



UMBILICAL CORD BLOOD BANKING

This is the second edition of the Scientific Opinion Paper on *Umbilical Cord Blood Banking*. It replaces the previous version published in October 2001.

1. Background

Since 1996, UK cord blood banking of haemopoietic stem cells (HSC) from umbilical cord blood has been undertaken largely by NHS facilities within the National Blood Service (NBS), funded initially through research and development funding^{1,2} and currently through the Department of Health. Women in selected maternity units in the UK are approached during the antenatal period and offered the option to donate cord blood to the NHS Cord Blood Bank (NCBB). Appropriate consent is obtained by trained NBS staff and the blood is collected by trained NBS operatives. These donations are sent to the NCBB for processing and storage for future potential use in unrelated transplantation, in a similar way to bone marrow donations. The donations are tested for a variety of parameters including markers of infection and for their tissue types (human leucocyte antigen, HLA). The tissue types of both unrelated cord blood and bone marrow donors are available for search for matches for any patient, anywhere in the world, for those who may require HSC transplantation. This established non-directed or altruistic cord blood banking service is to be distinguished from directed family or autologous cord blood storage now being offered commercially by a number of companies trading in the UK.

Commercial services offer mothers the opportunity to store their own baby's cord HSC long-term, in case that child or his/her siblings ever develop a metabolic, immunological or haematological disease that could only be treated by autologous or related cord blood stem cell transplantation. In addition, with the promise of stem cell therapy for cure or amelioration of degenerative diseases, commercial cord blood banks have added this potential benefit to the rationale given for personal storage of cord blood.

Advertising leaflets are distributed to antenatal clinics, to assisted conception units and to doctors' surgeries and there is also considerable advertising in women's magazines and on the worldwide web. The promotional literature for private cord blood banking appears persuasive: 'stem cells can only be collected at the time of birth'; 'unimaginable possibilities'; 'a once in a lifetime opportunity' that is 'like freezing a spare immune system'; 'saving the key components to future medical treatment'; 'saving something that may conceivably save his or her life someday'.

Clinicians have been approached directly by these banks but, like midwives, they are also being confronted with this issue by parents who request that their baby's cord blood be collected at the time of delivery and transported for storage. The aim of this revised document is to provide advice on the scientific basis behind umbilical cord blood storage, current clinical use, the safety and legal implications of collection, the dilemma between personal and altruistic cord blood storage and on the likely utility of cord blood stem-cells in the future.

2. What does umbilical cord blood contain?

Cord blood contains HSC. These proliferative cells are about one log fewer in number than can be obtained from bone marrow or peripheral blood HSC donation, but they have greater proliferative and colony forming capacity, and are more responsive to some growth factors. Also because they are more 'naïve' than proliferative cells from bone marrow, they seem to produce fewer complications associated with some aspects of HSC transplantation (see page 4).³

In the future, cord blood might be a useful source of stem cells other than haemopoietic precursors. Reports suggest that not only are mesenchymal and neural precursor cells present but that some cord blood cells, present in extremely low frequency, may have the capacity to develop into many different lineages including cartilage, fat cells, hepatic and cardiac cells.⁴ Research is still at an early stage and despite the amount of interest in the field,⁵ the therapeutic role for such cells remains speculative.

3. Sources of cord blood for storage

3.1 *Non-directed donations*

The use of allogeneic HSC is limited by the need to find an HLA-compatible donor. For those patients who need a bone marrow transplant with no suitable family member or unrelated bone marrow donor, cord blood banks have been set up alongside registries of bone marrow donors to facilitate matching (Bone Marrow Donors Worldwide <http://www.bmdw.org>). Over ten million bone marrow donors and cord blood units have been registered. In the UK there are three registries (Anthony Nolan, Welsh [WBMDR] and British Bone Marrow Registry [BBMR]) with over half a million registered donors. The BBMR administered by the NBS also on behalf of the Northern Ireland and Scottish Blood Services, holds HLA data on around a quarter of a million bone marrow donors and over 7000 cord blood donations collected and stored by the NHS Cord Blood Bank at Edgware, and participates in a global collaboration to find matches for patients in the UK and overseas.

The Netcord Foundation (<https://office.de.netcord.org/index.html>) is another organisation that provides search mechanisms and guidance on standards for affiliated cord blood banks. There are currently more than 85 000 cryopreserved cord blood units available through Netcord for clinical use.

In the UK, non-directed cord blood collection for banking for the NHS Cord Blood Bank is undertaken only at certain hospitals: Northwick Park Hospital in Harrow, Barnet General Hospital in Barnet and The Luton and Dunstable Hospital NHS Trust in Luton. Other sites are under evaluation or development. These hospitals have been selected for the ethnic variety of the local population; ethics permission has been granted and a service level agreement is in place. A good ethnic mix will increase access to transplantation for patients from ethnic minorities, because tissue types vary between populations. Currently only 3% of bone marrow donors are from minority groups, whereas 40% of the NCBB's donations are from these groups.⁶ Other university or blood services have banked smaller numbers of donations from the Royal Victoria Infirmary in Newcastle upon Tyne and the Mater Hospital Trust in Belfast. The Newcastle bank is not currently collecting but may do so again.

3.2 *Directed donations in at-risk families*

Some transplant centres recommend cord blood collection and storage from siblings born into a family where there is a known genetic disease amenable to HSC transplantation.⁷ If the cells are HLA-compatible, they may be used for the affected child. If not, they may be useable for a future HLA-compatible sibling. If the newborn child itself develops the disease, its own cord HSC may in future be useable as a vehicle for somatic gene therapy, when these techniques have been fully developed. The use of in vitro fertilisation with preimplantation genetic diagnosis to provide a 'saviour sibling'⁸ has been

the subject of ethical and legal controversy but is now allowed under UK law on a case-by-case basis with appropriate licensing from the Human Fertilisation and Embryology Authority (HFEA). As yet, no UK preimplantation genetic diagnosis service provides the facilities to undertake the appropriate HLA typing in conjunction with the embryo biopsy and those cases that have been undertaken have had their full treatment in the USA or the biopsied cells have been sent abroad for testing.

Cord blood can also be stored from siblings of a child with an acquired disease who may require HSC transplantation. However, improvements in chemotherapy mean that transplantation in childhood leukaemia, one of the main uses for related cord blood banking, is used less frequently, as over 80% of cases are 'cured' by chemotherapy. Related cord blood transplants have good outcomes when they are undertaken but the use of such donations means that related cord blood may need to be stored for a long period of time, perhaps decades, before they are needed, if ever. Such cord blood collections are normally initiated by the clinician caring for the sick potential recipient making appropriate arrangements with the NHS Cord Blood Bank but individual departments in hospital haematology units may also undertake this type of storage.

3.3 Directed donations in low-risk families

It is difficult to estimate the likelihood that a directed donation from a low-risk family would be used. Many of the projected usages of non-haemopoietic stem cells remain speculative and subject to research yet to be undertaken. At present, much more research is needed, including clinical trials, on the use of these cells in the treatment of non-haemopoietic disorders, before any realistic estimate can be made as to the potential use of umbilical cord stem cells in cellular therapy and regenerative medicine and on the utility of directed donations. Few of commercially banked units have been used in transplantation but this number is likely to increase, as more become available for this purpose and as the population of those donating ages.⁹

4. Clinical use of umbilical cord blood

4.1 Advantages and disadvantages

The major clinical use of cord blood has been for haematological malignancy in children. A survey from the International Bone Marrow Transplantation Registry (IBMTR) estimated that since 1998, one-fifth of stem cell transplants performed for young patients (less than 20 years old) are cord blood transplants, mostly for acute lymphoblastic leukaemia or acute myeloblastic leukaemia.¹⁰

The availability of cord blood as an alternative to bone marrow as a source of HSC for allogeneic transplantation has a number of potential advantages for both adults and children in clinical practice in comparison with other sources of allogeneic haematological stem cells.

These advantages include:

- faster availability: patients on average receive cord blood transplantation earlier than those receiving conventional bone marrow grafts¹¹
- extension of the donor pool: cord blood transplantation will tolerate a mismatch of tissue types between donor and the recipient greater than is acceptable with bone marrow or peripheral blood. In addition, because of the ethnic diversity of donors of cord blood, there is a higher frequency of non-Caucasoid HLA haplotypes available compared with bone marrow registries
- lower incidence and severity of graft versus host disease
- lower incidence of viral transmission: in particular, cytomegalovirus and Epstein-Barr virus
- lack of donor attrition: bone marrow donors may change their mind over time or may no longer be available.

There are also disadvantages of cord blood transplantation, including:

- low numbers of haemopoietic progenitor cells and stem cells in each cord blood donation,

- which may cause delayed engraftment. This deficiency is being addressed by the use of multiple units of cord blood for transplantation, and by efforts to expand the progenitor pool
- lack of availability of subsequent donations of stem cells and/or lymphocytes from the graft donor in graft failure or disease relapse.

4.2 Cord blood transplants from related donors

HLA-identical sibling cord blood transplantation has been performed almost exclusively in children. The lower risk of both treatment-related mortality and chronic graft versus host disease makes cord blood transplantation a particularly successful option for children with haemaglobinopathies.¹² Thus, collection and freezing of cord blood units should be considered strongly in families with a child affected with haemoglobinopathy or other genetic diseases.

4.3 Cord blood transplants in children from unrelated donors

Cord blood transplants from unrelated donors for children has been associated with sustained engraftment, a low incidence of graft versus host disease and no higher risk of leukaemic relapse. Cord blood transplantation is a good therapeutic choice for children with poor-prognosis acute myeloblastic leukaemia who lack a related donor. For children with genetic diseases such as Hurler syndrome, where the time from diagnosis to definitive treatment is crucial, cord blood transplantation should be considered strongly.

4.4 Cord blood transplants in adults from unrelated donors

A study of the outcome of HSC transplants from unrelated donors in adults with acute leukaemia, published in 2004, is encouraging.¹³ Although the number of nucleated cells that were infused from cord blood in this study was significantly smaller when compared to bone marrow grafting, the incidence of chronic graft versus host disease, transplant-related mortality, relapse mortality and leukaemia-free survival were not significantly different between those receiving cord blood compared to adult donation of HSC.

4.5 Future possibilities in haematological disease

The cell dose of cord blood grafts remains of critical importance for speed of engraftment and survival after unrelated cord blood transplantation from unrelated donors, particularly in adults. A minimum total nucleated cell dose of 2.0×10^7 /kg recipient body weight is essential and most centres use a threshold much higher than this. The median total nucleated cell yield of one cord blood unit is 1×10^9 . Thus, a single, autologous unit is unlikely to be adequate for any individual over 50 kg. Future research needs to focus on expansion of the pool of donors and strategies to augment the dose of HSC *ex vivo*, including transplantation of multiple cord blood units.^{14,15}

4.6 Non-haematopoietic uses

There is substantial speculation about the use of cord blood non-HSC in treatment of a variety of acute and chronic conditions but there is increasing evidence of the use of fetal-derived stem cells in the treatment of neurological disease¹⁶ and a number of preclinical studies in animal models, which suggest an improvement in cardiac function following infusion of umbilical cord stem cells for acute myocardial infarction.¹⁷⁻¹⁹ There has also been a report of the infusion of cord blood stem cells in a patient with longstanding spinal injury.²⁰ Commercial cord blood banks are citing such preliminary research as further potential uses in their literature. In addition, websites are now offering cell therapy using cord blood cells ahead of formal clinical trials.

5. Practical implications of collection of cord blood

5.1 Logistical issues

There are a number of practical issues that give cause for concern. A considerable logistic burden is imposed on the obstetrician, the midwife and the hospital involved in a request for personal umbilical cord blood storage:

- The consent procedure and associated paperwork place an additional load on already-overstretched midwifery staff.
- The collection procedure must be undertaken either during the third stage (while the placenta remains *in utero*) or shortly thereafter, a time where there is a risk of post partum haemorrhage and when both mother and baby require one-to-one care.
- There is pressure to ensure a sufficiently large volume is collected, since the likelihood of successful transplantation of cord blood HSC is related to the volume and cell dose collected.
- The cord blood can become contaminated with bacteria during collection unless stringent precautions are taken to avoid this.¹
- The use of midwifery or medical staff for cord blood collection may distract them from the care of other mothers and babies.

Samples might be incorrectly labelled or packed for shipping – although most companies provide appropriate kits and may also arrange a courier service to speed time to processing, another factor influencing successful stem cell harvest. Validation of storage prior to transportation (and subsequent transportation conditions) is essential to prevent loss of viability of cells during his phase.

Cord blood collection could jeopardise the mother's or the baby's health:

- if the normal practice for managing the third stage is altered or delayed to promote successful cord blood collection, e.g. withholding controlled cord traction in the presence of a postpartum haemorrhage or maternal risk factors such as severe pre-eclampsia, in an attempt to maximise the volume collected with the placenta still *in utero*
- if routine maternal or neonatal observations are neglected, or paired arterial and venous umbilical blood samples for blood gas status are overlooked or delayed.

The logistic burden of collection inevitably interferes with the accoucheur's attention, when it should be focused on minimising adverse neonatal outcome and postpartum haemorrhage. Some commercial banks suggest instead that no medical background is needed and that the birth partner can take the blood; this seems likely not only to jeopardise the adequacy of collection but also to lead to an infection risk from unskilled collection and blood dispersal. There are data to demonstrate that bacterial contamination rates fall with experienced trained staff undertaking collection.¹

Some specific issues in the third stage warrant attention:

- **Prematurity.** Early cord clamping appears to be disadvantageous to the preterm infant. Preterm babies are at risk of anaemia and haemodynamic instability. From a systematic review of seven randomised controlled trials there is some evidence that 30–120 seconds delay is associated with fewer transfusions for anaemia and fewer intraventricular haemorrhages.²¹
- **Nuchal cord.** Cord around the neck may need to be released or cut early to allow delivery. There should be no pressure on attendants to avoid cutting the cord.
- **Caesarean section.** Standard practice at caesarean delivery is to clamp the cord immediately and pass the infant to an attendant, then deliver the placenta, usually by cord traction but sometimes manually, and proceed to repair the uterine incision. Rapid action minimises maternal blood loss from surgery. Undue delay to effect collection or any delay where there is increased risk of haemorrhage would be inappropriate.
- **Maternal-infant contact.** It is important that cord collection does not interfere with immediate skin-to-skin contact of mother and baby and putting the infant to the breast. This is really a

matter of midwife priorities but any change would be avoided if a third party collected blood from a delivered placenta.

- **Multiple pregnancy.** The logistical burden of collection increases substantially at twin and high-order multiple deliveries, when the accoucheur's attention has to be even more focused on minimising adverse fetal outcome and postpartum haemorrhage. Identifying which cord blood is associated with which infant in non-identical multiple births is necessary if the cord is for autologous use and would require tissue typing or other matching techniques which not all commercial cord blood banks undertake.

The above difficulties apply predominantly to directed donations in low-risk families. For high-risk families, one-off arrangements will usually be made in advance and the delivery room staff will be aware of the importance of collection and the risk–benefit balance may differ from routine directed commercial storage collection. For altruistic non-directed donations, there is no pressure to ensure collection from any individual delivery.

An example of good practice is that used by NHS Cord Blood Bank, where cord blood is collected aseptically after delivery of the placenta by trained NBS staff within the delivery unit but outside the delivery room.^{1,22} This ensures privacy for the mother and removes any conflict between care of the mother and baby pair and the collection of cord blood. Donor mothers are interviewed antenatally to obtain written informed consent to use the cord blood for any patient who needs it, for testing for microbiological markers both current and future, and to ensure the mother meets with specific donor-selection criteria set by expert advisory groups.

5.2 *Timing of cord clamping*

There is considerable debate about the optimal time for cord clamping after delivery. Apart from evidence against early clamping in premature babies, there are no randomised trials in industrialised countries of early versus delayed clamping at term, although trials are in progress and a Cochrane review is awaited. The available controlled studies report a decrease in neonatal haematocrit with early clamping and a 12% decreased risk of hyperbilirubinaemia.²³ In developing countries, randomised trials show a decrease in haematocrit at 3 months with early clamping, although caution is urged because of statistical heterogeneity and high loss to follow up.²⁴ Delayed cord clamping may thus be advantageous where iron deficiency is endemic and associated with developmental disadvantage if untreated.²⁵ This is less likely to apply to the general healthy UK population, although it may be relevant to subpopulations of deprived or recent immigrant women and those with anaemia. A systematic review concluded that there was no clear evidence for defending any of the modalities for cord clamping in full-term newborns.²⁴

6. **Legal and ethical issues**

6.1 *Legal implications of parental requests to take cord blood*

The point at which the fetus becomes a person legally is when it emerges fully from the mother's body. Until that moment, the doctor is bound to respect the autonomy of the mother and she has an unfettered right to consent to everything that is done to her body. Once the child has fully emerged, the parents' right to dictate what shall be done to the child is coterminous with the child's best interests. The parents cannot demand that anything be done to the child that may have the effect of putting the child at risk, unless it is in the best interests of the child. This applies to the birth attendants as it does to the paediatrician. However, legally, the placenta is part of the body of the mother rather than the child. Either parent is competent to consent to anything done to or for the baby but only the mother can consent to anything done to her own body, including cord blood collection.

At the same time, professionals attending the mother in labour owe her a professional duty to meet her reasonable wishes. This means that if she wishes to have cord blood collected and the professional is

satisfied that it can be done safely in the circumstances, the attendants should assist. However the words 'safely in the circumstances' have to be interpreted broadly: the mother cannot demand that staff be made available specifically for the purpose or that other patients should be put at risk by being left unattended. It would be wise for hospitals providing obstetric services to have a clear policy on this issue and to make it available to patients. Where hospitals believe that they will be able to provide this service safely to those who demand it, we suggest that they should make it clear to prospective parents that this agreement will be conditional upon the clinical and logistical demands on the service locally at the time.

6.2 *Whose blood is it?*

The issue of whose owns cord blood has yet to be tested in the courts. On one hand, it has been suggested that the cord blood sample is more likely to be the property of the child on the basis that it is developmentally, biologically and genetically part of the child.^{26,27} On the other, it might be proposed that it is more likely that the sample is the property of the mother once the cord is cut: e.g. the mother's unfettered right to consent to what is done to her own body means that once the cord is cut she is free to refuse to consent to the removal of the afterbirth. Legal rights of property are not generally founded on genetic identity. The cord blood consigned to storage may be the subject of a gift from the mother to her child depending on the terms of the consignment. If right, this raises further issues as to the use of the products deriving from the sample taken.

If it is declared to be stored for the child's use then, until the time of majority, it will be held on trust for the child and its use may be seen as a right to be exercised in the best interests of the child by the trustee, who will probably be the mother, subject to the determination of the court in case of dispute. Directed donation for a sibling may be regarded as being in the best interests of the family and, thus, of the child from whose placenta it was taken. Once the child attains the age of 18 years, any trust will come to an end and the use of the stored cord blood will be decided by the individual described by the consignment contract as being the beneficial owner.

Cord blood donated to a bank raises different issues. Here, the decision to donate a product for use by other individuals is made by the mother and the cord blood, being taken from the maternal side of the clamp, is not part of the independent child's body. It is donated to the community and the decision to do so by the mother is made in the best interests of the society of which she and her child are members. Privacy is of special concern, since the source of the blood is the newborn, and it is widely agreed that it would be inappropriate to perform any genetic tests on the blood that would not be directly in the interests of the child until he or she is 18 years of age or is able to make such decisions.^{28,29} Whether or not the child at majority has any rights over their cord blood donated and stem cells stored in a bank by their parent has not been tested; however, it seems likely that they will be taken to have been the subject of a gift from the mother to the bank at the time of harvesting.

6.3 *Public versus private banking*

There has been debate about whether it is appropriate or necessary for individuals to store their child's cells in private commercial stem cell banks.^{26,29-33} While acknowledging the pressure on parents to do the best for their child, there are cogent arguments against the necessity of private banking:

- The individual's chances of using personal cord blood for haematopoietic disorders before the age of 20 years is low; estimates used vary from 1/20 000²⁶ to 37/100 000 (i.e. 1/2700).³³ However, it is not clear how many of those 37 people's needs could be met from allogeneic sources.
- There are alternatives to directed cord blood banking for those who require transplantation through international cord blood banking and bone marrow registries resources.
- Own cells may be inappropriate in conditions where the disease has a genetic origin, including some leukemias, and patients would be better served by a source other than their own-banked cells.

As a result, autologous low-risk commercial storage is unlawful in Italy and discouraged in some other European states. In 2004, the European Group on Ethics in Science and New Technologies advised European Commission that: ‘The legitimacy of commercial cord blood banks for autologous use should be questioned as they sell a service, which has presently, no real use regarding therapeutic options. Thus they promise more than they can deliver. The activities of such banks raise serious ethical criticisms’. The Group did not go as far as recommending banning this activity but they also recommended that: ‘any kind of advertising made by commercial cord blood banks in the media, including on the Internet, must be adequately controlled by public authorities’. They recommended that ‘support for public cord blood banks for allogeneic transplantations should be increased and long-term functioning should be assured’.³⁴

In Canada, the Fetal Medicine Committee of the Society of Obstetrician and Gynaecologists recommended that Canada should establish registration, regulation and accreditation of cord blood collection centres and banks and that commercial cord blood banks should be carefully regulated.³⁵

In the USA, on the recommendation of the Institute of Medicine of the National Academies, Congress voted US\$77 million for the establishment of a National Cord Blood Stem Cell Bank Network.³⁶

The RCOG strongly supports the concept of an NHS Cord Blood Bank for allogeneic storage of donated cord blood and would like to see it well funded. However, it remains unconvinced of the benefit of personal commercial banking for low-risk families. It is our view that if undertaken, advertising literature for commercial cord blood banks should be fair and informative and pricing structures transparent. Blood should be collected safely and in accordance with the EU Directive on Tissue and Cells 2004/23/EC³⁷ and should be stored only in facilities licensed by the Human Tissue Authority (www.hta.gov.uk/regulation). Where blood collection is arranged and undertaken in NHS facilities, full economic costs should be recovered.

7. RCOG advice and recommendations

Use of HSC obtained from umbilical cord blood has become an established alternative to bone marrow transplantation, especially in haematological, immunological and metabolic storage disorders in children and young adults. Storage of cord blood for therapeutic purposes will require a licence from the Human Tissue Authority under terms of the Human Tissue Act.³⁸

1. Collection of non-directed donations and directed donations for at-risk families are acceptable procedures through established public sector cord blood banks. There is still insufficient evidence to recommend directed commercial cord blood collection and stem-cell storage in low-risk families.
2. Future non-haematopoietic stem cell use is still speculative but it is understandable that some patients who can afford to do so may wish to avail themselves of commercial services offered. However, if this is done, it needs to be undertaken safely and will be dependent on the resources of the hospital in which the birth takes place.
3. Each NHS trust or hospital providing intrapartum care needs to develop its own policy on how to respond to prenatal requests for cord blood storage through commercial providers, including full economic cost recovery. Because some patients may incur financial obligations by registering with commercial providers before telling their doctors, we advise that this policy should be made available to prospective patients at an early stage. Written advice setting out the hospital’s policy should be made available to all patients when they book for maternity services.
4. The RCOG offers the following specific recommendations to NHS trusts who do decide to support cord blood collection:
 - a. There should be no alteration in ‘usual management’ of the third stage.
 - b. To maximise safety for the mother and infant, collection should be made from the *ex utero* separated placenta.

- c. Collection should be by a trained third party (that is, not by the attending obstetrician or midwife) using methods and facilities appropriate to meet the European Tissues and Cells Directive.
 - d. The service should not be made available in cases where the attending clinician believes it to be contraindicated: this will be likely to include all premature births and cases where there appear to the attendants to be specific contraindications, such as nuchal cord or maternal haemorrhage.
 - e. The details of the hospital's policy should be made available to all patients.
5. The NHS should consider an improved funding infrastructure for unrelated non-directed cord blood banking in the UK and directed donations for families with genetic disorders or for families with a member with an acquired disease treatable by HSC transplantation, in order to provide a broad coverage and equitable access for those in need of the benefits that stem cell transplantation can achieve now and those that may be available in the future.
 6. The RCOG recommends that research be performed to understand better the short- and long-term neonatal effects of third-stage practices.

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Additional reading

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