

The Future of Unrelated Donor Stem Cell Transplantation in the UK

Part 1

Findings and Recommendations



A Report from the UK Stem Cell Strategic Forum
July 2010



Foreword

Haemopoietic stem cell transplantation is a rapidly advancing area of science and medicine and is now firmly established worldwide as an important curative therapy for patients with leukaemia and other haematological malignancies. As a result of the increased availability of stem cells from unrelated donors, specifically adult unrelated donors and umbilical cord blood units, the number of patients transplanted year on year continues to grow, with consequent clinical benefit. It is particularly gratifying to note the recent increase in the use of cord blood in the UK following continued investment in the NHS-Cord Blood Bank since 1996.

Despite these advances, many patients in the United Kingdom cannot benefit from this potentially life-saving treatment because they lack a suitable donor. As a result more than 400 patients each year are denied access to a transplant; current trends show that over 200 of these lives could be saved by transplantation were a donor to be available. This loss of life disproportionately affects Black and minority ethnic patients because of the particular challenges in identifying suitable donors for members of these communities.

The UK Stem Cell Strategic Forum was set up at the request of the Minister of State for Public Health in January 2010 to advise on future options for the provision and use of stem cells derived from unrelated adult volunteer donors and cord blood. It was asked to report its findings to UK Health Ministers. This report is the result of three months of intensive effort by over forty scientists, clinicians, economists, and patient representatives.

This report sets out a strategy to save 200 lives each year by increasing the UK inventory of cord blood donations, and by improving the performance of UK-based stem cell registries to match the best in the world. This bold vision will take time to realise, but the recurring clinical and economic benefits are substantial.

In the current economic climate, it is more important than ever to ensure maximum patient benefit is derived from available funds. A focus on efficiency, effectiveness, quality and patient outcomes is therefore at the heart of our recommendations. Hence we advocate a process to performance manage the supply of adult stem cells and cord blood. We also advocate an overhaul of unrelated donor and cord blood stem cell transplantation commissioning. We recommend a framework to ensure equity of access to stem cell transplantation and identify the potential to improve patient outcomes by encouraging the consolidation of stem cells within Regional Centres of Excellence. The UK has an international reputation for excellence in basic and clinical research in stem cell transplantation. Our recommendations are intended to ensure the UK continues to play a major role in the translation of stem cell research into effective therapies.

As well as the 20 recommendations contained in this report, the UK Stem Cell Strategic Forum agreed the following consensus statements:

1. Stem cell transplantation from either adult unrelated donors or umbilical cord blood are highly effective treatment strategies for children and adults with high risk leukaemia and other haematological disorders who lack a sibling donor.
2. There is a clear and important need to significantly decrease the time it takes to identify suitably matched unrelated donors. This can be achieved through better tissue typing of volunteer donors and exploitation of information technology platforms which assist in the prediction of patient-donor compatibility.
3. Given the unique ethnic diversity of the United Kingdom, the UK should work towards a target of 50,000 banked cord blood units, accessible to all NHS patients. Improved access to adult unrelated donors and cord blood donations will cure around an additional 1000 people of an otherwise fatal condition over the next ten years and thereafter cure an additional 200 people annually when the expansion of the UK's cord blood inventory should be complete.
4. Research has demonstrated that stem cell dose is a critical determinant of outcome after cord blood transplantation. This should be reflected in the criteria used to select cord blood for banking to ensure inventory utilisation and clinical benefits are maximised.

5. 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.
6. Importation of cord blood units from international registries cannot substitute for the development of a UK cord blood inventory since it ignores this country's unique ethnic diversity and will not address the fundamental issue of lack of donor availability - particularly in Black and ethnic minority communities. Furthermore, it is not consistent with the economically sustainable development of cord blood transplantation over the medium and long term.
7. Unrelated donor transplants are complex treatments with a substantial procedure-related mortality. Regional Centres of Excellence for unrelated donor transplantation, specifically cord blood transplantation, should be established in order to optimise patient outcomes. Any savings accrued from this rationalisation should be considered for re-investment in the stem cell transplant programme of the NHS.
8. A system should be put in place for all units performing unrelated donor transplants to report immediate and long term patient outcomes to commissioners through a national transplant outcome registry. This should be a pre-requisite of obtaining transplant funding.
9. Given the significant morbidity and mortality associated with unrelated donor transplantation, it is highly desirable that transplants are performed according to disease specific registration studies and where possible, appropriately badged clinical trials. Commissioning authorities should encourage the development of appropriate studies for patients undergoing unrelated donor transplantation.
10. Substantial Government funding over the last two decades has resulted in the development of a world-class science base in stem cell biology within the United Kingdom. A clinical trials network of centres performing unrelated donor stem cell transplantation should be established. This will create one of the world's largest stem cell transplantation trials networks and consolidate the UK's international leadership role in translational research.
11. Collaborative links should be established between unrelated donor registries, UK cord blood banks, and the biopharmaceutical industry. Models in other countries identify such links as an important opportunity for income generation. This initiative, coupled with the establishment of a clinical trials network, has the capacity to attract inward investment to the UK which will create jobs in the knowledge rich biotechnology sector.

In presenting our findings and recommendations, we acknowledge that different strategic and policy frameworks operate in the four countries of the UK. As part of our recommendations, we strongly urge the Health Departments and service providers across the UK to continue the collaborative approach established by the UK Stem Cell Strategic Forum to ensure NHS patients achieve the best clinical outcomes.



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Executive Summary

The Provision of Unrelated Donor Stem Cells

Every year, transplantation of haemopoietic stem cells from unrelated donors, specifically adult volunteers or umbilical cord blood units, extends or saves the lives of hundreds of adults and children who are suffering from potentially fatal conditions such as leukaemia and lymphoma. For these patients, no alternative to transplantation exists. Advances in medical science have improved patient outcomes after transplantation, with more than 54% of patients now alive one year after unrelated donor stem cell transplantation compared to 42% ten years ago. Moreover, the increasing ability to transplant older patients continues to drive the growing number of transplants in the UK; around 750 unrelated donor transplants were performed in 2009 compared to approximately 300 in 2001. *Unrelated donor stem cell transplantation in the UK is described in Annexes 1 and 2.*

From the evidence received, the Forum clearly identifies a need for unrelated stem cell donors which is not being met through our current systems. **The evidence suggests that, each year, there are about 440 patients with fatal diseases who could benefit from a transplant if an unrelated adult stem cell donor or a cord blood donation could be identified in a timely manner.**

The UK developed the world's first ever bone marrow registry, established by the Anthony Nolan Trust (ANT) in 1974. Today the UK has three registries; the British Bone Marrow Registry (BBMR), the Welsh Bone Marrow Donor Registry (WBMDR) and the ANT. Between them, they list over 770,000 volunteer donors. Worldwide another 16 million donors are listed on 73 international registries.

Over the past decade, there have been considerable advances in the use of umbilical cord blood as an alternative source of stem cells for use in transplantation. As evidence for the clinical effectiveness of cord blood transplantation increases, so too does the number of transplants performed. In 2009, 13% of UK unrelated donor transplants used cord blood compared to 2% in 2001. This trend is forecast to continue; in France and Spain, 30% to 40% of unrelated donor transplants use cord blood. Evidence suggests that outcomes for children following cord blood transplantation are comparable, and in some situations superior, to using adult stem cells. In the adult setting, it has recently become clear that cord blood transplantation achieves similar results to adult stem cells where a fully matched unrelated donor cannot be identified and when the need for transplant is urgent.

The NHS-Cord Blood Bank has an inventory of 15,500 cord blood units (of which about 8,500 units contain the dose of stem cells typically requested for transplant) and has issued over 300 units for transplantation. The NHS-Cord Blood Bank collects cord blood from five hospitals in the London area, and by focusing collection in this way, 40% of banked units are from Black and minority ethnic donors. ANT, the Scottish National Blood Transfusion Service and the Northern Ireland Blood Transfusion Service have a combined inventory of 1137 units, and 1 donation has been provided for transplant (by the Northern Ireland Blood Transfusion Service). During 2009, the three stem cell registries provided 791 stem cell donations: 41% were sourced from UK donors and of these, 72% were provided by the ANT, 27% by the BBMR, and 1% by WBMDR. Ninety seven percent of non-UK stem cell donations were imported by the ANT.

However, despite this resource, and the fact that British registries are part of an international network providing access to over 16 million adult donors and 537,000 cord blood donations, significant challenges remain in the rapid identification of a suitably matched stem cell donor for many patients. This problem is greatest within Black and minority ethnic sectors of our population. There is a significant shortage of Black and minority ethnic donors on all major international registries; only 5% of BBMR donors and 8% of ANT donors are non-Caucasian. As a result, Black and minority ethnic patients are disadvantaged because HLA types (which determine genetic and biological compatibility between donor and patient) are related to ethnicity. Thus while around 90% of north European Caucasian patients may typically find a match, the matching rates for Black and minority ethnic donors may be 40% or lower, especially for patients of mixed genetic heritage. The length of time it takes to find a properly matched donation critically impacts on transplant outcome, and patients die because of delays in stem cell procurement. The Forum found that, each year, about 170 Caucasian and 90 Black minority ethnic patients fail to locate a suitably matched adult donor. Furthermore the Forum found that in the UK each year, around 110 patients with a matched donor die or deteriorate beyond transplantation while waiting to be transplanted.



The Patient Pathway

Unrelated donor stem cell transplantation remains a complex procedure, requiring considerable experience and expertise. The Review noted several recent studies showing that post-transplant outcomes are significantly worse for patients treated at centres performing relatively few procedures. In 2009, **54% of UK donor stem cell transplants were performed by the ten most active centres; the ten least active centres carried out just 10% of all transplants.**

Centralisation of specialised services has occurred across a range of fields in recent years, including cardiac care, trauma management, stroke treatment and other cancer divisions, with the guiding aim of improving the quality of patient care. Given the high overheads of each transplant centre, a similar approach should be considered for unrelated donor stem cell transplantation, to establish high performing facilities producing optimal patient outcomes while delivering improved cost efficiencies.

The patient pathway for an unrelated donor stem cell transplant recipient spans months or even years of pre- and post-transplant treatment. Typically, this involves input from multiple bodies and organisations, including hospitals, stem cell providers, specialised commissioning groups, and Primary Care Trusts. However, this Review found **divergent commissioning practices, variable cost allocations, and fragmented governance arrangements.**

In seeking to establish the economic case for developing stem cell transplantation in the UK, **the Forum found a lack of comprehensive, contemporary long-term outcome data.** In part this was due to a lack of nationally agreed protocols for stem cell transplantation in the UK. Historically, systems and funding for data collection and analysis have been *ad hoc*, although the British Society of Blood and Marrow Transplantation is now more formally collecting outcome data to inform commissioning processes. This work should be built upon to ensure that NHS patients, professionals and service providers benefit from robust outcome data that can be used to improve service provision.

The Review accepts that this area of NHS healthcare is a devolved matter, and as a result there will be divergence in policy and practice across the four countries of the UK. However, throughout this process, a strong willingness has been shown by all partners to develop frameworks and delivery systems that provide the best clinical outcome for patients and are cost effective and efficient. As part of our recommendations, we strongly urge the Health Departments and service providers across the UK to continue this collaborative approach to service provision with the aim of ensuring NHS patients receive the best outcomes.

Recommendations

Improve the Provision of Unrelated Adult Donor Stem Cells

To increase the number of UK patients finding an acceptable match within a clinically appropriate time period, **we recommend** that:

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.
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.
3. The UK should create or purchase predictive search technologies (such as those used by German and US registries) to increase the chance that selected donors are a match for the patient.
4. A 'graft identification advisory service' should be established to ensure optimal donor selection for each patient.
5. Registries should increase contact with donors, updating information on their contact details, health status and willingness to donate.

These measures are intended to create a 'fit panel' of volunteer donors. Collectively, they would a) increase the proportion of selected adult volunteers able to donate from 60% to 90%, b) reduce the number of donor searches by around 30%, c) reduce the number of extended HLA typings performed at donor selection by 75% and d) reduce search to transplant times by four to six weeks.

Improve the Provision of Cord Blood Stem Cells

A well utilised, genetically diverse inventory of cord blood is the most effective strategy to address the unmet need of UK patients. As the ethnic diversity of the UK, is unique, the inequality of access to donor stem cells cannot be effectively addressed by importation.

Based on an analysis of transplantation trends, and of patient and donor demographics (detailed at Annex 5), **we recommend** that:

6. The UK should increase its inventory of cord blood to 50,000 units over eight years. This time period represents a cost-effective approach to achieving the required inventory.
7. The inventory should contain 30% to 50% of donations from Black and ethnic minority women.
8. Newly banked units should have a high total nucleated count threshold (over 9×10^8 TNC from ethnic minority donors, over 12×10^8 TNC from Caucasian donors).
9. High resolution HLA typing should be performed on all of newly stored units and selected existing units.

Collectively, these measures would a) satisfy 85% of unmet Caucasian need (around 150 patients each year) and 50% of unmet Black and minority ethnic need (around 50 patients each year), b) improve search to transplant times (around 100 patients each year who fail to receive an adult stem cell transplant due to delays in provision would be able to be transplanted), c) improve donor/recipient matches (around 70 patients each year transplanted with a 9/10 matched adult donor could be transplanted faster or more effectively).

Operating with a feasible target of 1% annual utilisation, the cord blood inventory would, in the medium term, be capable of supplying cord blood donations at a significantly lower cost per unit (£16,000 each) than the current cost of an adult donation (£36,000), a domestic cord blood donation (£45,000) or an imported cord blood donation (around £25,000).

Drive Quality and Efficiency

Unrelated donor transplantation should reflect clinical best practice. Acknowledging differences in policy across the UK, **we recommend** that:

10. Educational tools and platforms should be developed to improve understanding among commissioning bodies. With the support of physicians, commissioners should align their strategies with the latest clinical guidance and patient outcome data.
11. Commissioning bodies should operate within a standardised funding framework, using a baseline figure adjusted to reflect market forces factors. This should detail the necessary costs for each stage of the patient's treatment to provide clarity and certainty to all service providers. This framework should cover the entire patient pathway, including pre- and post-transplant treatment.
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.
13. All centres performing unrelated donor stem cell transplantation should be accredited by the Joint Accreditation Committee of ISCT and EBMT (JACIE).
14. Local networks should be linked into designated centres and make appropriate referrals when necessary.
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.
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.
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.
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.
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.
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, the ANT, research organisations and charities to define research opportunities, to facilitate the translation of basic research into the clinical practice, and to maximise income through the commercialisation of intellectual property.

Health Economic Analysis

The Current Cost of Providing Unrelated Adult Stem Cells to UK Patients

The total cost of providing unrelated adult stem cells for UK patients was £25.4m during 2009. This includes organisational overheads, infrastructure costs as well as direct costs, and the cost of importing stem cell donations (ANT importation costs of £8.75m). Scottish donors are registered with the ANT. Northern Irish donors are registered on the BBMR.

The Current Cost of Providing Cord Blood to UK Patients

The total cost of providing cord blood donations for UK patients was £8 million during 2009. This includes organisational overheads, infrastructure costs as well as direct costs, and the cost of importing cord blood donations (ANT importation costs of £2.1m. Scottish donors are registered with the ANT; Northern Irish donors are registered on the BBMR.

The Economic Case for Improving the Provision of Adult Donor Stem Cells

Though the creation of a 'fit' panel would require considerable effort and investment, if designed correctly it could bring significant patient benefits and recover costs through improved utilisation rates and more efficient donor searches, with fewer deferrals and a lower number of extended typings for each donation issued. A preliminary cost benefit analysis looks promising, and has estimated around £9m of benefits over 10 years balanced by around £9m of costs. However, several significant costs and benefits are yet to be quantified, in particular concerning improvements in survival associated with earlier transplantation and costs of a Graft Identification Advisory Service (GIAS). Additional work will be needed to make an overall estimate of the economic case, drawing on results of the GIAS pilot currently being undertaken by ANT.

The Economic Case for Improving the Provision of Cord Blood

A health economic analysis of the projected expansion of the UK's cord blood inventory shows that the case for expanding the inventory to 50,000 looks broadly reasonable. This compared the proposal to expand to 50,000 units over eight years with the current strategy of achieving an inventory of 20,000 units within four years. All of the likely costs and benefits of improved provision were considered, including collecting, storing, and issuing cords, possible research and development, export cost recovery, costs of transplantation and the likely alternatives, and survival and quality of life improvements measured in Quality Adjusted Life Years (QALYs). Indeed the long run cost of an issued cord (£16,000) only represents around 16% of the overall cost of transplantation and follow-up (around £100,000), demonstrating the importance of estimating and including all likely costs and benefits, including any additional hospital investment required by the NHS. An annual utilisation of 1% for an expanded bank is considered to be achievable, given the level of unmet demand and comparisons with other major international banks. Utilisations in excess of this have also been modelled; while these would improve the economic case significantly (e.g. incremental cost per QALY of around £23k at 1.5% utilisation), they would rely significantly on large increases in exports to be achievable. An expanded bank may reasonably be expected to save around 1,000 QALYs per year. The incremental costs per QALY are in the region of £27k, typically considered to be justifiable in the context of public sector health spending.

Considerable uncertainty surrounds some of the inputs to the economic case however, in particular patient outcomes; there is currently limited information on long-term survival and quality of life, both with and without a cord blood transplant. However, as the practice of cord blood stem cell transplantation improves and survival rates rise further, the economic case for investment in cord blood banking is likely to improve.

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