practice at NHSBT and Anthony Nolan. Figure 4 shows the banking rate achieved by NHSBT and Anthony Nolan against targets agreed by the DH over the period.

20. Around 0.4% of 'fit panel donors' are selected each year compared to around 0.05% of donors from the wider registry.
21. 2013/14 data from Anthony Nolan.
22. This now more affordable with the advent of next generation sequencing – discussed in Part Two.
23. TNC is relatively simple to measure, and represents a useful surrogate indicator of stem cell content.
24. The original Strategic Forum recommendation was to bank only donations from BAME donors containing over 9×10^8 TNC, and donations from Caucasian donors containing over 12×10^8 TNC.

Figure 4: Incremental growth in the UK cord blood inventory, resulting from additional DH funding since 2011/12[25]

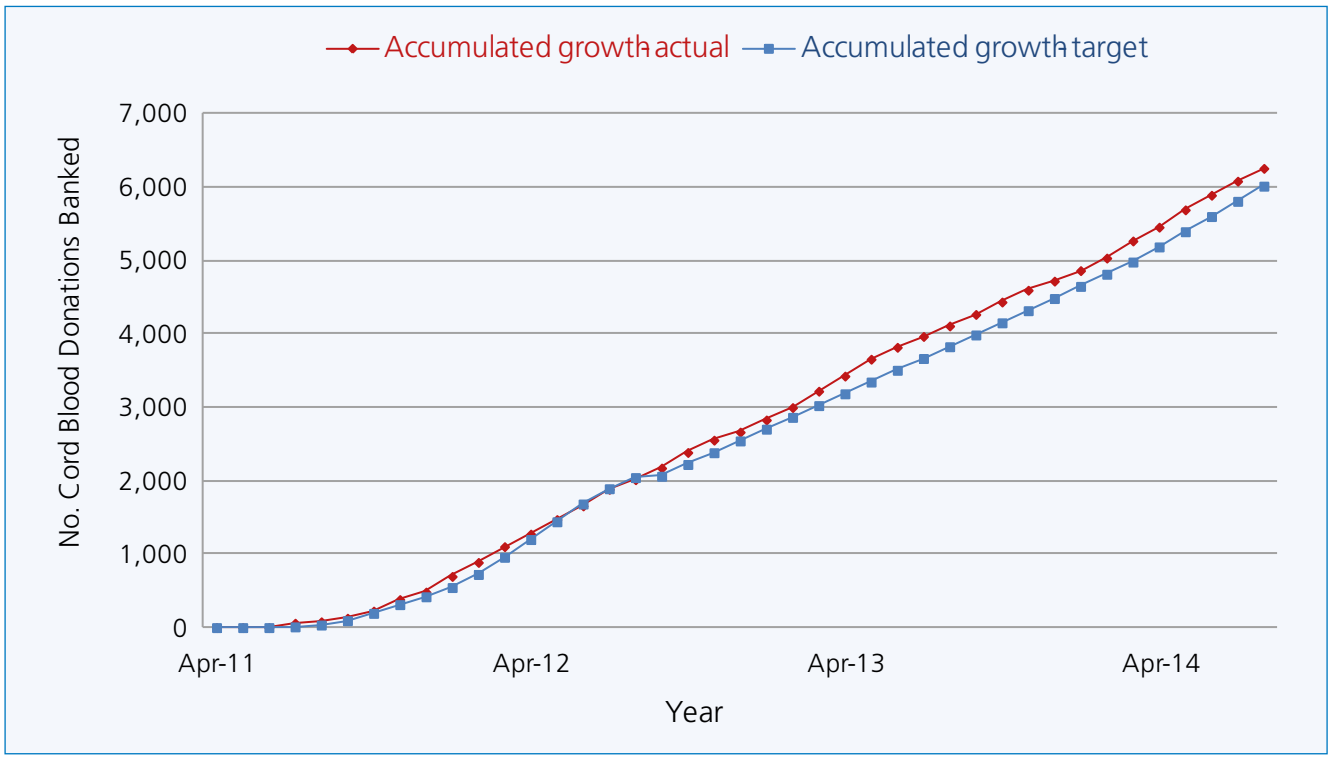


Table 1 shows how the inventory can be segmented according to post-processing TNC dose. For the purposes of this report, we distinguish between the clinical inventory and the research inventory. The clinical inventory comprises those donations containing a dose of stem cells sufficient for transplantation purposes. The research inventory, primarily acquired before 2011, remains in storage and is only rarely issued for transplantation. However, these donations are useful for research and development purposes. Within the clinical inventory, it is useful to further segment donations (grades A, B and C) according to utilisation rate as shown in Table 1. These utilisation rates are used to model the impact of different cord blood banking strategies (see Part Three).

25. This incremental growth is in addition to the growth achieved via NHSBT's and Anthony Nolan's 'baseline' funding.

Table 1: The UK's cord blood inventory

Inventory segment	Post-processing dose (x10^8 TNC)	Donations banked	% annual utilisation	Use
Grade A	> 19	1,288	3%	Clinical inventory
Grade B	14 – 19	3,446	1%	
Grade C	9 – 14	8,907	0.2%	
R&D	4 – 9	9,038	0.01%	Research inventory

Notes:
1. Shows inventory composition and utilisation rates as at January 2014.
2. Banking of donations containing less than 9 x 10^8 TNC (pre-processing) ceased 2011.
3. Banking of donations containing less than 14 x 10^8 TNC (pre-processing) ceased 2013.

Figure 5 further segments each grade of donation by ethnic composition. The data suggest that the largest donations may be biased towards Caucasian donors.

Figure 5: Composition of the UK's cord blood inventory by ethnicity.

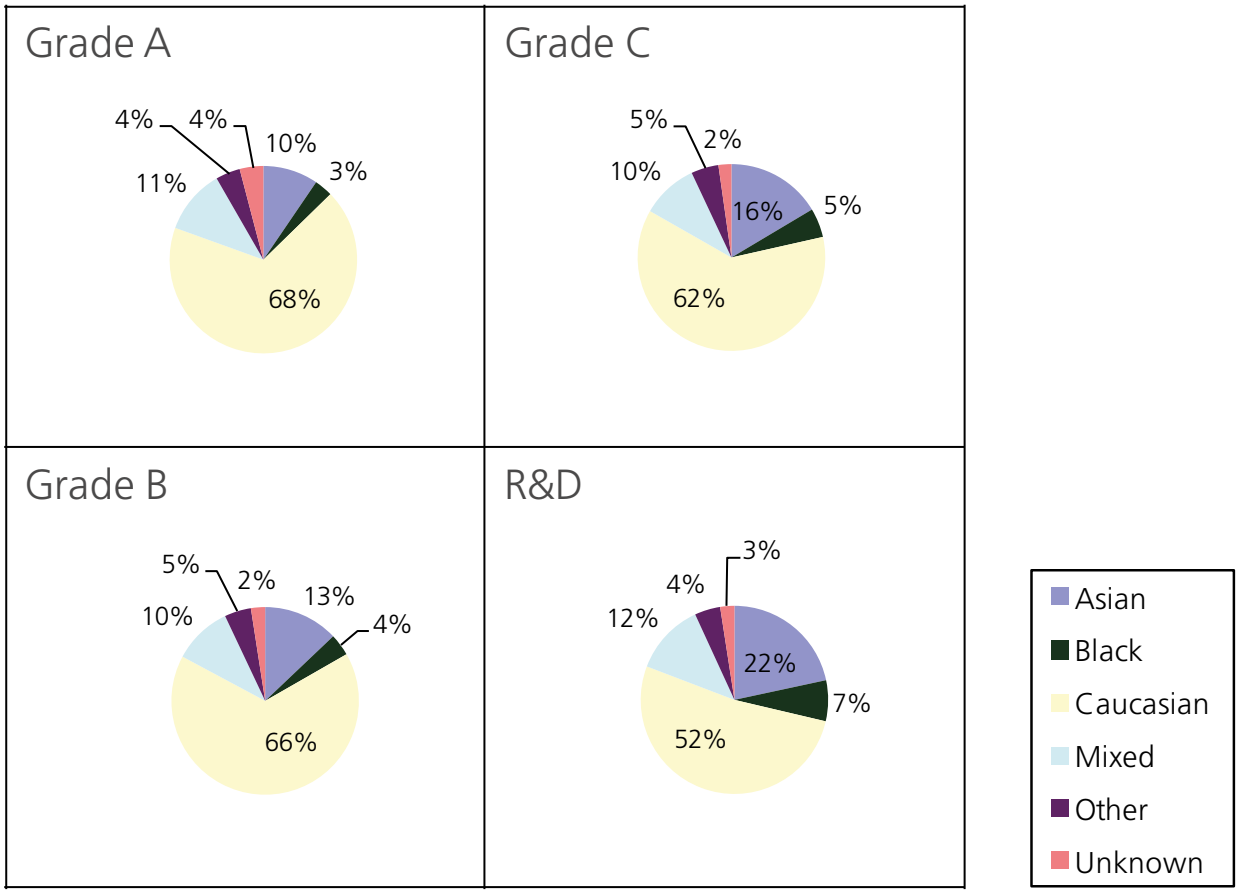


Figure 6 shows the cord blood inventory growth trajectory originally envisaged by the 2010 Strategic Forum; Figure 7 shows the actual growth achieved, and this reflects the change to cord blood banking criteria implemented in 2013. As at January 2014, the UK's operational inventory stood at around 13,600 donations.[26]

Figure 6: Inventory growth projection from 2010 Strategic Forum

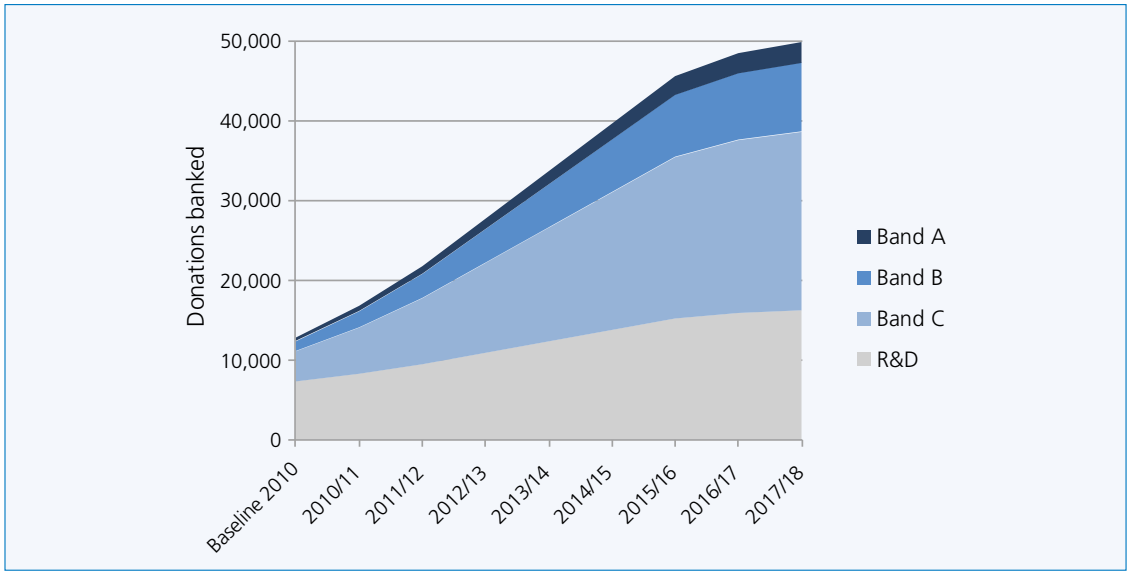
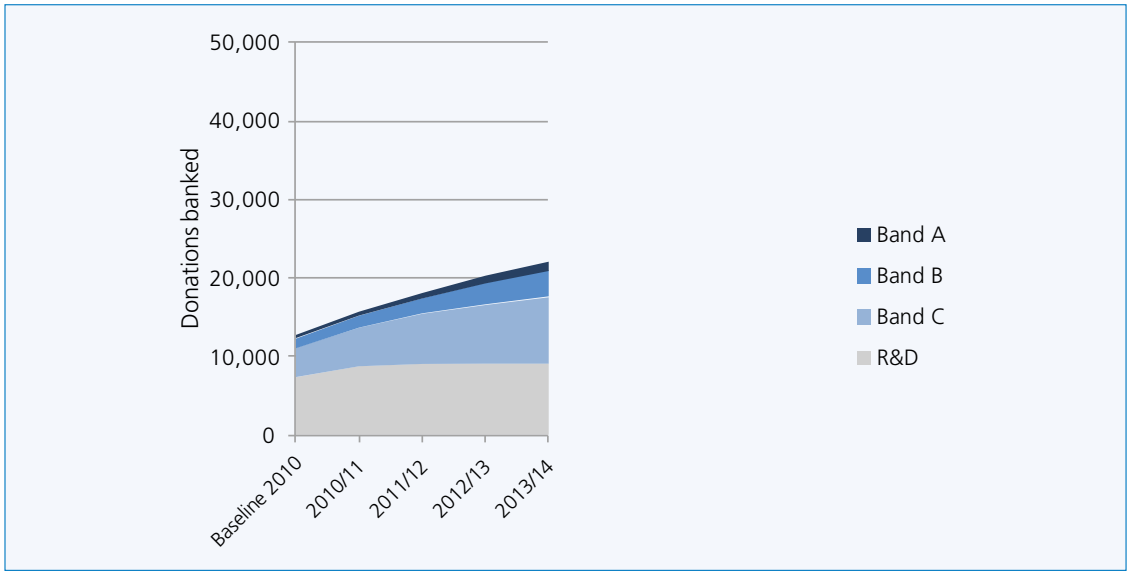


Figure 7: Actual growth in the UK cord blood inventory since 2010 demonstrating increased proportion of clinical grade cord blood units



26. In recommending the development of a UK cord blood inventory of 50,000 donations, the Strategic Forum anticipated a significant contribution from cord blood banks of the Scottish National Blood Transfusion Service (6,000 donations) and the Northern Ireland Blood Transfusion Service (3,000) donations. In the event, these cord blood banks have not developed significantly.

Improving equity of access to matched stem cells for BAME patients

A key aim of the 2010 recommendations was to improve equity of access to well-matched donor stem cells for BAME patients, given the poor representation of suitable donors on the international stem cell registries. As recently as 2000, only 30% of such patients were able to find an unrelated donor suitable for transplantation. In 2010 the Strategic Forum suggested that matching rates for BAME patients was around 40%, compared to around 90% for Caucasian patients.

In seeking to establish the position in the UK currently, the recent study by Lown *et al.* (2013)[27] provides a unique insight. Three hundred and thirty two patients consecutively admitted to four UK transplant units were prospectively followed from search request until last contact or death. Findings are summarised at Table 2. The median number of UK donors identified for white northern European (WNE) patients and non-WNE patients was 8 and 0 respectively; the median number of international donors was 127 and 5.5 respectively. Overall, 69% of WNE and 21% of non-WNE patients found a 10/10 HLA-matched donor; 96% of WNE and 61% of non-WNE patients found a 9/10 (or better) HLA-matched donor. Non-WNE patients had more cord blood transplants than WNE patients (21.3% vs 3.8%).

These data provide evidence that access to unrelated donors has improved over the last decade with around 60% of BAME patients now able to find an acceptably matched (but critically not an optimally matched[28]) donor. They also support a continued focus on improving the UK's cord blood inventory in order to benefit BAME patients.

Table 2: Outcomes for 332 patients requiring an unrelated donor allogeneic stem cell transplant (from Rob Lown, 2013)

	Number of patients	Potential UK donors per patient[1]	Potential inter-national donors per patient[1]	% patients with 10/10 match	% patients with 9/10 match[3]	% patients trans-planted	% patients with cord blood transplant	% patients with haplo-identical transplant
WNE[2] patients	248	8	127	69%	96%	63%	4%	1%
Non-WNE patients	84	0	5.5	21%	61%	56%	21%	11%

Notes.
1. Median number of unrelated adult donors available.
2. WNE = white northern European.
3. Includes patients with 10/10 match.
4. Haploidentical stem cell transplants are described in Part Two.

27. Lown, RN. *et al.* (2013) Equality of Access to transplant for ethnic minority patients through the use of cord blood and haploidentical transplants. Abstract. American Society for Haematology.
28. Patients receiving CMV incompatible 9/10 matched stem cells do less well that those receiving a 10/10 matched donation. Dr Bronwen Shaw, personal communication to the review.

Driving quality and efficiency

In 2010 the Strategic Forum recognised that quality and efficiency improvements could be encouraged through changes in commissioning processes. The Forum recommended that commissioning policy should be informed by rigorous patient outcome data, should encompass the entire patient pathway, and should encourage data collection and the creation of designated centres as a focus for unrelated donor stem cell transplantation and associated prospective clinical trials.

Since 2010 there have been significant changes to the commissioning landscape in England. The Health and Social Care Act 2013 created new commissioning arrangements, which came into effect on 1 April 2013. Significant progress has been achieved within this new environment. As part of the new commissioning structure, a Clinical Reference Group (CRG) for Blood and Marrow Transplantation was created. This CRG sits within the Cancer and Blood programme and is responsible for a range of areas relating to stem cell transplants for NHS England, including the drafting of service specifications, commissioning policy, quality dashboards, and Quality Innovation Productivity and Prevention (QIPP) agendas. The British Society of Blood and Marrow Transplantation (BSBMT) supports commissioning processes through engagement by office-bearers and the annual publication of detailed statistical analyses of patient outcomes.

A key component of the BMT CRG's service specification for adult transplantation has incorporated a central recommendation of the 2010 report by mandating that "centres which undertake umbilical cord transplants must be part of a provider network with a combined catchment population of at least 4 million people". The Oversight Committee, which has a UK-wide remit, also supports the work of the CRG through expert advice. This helps to ensure that policies in the four countries of the UK are developed consistently.

Until 2014, commissioning of double cord blood transplantation in England was unclear despite the majority of cord blood transplants requiring two donations (and ongoing DH investment in the UK cord blood inventory). In 2014 this 'paradox' was resolved. Acting on advice from the BMT CRG, the Clinical Priorities Advisory Group recommended to NHS England's Directly Commissioned Services Committee a policy of approving the use of double cord blood transplants. Moreover, the recommendations supported the use of relatively less expensive UK-sourced donations where suitable donations existed. It also supported continued investment in the UK cord blood inventory to continue to improve the availability of UK-sourced donation.

In 2010, the Strategic Forum recommended that all centres performing unrelated donor stem cell transplantation should be accredited by the Joint Accreditation Committee of ISCT and EBMT (JACIE). JACIE was established to provide a way for transplant centres across Europe to demonstrate compliance with accepted best practice in stem cell transplantation. JACIE accreditation in the UK is overseen by BSBMT. All allogeneic transplant centres in the UK have now been inspected, with all but one centre being JACIE accredited. The remainder are on schedule to receive re-accreditation during 2014.[29]

29. http://www.jacie.org/accredited-centres

Part Two: Realising the Potential of Technological and Medical Advances

Summary

In this appraisal of the impact of the Strategic Forum's 2010 recommendations, the Oversight Committee has undertaken an environmental scan in order to incorporate the most recent technological and medical advances in future recommendations. Broadly these are:

- Improved data on the relationship between HLA matching and patient outcomes;
- New conditioning regimens allowing transplantation in older patients;
- Improved patient outcomes following stem cell transplantation;
- Emerging evidence on the efficacy of haploidentical stem cell transplants;
- New data on the timing of umbilical cord clamping;
- The advent of affordable whole genome sequencing and next generation technology for allelic-level HLA typing;
- Emerging strategies to improve cord blood stem cell engraftment;
- The emergence of regenerative medicine as a focus for new therapies and inward investment;
- Improved IT inter-operability for donor search and provision activities.

The likely impacts of these advances on unrelated donor stem cell transplantation in the UK are considered below.

HLA matching and patient outcomes

Adult donor transplants

The Strategic Forum's 2010 report emphasised the important relationship between outcomes following unrelated adult donor stem cell transplantation and the degree of HLA mismatch demonstrated by high resolution matching for HLA-A, -B, -C , and –DRB1 alleles[30]. More recent data[31] have confirmed that patients receiving a 9/10 matched adult donor, especially if incompatible for CMV, do less well than patients receiving a fully-matched stem cell donation. These data continue to underpin the need to invest in adult donor stem cell registries in order to offer all patients the very best match possible.

30. Citing Lee, SJ *et al.* (2007). High-resolution donor-recipient HLA matching contributes to the success of unrelated donor marrow transplantation. Blood 110:4576-4583.
31. Dr Bronwen Shaw, personal communication to the review.

Cord blood transplants

In 2014 important new data emerged on allele-level matching at HLA-A, B, C and DRB1 and outcomes after cord blood transplantation. Eapen *et al.*[32] on behalf of CIBMTR and Eurocord reported a retrospective analysis of 1586 patients receiving a single cord blood donation transplant. Using a genotype prediction algorithm, they estimated that only 7% of donor-recipient pairs had been matched at HLA-A, -B, -C, -DRB1 (8/8). Non-relapse mortality was higher after 7/8, 6/8, 5/8, 4/8 and 3/8 HLA-matched transplants compared to 8/8. These data support a selection algorithm for cord blood donations which includes allele-level HLA-matches at HLA-A, -B, -C and -DRB1 (i.e. 8/8). They also suggested that, in the absence of a fully matched donation, mismatches at 1 or 2 alleles are acceptable. They recommended that cord blood donations mismatched at 4 or more alleles should only be considered along side developmental options such as haploidentical transplantation.

Patient Outcomes Database

Studies such as those described above provide important insight into the donor and patient-related factors which determine transplant outcomes. Such studies rely on the collection of medical, technical and demographic data, and the assembly and maintenance of databases which can be subjected to complex analyses. In the UK these activities are undertaken by different organisations, with BSBMT leading on the collection and analysis of patient-related data, and organisations of the Anthony Nolan and NHS Stem Cell Registry leading on the collection of donor-related data. The use of separate databases, combined with a lack of funding to optimally collect and collate post-transplant outcome data, hampers high quality retrospective analyses in the UK.

Recommendation

Funding should be identified to support and improve the collection and analysis of patient outcome data. A more complete outcomes database should be established and interrogated by consolidating the patient and donor-related data held by BSBMT and organisations of the Anthony Nolan and NHS Stem Cell Registry.

Single versus double cord blood transplants

The limited number of haematopoietic cells in a single cord blood donation has been associated with delayed haematopoietic recovery and higher mortality. For this reason, transplants using two cord blood donations have become the norm in adult patients. Wagner *et al.*[33] recently reported the first large prospective trial of single versus double cord blood transplants. A total of 224 patients with haematologic cancer were randomly assigned to undergo double-unit or single-unit cord-blood transplantation after a uniform myeloablative conditioning regimen and immunoprophylaxis

32. Eapen M *et al.* (2014). Impact of allele-level HLA matching on outcomes after myeloablative single unit umbilical cord blood transplantation for haematologic malignancy. Blood, 123:133-140.
33. Wagner JE *et al.* (2014) One-unit versus two-unit cord-blood transplantation for haematologic cancers. N Engl J Med. 371:1685-1694.

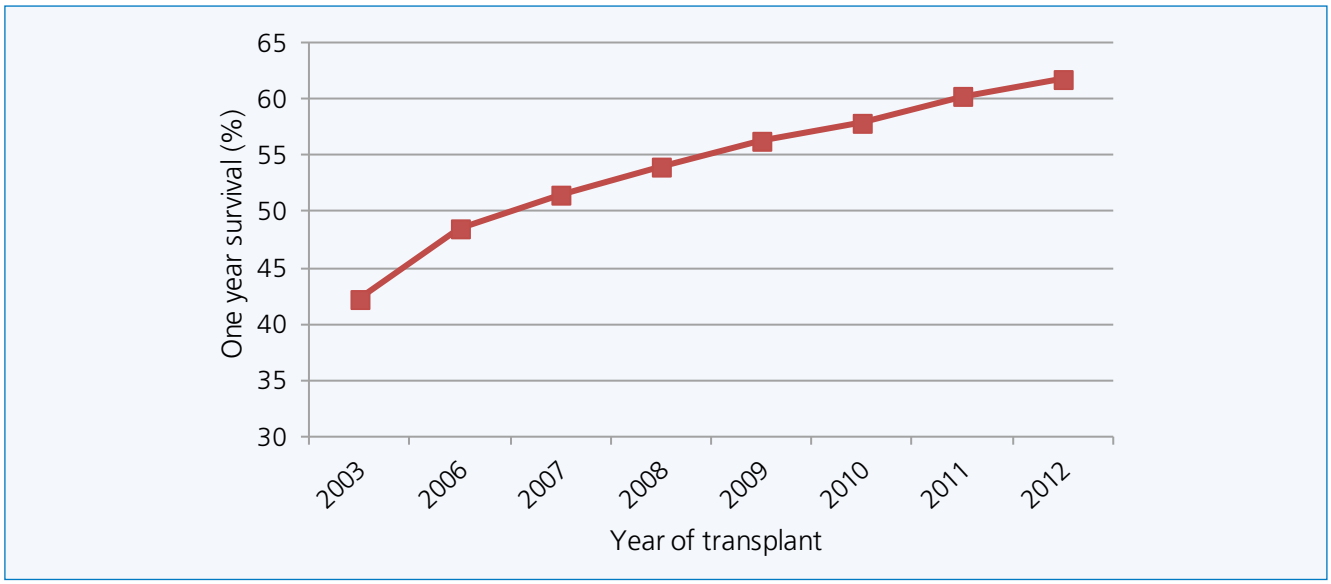
for graft-versus-host disease (GVHD). Overall survival rates at one year were 65% and 73% among recipients of double and single cord-blood units, respectively. Similar outcomes in the two groups were also observed with respect to the rates of disease-free survival, neutrophil recovery, transplantation-related death, relapse, infections, immunologic reconstitution, and grade II–IV acute GVHD. However, improved platelet recovery and lower incidences of grade III and IV acute and extensive chronic GVHD were observed among recipients of a single cord-blood unit.

The study concluded that, among children and adolescents with haematologic cancer, survival rates were similar after single-unit and double-unit cord blood transplants; however, a single-unit cord blood transplant was associated with better platelet recovery and a lower risk of GVHD.

Improved patient outcomes following stem cell transplantation

The Strategic Forum's 2010 report described the well-established historic trend towards improving patient outcomes after unrelated donor stem cell transplantation. Figure 8 shows this long-term trend continuing. Overall, outcomes after (well-matched) unrelated donor transplants are approaching those observed with related donors. This trend is observed in patients younger and older than 50 years. Improvements in HLA-matching techniques, with consequently better donor selection, better overall patient selection for transplantation, and improvements in supportive care are the likely explanation for this trend.

Figure 8: Overall one year survival following unrelated donor stem cell transplantation[34]



34. Worldwide trend data, acute leukaemia, CML and MDS, from CIBMTR (2014). Survival numbers are means of all transplants performed over 2 to 4 year periods, ending in the year shown. Note that late transplant related mortality and death from relapse beyond one year are not included in this analysis.

In this report, we summarise data published after 2010 in order to update and more accurately capture the outcomes being achieved currently in children and adults receiving adult and cord blood-derived stem cell transplants. Data sources comprised published reports of clinical trials as well as retrospective analyses of patient outcomes recorded in BSBMT and Eurocord databases. These reports are listed as part of our health economic assessment in Appendix Two. UK patient outcome data from the most recent report from the BSBMT to specialist commissioners[35] are summarised in Table 3.

Table 3: Patient outcomes by transplant type

	Overall survival at 5 years (%)	
	Unrelated adult donation	Cord blood donation
Paediatric patients	70	69
Adult patients	41	34

Haploidentical transplantation

In refreshing its recommendations on unrelated donor stem cell transplantation, the Oversight Committee has paid close attention to developments in the field of haploidentical stem cell transplantation. These donations, derived from partially-matched family donors, have the potential to reduce the requirement for stem cells from unrelated donors, particularly for patients from ethnic minority and mixed-race backgrounds where no adult unrelated or cord blood donor exists. Almost all patients have an available related donor with whom they share a single HLA haplotype (i.e. a haploidentical donor). Early attempts to use T-cell replete grafts from haploidentical donors using conventional preparative regimens were associated with unacceptable rates of graft-versus-host disease (GvHD) and graft rejection. Prior attempts to overcome these obstacles entailed costly *ex vivo* T-cell depletion, often combined with intense preparative regimens.

Recently, an alternative approach to haploidentical stem cell transplantation has been developed, which uses a T-cell–replete graft in combination with post-transplantation cyclophosphamide to prevent GvHD and graft rejection. This experimental approach has demonstrated promising initial results, including acceptable rates of non-relapse mortality and severe GvHD[36] although there are reports of a higher than anticipated relapse risk. However, randomised trials to compare longer term outcomes with alternative donor sources have yet to report, and given the short follow-up to date the BSBMT consensus guidance on donor selection currently recommends that haploidentical donors should only be considered in the absence of unrelated donors matched at 10/10 or 9/10 alleles or a suitable cord blood unit.

35. BSBMT 5th Report to Specialist Commissioners. The outcome of haematopoietic stem cell transplantation: an analysis of registry data for UK transplants performed 2006-2011 inclusive, and a detailed analysis of transplant activity and outcomes in 2012.
36. Bashey A *et al.* (2013) T-cell–replete HLA-haploidentical haematopoietic transplantation for haematologic malignancies using post-transplantation cyclophosphamide results in outcomes equivalent to those of contemporaneous HLA-matched related and unrelated donor transplantation. J Clin Oncol. 31:1310-1316.

The timing of cord clamping

In 2011 a randomised trial showed that delaying cord clamping by over 3 minutes resulted in increased haemoglobin concentration and iron stores in the newborn[37]. A systematic review by the Cochrane Library[38] published in 2013 confirmed these findings, noting additionally that babies who had later cord clamping had a small increased risk of jaundice requiring phototherapy. The Royal College of Obstetricians and Gynaecologists subsequently reiterated its recommendation that the umbilical cord should not be clamped earlier than is necessary.

Procedures used by NHSBT and Anthony Nolan for cord blood collection are designed to ensure there is no possibility of interfering with the birthing process. Accordingly, a survey was undertaken at six collection sites to determine whether any future move towards longer delays in cord clamping might affect stem cell collection yields. This review of 760 deliveries found that cord clamping after 3 minutes was rare (less than 2% of deliveries), and that there was no significant relationship between cord clamping time and collected volume or nucleated cell content. Recent NICE guidance has recommended clamping at least one minute after delivery. There is anecdotal evidence that this is beginning to influence the mother's choice in favour of delayed clamping and consequently midwife practice, and NHSBT and Anthony Nolan are monitoring the impact of any changes in obstetric practice on stem cell yields.

Recommendation

Anthony Nolan and NHSBT should work with midwives and community groups with direct access to families, especially those from ethnic minorities, in order to raise awareness of the medical benefits of unrelated donor stem cell transplantation.

37. Anderson O *et al.* (2011) Effect of delayed versus early umbilical cord clamping on neonatal outcomes and iron status at 4 months: a randomised controlled trial. BMJ: 343: 7157.
38. McDonald SJ, *et al.*: The effect of timing of umbilical cord clamping of term infants on maternal and neonatal outcomes. Cochrane Review, Issue 7 (2013).

Next generation DNA sequencing for allelic-level HLA typing

Recent developments in next-generation sequencing (NGS) offer the imminent prospect of cost-effective and high-throughput HLA typing to obtain unambiguous, phase-resolved HLA sequences in a single assay. Furthermore, NGS has the power to provide information about lesser known HLA regions, which may lead to discoveries that improve transplant outcomes. These platforms therefore offer the potential to improve patient outcomes, and to further increase donor registry and cord blood utilisation, by providing unambiguous (allelic-level) HLA-types in a cost-effective manner (see Figure 9).

Figure 9: HLA nomenclature and typing resolution

Four levels of HLA typing are often distinguished – low, medium (or intermediate), high and allelic. As resolution increases, the ambiguity of the result diminishes. In the example below, a medium resolution HLA type is inferred to include five different alleles. High resolution typing reduces this ambiguity to two alleles. Allelic level HLA typing is the only means of unambiguously distinguishing between alleles as defined by a unique DNA sequence.

HLA Typing Resolution	Interpretation
Low	A*30:01 - 30:92
Medium	A*30:02/10/12/25/33
High	A*30:02/33
Allelic	A*30:02

The majority of adult volunteer donors worldwide are typed at medium resolution. As a result, transplant centres require that further typing of selected donors is undertaken in order to confirm suitability for transplant. This is often referred to as extended typing (ET). This requirement inevitably delays the provision of donor stem cells. Transplant centres therefore increasingly select unrelated adult stem cell donors from registries listing HLA types at high or allelic level resolution. Given recent data on the importance of allelic-level matching for cord blood transplantation (discussed above), a similar trend might be anticipated for selection of cord blood donations.

Both NHSBT and Anthony Nolan are currently investing in NGS technology (Illumina (MiSeq) and Pacific Biosciences (PacBio RS II) platforms, respectively).

Recommendation

UK stem cell supply organisations should continue to implement next-generation DNA sequencing platforms for unambiguous HLA typing of selected adult donors and cord blood donations. The combined strengths of UK partners in the genomics of histocompatibility with particular reference to transplantation should be exploited to advance the UK Government's Life Sciences strategy.

IT interoperability for donor search and provision

The timely import and export of stem cells from unrelated adult donors and cord blood relies on effective IT interoperability between registries. Within the UK, the alignment of registry activities similarly required IT systems to provide Anthony Nolan with access to anonymised donor information held by the BBMR and WBMDR. To achieve this, NHSBT adopted the Prometheus system which incorporates the European Marrow Donor Information System (EMDIS). This international computer network now covers 34 registries and more than 90% of BMDW-listed donors worldwide.

The EMDIS system continues to evolve and, in 2015, NHSBT is planning to complete implementation of the 'EMDIS-cord' system. This will make UK cord blood donations increasingly visible to international registries, and should significantly increase provision to overseas patients.

The EMDIS-cord system involves the 'mirroring' of cord blood-related data at each registry. This removes the latency of peer to peer interactions as currently required by the EMDIS system for adult donor provision. It also allows registries to apply bespoke donor-selection algorithms to locally-held global data sets. A similar solution is being developed for adult donor provision, likely centred on a limited number of data-holding hubs to which smaller registries might connect. Anthony Nolan and NHSBT are reviewing options for an aligned IT strategy for adult donor provision which will improve stem cell provision by exploiting these developing opportunities.

Recommendation

The Anthony Nolan and NHS Stem Cell Registry should continue to develop and implement IT platforms to facilitate the rapid import and export of stem cell donations.

Whole genome sequencing

In July 2013 the Secretary of State for Health announced the creation of Genomics England, and a flagship project to sequence 100,000 genomes – a £300 million investment over four years. The project has the potential to transform the future of healthcare by helping to develop new and better tests, drugs and treatments. Just as unrelated donor stem cell transplantation may be viewed as a first generation regenerative medicine (see below), it also provides a firm foundation on which to realise many of the benefits envisaged of the 100,000 genomes project. Working daily in partnership with experts in molecular genetics and bioinformatics, stem cell physicians already use genetic information to stratify clinical risks, predict disease susceptibility, and to optimise the administration of drugs to achieve the best possible outcomes in individual patients.

Haematological malignancies are characterised by substantial inter-patient variability in treatment-induced morbidity, a component of which will be genetic. The 100,000 genomes project offers the near-term prospect of better understanding how combinations of genes might act in concert to determine a patient's response to different therapeutic regimens – both drugs and cell therapies. Through its structured and consolidated approach to the treatment of haematological malignancies, with established procedures for data collection and analysis, and drawing on established relationships with histocompatibility and immunogenetics laboratories, the UK provides an effective network of clinics and laboratories to bring novel genetic observations into clinical practice.

Delivering regenerative medicine therapies in the UK

Regenerative medicine is considered by the UK Government to be one of its eight great technologies, given the possibilities of transforming clinical management of degenerative disease for both health and economic benefit. As established by the "Taking Stock of Regenerative Medicine in the UK" report[39] the UK retains a strong position in Europe and globally in the science of stem cell and regenerative medicine, but there are concerns around our ability to translate this to clinical and commercial benefit. On 1st July 2013 the House of Lords Science and Technology Committee published a report on Regenerative Medicine[40] in which they made a number of recommendations, including the establishment of a group tasked with co-ordinating and maintaining momentum in the delivery of regenerative medicine treatments. In its response in October 2013, the UK Government agreed to establish a Regenerative Medicine Expert Working Group (RMEG) to deliver a NHS regenerative medicine strategy and action plan by December 2014.

RMEG, under the chairmanship of Sir Michael Rawlins, is considering a number of issues related to the regulatory environment, commissioning and assessment of these novel products, and the delivery of cellular therapies both for clinical trial and routine clinical practice by the NHS. It is clear that any such delivery will need to leverage existing human and physical infrastructure, resources and capabilities if widespread application of these novel therapies is going to get traction in an already busy and cost constraint clinical environment.

Haematopoietic stem cell transplantation represents the only form of regenerative cell therapy in routine use. As such, it provides a tested and proven model of the value chain required for the delivery of novel cellular therapies from networks of centres of excellence. Donors must be recruited, selected and screened and give appropriate informed consent; cellular tissue must be procured at minimum and acceptable risk to the donor; and the product processed or manipulated and thereafter stored and transported under controlled conditions to the clinical area where it is administered to the patient. The complexity of cell therapy manufacture can be categorised according to the extent of cell manipulation involved.

Category 1: Minimally Manipulated Cell Therapies include standard HSCT from bone marrow, mobilised peripheral blood or umbilical cord blood, but also the preparation of enriched cell populations on the basis of immunological markers such as CD34 or CD133 either for haematopoietic transplantation (homologous use) or other indications where they are classified as medicinal products (heterologous use) – for example to treat post-myocardial infarction.

Category 2: Somatic Cell Therapies in which autologous or allogeneic cells are isolated and cultured for a limited period of time *in vitro* (usually for a matter of days up to a week or two) prior to transplantation to one or a handful of recipients. Examples include EBV-specific cytotoxic T lymphocytes, mesenchymal stromal cells for immunomodulation, or dendritic cells for the treatment of certain forms of cancer. Some Category 2 products may be genetically modified, for example transduction of T cells with modified T cell receptors or chimeric antigen receptors, in order to alter their specificity.

39. Department of Business, Innovation and Skills, Taking Stock of Regenerative Medicine in the United Kingdom. July 2011.
40. House of Lords Science and Technology Committee, Regenerative Medicine Report. July 2013.

Category 3: Stem Cell Lines derived either from *in vitro* blastocysts (human embryonic stem cells) or reprogramming of adult cells (induced pluripotent stem cell; iPS cell). Such cellular lines will proliferate indefinitely in culture and will also differentiate into most if not all of the cell types present in an adult. This affords the prospect of scalability and of a single (allogeneic) donor contributing to the manufacture of multiple cellular products which may be administered to multiple recipients over an extended period of time. UK-lead examples include iPS cell-derived retinal pigment epithelial cells for treatment of macular dystrophy disorders, and iPS cell-derived red cells and platelets.

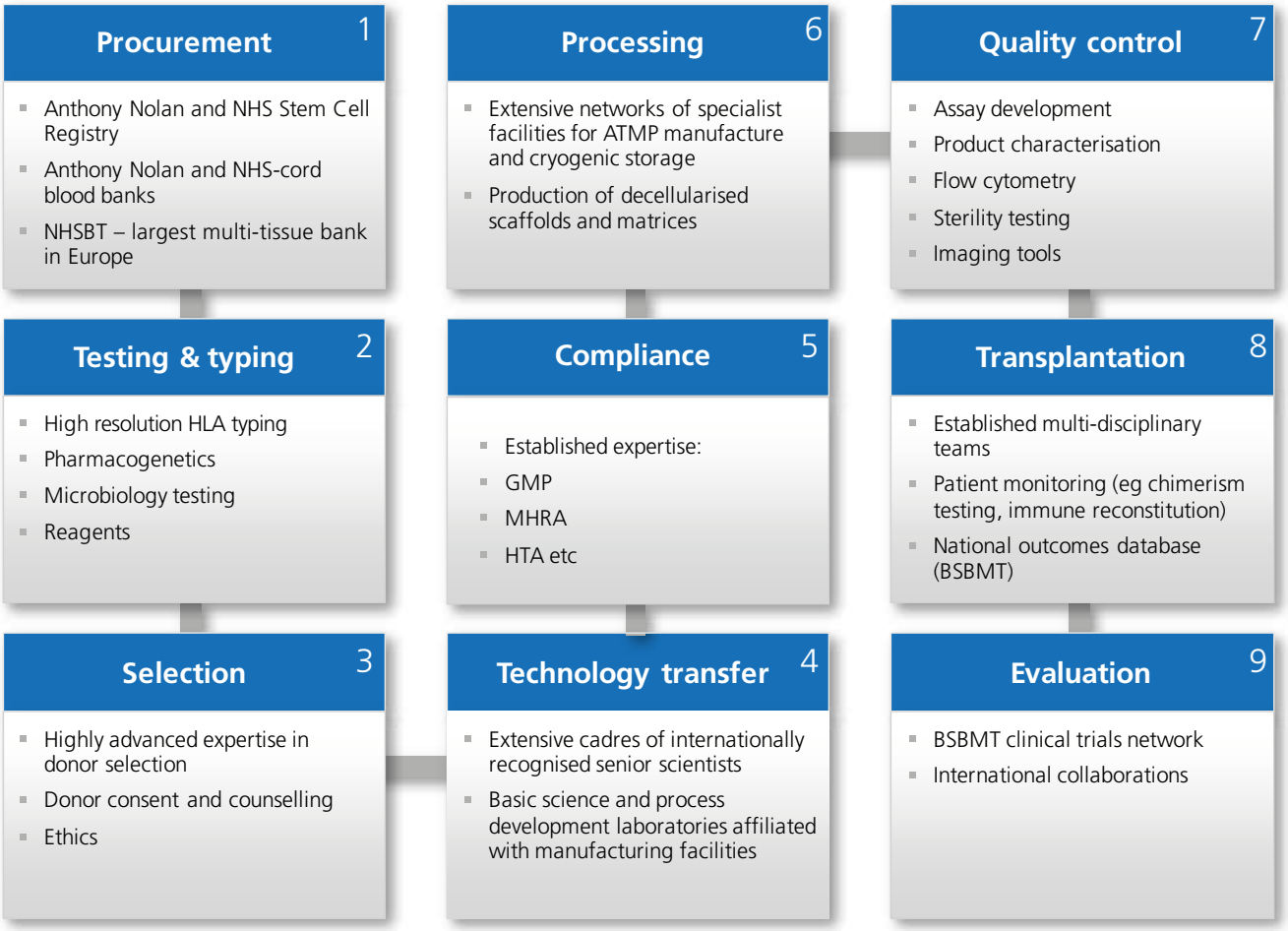
Category 4: Tissue Engineered Products. Human tissues do not consist of single cell suspensions but of complex three dimensional structures involving a variety of cell types and extracellular matrix components. The cell types contributing to such tissue-engineered structures may be derived from any of the above categories. Examples include the decellularised cadaveric human trachea and oesophagus to provide a scaffold which can be re-cellularised with autologous cells used in the treatment of tracheal stenosis.

Category 2 to 4 products are regulated as Advanced Therapy Medicinal Products (ATMPs) and require very significant commercial investment and expertise in order to drive them through to regulatory authorisation and clinical application. Many UK facilities processing HSCT for treatment of bone marrow disorders also product ATMPs for early phase clinical trials.

Mononuclear cells from bone marrow, cord blood or peripheral blood can form the starting material for the manufacture of many of these forms of cellular product. As in HSCT, the key donor selection criterion will be HLA type given that the closer the tissue match between donor (and therefore cell therapy product) and recipient(s) the lower the risk of immunological rejection and the less immune suppressive therapy will be required. In some ways the new generation of cellular therapies are likely to be the ultimate in stratified medicines in that, like HSCT, a degree of immunological matching and tailoring of the clinical therapeutic to the condition of the patient will be required.

It is important therefore that we continue to build on the panels of potential voluntary stem donors and cord blood donations in order to leverage the widest possible breadth of compatible regenerative medicine products for individual patients. It is important that the NHS explores new ways of working with commercial manufactures to facilitate the development of the next generation of cellular therapies. The delivery of these therapies will require suitable infrastructure including procurement services, manufacture or secondary processing facilities, quality assurance systems to GMP grade, regulatory approval, controlled storage and distribution and clinical transplantation including immune suppression management. Much of this infrastructure is already provided by HSCT units in blood services and major teaching hospitals (illustrated at Figure 10).

Figure 10: Summary of the established infrastructure for HSCT which should underpin the delivery of early phase clinical trials for novel regenerative medicine therapies.



Development of existing facilities and clinical networks into Centres of Excellence will be a more cost effective, efficient and rapid approach to delivering the infrastructure required to prove the clinical efficacy of regenerative medicine therapies than attempting to build this infrastructure de novo.

Recommendation

The well established human and capital infrastructure currently supporting regenerative cell therapies for patients with bone marrow disorders should be fully exploited in delivering innovative regenerative cell therapies for other disorders.

Improving stem cell engraftment after cord blood transplantation

Although overall survival after cord blood transplantation is comparable with matched unrelated adult donors, cord blood transplantation is associated with slow engraftment, delayed immune reconstitution, and an increased incidence of opportunistic infections. Compared to adult donations, cord blood donation generally contains fewer stem cells, which home relatively poorly to the bone marrow. A number of promising techniques are now entering clinical trials to improve engraftment and immune reconstitution[41]. Broadly these trials are examining the safety and efficacy of biologics which enhance homing of stem cells to the bone marrow or which can be used to expand cord blood stem cells[42] prior to infusion. These strategies are reviewed briefly below.

Biologics to enhance stem cell homing to bone marrow

The homing defect in cord blood stem cells (and their progeny) is related to the expression of homing receptors and adhesion molecules. Clinical trials underway at time of writing are investigating:

1. ***Systemic infusion of stigaliptin, a CD26 inhibitor.*** Initial outcomes indicate that oral treatment with stigaliptin improves median time to neutrophil recovery (21 days). A multicentre phase two trial has commenced.

2. ***Ex vivo treatment of cord blood donations using prostaglandin E2 or alpha-1,3 fucosyltransferase.*** These approaches aim to enhance stem cell entry to the bone marrow niche by upregulation or fucosylation of homing receptors. In clinical trials, these strategies demonstrated improved time to neutrophil recovery (median 14.5 and 17.5 days respectively).

Ex vivo *expansion of stem cells prior to infusion*

It has been predicted that a 4 fold expansion of stem cells in cord blood donations would allow the majority of banked donations worldwide to be used for adult patient transplantation. There are several approaches to stem cell expansion, and clinical trials generally transplant an unmanipulated donation with an *ex vivo*-expanded donation; the former donation generally engrafts over the long term, while the latter donation contributes to early neutrophil recovery.

Current approaches include exposure or co-culture of cord blood with:

- Notch ligand;
- Bone marrow-derived mesenchymal progenitor cells (Mesoblast);
- Tetraethylenepentamide (StemEx, Gamida Cell);
- Nicotinamide (NiCord, Gamida Cell).
- StemRegenin1 (Novartis)

Delaney *et al*. reported that TNC expansion averaged 562 fold and CD34+ cell expansion averaged 164 fold after notch-mediated expansion[43]. Expanded cells in several clinical trials have contributed to early haematological recovery. For example, in a clinical trial of Nicord, median time to neutrophil engraftment was 11 days, and hospital stay was reduced from 40 to 23 days.

41. Reviewed by Danby R and Rocha V (2014). Improving engraftment and immune reconstitution in umbilical cord blood transplantation. Frontiers in Immunology 5:68.
42. Here, the term 'stem cells' is intended to encompass a range of haemopoietic progenitor cells.
43. Delaney C *et al.* (2010) Notch-mediated expansion of human cord blood progenitor cells capable of rapid myeloid reconstitution. Nat Med 16:232-236.

Our understanding of how cord blood stem cells home, divide and differentiate is growing rapidly, and candidate technologies for *ex vivo* graft manipulation are emerging. The potential to utilise low dose cord blood donations to improve patient outcome is significant, but larger and longer-term clinical studies are required. Ongoing clinical trials generally exclude the UK. The absence of an appropriate clinical trials infrastructure in the UK to allow NHS patients to benefit quickly from these (and other) discoveries is discussed next.

Translating scientific discovery into improved patient outcomes

Stem cell transplantation remains a complex procedure and approximately 50% of patients die following a transplant due to complications or resistant disease. In the past two decades an extensive portfolio of new drug and cellular treatments with capacity to substantially improve the outcome of transplant patients has been developed. Before such therapeutic advances can be embedded into routine clinical practice their safety and efficacy must be assessed. This can only be done in the context of a well developed clinical trial network of sufficient size to ensure rapid recruitment.

Recognising this urgent clinical need and the strategic opportunities offered by the UK's excellence in basic science and the coherent structures afforded by the NHS, the Strategic Forum recommended the establishment of a clinical trials network to allow UK patients to benefit from ongoing developments in stem cell transplantation. Three years later, no such network exists in the UK and consequently patients continue to be denied rapid access to new, potentially life-saving therapies. At the same time there is no systematic process allowing prospective evaluation of novel transplant technologies in regenerative medicine where the UK has unique strategic strengths. The Oversight Committee wishes to reinforce the ongoing need to establish a national stem cell transplantation clinical trials network.

National and international context

The importance of ensuring the rapid assessment of novel drug and cellular therapies has been highlighted by both national governments and the pharmaceutical sector. Not only does the current lack of a clinical trials infrastructure prevent patients from benefiting from treatment advances in a timely manner, but it also represents a rate-limiting step for the rapid development of new drugs by the pharmaceutical sector. In 2010 the Prime Minister identified Life Sciences as a major engine of growth in the UK economy. Highlighting the UK's strategic strengths in Life Sciences he identified the importance of developing a translational infrastructure which would allow the economic potential resident within the NHS to be fully realised. In the same year, the Strategic Forum recommended the establishment of a clinical trials network to hasten the development of new drug and transplant technologies in stem cell transplantation. Such an initiative would establish a uniquely effective international trials network attractive to pharmaceutical and biotechnology companies and thus make a major contribution to UK inward investment and growth.

Current UK and international models of early phase clinical trials networks

The coherent structure of the NHS and its strong track record of delivering advanced medical technologies to a large patient population coupled with its world class science base gives the UK unique strategic advantages in the delivery of clinical trials. This is reflected in the UK being one of the biggest recruiters to late phase clinical trials but, in common with the rest of the developed world, our ability to deliver early phase clinical trials lags far behind.

The current situation reflects two major deficits. First, the UK lacks a central regulatory hub to facilitate the rapid work up of often complex early phase trials. Second, the UK lacks a network of research nurses with the time and expertise required to recruit patients.

The UK's unique opportunity to develop globally competitive early phase trials has recently been recognised by a number of funders. In 2012 for example, Leukaemia and Lymphoma Research opened a Trials Acceleration Programme (TAP). This provides an excellent 'proof of principle', with rapid progress made in creating an infrastructure capable of rapidly accessing new drug, antibody and transplant therapies which has allowed more than 400 patients to be recruited to a portfolio of early phase studies since 2012. Crucially all studies have integrated biological endpoints thereby maximising the scientific value of the studies and permitting the identification of molecular biomarkers of response. As a result of its success to date the TAP initiative has already been highlighted by Novartis and other global pharmaceutical companies as a uniquely attractive national resource.

Perhaps the best example of a highly effective clinical trials network in stem cell transplantation is provided by the US Blood and Marrow Transplant Clinical Trials Network. The BMT CTN is a collaboration between NMDP (the US National Marrow Donor Program), the CIBMTR (US Center for International Blood and Marrow Transplant Research) and EMMES (a contract research organization) which has randomised more than 4,000 patients into prospective transplant trials in the last decade. In contrast, in the UK fewer than 5% of transplant patients are entered into prospective clinical trials of any kind. The Clinical Trials Committee of the British Society of Blood and Marrow Transplantation is strongly supported by the UK transplant community and has a good track record in the delivery of retrospective studies of transplant outcome but does not have the infrastructure or staff required to support prospective randomised trials. Nonetheless the CTC does have the enthusiastic support of major transplant centres and represents an appropriate and informed forum for formulating future studies and a strong base on which to build a prospective trials network.

By integrating clinical trial activity with the UK's world class stem cell biology teams, an internationally competitive transplantation and regenerative medicine trials programme would be established. Not only would the recommended network play a major role in improving transplant outcome but, since medical technology clusters have been shown to be an extremely effective mechanism of generating inward investment, it would also serve as an effective engine of UK growth by confirming our global leadership in clinical trials and the Life Sciences.

Recommendation

A national stem cell transplantation trials network should be established to facilitate and promote high quality prospective, randomised and controlled early phase clinical trials of new molecular and cellular therapies for patients with haematological malignancies.

Basic science laboratories should be encouraged to participate in relevant clinical trials to derive novel information on predictive biomarkers, in this way developing a stratified and personalised approach to stem cell transplantation.

Part Three: The Stem Cell Supply Chain

Summary

In order to develop a robust stem cell strategy for the next decade, it is necessary to gain a clear idea of the incremental costs and benefits that accompany various service models. The NHS has finite resources and these must be channelled as effectively as possible to ensure that services represent value for money in terms of clear healthcare benefits.

Here we reflect on the dramatic success of the strategy to create a 'fit panel' of young donors typed at high resolution. We advocate the continuation of this strategy towards an UK 'fit panel' of 150,000 donors. We have revisited the Strategic Forum's recommendation to develop a UK cord blood inventory of 50,000 donations. Our health economic analysis continues to show a strong case in terms of cost per QALY gain. We affirm the existing strategy that the UK should work towards an inventory of 50,000 donations, but we recommend that this should be achieved in two phases. In the first phase, Anthony Nolan and NHSBT should continue to increase the current clinical inventory of around 16,500 donations to 30,000 donations by 2018. Towards the end of this phase, there should be a further review to assess the rate of inventory utilisation and current stem cell transplant practice. Given inventory utilisation rates in the order of 1% *per annum*, phase two would see cord blood sales income fund the incremental growth of the inventory to 50,000 donations. Given utilisation rates significantly less than 1%, the inventory would be maintained at 30,000 donations, and price reductions offered to NHS customers.

We have subjected these recommendations to a detailed health economic assessment, using the same analytical approach as set out in the 2010 report. We have confirmed a significant level of unmet demand in the UK for optimally-matched stem cell donations, driven in part by advances in clinical transplantation which now numbers 355 patients each year. Of these, around 257 (72%) would be able to proceed to transplant if there were to be a UK cord blood inventory of 30,000 donations, 298 patients (83%) benefitting from an inventory of 50,000 donations. We find that the incremental cost per QALY between the status quo and inventories of 30,000 donations and 50,000 donations is around £10,400 and £9,400 respectively, substantially below the £15,000 threshold used by DH to evaluate the effectiveness of NHS spending decisions, and a significant improvement in the cost per QALY of £27,000 given in the 2010 report. Moreover, we find that the cost per additional QALY resulting from expanding the fit panel to 150,000 donors is of the order of £8,500.

Improving the provision of stem cells from unrelated adult donors

Around 85% of patients without a matched sibling donor receive a graft from an unrelated adult donor (rather than cord blood or haploidentical donor). This proportion is unlikely to change significantly in the next few years. Recognising the ongoing importance of unrelated adult donors, the Strategic Forum recommended a series of measures to decrease the time taken to provide well-matched adult donor stem cells. In brief they recommended:

- The streamlining of UK stem cell registry activities;
- The focussed recruitment of young, ethnically-diverse donors;
- The high-resolution HLA typing of 75,000 donors.

The UK's 'fit panel' now stands at around 60,000, and NHSBT, WBMDR and Anthony Nolan continue to focus recruitment and high resolution HLA typing towards young male donors. The effectiveness of the strategy (discussed in Part One) is evidenced by:

- Fit panel donors are eight times more likely to go on to be a final donor compared to other registry volunteers;
- 80% of requests for donor samples for confirmatory HLA typing are fulfilled within 15 days compared to 35% in 2010.

Based on the rate of issue of 'fit panel' donors, we have estimated the additional benefits of extending the panel (Table 4)[44]. Acknowledging that this extrapolation makes a number of assumptions,[45] it might be estimated that a fit panel of 150,000 young male donors would result in an additional 90 lives saved each year.

Table 4: An estimation of additional lives saved through expansion of the UK 'fit panel'

Fit Panel Size	Additional Fit Panel Donors	Additional Fit Panel Donations	Additional Market Share	Total Market Share	Additional Lives Saved
45,400	–	–	–	34.7%	–
75,000	29,600	51	1.3%	36.1%	26
100,000	54,600	94	2.5%	37.2%	47
120,000	74,600	129	3.4%	38.1%	64
150,000	104,600	181	4.7%	39.5%	90
200,000	154,600	267	7.0%	41.7%	134

44. Data from Anthony Nolan.
45. Limitations of this estimations include:
    - Based on 'fit panel' size and utilisation as at April 2014;
    - Assumes the utilisation rate of 'fit panel' donors for UK-to-UK provision over the last 2 years will apply in the future;
    - Assumes the number of fit panel donors selected by UK transplant centres would grow in proportion with the size of the panel (i.e. does not take into account the possible impact of improved provision of cord blood donations);
    - Assumes a post-transplant survival rate of 50%.

Health economic evaluation of expanding the UK's 'fit panel'

We have also carried out an indicative cost effectiveness analysis, based on a simplified version of the analysis for expansion of the cord blood bank. This suggests that the cost per additional QALY resulting from expanding the 'fit panel' from 45,000 to 150,000 is of the order of £8,500.[46] For the purposes of this analysis, we have based the QALYs gained following unrelated adult donor transplantation on BSBMT's 5th report to Specialist Commissioners (2014).

The evidence shows that the UK's strategy to invest in the creation of a 'fit panel' to have been hugely successful. Moreover, with the advent of next generation HLA typing technologies, the opportunity exists to build the fit panel more cost effectively, and to HLA-type donors with even greater resolution. We have noted that Germany has 1.2 million donors typed at high resolution which ensures that they can meet the needs of 90% of German patients.

Recommendation

The Anthony Nolan and NHS Stem Cell Registry should continue to expand the UK's 'fit panel' to 150,000 donors.

There should be a continued emphasis on recruiting male, ethnically-diverse donors aged predominantly between 16 and 30.

All donors should continue to be typed at high or allelic-level resolution.

Optimising the UK cord blood inventory

In reviewing the UK strategy for cord blood banking, the Oversight Committee has reflected on the various factors which need to be balanced in order to maximise cost-effectiveness. The key factors are:

- Clinical trends in donation selection including BSBMT consensus guidance;
- The influence of allelic-level matching on optimal inventory size;
- Inventory utilisation and income generation through cord blood provision.

Recent trends in the use of UK-sourced cord blood donations

In 2011 the UK accounted for around 10% of the cord blood donations used in UK transplants, with the rest being imported. This year (2014) more than 25% of UK cord blood provision is predicted to come from the UK. This trend has been driven by increased confidence in the quality of UK-sourced cord blood donations, and by measures taken to streamline processes and reduce costs. A UK cord blood donation now costs around £16,000 to provide, compared to an average (price) of around £30,000 for an overseas donation. The use of UK donations rather than imported donations represents an avoided cost of around £270,000 *per annum* in 2014.

46. Based on costs provided by NHSBT; information on other assumptions is provided at Appendix Two.

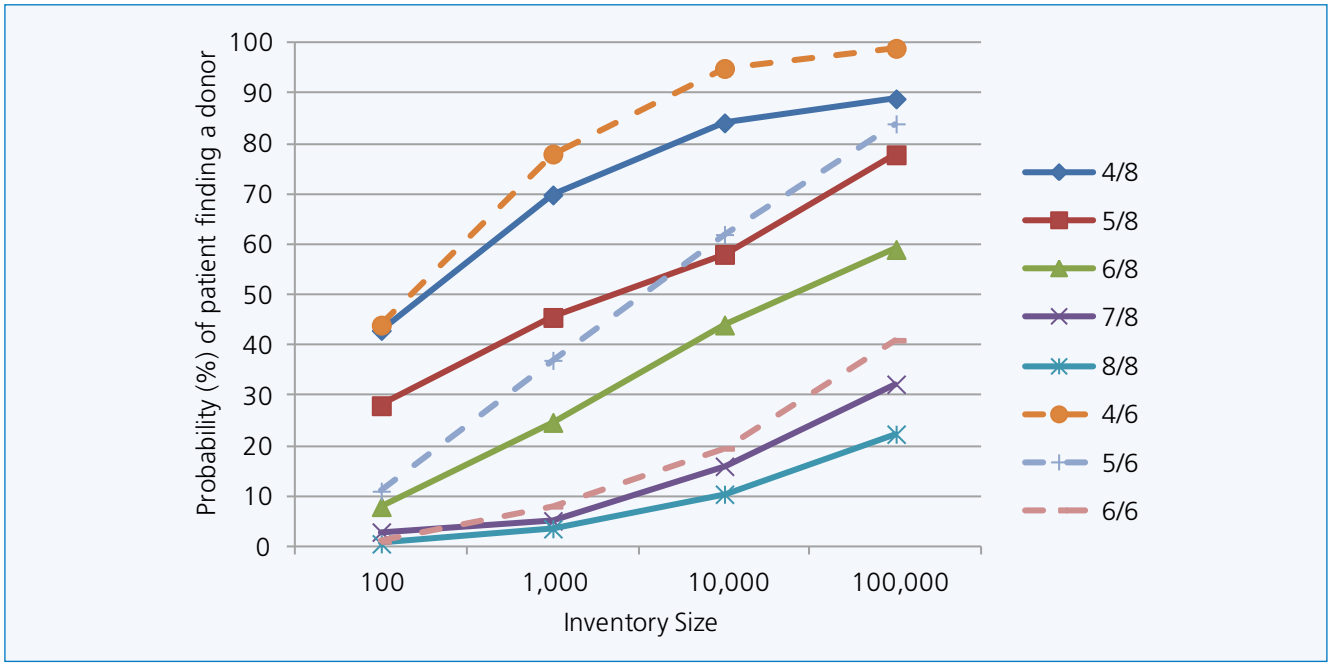
The improved provision of cord blood remains key to our ambition to improve outcomes for BAME patients with haematological malignancies. A recent study by Lown *et al.*[47] suggests that the strategy is starting to improve access to transplant for BAME patients, with around 60%[48] now able to find an acceptably matched donor (data reviewed in Part One). Importantly, the needs of 21% of BAME patients were met with a cord blood transplant compared to around 4% of white northern European patients.

Allelic-level matching for cord blood transplantation

Recent evidence on the benefits of allelic-level matching for cord blood transplantation is considered in Part Two.

In 2010, based on information available the time, the Strategic Forum made recommendations on optimal cord blood inventory size based on matching donor-recipient pairs at an allelic-level for HLA-A, B and DRB1.[49] It was estimated that an inventory of 50,000 cord blood units would be able to treat an additional 380 patients *per annum* against an unmet need of 440 patients. The adoption of stricter matching criteria for cord blood selection will reduce the number of cord blood donations available for individual patients; this is shown diagrammatically in Figure 11.

Figure 11: Relationship between inventory size and probability of finding a match



47. RN Lown *et al.* (2013) Presentation to the American Society for Haematology.
48. In 2010, the Strategic Forum estimated that around 40% of BAME patients would find a well-matched donor.
49. Based on Querol, S *et al.* (2009). Cord blood stem cells for haemopoietic stem cell transplantation in the UK: how big should the bank be? Haematological, 94:536-541.

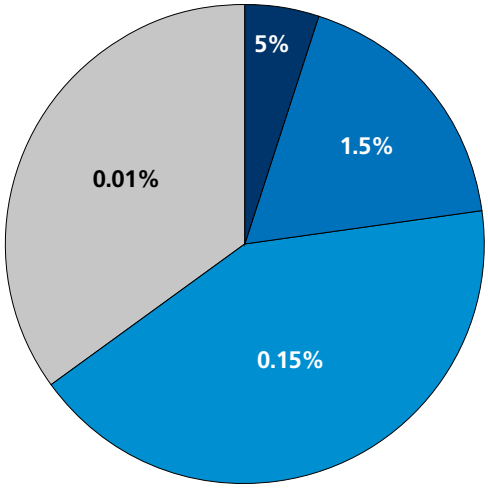
Below, we have assimilated the impact of these recent observations in reviewing the optimal size of the UK's cord blood inventory.

Inventory composition and utilisation

In Part One we described how the cord blood inventory can be segmented into clinical and research inventories. The clinical inventory comprises only those donations containing a dose of stem cells sufficient for transplantation purposes. This can be further segmented (donation grades A, B and C) according to cell dose. Utilisation rates for each cell dose are used to model the impact of different cord blood banking strategies (see below) taking due account of the likely impact of planned initiatives to type donations at allelic level, and to achieve improved visibility with international registries through implementation of EMDIS-cord (discussed in Part Two). Figure 12 compares the utilisation of the 50,000 donation inventory originally recommended by the Strategic Forum with the utilisation of a 30,000 donation clinical inventory recommended below. This emphasises the importance of inventory composition in optimising cost-effectiveness and patient benefit.

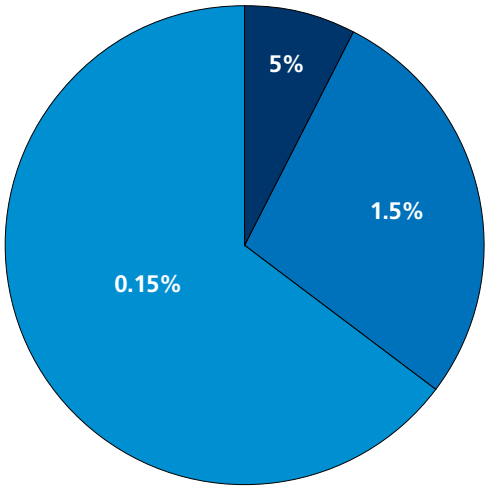
Figure 12: Cord blood inventory composition and utilisation

Strategic Form recommendation: 50,000 donation inventory



- Utilisation estimated to be around 0.54%
- 272 donations issued *per annum*

Revised recommendation (phase 1): 30,000 donation operational inventory



- Utilisation estimated to be around 0.94%
- 285 donations issued *per annum*

Key:

- Grade A donations: post-processing cell dose >19 x 10^8 TNC
- Grade B donations: post-processing cell dose 14-19 x 10^8 TNC
- Grade C donations: post-processing cell dose 9-14 x 10^8 TNC
- R&D donations: post-processing cell dose <9 x 10^8 TNC

It is useful to benchmark estimated inventory utilisation rates against those achieved by other cord blood banks. However, comparisons are complicated by the different composition of bank inventories; many banks contain a predominance of low quality donations which are unlikely to be selected for donation. Table 5 summarises WMDA's global utilisation rate for cord blood banks.[50]

Table 5: WMDA global cord blood inventory utilisation rates

	2010		2012	
	Total inventory	% utilisation	Total inventory	% utilisation
< 9.0 x 10^8 TNC	214,200	0.04%	205,373	0.08%
9.0-12.4 x 10^8 TNC	168,300	0.34%	190,079	0.21%
12.5-14.9 x 10^8 TNC	61,200	1.19%	76,620	0.56%
15.0-19.9 x 10^8 TNC	51,000	2.54%	62,515	1.32%
>20.0 x 10^8 TNC	15,300	9.01%	20,164	5.63%
Global inventory	510,000	0.80%	554,751	0.53%
Global inventory of units >9.0 x 10^8 TNC	295,800	**1.34%**	349,378	**0.80%**

Proposed inventory growth and financial sustainability

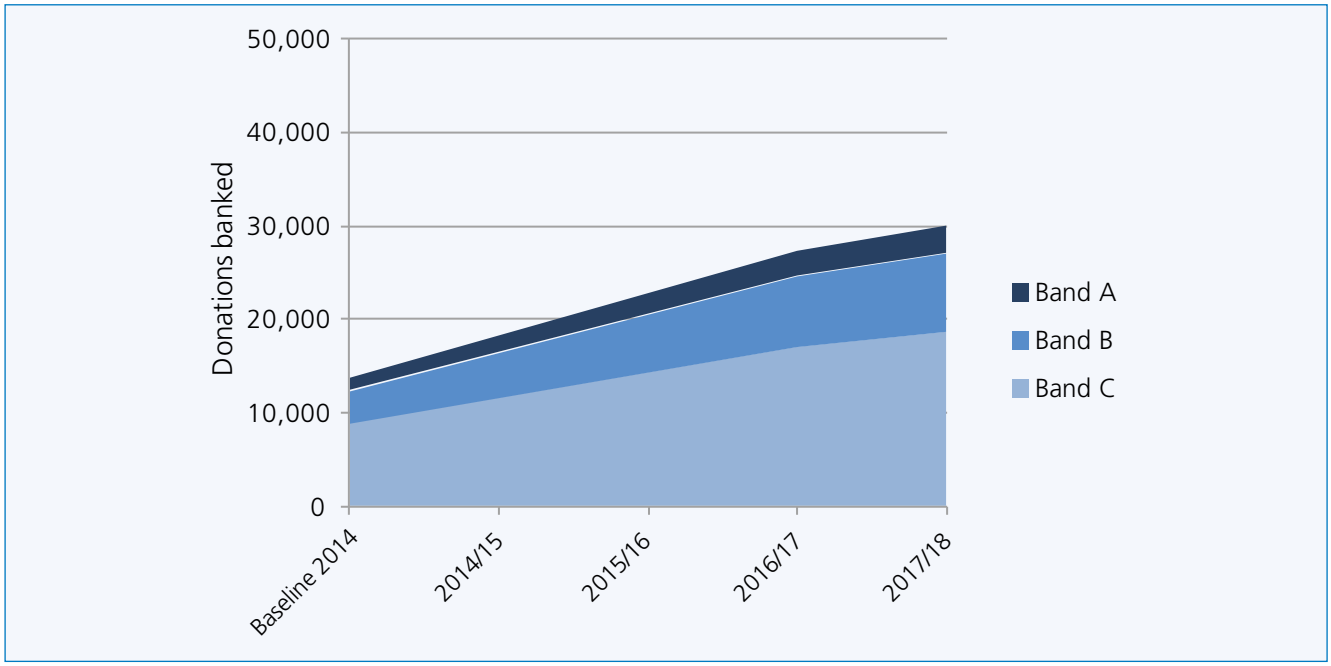
In working towards a clinical inventory of 50,000 donations to best meet the needs of UK patients (see below), we recommend a two phased approach. Phase one, sustained in part through continued central funding, would see Anthony Nolan and NHSBT continue to increase a clinical inventory of around 16,500 donations (April 2015) to 30,000 donations by 2018. In phase two sales income would fund continued growth towards a clinical inventory of 50,000 donations. The feasibility of phase two growth critically depends on the annual rate of inventory utilisation and the income derived through the provision of cord blood to UK and overseas transplant centres.

We have therefore modelled the cord blood collection and banking rates required to develop a clinical inventory of 30,000 donations focussing on measures to achieve overall utilisation of the inventory in the region of 1% *per annum* by 2018. The required growth rate, shown diagrammatically at Figure 13, is achievable at current activity levels at NHSBT and the Anthony Nolan. Broadly, NHSBT would bank 20,000 donations, and Anthony Nolan would bank 10,000 donations. We use the associated costs and utilisation rates to derive the health economic analysis shown below.

50. WMDA = World Marrow Donor Association. Data provided by S. Querol, 2014.

A key objective for the UK's cord blood banking strategy must be to achieve the long-term financial sustainability required to grow the inventory from 30,000 donations to 50,000 donations beyond 2018. At current NHS prices, an inventory of 30,000 donations, achieving 1% utilisation *per annum*, would generate around £4.5m *per annum* in sales income. After 2018, the cost of maintaining three to four collection sites, and of banking sufficient cord blood donations to improve inventory quality and to off-set inventory attrition is estimated to be around £3m *per annum*. Further economies of scale might be achieved by consolidating cord blood processing and/or storage activities, but due consideration would need to be given to operational resilience. Thus, continued income-funded growth beyond 2018 looks broadly reasonable, although the rate of growth will be dependent on inventory utilisation.

Figure 13: Proposed inventory growth towards at target of 30,000 donations by 2018



Importantly, we recommend a review of cord blood banking in 2017 before committing further resources towards increasing the inventory beyond 30,000 donations. Should utilisation rates be significantly less than 1% in 2017, due to medical or technical advances, then the recommendation would be to reduce the price of cord blood offered to NHS customers, in this way generating sufficient income to maintain (but not expand) the inventory at 30,000 donations.

Below, we summarise our health economic analysis of cord blood transplantation in the UK, focusing on an inventory of 30,000 donations. The analysis for expanding to inventories of both 30,000 and 50,000 donations is given in detail in Appendix Two.

The health economics of cord blood transplantation in the UK

Table 6 sets out the rationale underpinning the health economic analysis summarised here and detailed in Appendix Two.

Table 6: Health economic assessment of the proposed strategy for cord blood banking in the UK

Step	Rationale
1. Estimate the unmet demand for optimally-matched donor stem cells as patients: • without an acceptable adult donor • who deteriorate while waiting for transplant • with a sub-optimal adult donor match.	Consider BSBMT consensus on selection criteria for adult and paediatric patients with malignant and non-malignant disorders.
2. Calculate the number of additional lives saved via a cord blood clinical inventories of 30,000 donations.	Consider relationship between inventory size and matching probability for white northern European and BAME patients. We assume that the cord blood inventory will achieve an annual utilisation rate of 1% *per annum* by 2018.
3. Calculate the net QALY gain following an unrelated stem cell transplant for adult and paediatric patients with malignant and non-malignant disorders.	Literature review and expert medical opinion on patient outcomes versus alternative treatment options. Benchmark against Office for National Statistics data.
4. Estimate the extra cost of a stem cell transplant versus alternative treatments.	Published data on transplant unit-associated costs: • personnel, facilities, medicines • purchase of stem cell • transplant and follow-up • consider infrastructure costs • subtract cost of alternative treatment.
5. Estimate the cost of providing stem cells from a cord blood clinical inventory of 30,000 donations.	• Size versus fixed costs • Annual utilisation • Genetic diversity • International benchmarks.
6. Determine cost per QALY from expanding the cord blood inventory to 30,000 donations.	Derived from 2 to 5 above.
7. Undertake sensitivity analyses.	Determine the extent to which the cost per QALY may be influenced by individual assumptions and estimates.
Key: QALY = quality adjusted life year	

Step 1 – Estimate unmet demand for cord blood stem cells in the UK

In 2012, 875 unrelated adult stem cell transplants were performed in the UK.[51] An analysis among a group of 401 patients[52] found that, for every 100 unrelated adult donor transplants, there are a further 30 patients for whom no well-matched unrelated adult donor can be found. From this, it can be estimated that the total number of patients considered for unrelated stem cell transplantation is in the order of 1140 *per annum*.

An expanded cord blood inventory would increase the number of these patients able to receive a transplant, as well as being able to help other patients. This unmet demand stems from:

- Failure to find a suitably matched adult donor;
- Patient deterioration while waiting for an adult donation to be provided;
- Less than optimal outcomes for patients who receive a mismatched adult donation or a haploidentical donation.

Table 7 summarises the unmet demand for well matched unrelated donor stem cells in the UK, and then, based on BSBMT guidance on donor selection preferences, shows the number of those patients likely to benefit from a cord blood inventory of 30,000 donations.

Table 7: Summary of unmet demand for unrelated donor stem cells, and the level of demand met by a cord blood inventory of 30,000 donations

	Unmet demand: UK patients	Patients benefiting from 30,000 cord blood inventory
No matched adult donor	140	79
Patients deteriorating while waiting	138	117
Patients receiving sub-optimal adult matches	50	42
Patients receiving haploidentical transplants	23	19
Total unmet demand	**351**	**257**

The additional UK patients treated annually from a cord blood inventory of 30,000 donations would be around 257 (out of a potential 351).

Assuming that, on average, 1.59[53] cord blood donations are used per transplant, this would amount to around 400 cord blood donations per annum.

51. British Society of Blood and Marrow Transplantation: 5th report to specialist commissioners.
52. Lown *et al.* (2013). Presentation to the American Society of Haematology.
53. From information provided by Anthony Nolan on cords provided for transplant in 2013.

Step 2 – Calculate the number of additional lives saved via a cord blood inventory of 30,000 donations

An expanded inventory will have a broader range of HLA types and can therefore provide a greater number of patients with a match. Up to a point, we expect this to raise the number of units issued each year, and to increase the utilisation of the cord blood inventory. With the decision to add only donations containing over 14 x 10^8 TNC, as the inventory is built up, the proportion of donations with a high dose will also grow. We estimate that an inventory of 30,000 donations built up in this way will achieve a utilisation rate of 1%.

We use this utilisation rate to estimate how many donations will be issued as the inventory is built up, and then for the lifetime of the donations in the bank. We then count the life-years saved as a result of the domestic transplants that these supply.

The revenue gained by the sale of donations for export is subtracted from the cost of developing the inventory.

Step 3 – Calculate the net QALY gain following an unrelated stem cell transplant for adult and paediatric patients with malignant and non-malignant disorders

In gauging the benefits of unrelated donor transplantation, the standard measurement is the Quality-Adjusted Life Year (QALY). The purpose of the QALY is to provide a more nuanced picture of the value of a therapy by considering not only the net gains in terms of overall survival, but also the improved quality of life it may bring to the patient. This involves a range of factors and varies considerably.

The methodology used for QALY gain calculations was as follows:

1. Obtain published survival information on cord blood transplant patients;
2. Extrapolate long-term survival rates from this to identify the life expectancy of transplant patients;
3. Make adjustments for quality of life to derive the number of QALYs expected following a transplant;
4. Carry out these calculations for similar patients who do not receive a transplant;
5. The QALY gains from a transplant is defined as the difference between QALY expectancy with a transplant and QALY expectancy without a transplant.

From this, we obtain an average QALY gain per unrelated donor stem cell transplant of 7.3

Step 4 – Estimate the net cost of performing a cord blood transplant

In order to deduce the cost per QALY, it is first necessary to estimate the net cost of a cord blood transplant (i.e. full cost less the cost of an alternative treatment). There are two elements to this, namely the cost of providing the donation, and then the cost of the clinical procedure including patient follow-up.

In Appendix Two, we estimate the approximate costs of transplantation, including post-transplant care. This has been based on the methodology used by van Agthoven *et al*. (2002),[54] but some of the components have been updated to reflect current UK cord blood transplant practice.

We estimate the total cost of a single cord blood transplant to be around £98,200 per patient, with cost up to 100 days post-transplant in the order of £72,000

However, patients would have received some form of treatment if they did not receive a transplant. We estimate this to be around £20,000. As a result, we estimate the extra cost of performing a stem cell transplant to be £78,200.

Step 5 – Estimate the cost of providing stem cells from a cord blood inventory of 30,000 donations

As well as the cost of performing the transplant, we also need to estimate the cost of providing the stem cells. NHSBT provided estimates of the cost of each stage of the process from collecting an umbilical cord blood donation, through processing, cryopreservation and storage, to selection, evaluation and issue. We have used these costs to estimate the cost of building up an extended inventory, and then issuing donations as they are selected through their life in the inventory. Table 8 shows these costs for the status quo, and for expanding the inventory to 30,000. These costs were forecast using information provided by NHSBT.

Table 8: Discounted costs of option 1 (status quo) and option 2 (expansion to 30,000 donations).

	Activity	Lifetime cost (£m)
Option 1: Status Quo	Collection costs	4.8
	Processing and storage costs	5.6
	Issue costs	0.5
	Total	**10.9**
Option 2: 30,000 Inventory	Collection costs	14.9
	Processing and storage costs	6.3
	Issue costs	0.8
	Total	**22.0**

54. Van Agthovem M *et al.* (2002). Cost analysis of HLA-identical sibling and voluntary unrelated allogeneic bone marrow and peripheral blood stem cell transplantation in adults with acute myelocytic leukaemia or acute lymphoblastic leukaemia. Bone Marrow transplantation 30:243-251.

Step 6 – Determine cost per QALY from expanding the cord blood inventory to 30,000 donations

This estimate draws on the estimates and assumptions described above, summarised at Table 9.

Table 9: Key assumptions and data used to derive the cost per QALY gained.

Data	Value	Source
Unmet need	351	Lown *et al.* (2013)
Unmet need met by 30,000 bank	257	BSBMT donor selection consensus
Forecast inventory utilisation	1%	Extrapolated from existing rates
Imported CB *per annum*	122	Anthony Nolan NHS Stem Cell Registry
Import price	£29,879	Anthony Nolan NHS Stem Cell Registry
Export price	£21,500	Anthony Nolan NHS Stem Cell Registry
Healthcare costs without transplant	£20,000	Costa *et al*. (2007)
Healthcare costs with transplant	£98,200	van Agthoven *et al*. (2002) and expert opinion
Transplant QALY gain	7.3	Collation from various papers
Cord blood donations per transplant	1.59	Anthony Nolan NHS Stem Cell Registry
QALY value	£60,000	DH Impact Assessment Guidance
Opportunity cost uplift	4	DH Impact Assessment Guidance

Based on these assumptions, it is estimated that:

The incremental cost per QALY between the status quo option and the 30,000 donation inventory is around £10,400. This is below the £15,000 threshold used by DH to evaluate the effectiveness of NHS spending decisions. The case for a 30,000 donation inventory appears broadly reasonable.

Step 7 – Sensitivity analyses

As this health economic analysis includes a number of assumptions based on expert opinion (see above), there will be a level of uncertainty surrounding the estimates derived. A univariate sensitivity analysis serves to verify that a result is not driven by any single overarching assumption. In this way, a sensitivity analysis can be considered to improve the robustness of the potential conclusions drawn from the cost benefit analysis.

From these analyses (shown in Appendix B), the following conclusions can be drawn:

1. There is significant weight attached to uncertainty in health benefits. Altering the QALY gain associated with a transplant by a small amount results in a significant change in both the cost per QALY and the net present value. This is a key uncertainty as the QALY gain following a transplant varies across age groups.

2. Alternative costs, transplant costs, and utilisation rate have a large influence on the net present value. Hence, there is uncertainty about the overall cost to the NHS and not just around the collection of stem cells.

3. Changing the price of exports or varying the R&D sales price does not make a significant impact, unless there are a large number of exports.

4. We also carried out a Monte Carlo analysis, allowing various parameters to change at the same time within specified ranges. This showed that there are scenarios where the cost per QALY exceeds £15,000.

Conclusion

The health economic analysis broadly supports the investment case for a cord blood inventory of 30,000 units. The base case estimate of cost per QALY gained (£10,400) is within the typical DH threshold of £15,000. However, sensitivity analyses demonstrate a level of uncertainty surrounding the result.

Recommendation

The Anthony Nolan and the NHS Cord Blood Bank should establish a clinical inventory of 30,000 cord blood donations by 2018. Beyond 2018, inventory growth to 50,000 donations should be funded via income generated through donation provision.

Inventory utilisation should be maximised by banking only those donations likely to contain a clinically-useful dose of stem cells, equivalent to 14 x 10^8 total nucleated cells.

30%-50% of donations should include BAME parentage.

The recruitment and retention challenge

In its 2010 report, the Strategic Forum stated that "a collaborative approach to working with third sector organisations is required to better engage with potential stem cell donors, and especially those from Black and ethnic minority communities. Education is essential to increase the representation of these communities on unrelated donor registries and cord blood banks." Since 2010 Anthony Nolan and NHSBT have undertaken work with a number of third sector groups. The DH established the National Black, Asian and Minority Ethnic Transplant Alliance (NBTA), a coalition of organisations seeking to promote awareness of organ and stem cell donation amongst BAME people and to increase the number of donors from these communities. In addition, Anthony Nolan has carried out a number of campaigns targeted at increasing BAME representation on the registry. This vital work should continue, although this is reliant upon continued funding to target and recruit young male donors, in particular, from BAME communities.

Given the time that can elapse between joining a registry and being identified as a potential stem cell donor, a significant proportion of volunteers may no longer be contactable, or may decide not to proceed when contacted. Twenty-two per cent of requests for confirmatory typing samples are cancelled for donor-related reasons.[55]

Lack of donor reliability leads to a missed opportunity to provide a UK donor in 16% of cases, thus increasing the need to import donor stem cells, sometimes at increased cost to the NHS (depending on the registry). Delays caused by poor donor reliability have a detrimental impact on a patient's chance of survival. Patients experiencing donor attrition on more than two occasions tend to have fewer 10/10 matched donors, fewer CMV-compatible donors, and fewer donors under 30 years of age.[56] Almost one in ten patients (9%) do not achieve a transplant due to donor unavailability. Ethnicity, the time a volunteer has been on the registry and gender are all associated with donor availability.[57] Given the demographic profile of the 'fit panel' volunteers, they tend to be more available and willing to donate when selected. This has led to a significant improvement in donor reliability rates for UK-to-UK transplants compared to international-to-UK transplants. In 2013/14, the attrition rate for requests for international confirmatory typing samples was 60%, compared to less than 38% for UK donors.[58]

Recommendation

The Anthony Nolan and NHS Stem Cell Registry should continue to develop evidence-based strategies to further improve donor availability when approached for donation.

Stem cell supply organisations should undertake or commission research to better understand donor behaviours in relation to stem cell donation and consider prospective clinical studies of novel interventions aimed at improved retention.

Improving donor selection

HLA genetics and unrelated donor selection and provision are complex fields, and transplant centres rely on excellent advice and communications from supporting experts. Advice is typically provided by the histocompatibility and immunogenetics laboratories associated with each transplant team. Anthony Nolan provides an excellent support service called GIAS (graft information advisory service) to several major transplant groups. The Strategic Forum recognised in its 2010 report that an important aspect of minimising the time from search-to-transplant is the provision of expert advice on the suitability of potential donors.

55. Data from Anthony Nolan.
56. Bronwen Shaw, personal communication to the Review.
57. Lown RN *et al.* Ethnicity, length of time on the register and sex predict donor availability at the confirmatory typing stage. Bone Marrow Transplantation 49:525-531.
58. Data from Anthony Nolan.

During 2013, Lown *et al.* examined the impact the GIAS service on a number of clinically important performance indicators. Some findings are summarised in Table 10.

Table 10: Impact of GIAS support on time to transplantation and donor selection behaviours

	GIAS	Non-GIAS	
Median time from search request to CT request (days)	4	10	$P < 0.001$
Median time from CT request to donor work up request (days)	48	63	$P < 0.001$
Median time from search request to transplant	109	141	$P < 0.001$
UK donors selected for transplant	37.3%	26.6%	$P = 0.031$
Key: CT = confirmatory typing			

These data point to an important opportunity to improve and standardise the quality of advice provided to transplant teams. This is especially required to ensure an optimal and consistent approach to the selection of cord blood donations, where opportunities exist to:

1. Select UK-sourced cord blood, where well-matched donations exist;
2. Optimise the utilisation of the UK inventory by maximising the selection of lower dose donations where clinically appropriate;
3. Encourage the selection of cord blood donations on the basis of non-inherited maternal antigen (NIMA) types.[59]

Recommendation

Anthony Nolan, NHSBT, WBMDR, BSBMT and BSHI should collaborate to improve the selection and provision of adult donor and cord blood stem cells by gathering and sharing performance data, providing expert guidance, and supporting education.

59. Non-inherited maternal antigens (NIMA) are defined as the HLA antigens of the mother which are not inherited by the fetus. Fetal exposure to NIMA during leads to sustainable antigen-specific immunological tolerance. This tolerance permits the use HLA-incompatible transplants. Thus, substituting inherited HLA mismatches for a non-inherited mismatches yields new "clinically permissible" matches. The NHS-CBB has listed over 4,700 maternal NIMA types providing over 70,000 new virtual phenotypes. In a retrospective analysis of 437 donations issued by the NHS-CBB, only 18% of patients received donations matched at 6/6. Consideration of NIMA matches could have provided a "virtually fully matched donor" for an additional 35% of patients.

Commissioning stem cell transplantation

In 2010, the Strategic Forum recommended that a commissioning framework should be developed to cover all aspects of unrelated donor stem cell transplantation. This recommendation was in part realised in 2013 with creation of the Health and Social care Act 2013 and the establishment of the Clinical Reference Group (CRG)[60] for Blood and Marrow Transplantation. This presaged an entirely new approach for commissioning stem cell transplantation. NHS England is responsible for specialised commissioning, and commissions treatment from 30 days pre-transplant until 100 days post-transplant. After 100 days, responsibility moves to the Clinical Commissioning Groups. The commissioning of care is therefore fragmented for patients who are likely to suffer long-term physiological and psychological effects of stem cell transplantation. The risk therefore is that there will be a lack of coordinated planning between teams delivering specialist services and those involved in the complex long-term care[61] so vital to the quality of life for stem cell transplant patients. These issues have recently been explored in depth.[62]

Recommendation

Commissioning processes should encourage the development of regional centres of excellence for recipients of alternative donor transplants consistent with broader national policies including the delivery of early phase trials in regenerative medicine. There should be a consistent national approach for commissioning patient care after 100 days post-transplant.

60. Clinical Reference Groups act as a source of clinical advice to NHS England.
61. For example extracorporeal photopheresis for GvHD.
62. Beer G *et al.* (2013). A Road Map for Recovery – a study commissioned by Anthony Nolan.

Appendix One: Progress Against the Stem Cell Strategic Forum's 2010 Recommendations.

Improve the provision of unrelated adult donor stem cells
1. ***In collaboration with third sector organisations, there should be greater engagement with Black and minority ethnic donors to increase their representation on donor registries and cord blood banks.***
• Anthony Nolan has carried out a number of targeted campaigns at increasing BAME representation on the registry. In 2011 the charity's Man on a Mission campaign, fronted by presenter and comedian Hardeep Singh Kohli, recruited around 2,000 BAME volunteers from Birmingham and London over a two-week period and increased awareness of the importance of BAME donors through social and traditional media.
• In 2013 Anthony Nolan's 'The Six Percent' campaign led to a 160% increase in the number of Asian people joining the registry (in comparison with 2011) after it highlighted that 94% of Britain can't help an Asian person with blood cancer because they are not a suitable match.
• 61.4% of BAME patients are able to find a 9/10 or 10/10 matched donor in 2014. This represents a significant improvement on the 40% figure cited in the 2010 report.
• The National Black, Asian and Minority Ethnic Transplant Alliance (NBTA) was established in 2012. This is a coalition of organisations seeking to promote awareness of organ and stem cell donation amongst BAME people and to increase the number of donors from these communities. NBTA membership includes ACLT, The Afiya Trust, Anthony Nolan, DWIB Leukaemia Trust, Hindu Forum of Britain, Kidney Research UK, National Kidney Federation, NHS Blood and Transplant, Organ Donation and Transplantation Research Centre (University of Bedford), Race Equality Foundation, Rik Basra Leukaemia Campaign, Seventh Day Adventist Church and South Asian Health Foundation.
2. ***Selected donors should be prospectively HLA typed to high resolution to obviate the need for this test as part of the donor selection process.***
• 60,000 young donors have been typed to a high resolution and added to the 'fit panel'; numbers continue to increase.
• 'Fit panel' donors are eight times more likely to be selected as a donor compared to other registry volunteers.
• 0.4% of 'fit 'panel' donors are now being selected each year compared to 0.05% from the wider registry. This has resulted in at least 40 additional lives being saved in the last year alone.
• 34% of all UK-to-UK provisions are now supplied by 'fit panel' donors.
• Anthony Nolan has created the "Phenotype Project", to supplement the listed information on donors who have the most frequently requested HLA types. These donors are contacted as part of the retyping process to ensure they are still willing to donate. This improves the time from search-to-transplant following a request from a transplant centre.
3. ***The UK should create or purchase predictive search technologies to increase the chance that selected donors are a match for the patient.***
• Since the creation of the Anthony Nolan and NHS Stem Cell Registry, work has been undertaken to build predictive search technologies into the registry's database. This work is almost complete. The necessary algorithms have been developed and are currently in final testing with good results. The predictive search technology, which is based on 20,000 HLA types representing the predominant UK ethnic group, will go live in 2015.

Improve the provision of unrelated adult donor stem cells *continued*

4. *A 'graft identification advisory service' should be established to ensure optimal donor selection for each patient.*

- Anthony Nolan has gathered additional information of the effectiveness of its 'graft identification advisory service', demonstrating:
  - Improved efficiency in selecting donors for confirmatory typing;
  - Reduced waiting times before donation availability;
  - Better selection of UK donors.
- A graft identification advisory service now operates across hospitals supported by Anthony Nolan WBS, and NHSBT H&I laboratories. A similar service is provided to other transplant centres by associated H&I laboratories.

5. *Registries should increase contact with donors, updating information on their contact details, health status and willingness to donate.*

- Anthony Nolan regularly runs 'Update Your Details' campaigns and regularly updates details through day-to-day contact with donors when requesting samples. A similar campaign was run by NHSBT in 2012/13, with another planned for 2014. Similarly, the WBMDR contacts lapsed blood donors to check individual donor's fitness and commitment to donate.

Improve the provision of cord blood stem cells

6. *The UK should increase its inventory of cord blood to 50,000 units over eight years.*

- The rate of cord blood collection has tripled compared to the steady state in 2011. There are now 14 NHS hospitals operating a cord blood collection system:
  - Barnet General Hospital (NHSBT)
  - Birmingham Women's Hospital (Anthony Nolan)
  - King's College Hospital in London (Anthony Nolan)
  - Leicester Royal Infirmary (Anthony Nolan)
  - Leicester General Hospital (Anthony Nolan)
  - Luton and Dunstable Hospital (NHSBT)
  - Northwick Park Hospital, Harrow (NHSBT)
  - Nottingham City Hospital (Anthony Nolan)
  - Queen's Medical Centre in Nottingham (Anthony Nolan)
  - The Royal Free Hospital in London (Anthony Nolan)
  - St George's Hospital, London (NHSBT)
  - Saint Mary's, Manchester (Anthony Nolan)
  - University College Hospital, London (NHSBT)
  - Watford General Hospital (NHSBT)
- DH funding since 2011 has been used to support cord blood collection at three Anthony Nolan sites and six NHSBT sites.
- The UK's cord blood inventory stands at around 15,000 clinical donations at time of writing; the quality of the donations banked is higher than recommended in 2010 – this 'mid-course' adjustment in banking policy was taken in light of new data on cord blood selection criteria and inventory utilization.
- The planned contribution to inventory growth from the Scottish National Blood Transfusion Service and Northern Ireland Blood Transfusion Service has not been realised.

7. *The inventory should contain 30% to 50% of donations from Black and ethnic minority women.*

- 40% of the UK cord blood inventory is currently from BAME women

Improve the provision of cord blood stem cells *continued*

8. *Newly banked units should have a high total nucleated count (TNC) threshold (over 9 x 10^8 TNC from ethnic minority donors, over 12 x 10^8 TNC from Caucasian donors).*

- Processes for clinical cord blood banking have been aligned across NHSBT and Anthony Nolan.
- The quality of donations banked has further increased from 2012 onwards by increasing the threshold to 14 x 10^8 TNC from 2012 onwards.

9. *High resolution HLA typing should be performed on all of the newly stored and selected existing cord blood units.*

- Cord blood donations entering the inventory are routinely typed at high resolution.
- Anthony Nolan and NHSBT have completed an exercise to retrospectively type existing high dose donations at high resolution.

Drive quality and efficiency

10. *Educational tools and platforms should be developed to improve understanding among commissioning bodies. Commissioners should align their strategies with the latest clinical guidance and patient outcome data.*

- Since 2010, there have been significant changes to the commissioning landscape in England. The Health and Social Care Act 2013 created new commissioning arrangements, which came into effect on 1 April 2013. The Oversight Committee provides expert advice to the Clinical Reference Group for Blood and Marrow Transplantation.
- The British Society for Blood and Marrow Transplantation produces annually a detailed statistical analysis of patient outcomes to inform commissioning practice and policy.

11. *Commissioning bodies should operate within a standardised funding framework, using a baseline figure adjusted to reflect market forces factors. This framework should cover the entire patient pathway, including pre- and post-transplant treatment.*

- Stem cell transplantation is currently only nationally commissioned from 30 days pre-transplant to 100 days post-transplant, at which point commissioning responsibility is transferred to the patient's Clinical Commissioning Group.
- This fragmentation in commissioning of specialist care, coupled with the lack of national guidance on how post-transplant care should be delivered, leads to differentiation in the post-transplant care received by patients in different regions of the UK.

12. *Resources and expertise for cord blood transplantation should be concentrated into designated Regional Centres of Excellence, promoting high quality care and the best use of resources. Regional Centres of Excellence should undertake a minimum of 5, preferably 10, cord blood transplants per annum and serve a minimum population of 4-5 million.*

- A key component of the BMT CRG's service specification for adult transplantation has incorporated a central recommendation of the 2010 Strategic Forum report by mandating that "Centres which undertake umbilical cord transplants must be part of a provider network with a combined catchment population of at least 4 million people".

13. *All centres performing unrelated donor stem cell transplantation should be accredited by the Joint Accreditation Committee of ISCT and EBMT (JACIE).*

- In 2014, 32 UK centres performing unrelated donor stem cell transplantation had JACIE accreditation.
- The few remaining centres are on schedule to receive accreditation this year.

14. *Local networks should be linked into designated centres and make appropriate referrals when necessary.*

- There has been little progress on this recommendation to date.

Drive quality and efficiency *continued*

15. ***Standardised data collection and outcome monitoring should be integrated into every stage of the patient pathway so that reliable outcome data can be used to benchmark individual performance and promote best practice. Funding streams should be identified to support the collection and analysis of outcome data from Regional Centres of Excellence.***

- This recommendation has been largely met through the detailed report compiled and provided to commissioners by the British Society for Blood and Marrow Transplantation. However, substantial issues remain around lack of funding for data collection and reporting in transplant centres and Commissioners should mandate data management resource requirements according to transplant volume and complexity for individual transplant centres.

16. ***Designated transplant centres should work together to support an alternative donor clinical trials network. The commissioning process should encourage the development of registration studies and early and late phase clinical trials in alternative donor transplantation. Funding streams should be identified to develop what would be a uniquely important translational initiative worldwide.***

- Substantial progress has been made in formulating the structure of a UK Transplant Trials Network and gaining widespread support for this initiative from key partners including BSBMT, NHSBT, Anthony Nolan and LLR. However, despite widespread support for this initiative, it has not been possible to identify funding and the great majority of UK transplant patients still have no access to clinical trials.

17. ***Acknowledging differences in policy and process between the four countries of the UK, a commissioning framework should be developed and supported by a UK Stem Cell Advisory Forum to performance manage the provision of:***

- ***A UK stem cell registry;***
- ***A UK cord blood inventory;***
- ***A database of patient outcomes following transplantation.***

- The roles envisaged of the 'UK Stem Cell Advisory Forum' have, to a large extent, been subsumed into those of the Oversight Committee.
- Stem cell supply organisations report key performance indicators to the Oversight Committee on a regular basis. The Committee endorses changes to operational policies, ensuring consistency of practice across the UK.

18. ***Each element of the framework should be contracted; the Advisory Forum should advise on the specification of each contract. Provider organisations should report on key performance indicators annually.***

- Anthony Nolan, NHSBT and WBS have created a joint management committee to oversee activities of the Anthony Nolan and NHS Stem Cell Registry.
- The management committee produces regular performance reports for review by the Oversight Committee and the Department of Health.

19. ***The Stem Cell Advisory Forum should build on the work and membership of the UK Stem Cell Strategic Forum. It should develop standards and specify the service levels required of supplier organisations.***

- The Oversight Committee, which has a UK-wide remit, supports the work of the Clinical Reference Group for Bone Marrow Transplantation. This helps to prevent policies in the four countries of the UK being developed in isolation.

20. ***In addition to advising on the provision and use of stem cells for transplantation, the Stem Cell Advisory Forum should work with key stakeholders such as UK Blood Services, Anthony Nolan, research organisations and charities to define research opportunities, to facilitate the translation of basic research into the clinical practice, and to maximize income through the commercialization of intellectual property.***

- To date it has not proved possible to identify the funding required to sustain the clinical trials infrastructure which would provide a platform for these initiatives.

Appendix Two: Stem Cell Transplantation in the UK – Health Economic Analysis

Introduction

Part Three of this report provided an overview of the health economic analysis for expanding the UK's inventory of cord blood and registers of fit panel donors. This appendix provides more detail on the methodology used in the analyses, and the results for expanding the inventory to 30,000 or 50,000 donations, and the results for expanding the fit panel to 150,000 donors.

Estimating demand for cord blood stem cells in the UK.

Annex 3 of the 2010 Strategic Forum report presented an estimate of the unmet need for stem cells in the UK – around 440 patients *per annum*. Here we apply the same health economic analytical approach used in 2010, using recent clinical, performance and financial data, and reflecting on the continued evolution of clinical practices. We start by estimating the extent to which an expanded cord blood bank might:

- Meet the needs of patients without a matched adult donor;
- Enable a transplant for patients who currently deteriorate while waiting for an adult donation to be provided;
- Enable an improvement in the clinical outcome for patients who receive a mismatched adult donation or a haploidentical donation.

We then estimate the extent to which patient outcomes would be improved through a UK cord blood inventory of 30,000 or 50,000 donations, and the relative costs of achieving these outcomes.

Unmet demand due to failure to find a match

The failure to find an optimal match for a patient requiring a transplant is still a major problem. Patients without a matched sibling donor may receive a transplant using stem cells from an unrelated adult donor or cord blood donation. Developmental haploidentical protocols are also under investigation. However, a significant proportion of patients do not find a suitable match through any of these options. These patients represent part of the unmet demand for unrelated donor stem cells in the UK.

An analysis of a group of 401 patients across four transplant centres found that 228 patients received a transplant. Of these 228 patients, 185 received stem cells from an unrelated adult donor, 30 received cord blood transplants, and 13 received haploidentical transplants.[63]
A further 13 did not receive a transplant as no suitable donor could be found. This suggests that, for every 185 unrelated adult donor transplants, there are a further 56 patients for whom no well-matched unrelated adult donor can be found.

In 2012, 875 unrelated adult stem cell transplants were performed in the UK.[64] Applying the ratio from the above study to this national total, it is estimated that there are approximately 265 patients *per annum* for whom no matching unrelated adult donor is found (giving a total of 1140 patients). BAME[65] groups make up 17% of the UK population and so, for the purposes of this calculation, it is assumed that 194 of the total patients are from these groups.

BSBMT[66] also state that 79 transplants were carried out in the UK in 2012 using cord blood donations, and 46 transplants were carried out using stem cells from haploidentical donors.

Lown *et al.* also present information on the proportion of BAME and white northern European patients who receive each type of transplant; from this it can be estimated that BAME patients receive 7.5% of adult unrelated donor transplants, 57% of cord blood donations, and 67% of haploidentical donor transplants (data are summarised at Table 11).

These estimates give an overall unmet need due to failure to find a match at **140 patients *per annum.***

Table 11: Unmet demand for unrelated donor stem cells in the UK due to failure to find a match

	Total	White north European patients	BAME patients[1]
Total UK patients	1,140	946	194
Adult donor transplants	875	809	66
Cord blood transplants	79	34	45
Haplo-identical transplants	46	15	31
Unmet need	**140**	**88**	**52**

Key:
1. More accurately patients who are not white northern Europeans.

63. Lown *et al.* (2013). Time to Transplant Study. Presentation to the American Society of Haematology.
64. British Society of Blood and Marrow Transplantation: 5th report to specialist commissioners.
65. More accurately patients who are not white northern Europeans.
66. British Society of Blood and Marrow Transplantation: 5th report to specialist commissioners.

Unmet demand due to patient factors

At other times, a suitable match may be identified but a patient's disease can progress while they are awaiting transplant. The time taken from diagnosis to transplant is recognised to adversely affect patient outcome, and provision of unrelated donors has been identified as a key source of delay. Obstacles to timely provision are reviewed by Lown and Shaw (2013)[67] and include delays in referral to a transplant centre, delays while typing sibling donors, delays in obtaining samples for confirmatory and extended typing, donor ineligibility on grounds of health, and late donor refusal.

Patients may also fail to go to transplant due to the development of toxicities from salvage treatment or additional cycles of treatment given to maintain remission whilst waiting for a suitable donor.

Between 12% and 33% of patients with a matched unrelated adult stem cell donor do not proceed to transplant due to patient-related factors which develop while waiting for transplant.[68] It is assumed 50% of these patients would benefit from a rapid cord blood transplant. So unmet demand for these patients can be estimated as between:

(0.12/0.88) x 875 x 0.5 = **60** patients *per annum* and (0.33/0.67) x 807 x 0.5 = **215** patients *per annum*.

Taking the mid-point, the unmet demand from patient factors is around **138 patients** *per annum*.

Further opportunities to improve patient outcomes by substituting adult donations with cord blood

Optimal patient outcomes are achieved when transplanted with 10/10 matched adult donor stem cells (data reviewed in Part Two). Frequently, 10/10 matches are not available, and mismatched donors are provided in accordance with BSBMT hierarchical donor-selection algorithms. This guidance is summarised at Table 12.

Table 12: Summary of BSBMT guidance on selection of cord blood donations

For adult malignancies, an adult donor with a 9/10 match and a good cord blood donation (either a well-matched large single unit or a double unit) are generally regarded as equivalent. However, a cord blood donation may be preferred to a 9/10 adult donor match if there is a CMV mismatch, or if there is a need to perform the transplant quickly. We estimate that a cord blood donation might replace about 20% of 9/10 adult donor transplants and all 8/10 transplants for these patients.
For paediatric malignancies, an adult donor with a 9/10 match and a good cord blood donation are generally regarded as equivalent. However, a cord blood donation may be preferred to a 9/10 adult donor match depending on the disease type or if a quick transplant is needed. We estimate that a cord blood unit might then replace about 35% of 9/10 adult donor transplants and all 8/10 transplants.

67. Lown RN and Shaw BE (2013). Beating the odds: factors implicated in the speed and availability of unrelated haemopoietic cell donor provision. Bone Marrow Transplantation 48:210-219.
68. The future of unrelated donor stem cell transplantation in the UK (2010).

For paediatric bone marrow failure, an adult donation with a match of 8/10 will generally be preferred to a cord blood unit, given the difficulty in achieving a successful cord blood transplant. As a result, we estimate that no adult donor transplants might be replaced by cord blood donations.

For paediatric immune deficiency and metabolic diseases, a large cord blood donation with an 8/8 match is generally regarded as equivalent to an adult donor with a 10/10 match, and a good cord donation as equivalent to an adult donor with a 9/10 match. As a result, an 8/8 matched cord unit might replace any adult mismatched donor transplants. However, we estimate that a cord blood donation with a 5/6 or 7/8 match might replace 25% of 9/10 adult donor transplants. As 8/8 matches are rare, we here use the lower figure of 25%.

Reflecting on the above consensus guidance, the BSBMT Cord Blood Working Group reviewed the clinical benefits of substituting mis-matched adult donations with cord blood donations. Considering each patient group in turn, and using the information from Anthony Nolan on levels of matching within each group, it was estimated that around 23% of unrelated adult donor transplants are from donors with at least one mismatch[69] and that around 25% of these mismatched transplants could be replaced with a cord blood transplant to the benefit of the patient.

These estimates give an overall scope to replace mis-matched adult donations with cord blood donations at **50 patients *per annum.***

Long-term outcome data following haploidentical transplants is being accumulated at time of writing. There is therefore uncertainty regarding the extent to which better patient outcomes might be achieved through provision of a well-matched cord blood transplant. For the purposes of this analysis, we have assumed that 50% of the 46 haploidentical transplants performed in 2012 may have benefited from the availability of a well-matched cord blood donation.

This estimate gives an overall scope to replace haploidentical transplants with cord blood donations at **23 patients *per annum.***

Consolidating these estimates it follows that:

The **maximum** possible **extra** demand for cord blood stem cells is circa 88 + 52 + 138 + 50 + 23 = **351 patients *per annum.***

69. From information provided by Anthony Nolan on the level of matching of adult donors who were "worked up" in 2013, it can be estimated that around 23% of unrelated adult donor transplants are from donors with at least one mismatch.

Meeting unmet demand via an increased inventory of cord blood donations

Querol *et al*. (2009)[70] estimated that a UK inventory of 50,000 cord blood donations would provide a 5/6 or 6/6 match for:

- 85% and 50% of white northern European patients and BAME patients respectively;
- 90% of patients whose conditions deteriorate while waiting for an adult donor;
- 100% of the patients who would have received a 9/10 HLA matched bone marrow donation.

Extrapolating from Querol's formulae, we estimate that an inventory of 30,000 cord blood donations would provide a 5/6 or 6/6 match for 80% and 43% of while northern European patients and BAME patients respectively.

Turning to unmet demand, and allowing for the more stringent matching protocols now recommended (described in Part Two), we estimate that a UK inventory of 30,000 cord blood units would be able to meet:

- 60% and 50% of the unmet demand for white northern European patients and BAME patients respectively;
- 85% of patients of the unmet demand whose conditions deteriorate while waiting for an adult donor;
- 83% of the unmet demand for patients who would have received a 9/10 HLA matched adult donation;
- 83% of the unmet demand for patients receiving a haploidentical transplant.

Thus, the extra number of UK patients who would be treated from a UK cord blood inventory of 30,000 units would be:

- White northern European patient unmet demand met: 60% x 88 = **53** patients *per annum*
- BAME patient unmet demand met: 50% x 52 = **26** patients *per annum*
- Patient factor demand met: 85% x 138 = **117** patients *per annum*
- Mismatched adult donor substitution demand met: 83% x 50 = **42** patients *per annum*
- Haploidentical transplant substitution demand met: 83% x 23 = **19** patients *per annum*

The additional UK patients treated annually from a cord blood inventory of 30,000 donations would be around 257 (out of a potential 355).

Assuming that, on average, 1.59[71] cord blood donations are used per transplant, this would amount to around 400 cord blood donations per annum.

70. Querol S *et al.* (2009) Cord blood stem cells for haemopoietic stem cell transplantation in the UK: how big should the bank be. Haematological 94:536-541.
71. From information provided by Anthony Nolan on cord blood donations provided for transplant in 2013.

QALY gains following unrelated donor stem cell transplantation

In order to develop a robust stem cell strategy for the next decade, it is necessary to gain a clear idea of the incremental costs that accompany various service models. The NHS has finite resources and these must be channelled as efficiently as possible to ensure that services represent 'value for money' in terms of clear healthcare benefits. Though part of the focus of these discussions is financial, the central consideration is the patient and the possible improvement in both survival and quality of life that he or she receives.

In gauging the benefits of unrelated donor transplantation, the standard measurement is the Quality-Adjusted Life Year (QALY). The purpose of the QALY is to provide a more nuanced picture of the value of a therapy by considering not only the net gains in terms of overall survival, but also the improved quality of life it may bring to the patient. This involves a range of factors and varies considerably.

The methodology used for QALY gain calculations was as follows:

1. Obtain published survival information on cord blood transplant patients;
2. Extrapolate long-term survival rates from this to identify the life expectancy of transplant patients;
3. Make adjustments for quality of life to derive the number of QALYs expected following a transplant;
4. Carry out these calculations for similar patients who do not receive a transplant;
5. The QALY gains from a transplant is defined as the difference between QALY expectancy with a transplant and QALY expectancy without a transplant.

Published data of patient outcomes and alternative survival

Table 13 provides a summary of the publications and other data sources considered as part of this review.

Table 13: Summary of reports and studies reviewed

Report	Donor	Disease	Age range	Country, cord bank or registry	Years of study	Type of transplant survival	Alternative survival
Brunstein *et al.* (2012)	PBSC CB	ALL, AML	Adults	CIBMTR	2000-2009	DFS and OS at 3 years	Not stated
Eapen *et al.* (2010)	BM PBSC CB	AML, ALL	Adults	EUROCORD EBMT CIBMTR	2002-2006	DFS measured at 4 years	Not stated
Kai *et al.* (2013)	CB	AML, ALL, CML, MDS	Children Adults	Japan	2006-2010	DFS measured at 3 years	Not stated
Labopin *et al.* (2014)	CB	AML, ALL	Adults	France	2002-2009	DFS and OS at 3 years	Not stated
Locatelli *et al.* (2013)	CB	JML	Children	EUROCORD EBMT CIBMTR	1995-2010	DFS and OS at 5 years	Not stated
Nagler *et al.* (2012)	BM PBSC	AML	Adults	EBMT	2000-2007	DFS measured at 5 years	Not stated
Rodrigues *et al.* (2014)	MUD CB	HL, NHL, CLL, FL	Adults	EUROCORD EBMT NETCORD	2000-2008	DFS and OS at 5 years	Not stated
Ruggeri *et al.* (2014)	CB	ALL, AML	Adults	EUROCORD EBMT centres	2005-2011	DFS measured at 2 years	Not stated
Schlenk *et al.* (2010)	MRD MUD CB	AML	Adults	Germany Austria	1998-2004	DFS and OS at 5 years	Chemo-therapy
Schlenk *et al.* (2013)	Allo-HSCT	AML	Adults	International	1987-2009	OS measured at 5 years;	Chemo-therapy
Yoo *et al.* (2011)		AL, IE, MDS/JMML, SAA, CML	Children	Korea		DFS, & OS measured at 8 years	Not stated
Bergstrom *et al.* (2008)	BM	AML, ALL, CML, MDS, NHL, AA	Not stated	US	1987-2004	OS measured at 5 or 10 years	Mostly chemo-therapy

Report	Donor	Disease	Age range	Country, cord bank or registry	Years of study	Type of transplant survival	Alternative survival
Bhatia *et al.* (2007)	BM CB PBSC	AML, ALL, CML, NHL, SAA	Adults Children	US	1974-1998	OS measured at 5 years	Not stated
Bizzetto *et al.* (2011)	CB	Multiple	Adults Children	International	1994-2008	OS measured at 5 years	Not stated
Costa *et al.* (2007)	BM CB	AML, ALL,	Adults	International	1988-1996	OS measured at 5 years	None
Eapen *et al.* (2011)	BM PBPC	Severe AA	Adults Children	US CIBMTR	2000-2008	OS measured at 3 years	Not stated
Eapen *et al.* (2011)	CB	ALL, AML, CML, MDS	Adults Children	CIBMTR EUROCORD NETCORD	1996-2008	OS measured at 3 years	Not stated
Eapen *et al.* (2014)	CB	ALL, AML	Adults Children	CIBMTR EUROCORD NETCORD	2000 – 2010	OS measured at 3 years	Not stated
Fernandes *et al.* (2012)	BM PBSC CB	SCID or Omenn syndrome	Children	EUROCORD SCETIDE EBMT	2000 – 2005	OS measured at 5 years	Not stated
Howard *et al.* (2005)	BM CB	AML, ALL,	Adults Children	International	Large	OS measured at 5 years	Chemo-therapy
Marks *et al.* (2014)	BM PBSC CB	ALL	Adults	CIBMTR	2002 – 2010	OS measured at 3 years	Not stated
Scaradavou *et al.* (2013)	CB	ALL, AML	Adults	CIBMTR		OS measured at 3 years	Not stated
Schlenk *et al.* (2013)	Allo-HSCT	AML	Adults	International	1987 – 2009	OS measured at 5 years;	Chemo-therapy
Snowden *et al.* (2014)	CB	Multiple	Adults	UK	2000 – 2012	OS measured at 3 years	Not stated
Veys *et al.* (2014)	CB	ALL, AML, MDS/MPD, Immunodeficiency metabolic, BMF, HLH	Children	UK	1998 – 2012	OS measured at 5 years	Not stated

Key:
AA = aplastic anaemia
AML = acute myeloid leukaemia
ALL = acute lymphoblastic leukaemia
BM = bone marrow
CB = cord blood
CML = chronic myeloid leukaemia
DFS = disease-fee survival
JML = Juvenile myelomonocytic leukaemia
MDS = myelodysplastic syndrome
NHL = non-Hodgkin's lymphoma
OS = Overall survival
PBSC = peripheral blood stem cells
SCID = severe combined immunodeficiency

Despite the variations between the studies, the evidence confirms the value of unrelated donor stem cell transplantation as a life-extending and life-enhancing therapy. In every disease category, alternative survival rates without transplantation were much inferior.

The literature suggests two alternative situations. For most patients, the survival rate without transplantation is expected to be very low, approximately 1% after five years. For some patients, primarily those suffering from acute leukaemia who would be treated with chemotherapy, the survival rate is better, estimated as being approximately 20% less than the survival rate following transplantation.

The transplant survival data in these studies has been integrated and benchmarked against an Office for National Statistics (ONS) model of life expectancy based on historic mortality rates. The QALY gains associated with transplantation are then calculated by measuring the difference between the net QALY expectancy with or without transplantation.

Drawing on expert opinion, we estimate that approximately 80% of adult patients have the lower alternative survival rate as will approximately 80% of children suffering from acute myeloid leukaemia (AML) or acute lymphoblastic leukaemia (ALL), and all children with non-malignant conditions. As there are approximately equal numbers of child patients in the two groups, we estimate that approximately 90% of child patients have the lower alternative survival rate.

Information provided by Anthony Nolan on patients for whom a registry search was carried out in 2013 indicates that 17% of patients are children.

Table 14 summarises the key assumptions therefore from which an overall average QALY gain from unrelated donor stem cell transplantation has been estimated.

Table 14: QALY gains for adults and children for a unrelated donor stem cell transplantation, compared to a alternative survival rates of 20% below transplant survival and 1% survival after 5 years

	Alternative survival scenario 1: 1% survival at 5 years		**Alternative survival scenario 2: 20% lower 5-year survival than transplant**	
	QALY gain	% of patients	QALY gain	% of patients
Adults (83% of patients)	6.2	80%	3.1	20%
Children (17% of patients)	16.7	90%	6.3	10%

From this, we obtain an average QALY gain per transplant of:

$0.83 \times (0.8 \times 6.2 + 0.2 \times 3.1) + 0.17 \times (0.9 \times 16.7 + 0.1 \times 6.3) = 7.3$

Cost of a stem cell transplant

In order to deduce the cost per QALY, it is first necessary to estimate the total cost of a cord blood transplant. There are two elements to this, namely the cost of providing the donation, and then the cost of the clinical procedure including patient follow-up. Both are considered below.

Stem cell provision costs

A proportion of the full cost of unrelated donor stem cell transplantation is associated with procuring and providing suitably matched stem cells. This, in turn, reflects the accumulated costs of each individual step in the supply chain including recruitment, collection, testing, cryopreservation, storage, registration, searching, shipping and issue. In the UK, a significant proportion of these costs is funded via central DH funding or charitable income (Anthony Nolan).

Registries and cord banks are collective resources with low lifetime utilisation rates; only a small fraction of adult volunteers and listed cord blood donations will ever be used for transplantation in a given year. The true provision cost of every stem cell donation must, therefore, include a share of the long-term running costs associated with the other adult donors or cord blood donations that are recruited or banked without ever being selected. This means that the true cost of each stem cell donation exceeds the costs allocated specifically to the selected donor or cord unit. Consequently, the overall costs of an adult donation or cord blood unit are weighted to reflect this (Table 15).

Table 15: Current long run costs of providing cord blood units for transplantation[1]

Component	Cost/Event (£)	Events per Transplant	Weighted Cost per Transplant (£)
Recruitment, collection, evaluation and discards	706	8	5,764
Typing and testing	123	8	1,004
Processing and registration	277	8	1,852
Maintenance of the cord blood bank	17	154	2,677
Extended typing	350	2	700
Final product evaluation	600	1	600
Issue and logistics	3331	1	3,331
Total per donation issued			**15,928**

Key
1. Costs derived from actual expenditure at NHSBT.

Stem cell transplant

Table 16 shows the approximate costs of transplantation, including stem cell provision and post-transplant care. This has been based on the methodology used by van Agthoven *et al*. (2002)[72] but updating some of the components to reflect current UK cord blood transplant practice. We have drawn on unit costs provided by the PSSRU Unit Costs of Health and Social Care 2013 database.[73] Where these were not available, costs have been scaled and converted from the original study. The costs of post-operative care have also been weighted to reflect the fact that, with every progressive phase of treatment, a smaller proportion of transplanted patients are alive to receive it. Costs were converted using 1999 pound/euro exchange rates and adjusted using the Health and Social Care Pay & Prices index to put them into 2012/13 terms. There are a number of caveats. The non-UK data may have only limited applicability, and only includes unrelated adult donor transplants, not cord blood transplantation. The patients are all adults and therefore paediatric patients are excluded.

Table 16: Summary of transplant costs per patient (extrapolated from van Agthoven *et al.* (2002).

Component	Average costs per living patient	% alive	Weighted costs per transplant patient
Transplant unit personnel	£20,720	100%	£20,720
Transplantation[1]	£38,183	100%	£38,183
Follow up 1[2]	£28,390	90%	£25,551
Follow up 2[3]	£19,502	48%	£9,361
Follow up 3[4]	£14,073	31%	£4,363
Total Costs	**£120,868**		**£98,178**

Key
1. Includes the price of a UK-sourced cord blood donation (£16,500).
2. Follow up 1 covers the period from the first discharge after transplantation to 6 months after transplant.
3. Follow up 2 covers the period from 6 to 12 months after transplantation date.
4. Follow up 3 covers the period from 12 to 24 months after transplantation date.

Thus we estimate the cost of a single cord blood transplant to be around £98,200 per patient, with cost up to 100 days post-transplant in the order of £72,000.

This cost should be set against the often considerable costs of not transplanting a patient, such as ongoing chemotherapy and supportive care. These costs have been estimated at around £20,000 per patient, though this may fluctuate significantly from case to case.

72. Van Agthovem M *et al.* (2002). Cost analysis of HLA-identical sibling and voluntary unrelated allogeneic bone marrow and peripheral blood stem cell transplantation in adults with acute myelocytic leukaemia or acute lymphoblastic leukaemia. Bone Marrow transplantation 30:243-251.
73. These can be found at http://www.pssru.ac.uk/project-pages/unit-costs/2013/ (webpage accessed 19 September 2014).

Economics of cord blood banking

There are a number of factors to consider when deciding on the best future model for the UK's cord blood inventory. These include:

Inventory size. A larger inventory will have higher costs, but may be more efficient in terms of costs per unit as the fixed costs and overheads are shared across a greater number of stored donations.

Inventory utilisation. This is the proportion of an inventory's stored donations issued every year. In principle, utilisation rates may fall as the size of an inventory increases, but in reality this relationship is more complex. Utilisation is one of the key determinants in whether a cord blood inventory is financially sustainable over the long term.

Genetic diversity. The genetic diversity of a cord blood inventory reflects the ethnic diversity of the cord blood donors. This is key to ensuring the UK cord blood inventory increasingly meets the needs of BAME patients.

These key considerations are reviewed below.

Inventory size

The optimal size of a cord blood inventory is one of the central considerations in its design. Clearly, the overall operational costs of a smaller cord inventory are likely to be less than for an expanded inventory. In theory, in the context of limited patient demand, a smaller bank should issue a higher proportion of its stored donations every year, even if the actual number of units is lower. In reality the relationship between size and utilisation is not so clear-cut.

Despite incurring greater overall costs, a larger inventory may prove more economic due to the significant portion of fixed overheads in staff, equipment and infrastructure. While many of the costs of adult donations are associated with donor work-up and stem cell collection, these processes are only undertaken once the donor has been selected for donation. In contrast, cord blood banking and storage costs are incurred before the selection and issue process. Expanding the size of the UK's cord blood inventory should therefore reduce the fixed cost component for each donation stored, provided a reasonable utilisation rate is maintained.

An expanded inventory will have a broader range of HLA types and can therefore provide a greater number of patients with a match. Up to a point, this may raise the number of units issued each year to maintain an acceptable utilisation rate. As its size increases beyond a certain level, however, utilisation rate will fall as donations added to the inventory less often represent a novel HLA type.

Table 17 shows the size of cord blood inventories recently agreed for three other countries, along with the implied number of donations available per million of population. Our analysis considers a 30,000 donation inventory for the UK, which is consistent with the sizes of inventories in other equivalent European regions.

Table 17: Recently agreed bank sizes, with number of cords per million of population

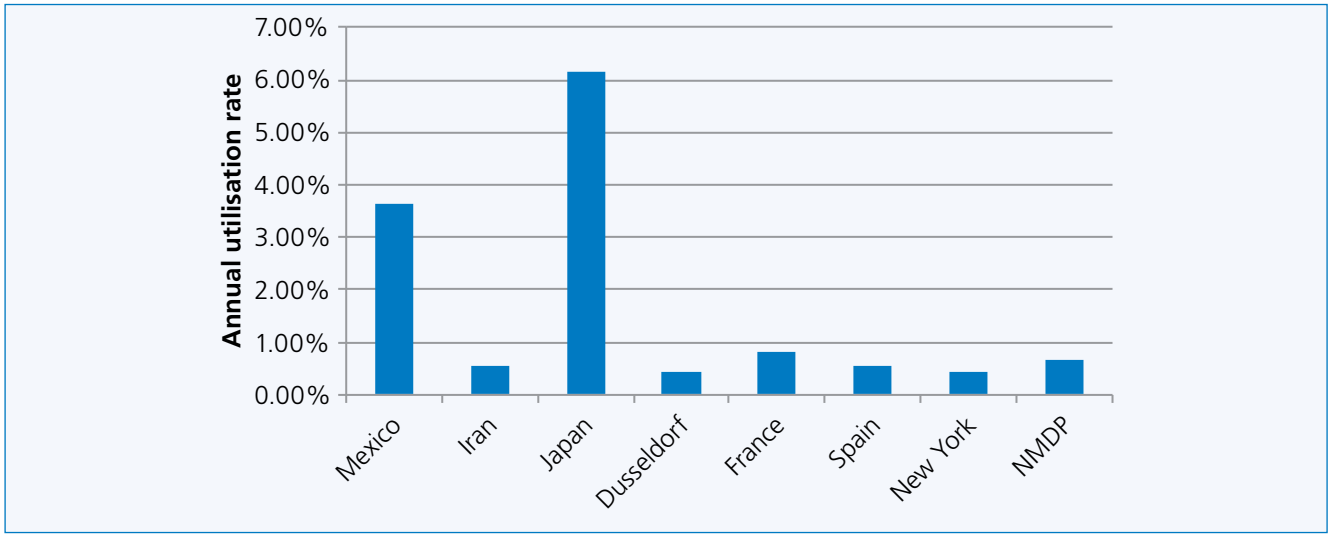
Region	Inventory size	Cord blood donations per million of population
Holland	10,000	592
Canada	18,000	516
France	30,000	478
UK (proposed)	30,000	471

Inventory utilisation

The utilisation rate of the inventory is the major determinant of its long-term financial sustainability. By increasing the utilisation rates of its inventory, the UK could significantly improve its cost effectiveness and lower the real costs per donation significantly.

In Part Three, we describe current and forecast inventory utilisation rates. In forecasting an average utilisation rate of around 1% for a UK inventory of 30,000 or 50,000 high dose donations, we have also sought to benchmark against other cord blood banks. These are shown in Figure 14.

Figure 14: International cord blood inventory utilisation rates



Overall there is no simple relationship between utilisation rate and inventory size. The cord banks of Mexico, Iran, Japan, Dusseldorf, France, New York and the NMDP together have the highest utilisation rates in the world. However, the inventories service different populations and vary greatly in size and composition. The high rate of utilisation in Mexico is due to the small size of the cord blood bank and the relative genetic homogeneity of the Mexican population. The NMDP, on the other hand, has a large inventory serving an ethnically diverse population; its utilisation rate is sustained by high levels of domestic demand. France with its cord blood inventory of 31,230 units provides a closer comparator for the UK; the French population has similar levels of ethnic diversity.

We expect that the utilisation rates presented in Figure 14 relate to cord blood banks with a lower proportion of high quality cord blood donations than we here propose for the UK. Applying utilisation rates based on information across the World Marrow Donor Association (WMDA)[74] to the projected composition of the recommended 30,000 and 50,000 inventories, we estimate that the future utilisation would be as set out in Tables 18 and 19:

Table 18: Projected utilisation rate of a cord blood inventory of 30,000 donations

Donation size (TNC x10^8)	Inventory size	Utilisation rate	Annual issues
>19	2,614	5%	131
14-19	8,301	1.50%	125
9-14	19,385	0.15%	29
Total	30,300		285
Overall utilisation rate			**0.94%**

Table 19: Projected utilisation rate of a cord blood inventory of 50,000 donations

Donation size (TNC x10^8)	Inventory size	Utilisation rate	Annual issues
>19	3,830	5%	191
14-19	14,224	1.50%	213
9-14	33,247	0.15%	50
Total	51,300		454
Overall utilisation rate			**0.89%**

The figures in Table 18 suggest that a utilisation rate of 1% is broadly achievable for an inventory of 30,000 donations. However, we anticipate a lower utilisation rate for an inventory of 50,000 donation due to the higher proportion of duplicated HLA profiles and limitations in global demand. Accordingly, we have based our analyses on a utilisation rate of around 0.85% for an inventory of 50,000 donations.

Genetic diversity

Patients from ethnic minorities are less likely to be able to find a suitable donor than Caucasian patients. This is because HLA types are related to ethnicity, and ethnic minority donors are underrepresented on adult donor registries. The challenge of identifying matched adult donors for BAME patients is further increased by other factors, including:

- The greater HLA heterogeneity among certain ethnic groups. The probability that two randomly selected African-Americans will have an HLA match is about a tenth of the equivalent probability of a match between two Caucasians;[75]
- A smaller donor pool. As ethnic minorities have a smaller population base, even with comparative levels of representation to Caucasians, ethnic minority patients will have a smaller selection of potential matches.

74. Personal correspondence from S Querol, using 2012 WMDA global data.
75. Bergstrom TC *et al.* (2009). One chance in a million: altruism and the bone marrow registry. American Economic Review 99:1309-1334.

The banking of umbilical cord blood offers an opportunity to reduce this inequality. Through targeted collection of cord blood at hospital maternity units serving populations with relatively high levels of ethnic diversity, currently underrepresented HLA types can be made much more available. This benefits not only ethnic minorities in the UK but also the same ethnic groups in other countries around the world. The NHS and Anthony Nolan cord blood banks have a combined ethnic minority representation of 38.4%.

Cost-benefit analysis – an expanded cord blood inventory

A cost-benefit analysis was carried out by comparing three options for expanding the current supply of cord blood donations. This was undertaken in order to determine the incremental costs and benefits of moving from the status quo policy to an inventory of 30,000 or 50,000 donations. Thus the options examined were:

1. Expand the cord blood inventory to 20,000 donations in one year (status quo).
2. Expand the cord blood inventory to 30,000 donations over four years. It is assumed that once the inventory reaches its target capacity, it will achieve a utilisation rate of 1% each year. Cord blood collection thereafter would be consolidated to maintain the inventory, aiming to maintain the proportion of ethnic minority cord blood units at 30%-50%.
3. Expand the cord blood inventory to 50,000 donations over eleven years. This is achieved by expanding the inventory to 30,000 over four years (as option 2), and then continuing to expand at the rate of the final two years until an inventory of 50,000 is achieved. It is again assumed that once the inventory reaches its target capacity, it will achieve an utilisation of 1% each year. Cord blood collection would then be consolidated to maintain the inventory, aiming to maintain the share of ethnic minority cord blood units at 30%-50%.

The analysis draws on the estimates set out above and is based on:

- Costs of donor recruitment, cord blood collection, storage and transplantation;
- Benefits measured in QALYs;
- The incremental cost per QALY of expanding to a 30,000 donation or a 50,000 donation inventory.

We demonstrate that results are broadly favourable to both a 30,000 and a 50,000 inventory, subject to the assumptions made, in particular the annual utilisation rate achieved.

General modelling sssumptions

These were as follows:

1. Cord blood units are assumed to have a 20-year shelf life.[76]
2. Once the inventory has reached its target capacity, the number of cord blood units will run down to 0 over 30 years through issues for transplants and expiry of donations after 20 years in the bank. This will not happen in reality; modelling has been done this way simply to ensure the costs align to the benefits.
3. In line with DH impact assessment guidance, discount rates of 3.5% for all costs (including NHS cost savings) and 1.5% for benefits (whether expressed in QALY or monetary terms) are applied.
4. All present and future costs are presented in real terms (i.e. there is no adjustment for inflation).
5. We take the value of a QALY to be £60,000.
6. An opportunity cost multiplier of 4 is applied to NHS costs for the calculation of the Net Present Value as specified in the Department of Health Impact Assessment Guidance.
7. The profile of expansion was agreed with NHSBT. The profile helps to inform how many donations would be collected and issued in a given year.
8. To expand the UK inventory to 30,000 donations, the number of donations banked annually remains constant in years 1 and 2, and then reduces for years 3 and 4 to reach 30,000. This collection profile has been chosen to allow a gradual phasing out of collection towards the end. This is to help mitigate the redundancy costs of consolidating collection activity.
9. The number of cord blood units stored each year is equal to the existing number of cord blood units in storage, plus the additional cord blood units collected, minus the cord blood units used or discarded.
10. During expansion, utilisation is assumed to be 1% of the average bank size that year.
11. The number of exports is assumed to be equal to the number of cord blood units needed to be used to bring utilisation to 1% on top of the cord blood units used domestically. This calculation takes double cord blood unit usage into account.[77]
12. It is assumed that 59% of transplants are double cord blood transplants. This figure is based on information on double cord transplants in 2013 provided by Anthony Nolan.
13. The total unmet need is estimated at 351 patients per year. Of this, we estimate that 257 patients each year might receive a transplant from a cord blood inventory of 30,000 donations, and 298 patients might receive a transplant from an inventory of 50,000 donations.
14. We assume that 78 transplants will be supplied by imported cord blood donations.
15. We assume that the cost of an imported cord donation is £29,879, and exported cord blood donations are sold at £21,500.

76. This assumption is for modelling purposes only.
77. This assumption has been made for modelling purposes to ensure that the separate assumptions about unmet need and bank utilisation are internally consistent. If higher utilisations are achieved, as modelled in the sensitivity analysis, then it is assumed that the proportion of exports will increase.

Based on these criteria, the expansion profiles for option 1 (status quo), option 2 (expansion to 30,000 donations), and option 3 (expansion to 50,000 donations) are shown at Tables 20, 21 and 22.

Table 20: Expansion profile for option 1 (20,000 donations; status quo)

Year	0	1	2	3	4	Total
Additions to inventory		4,550				4,550
Inventory size	15,300	19,700	19,600	19,500	19,300	
Donations issued		123	138	137	136	535

Table 21: Expansion profile for option 2 (expansion to 30,000 donations)

Year	0	1	2	3	4	Total
Additions to inventory		4,550	4,550	3,413	3,413	15,926
Inventory size	15,300	19,700	24,000	27,200	30,300	
Donations issued		176	220	257	289	941

Table 22: Expansion profile for option 3 (expansion to 50,000 donations)

Year	0	1	2	3	4	5	
Additions to inventory		4,550	4,550	3,413	3,413	3,413	
Inventory size	15,300	19,700	24,100	27,300	30,400	33,600	
Donations issued		149	187	219	246	273	
Year	**6**	**7**	**8**	**9**	**10**	**11**	**Total**
Additions to inventory	3,413	3,413	3,413	3,413	3,413	3,413	39,817
Inventory size	36,700	39,800	42,800	45,900	48,900	51,900	
Donations issued	300	326	353	379	404	430	3,820

Costs and cost savings

Cord blood inventory costs

Costs were forecast using information provided by NHSBT (Table 23).

Table 23: Discounted costs of options 1 (status quo) and options 2 and 3 (expansion).

	Activity	Lifetime cost (£m)
Option 1: 20,000 inventory (status quo)	Collection costs	4.8
	Processing and storage costs	5.6
	Issue costs	0.5
	Total	**10.9**
Option 2: 30,000 Inventory	Collection costs	14.9
	Processing and storage costs	6.3
	Issue costs	0.8
	Total	**22.0**
Option 3: 50,000 Inventory	Collection costs	33.6
	Processing and storage costs	9.4
	Issue costs	1.0
	Total	**44.0**

Transplant costs

A base estimate of £98,200 per transplant is used (see above).

Alternative costs

The cost of the alternative treatment is assumed to be £20,000 per patient (see above).

Export cost recovery

Some costs will be recovered through exporting cord blood. The current price of £21,500 charged by NHSBT per exported donation is assumed to remain constant over the 30 years of the analysis, with alternative options explored in the sensitivity analysis.

R&D cost recovery

£200 net income assumed to be received per cord blood donation after taking the cost of processing into account. Demand from the research community is forecast to be 1000 donations *per annum*. There will be sufficient supply to meet demand under either status quo for the 30,000 option during the expansion phase, hence R&D cost recovery will have little effect on the incremental costs of expansion.

Health gains

Population life expectancy and QALY expectancy

Future life expectancy for different age groups was constructed, based on historic ONS survival data. Each age group was assigned average QALY values, which were discounted at 1.5% *per annum* (the standard DH rate).

Mortality rates

Survival data were taken from a selection of published papers, with and without transplant (see above).

QALY gains

Adjusted mortality rates are used to calculate life expectancy with and without a transplant. Life Year values are adjusted by a factor of 0.8, to reflect co-morbidities and continuing lower health-related quality of life. Future QALY expectancy with and without transplant is netted to give the incremental QALY gain.

QALY assumptions

A QALY gain of 7.3 per transplant has been used (see above). Other QALY gain values are tested in the sensitivity analysis.

The overall QALY gain was calculated by taking the product of 7.3 and the number of domestic transplants. For the net present value calculation (NPV) the QALY gain was converted to a monetary equivalent assuming a value of £60,000 per QALY.[78]

78. DH Impact Assessment Guidance.

Cost per QALY Gain

Table 24 summarises the discounted total costs for each options 1 and 2, and for the difference between the two.

Table 24: Costs per QALY for expansion of the cord blood inventory from 20,000 to 30,000 donations

Status quo (20,000 donations)	Discounted total costs	£241m
	Discounted QALY	20k
Expansion (30,000 donations)	Discounted total costs	£389m
	Discounted QALY	34k
Incremental	Discounted total costs	£148m
	Discounted QALY	14k
TOTAL	**Cost per QALY**	**£10,375**

The incremental cost per QALY between the status quo and the 30,000 inventory option is £10,400. This is below the £15,000 threshold used by DH to evaluate the effectiveness of NHS spending decisions. The case for a 30,000 donation inventory appears broadly reasonable.

Table 25 summarises the discounted total costs for options 1 and 3 and for the difference between the two.

Table 25: Costs per QALY for expansion of inventory from 20,000 to 50,000

Status quo (20,000 donations)	Discounted total costs	£241m
	Discounted QALY	20k
Expansion (50,000 donations)	Discounted total costs	£432m
	Discounted QALY	40k
Incremental	Discounted total costs	£191m
	Discounted QALY	20k
TOTAL	**Cost per QALY**	**£9,437**

The incremental cost per QALY between the status quo and the 50,000 inventory option is £9,400. This is below the £15,000 threshold used by DH to evaluate the effectiveness of NHS spending decisions. The case for a 50,000 donation inventory appears broadly reasonable.

Sensitivity analyses

Univariate sensitivity analysis

As this health economic analysis includes a number of assumptions based on expert opinion (see above), there will be a level of uncertainty surrounding the estimates derived. This section presents the results of a sensitivity analysis on the key parameters in the model. It serves to verify that a result is not driven by any single overarching assumption. In this way, a sensitivity analysis can be considered to improve the robustness of the potential conclusions drawn from the cost benefit analysis.

The analysis works by varying individual parameters one by one while holding the remaining parameters constant. This makes it possible to observe the impact that individual parameters have on the final results and thus assess the degree of uncertainty surrounding the results.

Table 26 presents the results of this univariate sensitivity analysis for the incremental cost per QALY for expanding the cord blood inventory to 30,000 donations and Table 27 shows corresponding results for expanding the inventory to 50,000 donations. The following conclusions can be drawn:

1. There is significant weight attached to uncertainty in health benefits. Altering the QALY gain associated with a transplant by a small amount results in a significant change in both the cost per QALY and the net present value. This is a key uncertainty as the QALY gain following a transplant varies across age groups.
2. Alternative costs, transplant costs, and utilisation rate have a large influence on the net present value. Hence, there is uncertainty about the overall cost to the NHS and not just around the collection of stem cells.
3. A higher level of utilisation would strengthen the case for a cord bank expansion. However, a higher level of utilisation than 1% is not supported by international comparisons.
4. Changing the price of exports or varying the R&D sales price does not make a significant impact, unless there is a large number of exports.

Table 26: Results of the univariate sensitivity analysis for expanding the cord blood inventory to 30,000 donations

Parameter	Original Value	Sensitivity Value	Cost per QALY	Net Present Value
Base Case			**£10,375**	**£263.9m**
Alternative costs	£20,000	£40,000	£8,091	£394.2m
		£10,000	£11,518	£198.7m
Transplant costs	£98,200	£73,200	£7,520	£426.8m
		£123,200	£13,231	£100.9m
QALY gain	7.3	5	£15,078	-£3.1m
		6	£12,565	£114.7m
		7	£10,770	£232.5m
		8	£9,424	£350.3m
		9	£8,377	£468.1m
Utilisation (future)	0.85%	0.50%	£13,763	£23.9m
		1.50%	£7,433	£405.8m
		2.00%	£4,349	£536.5m
Met unmet demand in long run	257	150	1.00	£7,885
		400	2.00	£10,954
Double cord ratio	1.59	1.00	£10,000	£10,000
		2.00	£14,500	£10,147
Export price	£21,500	£10,000	£25,000	£10,490
		£14,500	£0	£10,415
		£25,000	£100	£10,395
R&D sales price	£200	£0	1.00	£7,885
		£100	2.00	£10,954

Table 27: Results of the univariate sensitivity analysis for expanding the cord blood inventory to 50,000 donations

Parameter	Original Value	Sensitivity Value	Cost per QALY	Net Present Value
Base Case			**£9,437**	**£450.4m**
Alternative costs	£20,000	£40,000	£7,309	£622.7m
		£10,000	£10,502	£364.2m
Transplant costs	£98,200	£73,200	£6,777	£665.8m
		£123,200	£12,098	£235.0m
QALY gain	7.3	5	£13,715	£71.6m
		6	£11,429	£238.7m
		7	£9,797	£405.9m
		8	£8,572	£573.0m
		9	£7,620	£740.2m
Utilisation (future)	1%	0.50%	£11,491	£183.7m
		1.00%	£8,418	£523.8m
		1.50%	£4,942	£755.6m
Met unmet demand in long run	257	200	£5,429	£320.9
		450	£10,049	£511.3
Double cord ratio	1.59	1.00	£7,229	£509.4
		2.00	£10,483	£370.8
Export price	£21,500	£10,000	£9,621	£435.5
		£14,500	£9,549	£441.3
		£25,000	£9,382	£454.9
R&D sales price	£200	£0	£9,616	£436.0
		£100	£9,527	£443.2

Monte Carlo analysis

A Monte Carlo analysis allows the overall uncertainty of the results to be assessed. The simulation is run by allowing the parameters of the model to be drawn from uniform distributions between pre-specified values. The parameters are then picked at random from their distributions and plugged into the model. The process is repeated 10,000 times, allowing a distribution of results to be constructed.

We have performed this analysis for expanding the cord blood inventory to both 30,000 and 50,000 donations. Table 28 lists the parameters of the model, as well as their lower and upper bounds between which their values are distributed uniformly.

Table 28: Parameter ranges for the Monte Carlo analysis

Parameter	Base Case	Lower Bound	Upper Bound
Alternative costs	-£20,000	-£10,000	-£30,000
Transplant costs	£98,200	£73,200	£123,200
QALY gain	7.3	5	9.6
Unmet need met at steady state: 30.000 donations 50.000 donations	 257 298	 150 150	 350 450
Future utilisation: 30.000 donations 50.000 donations	 1.00% 0.85%	 0.50% 0.35%	 1.50% 1.35%
Export revenue	-£21,500	-£21,000	-£22,000
Double cord transplant frequency	1.590	1.290	1.890

Figure 15 shows the frequency distribution of the incremental cost per QALY of expanding the cord blood inventory to 30,000 donations resulting from the 10,000 simulations, and Figure 16 shows a corresponding distribution of expanding to 50,000 donations. The base case cost per QALY (£10,400 and 9,400 respectively) and the 10th and 90th percentiles are marked.

Figure 15: Cost per QALY distribution for expansion of the cord blood inventory to 30,000 donations

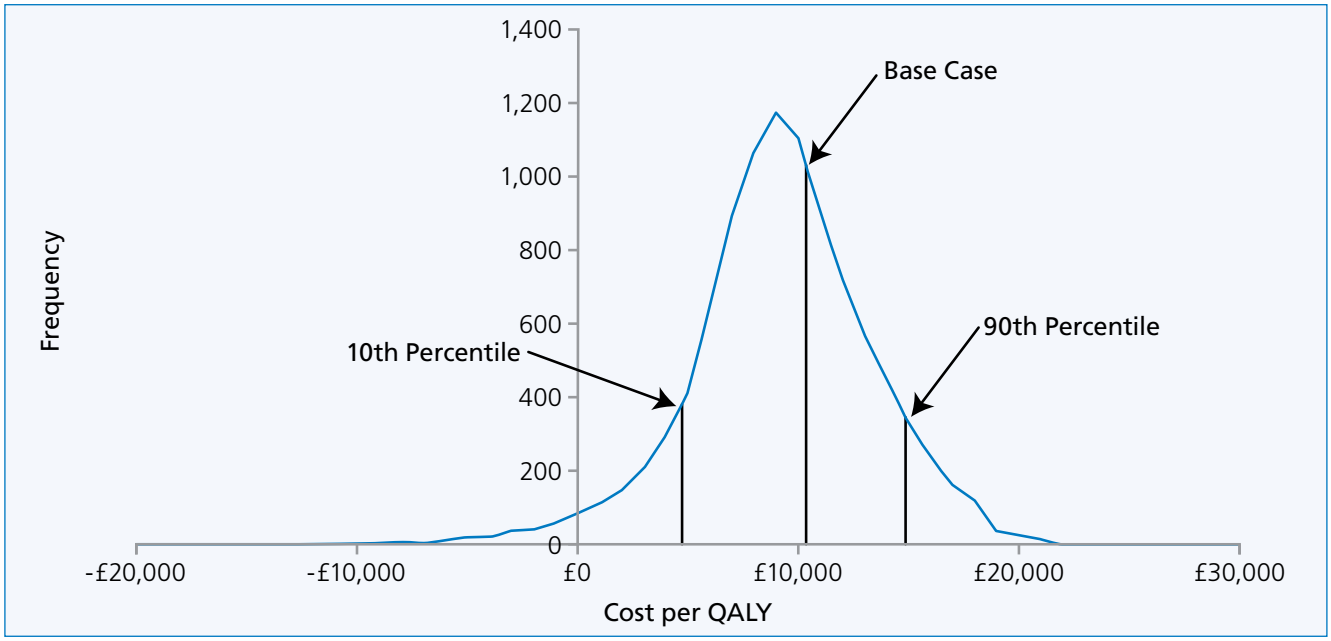
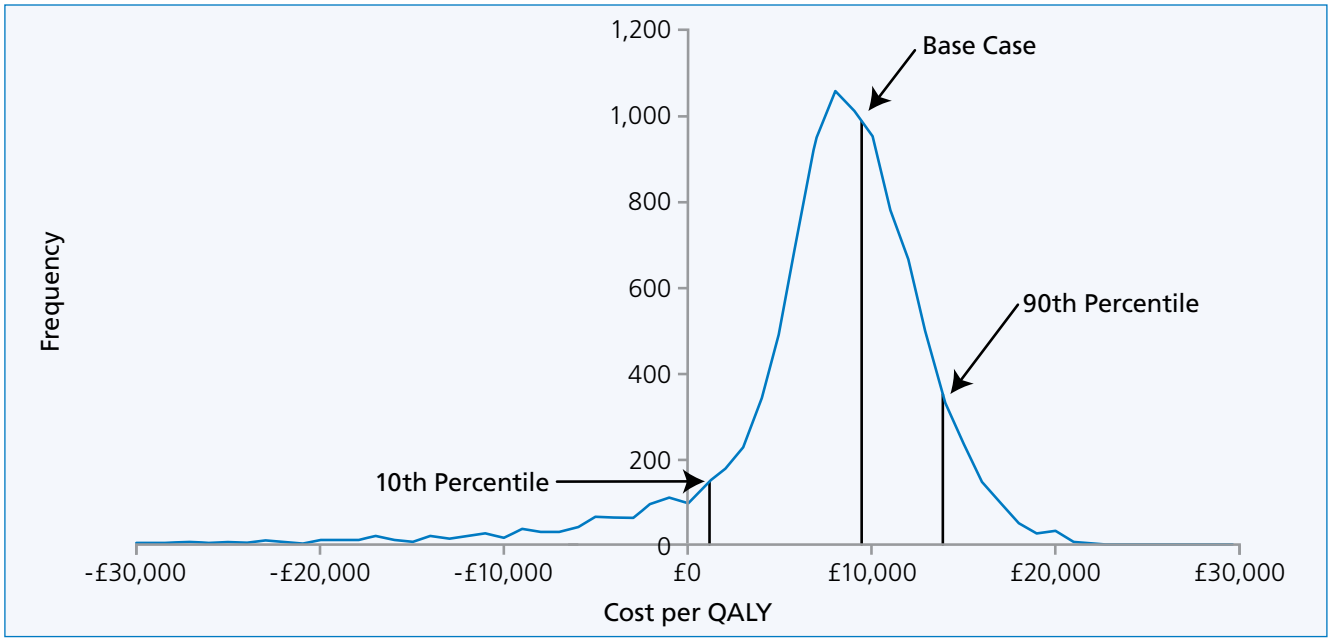


Figure 16: Frequency distribution of net present value for expansion of the cord blood inventory to 50,000 donations



Figures 17 and 18 show the frequency distribution of the net present value of incremental benefits or expansion to banks of 30,000 and 50,000 donations, respectively. Results are summarised in Tables 29 and 30.

Figure 17: Frequency distribution of net present value for expansion of the cord blood inventory to 30,000 donations

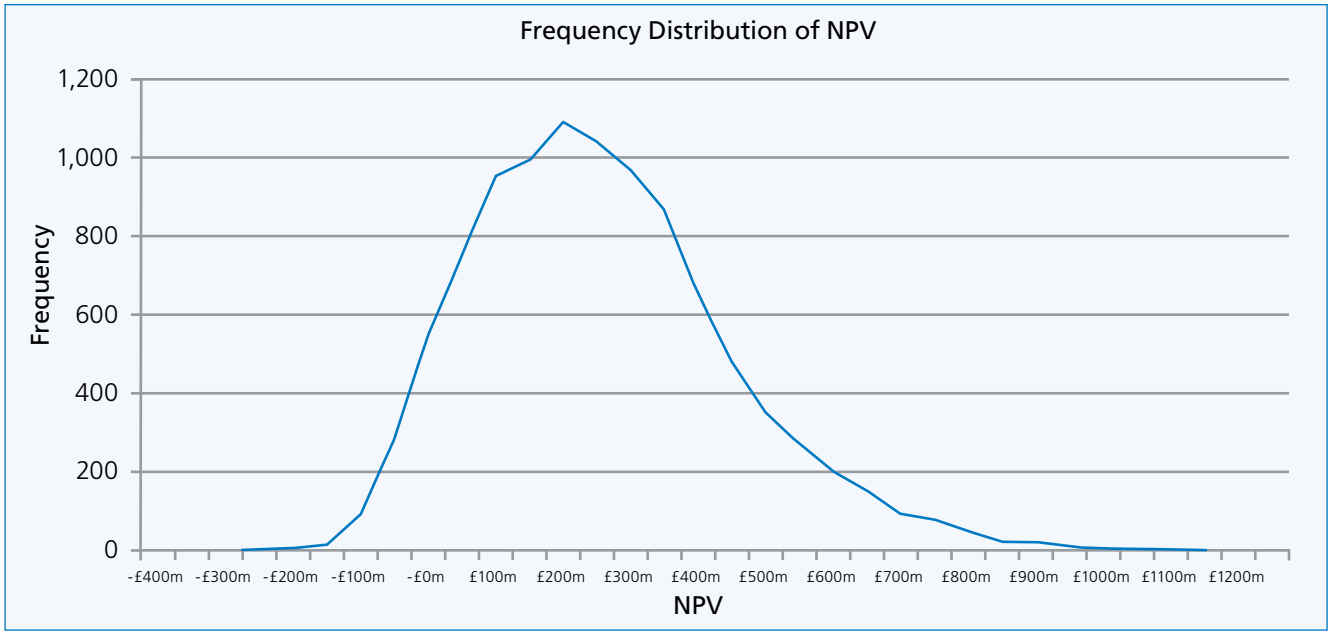


Figure 18: Frequency distribution of net present value for expansion of the cord blood inventory to 50,000 donations

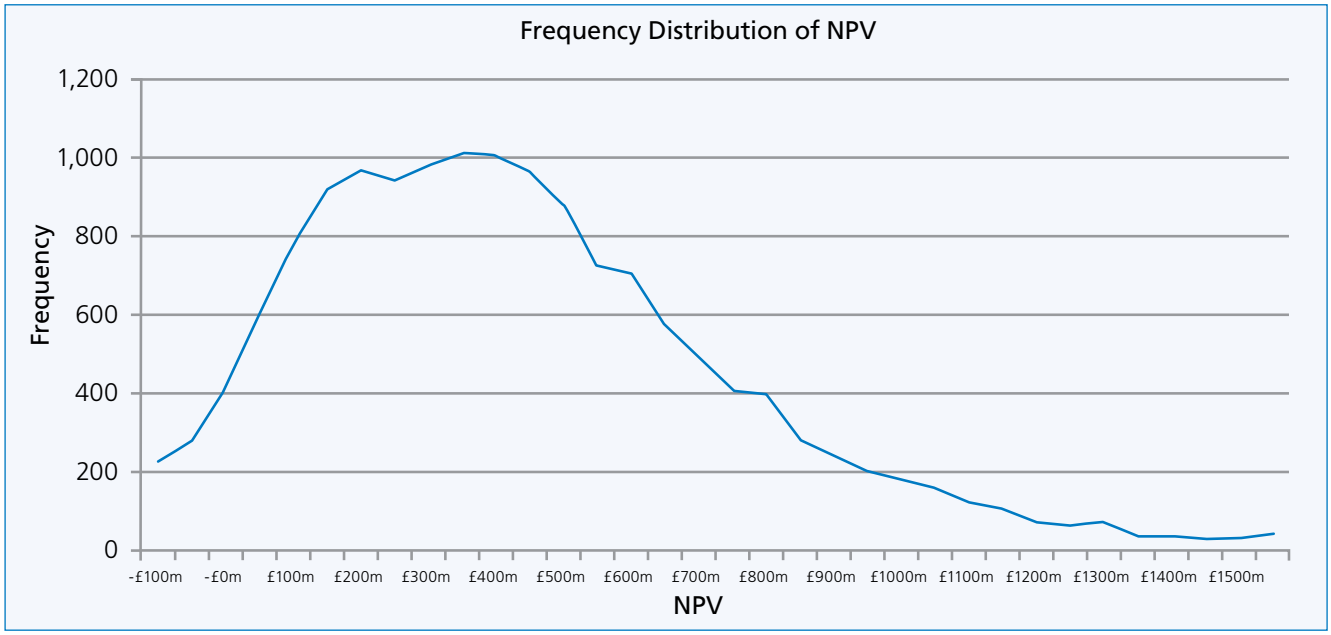


Table 29: Summary of Monte Carlo analysis results for expansion of the cord blood inventory to 30,000 donations

Variable	Mean	Median	10th Percentile	90th Percentile
Cost per QALY	£9,624	£9,773	£4,744	£14,867
NPV	£231.6m	£212.5m	£485.0m	£3.8m

Table 30: Summary of Monte Carlo analysis results for expansion of the cord blood inventory to 50,000 donations

Variable	Mean	Median	10th Percentile	90th Percentile
Cost per QALY	£8,753	£8,872	£1,153	£13,889
NPV	£409.7m	£368.1m	£833.4m	£48.2m

This analysis quantifies the uncertainty in the model. The range of possible costs per QALY is wide and although the base case estimate falls under the £15,000 threshold, there is a possibility that the cost per QALY could exceed the threshold.

Cost-effectiveness of expanding the "fit panel"

We have also assessed the cost-effectiveness of expanding the fit panel from 45,400 to 150,000. To do this, we have compared the costs and benefits of expanding the panel to 150,000 registered donors with those for a panel that continues at 45,400 donors to derive a cost per additional QALY gained.

This has broadly followed the same methodology as for the expansion of the cord blood bank described above. In particular, we have assumed that:

- The fit panel will reach 150,000 by the end of 2019/20;
- The utilisation rate will depend on the size of the panel, starting at the current level of 0.4% but reducing to 0.3% for a panel of 150,000;
- The proportion of donations exported is 31% (based on information for 2013/14);
- The individuals in the fit panel, and the new recruits, are evenly spread across the age range of the fit panel;
- Around 0.6% of fit panel members will leave the panel each year (based on data from Anthony Nolan for 2012/13) and that the leavers will be evenly spread across the age range;
- Each transplant will result in a benefit of 9.7 QALYs. This is derived from survival rates for unrelated donor stem cell transplants (BSBMT 5th report to Specialist Commissioners) using the methodology reported above;
- The cost of a transplant, and of alternative treatment, will be the same as for a cord blood transplant;
- We use cost information provided by NHSBT.

This analysis suggests that the cost per additional QALY from expanding the fit panel is of the order of £8,500. This is well within the typical DH threshold of £15,000 per QALY.

Univariate sensitivity analysis

Table 31 presents a univariate sensitivity analysis for selected variables for the expansion of the fit panel.

Table 31: Results of the univariate sensitivity analysis for expanding the fit panel to 150,000 volunteers

Parameter	Original Value	Sensitivity Value	Cost per QALY	Net Present Value
Base Case			**£8,500**	**£520m**
Alternative costs	£20,000	£40,000	£6,700	£650.0m
		£10,000	£9,400	£450.0m
Transplant costs	£98,200	£73,200	£6,300	£690.0m
		£123,200	£10,700	£340.0m
QALY gain	9.7	7	£11,800	£190.0m
		8	£10,300	£310.0m
		9	£9,200	£430.0m
		10	£8,300	£550.0m
		11	£7,500	£670.0m
		12	£6,900	£790.0m
Utilisation of 150,000 panel (future)	0.3%	0.40%	£8,200	£730.0m
		0.25%	£8,700	£410.0m
		0.20%	£9,100	£300.0m
Export rate	31%	21%	£8,600	£580.0m
		41%	£8,400	£450.0m

Conclusions

The results are broadly favourable to a move to a cord blood inventory of 30,000 donations or 50,000 donations, based on the base case assumptions. The base case estimates of cost per QALY (£10,400 and £9,400 respectively) are both within the typical DH threshold of £15,000. However, both sensitivity analyses demonstrate a level of uncertainty surrounding the estimates, and suggest that there are scenarios where the cost per additional QALY exceeds the typical threshold.

Abbreviations and acronyms

BAME	Black, Asian and minority ethnic
BM	Bone marrow
BMT	Bone marrow transplant
BSBMT	British Society of Blood and Marrow Transplantation
BSHI	British Society for Histocompatibility and Immunogenetics
CB	Cord blood
CBT	Cord blood transplant
CCG	Clinical Commissioning Group
CTC	Clinical Trials Committee (BSBMT)
CIBMTR	Center for International Blood and Marrow Transplant Research
CMV	Cytomegalovirus
CQUIN	Commissioning for Quality & Innovation
CRG	Clinical Reference Group
EBMT	The European Marrow Group for Blood and Marrow Transplantation
EMDIS	European Marrow Donor Information System
FACT	Foundation for the Accreditation of Cellular Therapy
GCSF	Granulocyte colony stimulating factor
GIAS	Graft identification advisory service
GvHD	Graft versus host disease
HLA	Human leukocyte antigen
HSCT	Haemopoietic stem cell transplantation
HTA	Human Tissue Authority
IPS	Induced pluripotent stem cell
JACIE	The Joint Accreditation Committee – ISCT & EBMT
LLR	Leukaemia and Lymphoma Research
NGS	Next generation sequencing
NHSBT	NHS Blood and Transplant
NHS-CBB	NHS Cord Blood Bank
NMDP	National Marrow Donor Programme
ONS	Office for National Statistics
PBSC	Peripheral blood stem cells
QALY	Quality-adjusted life year
QIPP	Quality Innovation Productivity and Prevention
R & D	Research and development
SNBTS	The Scottish National Blood Transfusion Service
TAP	Trials acceleration programme
TNC	Total nucleated cell count
WBMDR	Welsh Bone Marrow Donor Registry
WBS	Welsh Blood Service
WMDA	World Marrow Donor Association
ZKRD	German National Bone Marrow Donor Registry

NHS Blood and Transplant

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