An analysis of the NHS Cord Blood Bank; Barriers to Cord Blood Donation and Quality Parameters Limiting Storage

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Abstract
The NHS Cord Bank was established in 1996 to build an inventory of altruistically donated cord blood units to provide equity of access to all patients eligible for a stem cell transplant. Fixed cord blood collection sites were selected in areas of high black and minority ethnic (BAME) populations and a performance indicator was set routinely to bank 40-50% of cord blood units from BAME donors. As well as providing an ethnically diverse inventory, the cord donations should be of high quality in terms of nucleated cell count to achieve the best possible outcomes for patients regardless of ethnicity.

Objectives were:
To validate the objective to bank at least 40% of donations from BAME donors at each of the six collection sites.
To analyse the nucleated cell content of banked BAME donations.
To monitor the provision of cord blood transplants to BAME patients
To understand barriers to donation through a qualitative research study with healthcare professional involved with the NHS cord blood banking programme.

Methods
Data were extracted from NHSBT software using a database query and analysed for both banked cord blood units and for cord units provided for transplant.
Data relating to the self-reported donor ethnicity and collection site were extracted and analysed as a proportion of the whole bank, as a contribution of BAME donors from each collection site and to ascertain the proportion of BAME donations with a high TNC. Interviews and a focus group with fifteen healthcare professionals, comprising five midwives, five community midwives and five cord blood collectors were undertaken to understand barriers to cord blood donation and collection. Thematic analysis was used to interpret the interviews with participants.

Results

Banking of at least 40% BAME donations was routinely met. Representation from all groups listed on the NHS Cord Bank ethnicity form was demonstrated in the collected and banked cord donations. Non-BAME donations comprise the greater proportion of high TNC cord units. The proportion of NHS Cord Bank cord blood transplants provided to BAME patients remained constant across the period studied. Changes to, and sharing of, best practice across sites were identified which could remove or reduce the barriers to cord donation and collection.

Discussion
The initial strategy to select collection sites in areas of high BAME birth rate has been successful in building an inventory with a high proportion of BAME donations. Further work to understand and determine any link between the volume and TNC of collected cord blood with ethnicity and subsequently to improve the efficiency of collections from BAME donations is needed to improve availability of HLA matched cord. The importance of communication and information for both healthcare professionals working together and potential donors was highlighted as a means of improving donation and collection of cord blood.

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This work is dedicated to my dear mum and dad; much loved and missed.

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Abbreviations

BAME	Black, Asian and minority ethnic
BINE	British, Irish and North European
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
CBU	Cord blood unit
CCG	Clinical Commissioning Group
CD34+	Cluster of differentiation 34
CIBMTR	Center for International Blood and Marrow Transplant Research
CMV	Cytomegalovirus
CRG	Clinical Reference Group
CTC	Clinical Trials Committee (BSBMT)
DHSC	Department of Health and Social Care
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 leucocyte antigen
HPC	Haematopoietic progenitor cells
HSCT	Haemopoietic stem cell transplantation
HTA	Human Tissue Authority
JACIE	The Joint Accreditation Committee
NGS	Next generation sequencing
NHS	National Health Service
NHSBT	NHS Blood and Transplant
NHS-CBB	NHS Cord Blood Bank
NICE	National Institute for Health and Clinical Excellence
NMDP	National Marrow Donor Programme
ONS	Office for National Statistics
PBSC	Peripheral blood stem cells
R & D	Research and development
TNC	Total nucleated cell count
WMDA	World Marrow Donor Association

1 Introduction

1.1 History of cord blood as a haematopoietic stem cell transplant

1. Allogeneic transplantation of haematopoietic progenitor cells (HPCs) where the cells are donated from one individual to another has been a potentially curative therapy for both malignant blood diseases and some non-malignant diseases for several decades, using the ability of the HPCs to home to the patient's bone marrow and repopulate their immune system. The first successful bone marrow transplant from a related donor to recipient was performed in 1956 by Dr Donnall Thomas in New York. The patient, who had leukaemia, was given radiotherapy and then transplanted with bone marrow donated from their identical twin. In 1968 a paediatric patient with a non-malignant disease, severe combined immunodeficiency syndrome (SCID), was treated with a bone marrow transplant from their sibling (Kenny, 1979) and in 1975 the first successful unrelated bone-marrow transplant took place to treat a patient with lymphoma (McGlave, 1982). Some years later in the 1990's the use of the drug G-CSF in healthy adult donors facilitated mobilisation of haematopoietic stem cells, previously harvested from the bone marrow, into the peripheral blood which could then be harvested from the donor using apheresis techniques (Dreger, 1999). While the number of allogeneic bone marrow transplants remained relatively stable year on year, the number of transplants from peripheral blood stem cells (PBSC) rose rapidly (WMDA data, Figure 1.1) after G-CSF was licensed for use in healthy donors. Alongside these two sources of

HPC, a third source was about to come into use in unrelated stem cell transplant. In 1989 the first transplant using umbilical cord blood as the source of haematopoietic stem cells was performed using sibling umbilical cord blood to treat an older sibling who had Fanconi's anaemia (Gluckman, 1989).The child engrafted with the newly replaced haematopoietic stem cells from their sibling's cord blood and was still well five years post-transplant. This proof of principle opened the door for cord blood to be used as a viable and alternative transplant source to bone marrow or peripheral blood derived haematopoietic stem cell transplants. One of the key drivers for cord blood use as a transplant has been to provide equity of access for patients eligible for a stem cell donor but unable to find one due to their ethnicity. Potential stem cell transplant patients from Black, Asian and minority ethnicities (BAME) are less likely to find a suitable transplant than Caucasian patients (Barker, 2019). Some of the milestones in haematopoietic stem cell transplantation are listed in Table 1.1 from the first description of bone marrow through to advanced therapies using cord blood that has been expanded *ex vivo.*

Table 1.1 Milestones in hematopoietic cell transplantation and cord blood transplantation

Year	Milestones in haematopoietic stem cell transplantation (HCT)	Reference
1868	Bone marrow first described as a blood-forming tissue	Cooper, 2011
1968-69	First successful allogeneic bone marrow transplant (BMT) for patients with severe combined immunodeficiency syndromes (SCID)	Kenny, 1975
1975	First successful allogeneic SCT for patient with leukaemia	McGlave, 1982
1988	First sibling cord blood transplant for patient with Fanconi's anaemia	Gluckman, 1989
1990	Donnall Thomas awarded Nobel Prize in Medicine for the development of HCT as a treatment in haematological diseases	Thomas, 1994
1996	First unrelated cord blood transplant in children	Kurtzberg, 1996
1996	First unrelated cord blood transplant in adults	Laporte, 1996
1997	Eurocord-Netcord network formed	Hakenberg, 1998
2000	Cord blood transplants in HLA identical siblings had similar survival to that of BMT in children	Rocha, 2000
1996-2001	Demonstrated that long-term, relapse-free survival was similar for cord blood and HLA matched unrelated donor BM transplant	Rubinstein, 1998 Sanz, 2001
2002	Transplantation of *ex vivo* expanded cord blood	Shpall, 2002
2005-2010	Improving results with double cord blood transplants and nonmyeloablative conditioning regimens	Barker, 2005 Brunstein, 2007

Following the first allogeneic cord blood transplant in 1989, cord blood banks that stored altruistically donated, publicly available cord blood transplants began to be established. Some of the milestones in cord blood banking and transplantation are shown in Table 1.2. The first of these was at the New York Blood center, set up by Dr Pablo Rubinstein in 1989 (Rubinstein, 1993). As more cord banks around the world began to store cord blood donations the availability of cord blood transplants grew alongside the ability of transplant centres to search stem cell registries for

suitably matched donors for their patients. Consequently, as the worldwide inventory grew (Fig 1.1), the number of cord blood transplants performed using this readily available source also grew (Fig 1.2). Since cord banks started building their inventories the growth in transplant of unrelated cord bloods for a variety of diseases has increased worldwide from less than fourteen transplants in 1997 to over four thousand in 2010. Since this peak around 2010-2012 numbers of cord blood transplants have plateaued and have since dropped as other transplant regimes have been developed (WMDA Global report 2015).

During this period a treatment regime came into use that has affected the number of cord blood transplants performed. This is termed a haplotype transplant and has opened up access to patients who otherwise were unable to find a suitably HLA matched donor. Haplotype transplants are derived from partially matched family donors and 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 exist (see also 1.5). Almost all patients will have an available related donor with whom they share a single HLA haplotype i.e. a haploidentical donor. Early attempts with haplotype transplants using conventional conditioning regimens were associated with unacceptable rates of graft-versus-host disease (GvHD) and graft rejection (Aversa, 1998)but development of a reduced intensity conditioning regimen and use of the drug cyclophosphamide post-transplant to prevent GvHD and graft rejection produced good results in terms of non-relapse mortality (Ciurea SO, 2018), although the longer term likelihood of disease relapse is less clear and current guidance still recommends that a well matched unrelated donor or cord transplant is considered first if a sibling match is not available (BSBMT Guidelines,

2013). Nonetheless, haplotype HPC transplants have had a significant effect on the number of cord blood transplants carried out each year (Raiola, 2014) yet cord transplant remains an important treatment option for patients where a suitably matched adult donor is hard to find, usually within BAME patients (Barker, 2019). Transplant of haematopoietic stem cells derived from the bone marrow, peripheral blood or umbilical cord blood from unrelated donors is now a standard treatment for several paediatric and adult malignancies (BSBMT, 2013). Clinical trials have been undertaken to determine which source provides the most favourable outcome (Hwang, et al., 2007) (Eapen, et al., 2007) (Rocha, et al., 2001). As well as comparing sources of HPCs for differing disease conditions, trials have analysed outcomes after transplant using a single cord donation or a double cord transplant to overcome issues of cell dose for adult patients (Avery, 2010). Additionally, combined sources of HPC transplants have been trialed; in one study good outcomes were seen following combined haplotype and cord blood transplant in patients with aplastic anaemia (Purev, et al., 2016).

1.2 Growth in haematopoietic stem cell transplants

By the year 2000, 77,000 cord blood donations had been banked and were available for transplant, their use starting to become evident in the number of cord transplants undertaken globally (Figure1.1). By 2015, 755, 000 cord blood donations were available but by this time the use of cord blood transplants had peaked between 2010-2013 and then started to drop with a year-on -year decrease to a current plateau of c.3,000 cord blood transplants per annum globally (Figure 1.2). Bone marrow transplants have remained fairly stable in number between 3000 and 4000 per annum globally since 1997, with peripheral blood

stem cell transplants accounting for the highest proportion of HPC transplants (WMDA, Global report 2019). Some of the loss in cord blood transplants is attributable to the increase in haplotype transplants using PBSC donations from related donors.

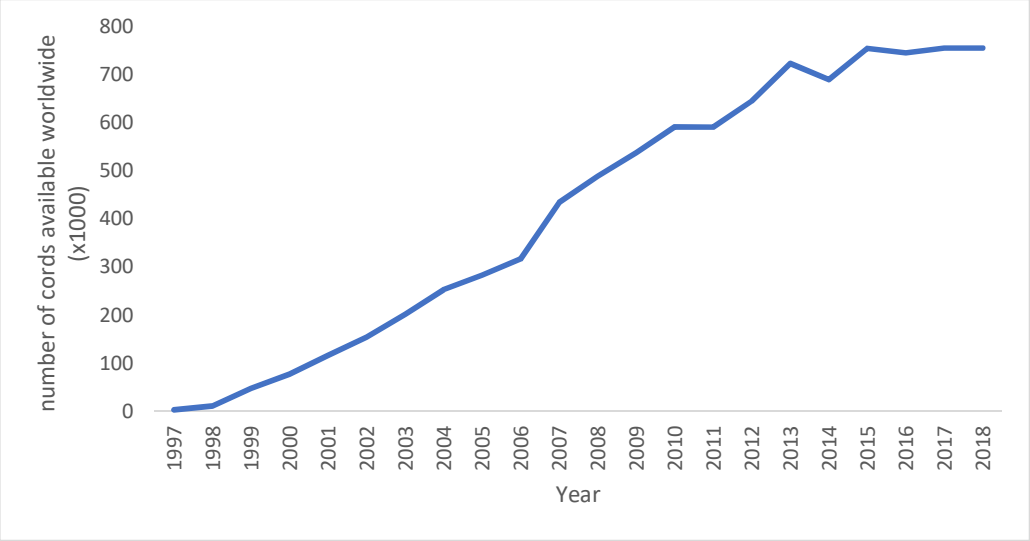

Figure 1.1 Growth in the number of cord donations available worldwide from 1997 to 2018 (data derived from WMDA Global Report 2019)

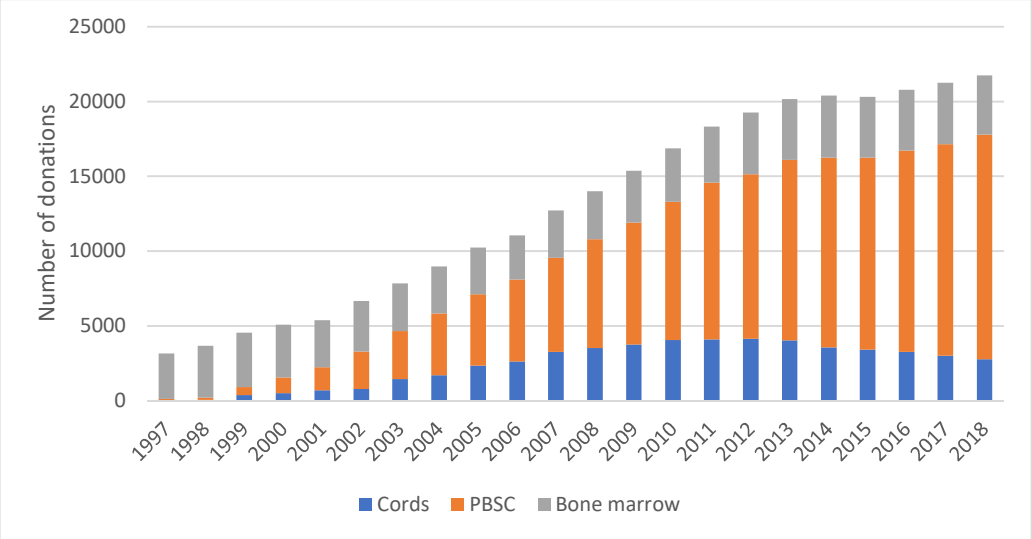

Figure 1.2 The number of haematopoietic stem cells issued for transplant worldwide by stem cell source (data derived from WMDA Global Report 2019)

1.3 Advantages and disadvantages of different sources of haematopoietic stem cells

The three sources of haematopoietic stem cells each offer their own advantages and disadvantages for both donor and recipient patient. These are summarised in Table 1.2.

Table 1. 1 Advantages and disadvantages for the donor and recipient of haematopoietic stem cells sourced from umbilical cord blood, peripheral blood or bone marrow (Adapted from the literature)

Source	Advantages	Disadvantages
Cord Blood	• Widely available • Ease of collection (donor) • Less GvHD (recipient) • Less rejection of graft (recipient)	• Low stem cell dose (slower engraftment) (recipient) • No extra cells for storage or top-up post-transplant (recipient)
Bone Marrow	• No requirement for drugs to mobilise stem cells (donor) • Faster engraftment than a cord blood transplant (recipient) • 1-2 weeks off work (donor)	• Requires general anaesthetic • May render the donor anaemic (donor) • 1-2 weeks off work (donor)
Peripheral Blood	• Ease of collection (donor) • No general anaesthetic (donor) • Attain high stem cell doses (recipient) • Faster engraftment after transplant (recipient) • 2-3 days off work (donor)	• Requires mobilisation with G-CSF (donor) • May require central venous catheter if inadequate peripheral access (donor) • More GvHD after allogeneic transplant (recipient)

Umbilical cord blood is rich in haemopoietic stem cells which are biologically naïve compared with those found in the bone marrow and peripheral blood and demonstrate a greater potential to proliferate and engraft in the recipient (Gluckman, 2011). Outcomes from a study (Ponce, 2013) have shown that cord blood stem cell transplants are less prone to rejection than bone marrow or PBSC, probably because the cells are less mature and have not yet developed the features that can be recognised and attacked by the recipient's immune system.

A University of Colorado Cancer Center study (Gutman, 2016) compared outcomes of leukemia patients receiving bone marrow transplants from 2009-2014, finding that three years post-transplant, the incidence of severe chronic graft-versus-host disease was far lower in patients who had received umbilical cord blood transplants than in patients who had received transplants from matched, unrelated donors (8% and 44% respectively), with no difference in overall survival between these two techniques. The patients who received cord blood transplants were also less likely to need immunosuppression and less likely to experience late infection and require readmission to hospital.

However, it is not possible to return to the donor for additional 'top-up' cells as with adult donors and, although the cells are less mature and the requirements for dosage differ, the cell content may not be sufficient and may require a double transplant for an adult patient. The nucleated cell dose in a single cord blood will be relatively small compared with bone marrow and peripheral blood, though this

can be partially mitigated by use of a double cord transplant but may still not provide a clinically suitable dose of cells for an adult patient.

Hospital stays following a cord transplant are generally longer and more expensive due to the prolonged period of engraftment seen with cord blood transplants; typically 22-27 days (Rocha, 2010) as opposed to 18 days for a bone marrow (Laughlin, 2001) and 12 days for PBSC transplant (Medd, 2013). Consequently, the risk of infection in this post-transplant neutropenic period is also greater. In a comparative study the median length of hospital stay for patients who had undergone a cord blood transplants was 121 days compared with 89 days for patients receiving bone marrow or peripheral blood transplants (Takahashi, 2007). Due to the prolonged neutropaenic period and greater risk of infection, cord transplants are generally viewed as a higher risk transplant than bone marrow or PBSC transplants. Additionally, as cord transplants are performed less frequently than bone marrow or PBSC transplants, transplant centres may be less used to physically handling this type of transplant and consequently less confident in their use.

1.4 Factors affecting the choice of a cord blood transplant

1.4.1 HLA match and Cell dose

Once a cord blood transplant has been determined by the transplant team as the preferred option, there are two primary factors that are considered when deciding on the best cord blood transplant for the patient and these are the match between the donor and recipient human leukocyte antigens (HLA) and the total nucleated cell (TNC) dose in the cord blood unit (Hough, 2016). There are six highly polymorphic, HLA molecules (HLA-A, -B, -C, -DRB1, -DQB1 and -DPB1) that are

encoded by the MHC on chromosome 6. They are ubiquitous cell surface markers with a key role in recognising foreign antigens and the formation of tolerance to self and foetal antigens (Lown, 2013). There can be a greater degree of tolerance for HLA mismatches between cord transplant and recipient than with other adult stem cell sources. Typically, cords are matched ideally to find a 6/6 match, whereas adult stem cell donors would be matched at 10/10 (Eapen, 2011 December). One antigen is inherited from both parents at each loci and so a 6/6 match refers to the antigen matches at HLA-A, HLA-B and HLA-DRB1. The 10/10 match for adult stem cell donors includes HLA-C but the DPB-1 loci is usually excluded from this. More recently improving the level of match between cord and recipient has been implicated with better outcomes for engraftment of the HSCs and reducing the incidence of GVHD (Akahoshi, 2020;).Furthermore, increasing the TNC dose in the cord transplant can offset HLA disparities to provide equivalent outcomes to a better matched cord transplant with a lower cell dose (Wroe, 2014; Barker, 2010). Other factors play an important part in decision-making between potential cords such as the CD34+ content; a surface marker on haematopoietic stem cells, ABO blood group compatibility and whether the cord blood donation comes from an accredited bank (Hough, 2016).

1.4.2 Indications for treatment

Diseases that can be treated by cord blood transplant include haematological malignancies, bone marrow failure syndromes, metabolic disorders and primary immunodeficiencies. In 2008 the most common indications for allogeneic cord blood transplants were acute myeloid leukaemia (33.4%), acute lymphoblastic leukaemia (13.4%), myelodysplastic syndrome (10.6%), non-Hodgkin lymphoma

(9.9%) and anaemia (5.7%) (BSBMT, 2009). The commonest indication for cord transplants provided by the NHS Cord Bank is acute myeloid leukaemia and cord transplants have also been provided for a number of non-malignant conditions in paediatric patients such as Hurler's syndrome and other enzyme deficiency conditions (NHS Cord Bank data, 2018). In some settings, particularly where minimal residual disease persisted at the time of transplant, favourable outcomes with cord blood transplant as compared with bone marrow or PBSC transplant have been shown (Milano, 2016).

1.4.3 Speed of access to stem cell transplant sources

Cord blood stem cell transplants are a readily available source. Typically a request for a cord blood transplant from the NHS Cord Bank can be turned around within a day (NHS Cord Bank standard operating procedures SOP1714 2019, SOP1715 2020) unlike that for an adult donor, which would take a minimum of 28 days to work up and prepare for donation of stem cells (British Bone Marrow Registry data, 2018). Additional delays can be incurred if the adult donor is unable to be contacted if records have not been kept up to date or there is a contra-indication to donation which becomes apparent during the work-up phase. The NHS Cord Bank data show that about half of the cord blood transplants reserved by transplant centres are kept as a back-up option to adult stem cell sources, should they fail to yield a successful transplant.

Following collection and processing, by the time cord blood donations have been made searchable on stem cell registries they have been through stringent quality control checks and have been medically cleared and passed fit for use as a transplant. This came to the fore during the early stages of the COVID-19

pandemic in 2020, when cord blood transplants were identified as back-up sources of transplant for every patient undergoing a stem cell transplant in the event that the adult donor was unable to donate due to COVID-19 infection and the consequent risk of transmission to the patient (Lee, 2021).

1.5 HLA, ethnicity and haematopoietic stem cell transplants

The proportion of unrelated cord blood donations from black and minority ethnic groups (BAME) has increased over the last decade but, compared with the likelihood of provision of an allogenic transplant for a Caucasian donor, the likelihood of finding a suitably matched cord blood transplant is still far lower. Data from the British Bone marrow registry suggest that Caucasian patients are more than twice as likely (88%) to find a suitably matched donor than mixed-race patients (40.7%) (BBMR, 2004/5). Although the proportion of BAME donors among those registered with the British Bone Marrow registry has risen from 11% in 2013 to 15% in 2016 (Figure 1.3), it is unlikely that this proportion will continue to rise, given blood donation statistics (NHSBT Blood Donation annual report, 2018). Consequently, there is still an unmet need for adult stem cell donations from black and minority groups but the extent for individual BAME groups is unclear and hence research is required to determine which groups need to be targeted to increase donation rates and by how much. The recruitment of cord blood donors from BAME groups is perceived to be more readily attainable than is the case with adult stem cell donors (Lown, 2012), which has supported the growth of cord banks worldwide to provide greater donor diversity.

While the Stem Cell Strategic Forum in the 2014 report noted that provision of stem cells from unrelated adult donors was the most effective way of meeting the

needs of the majority of UK stem cell transplant patients, it recommended that the continued development of a genetically diverse UK inventory of cord blood was the best way of addressing the needs of BAME patients. They estimated that with the number of donations available at the time of the report at least 90 patients of black and minority ethnic groups per annum were unable to receive a potentially lifesaving transplant (Stem Cell Strategic Forum, 2014). Since then the number of patients in the UK able to proceed to a potentially life-saving unrelated donor transplant has increased by over 30% but there is still a persistent problem in finding a well matched donor within a reasonable timeframe for patients from BAME communities (Stem Cell Strategic Forum, 2014). A similar picture was seen in America in 2006 when cord banks were being established and inventories built up: the likelihood of a BAME patient's finding a suitably matched adult stem cell donor was about half that of a Caucasian patient; 50% versus 93% respectively (Figure 1.4).

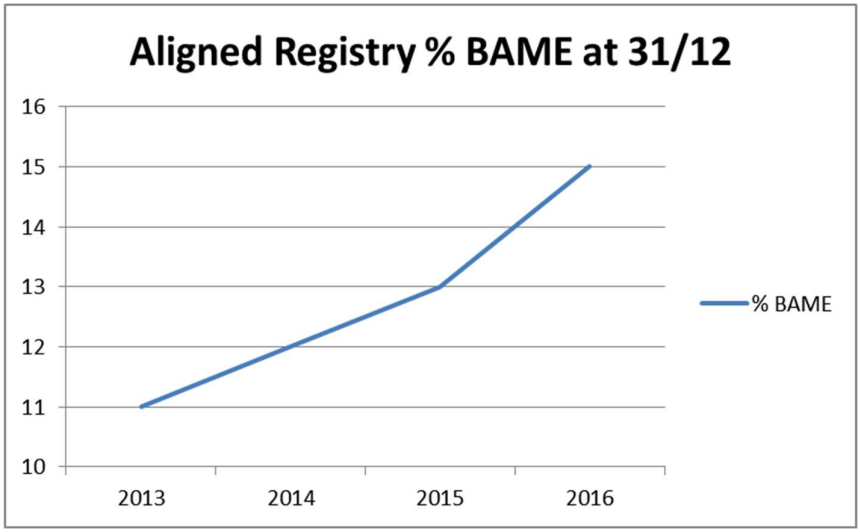

Figure 1.3 Proportion of BAME adult donors registered on the British Bone Marrow Registry in 2018 (BBMR data 2019)

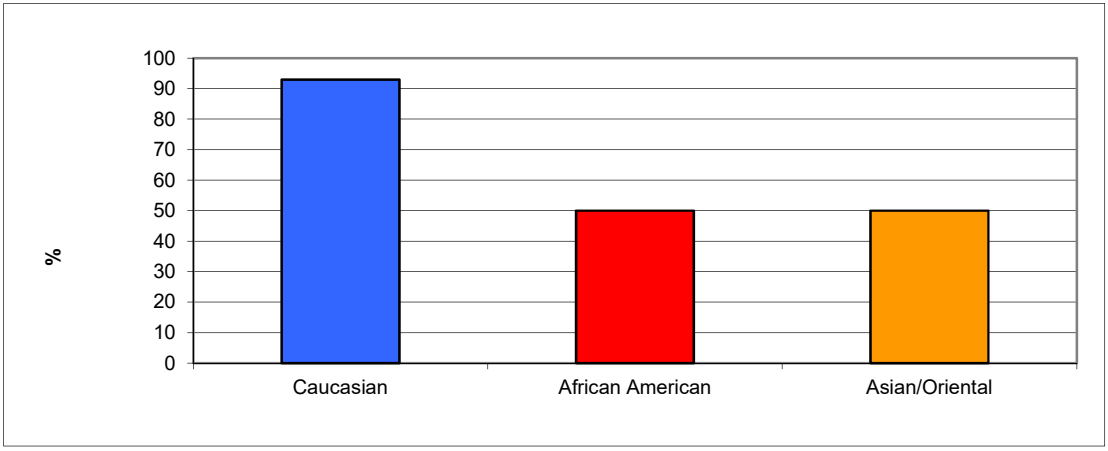

Figure 1.4 Likelihood of finding a 6/6 HLA matched BM/PBSC donor according to patient ethnicity, National Cancer Institute, USA, 2006

1.6 The NHS Cord Blood Bank

1.6.1 History

The NHS Cord Blood Bank was established in 1996 as The London Cord Blood Bank with an initial remit to bank ten thousand cord blood (CB) donations (Armitage 1999). By 2009, with the promise of cord blood transplants as an 'off the shelf' stem cell transplant, this was revised to bank 20,000 CB donations containing a high enough cell count to be clinically suitable to reconstitute an immune system by transplanting the cells into a recipient patient (Recommendations of the Stem Cell Strategic Forum, 2009). Data from Querol indicated that the optimal UK bank size to serve a UK patient population of 2000 would be 50,000 units (Querol, 2009). The aim was to meet this target through funding of two UK banks working closely together; the NHS Cord Bank and the Anthony Nolan Cord Bank. The UK Stem Cell strategy which comprises key opinion leaders from the NHS and Department of Health and Social Care (DHSC) set out its aims in relation to cord banking and stated an additional aim that the

units should be ethnically diverse to meet the gap found in the adult bone marrow donors registries which have a high proportion of Caucasian donors and consequently cannot provide a transplant for all ethnic groups since one of the primary factors in sustained engraftment is the degree of HLA (human leucocyte antigen) match, which differs between ethnic groups. The ability to build a diverse inventory of cord blood donations and improve equity of access for BAME patients was a vital determinant in funding the NHS Cord Bank.

1.7 Operating Model of the NHS Cord Bank

1.7.1 Location

The NHS Cord Blood Bank is sited in Colindale, North London and in Filton, Bristol and is part of NHS Blood and Transplant (NHSBT). It is one of the largest public cord banks worldwide (WMDA data 2018). During the growth phase of the cord bank when the inventory was being rapidly built there was a maximum of six collection sites, based at NHS Hospital Trusts in and around London. The dates each site opened are shown in Table 1.3. These sites were initially located around the London area in accordance with the number of available births and the ethnically diverse population that the hospitals served, with the potential for 40% of banked cords to come from black and other minority ethnicity (BAME) donors in an attempt to provide equity of access by improving the unmet need of stem cell patients from BAME background. The Strategic Stem Cell Forum had estimated that 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 with around 90% for Caucasian patients. This translated to an estimated 351 patients per year who

were unable to find a suitably matched transplant, whose likelihood of finding a suitable match would be increased by building a cord blood inventory of 30,000 donations. A legal agreement was signed with each of the hospitals, which details the roles and responsibilities of each party, including the requirement for the hospital to support and engage with the cord banking programme

Table 1.3 Dates collection sites commenced cord blood collections.

Site	Opened
Barnet General Hospital	Feb-96
Northwick Park Hospital	Mar-97
Luton and Dunstable Hospital	Jul-03
Watford General Hospital	Aug-07
St George's Hospital	Oct-09
University College Hospital	Nov-11

1.7.2 Overview of the cord blood banking process

1.7.2.1 Donor recruitment and consent

The cord blood collectors are employed by the NHS cord bank and hold honorary contracts at the hospital trust where they are based. Not all cord banks operate in this way: some banks contract with midwives who are employed by the hospital where they collect cords to act as cord blood collector. The NHS Cord Bank cord collection team are highly experienced, many having worked for the cord bank for more than ten years according to electronic staff records and information volunteered during the interviews undertaken as part of this research, and are

consistent in their practices at each site since they work for a national organisation with controlled and documented procedures which are the same at all collection sites.

The cord collectors are responsible for consenting maternal donors and documenting a donor screen which reviews lifestyle, travel history and family medical history for transmissible genetic disease, as well as maternal risk factors for transmission of communicable disease, taking samples from them for mandatory virology markers. Information leaflets are supplied to maternity staff involved in the Antenatal Clinic (to be included as part of booking-in pack) and in the antenatal areas to promote cord blood donation to potential donor mothers (Appendix 1). Initial consent to collect the cord blood is often provided prior to delivery after potential donors have received information at antenatal clinics at the cord collection sites. The medical history, samples for virology markers and consent for storage and use a stem cell transplant is generally obtained soon after delivery and has to be obtained within seven days of delivery to comply with regulatory requirements (HTA 2004).

1.7.2.2 Collection of umbilical cord blood

The attending midwife checks the placenta once it had been delivered and then hands it into the care of the cord blood collector. A dedicated room within the delivery suite is used to carry out collection of the umbilical cord blood. The placenta is suspended using a clamp stand to allow the umbilical cord to hang freely. A stringent cleaning process of the cord is undertaken to minimise bacterial contamination and the cord is then venesected with a needle attached to a bag

filled with anticoagulant. The blood from the placenta drains by gravity through the cord into the bag.

If the cord blood does not reach a minimum volume of 60ml, it is discarded at the hospital site in accordance with local procedures. Cord collections above 60 ml are held at ambient temperature prior to transport to the laboratory at Colindale for evaluation of the cell count.

1.7.2.3 Evaluation

All cord blood units and samples that have been collected at the sites and are above 60ml in volume are sent to a central laboratory for preliminary evaluation in Colindale, North London. A sample of well mixed cord blood is taken from a sealed segment of the bleedline and a full blood count (FBC) is performed using a haematology analyser (Sysmex XN1000).

The total nucleated cell count (TNC) for the cord blood unit (CBU) is calculated. On current acceptance criteria (Appendix 2) any CBU with a TNC greater than $135x10^7$ passes preliminary evaluation and is sent to NHSBT at Filton, Bristol for processing, storage, listing on registries and distribution for transplant.

1.7.2.4 Processing and storage

The cord blood donations are processed in a closed system to maintain sterility and at this stage are referred to as a cord blood unit (CBU), making a distinction between the maternal donor and the product derived from the donation. Accreditation guidelines from FACT Netcord require CBU to be cryopreserved within 48 hours of collection, the NHS Cord Bank cryopreserves CBU within 24

hours to maximise potency and viability of the cells, based on work in 2000 during development of the Bristol Cord Bank pilot (Donaldson, 2000) and the London Cord Bank (Armitage, 1999)The CBU is frozen as a volume of about 21ml with 10% DMSO to preserve the integrity of the cells and stored indefinitely in liquid nitrogen tanks at cryogenic temperatures (NHSBT Standard operating procedures).

1.7.2.5 Discards from the bank

CBUs can be discarded after storage during quality control checks for reasons such as bacterial contamination, maternal medical history, positive mandatory viral marker or withdrawal of donor's consent. Discards such as these account for a very small percentage of CBUs since by the time of banking detailed maternal histories have been taken, which mostly preclude collection of cord donations where there is likely to be a reason for discarding the CBU. Stringent cleaning protocols for the cord are applied during the collection process and with processing carried out in a closed system the rate of bacterial and fungal contamination has been consistently low (NHS Cord Bank trending data, 2020)

1.7.2.6 Review, release to registry, reservation and shipment

All records of processing, cord collection and maternal history are reviewed and signed off for each CBU that is banked prior to release of information such as HLA type, cell dose and viability to stem cell registries in the UK and worldwide. This allows the CBUs to be viewed by transplant centres searching for suitable adult HPA donors or cord HPC donations for their patients. Once a CBU has been

selected as a potential transplant several pre-release checks are undertaken to ensure that the integrity of the CBU has been maintained during the freezing process and subsequent storage. These checks include verification of the HLA match between the patient and cord and the maternal donor. Once final reports have been released the CBU can be transported to the transplant centre for infusion. This usually takes place prior to the start of patient's conditioning unless the CBU is being provided in an emergency scenario, for example when the adult stem cell donor has been unable to donate their cells.

1.7.2.7 Research uses

During the cord collection process, when paperwork is being completed for the maternal donor, the donor is asked whether they consent to their cord donation's being used for research and development purposes if the cord donation is not clinically suitable, for example if the TNC is too low. These CBUs can then be provided either fresh or cryopreserved to research groups. This has been an area of growth for the cord bank with continued growth in attempts to expand cord blood or manipulate cell markers to improve anti-leukaemic effects, for example. (Berglund, 2017)

1.8 Barriers to public cord blood donation and collection

1.8.1 Attrition through the process

For every cord that is banked for potential clinical use there will be one to three cords that have not proved suitable (NHS Cord Bank cord performance data, 2018) and are either discarded prior to leaving the collection site or discarded after evaluation of the cell count, if not used for approved R&D purposes. Some

reasons for not proceeding with collection of a cord donation concern medical guidance, for example on twin delivery, gestation below 37 weeks or temperature spikes during delivery which could indicate infection. Other reasons such as delayed clamping of the umbilical cord might be reviewed for changes in practice that could reduce the attrition in the donation and collection process and contribute to an improved conversion rate between cords donated and banked.

The impact of delayed or deferred clamping of the umbilical cord has been well documented and can be a significant impediment to collection of a clinically suitable CBU. The practice refers to a wait after delivery of the baby before cutting the umbilical cord and was first introduced for pre-term babies to top up blood volume, reduce the incidence of anaemia and improve iron stores (Ashish 2017, Chopra, 2108) but has been adopted at term deliveries. Delayed clamping has been explored in Study 2 to understand opinions from healthcare professionals directly involved in the cord banking programme and to determine whether any changes could be made to minimise or mitigate the impact of its adoption.

1.8.2 Other models of cord banks

Private cord banks, also called family banking, were set up to enable parents to store their offspring's cord blood for potential use by compatible family members. Quality parameters which assess the clinical suitability of a cord blood unit are often less rigorous than those used in public banking (Sun, 2010). The cord blood remains the property of the child and is not searchable on registries for use by an unrelated patient. The likelihood of an individual's developing a disease that would be treatable with their own cord blood is very small; one study estimating this at between 0.005% and 0.04% (Annas, 1999) and more recently it has been

suggested that there is still not enough scientific data to support autologous cord banking (Armitage, 2016). However, as the field of regenerative medicine continues to grow, with possible autologous applications, the case for private banking may be more attractive to parents if there was mounting evidence to support potential use of the stored cord blood for a wider range of conditions.

More recently, a third choice called a hybrid bank for parents has emerged, combining both public and private banking, which enables them both to store and potentially donate their child's cord blood (Mayor, 2007; Wagner, 2013)) The typical model for this hybrid bank allows parents to donate their cord blood, consenting to its being publicly available for search and to its use in an unrelated patient as a transplant if requested. Until this point the parents typically pay an annual storage fee which ceases as soon as the cord blood is used. This model may have an advantage in terms of the quality control required to retain licenses and accreditation as needed for public banks, but these types of bank which act as a sort of biological insurance with a small likelihood of use have been discouraged (Royal College of Obstetricians and Gynaecologists position statement, 2011).

1.9 Challenges and opportunities for cord blood banks

While clinical practice in stem cell transplantation has evolved, an important niche remains for cord blood as a transplant source either as a back-up to bone marrow or PBSC stem cell transplants in the event of graft failure or as a first choice in some clinical circumstances. To maintain and improve the market share currently held (Anthony Nolan Aligned Stem Cell registry data 2020) the NHS Cord Bank must continue to provide high quality cord blood transplants that contain clinically

suitable cell doses as well as providing a diverse range of HLA types to meet the needs of patients awaiting a stem cell transplant in the UK and worldwide. This research was undertaken to establish whether initial targets for the cord bank had been met and, importantly, to identify ways that maximise efficiency in cord blood donation, collection and quality of stored cord blood available for transplant.

In 2018 funding by the Department of Health to continue building the NHS Cord Bank inventory to 20,000 banked donations ceased since this target had been met and the bank began to enter a maintenance phase during which a number of cord blood units reduced from that which had been collected previously per annum would be banked to maintain and adapt to requirements for HLA diversity and TNC content of the cord blood units. This research aims to contribute to decisions enabling this by determining the content of the bank in terms of quality and ethnic diversity and identifying gaps or disparity in provision of BAME and BINE transplants for black, Asian and ethnic minorities (BAME) and British, Irish and North European patients (BINE). One of the local strategy objectives for the NHS Cord Bank is to reduce and refine the inventory to ensure only clinically suitable units are stored in the bank and that plans are made to reduce the number of other units held in stock through use in new applications of clinical and molecular therapy. It is important in doing this that ethnically diverse units are maintained and that future donations are of good quality in terms of cell count, as it has been previously shown that these donations frequently yield lower volume cord collections and contain fewer cells but may be from a rare but significant HLA type (5) in the patient population (unpublished data, NHS Cord Blood Bank).

1.11 Aims and Objectives

This research consists of two studies using mixed methods. The first quantitative study explores the quality of the cord blood donations related to TNC and whether the NHS cord bank has met its targets for banking in terms of BAME donations and if provision of BAME cord transplants has changed over time. The second qualitative study explores barriers and potential changes to practice to improve donation rates and the quality of banked cord blood units based on the findings of Study 1.

Aim 1

- To provide a retrospective analysis of the NHS cord bank inventory by donor-reported ethnicity and nucleated cell count.
- To undertake a retrospective analysis of the cord transplants issued from the NHS Cord bank in terms of ethnicity, cell dose and HLA match using existing data.
- To analyse data from the Anthony Nolan Aligned UK stem cell registry on searches undertaken for patients who were eligible for a transplant but could not find a suitable HLA matched transplant to assess changes in availability over time.
- To use these data to identify areas for improving rates of donation and collection, these to be investigated in the second part of this research.

Objective 1

i. Existing data on the NHS Cord Bank inventory will be reviewed to establish its ethnic composition and to determine whether the strategic aim of banking 30-50% of donations from BAME groups has been achieved.

ii. Existing data on cord transplants issued from the NHS Cord Bank will be analysed to determine the proportion of BAME transplants issued to patients in the UK and worldwide and to understand if this has changed over time.

iii. Search data from transplant registries will be analysed to identify the numbers of patients that were eligible for a haematopoietic stem cell transplant but did not receive one because an HLA-matched transplant was not available.

iv. Should the existing data in these reports be insufficient to address Aim 1, additional queries will be written to extract the data from databases available at NHSBT.

Aim 2

Using data from study 1, to examine the reasons for not engaging, or for engaging, with cord donation and collection through development of semi-structured interviews or focus groups.

Objective 2

i. To select two or three groups to seek opinion(s) based on data from Study 1. Need to ensure clear differentiation between these barriers to donation and the issues in the collecting and processing stages

ii. To identify a suitable location and forum, through NHSBT blood donor links, and organise a focus group for each group or interviews with individuals.

iii. A semi-structured plan of questions will be used to elucidate thoughts, feelings and barriers to donation of cord blood.

Aim 3

To suggest interventions aimed at increasing donation rates based on the findings of the focus groups and interviews.

Objective 3

i. To seek feedback on proposed interventions with those interviewed for the study and the wider NHS Cord Bank team.

2 Study 1 Methods

This chapter presents the context and setting for study 1 and describes the collection and analysis of data. The following data sets were analysed:

1. The NHS cord bank inventory from the start of banking in February 1996 to December 31st, 2017. In 2018 the cord bank went from a growth to a maintenance phase with significant changes in staff numbers and shift patterns. The data were analysed to the end of the growth phase to inform practice during the maintenance phase of banking when collection numbers would be reduced.
2. Cord blood unit (CBU) transplants provided to patients from the NHS Cord Bank Inventory from the first transplant that was issued from the bank in 1998 to the end of calendar year 2018.
3. Anthony Nolan Aligned Registry searches for HLA-matched adult and cord blood donors between 2006 and 2016. These data were provided from a source external to the NHSBT and the data were provided from when records of ethnicity began to the time at which the application was made.

2.1 Context and setting

Data for this study relating to the cord bank inventory and transplant provision were obtained from NHSBT databases and software that records information on the cord blood maternal donor and the donation of cord blood itself, the product. These data include all cord donations stored in the bank since it commenced in 1996 up to 31/12/2017 and all cord donations provided for transplant from the

bank between 1998 and 31/12/2018. By the end of 2018 cord blood donations that were collected in 2017 were available for search.

An application including ethics approval was made to the Anthony Nolan registry (Appendix 3) for data relating to searches undertaken to find an adult or cord blood stem cell donation for patients. These data covered a ten-year period from 2006 to 2016. This period was chosen because prior to 2006 the data were not recorded in a format that could be retrieved without accessing multiple data sources.

Using descriptive statistics in Excel and IBM SPSS the composition of the NHS cord blood bank was first assessed by donor reported ethnic groups, which were initially divided into Black, Asian and Minority Ethnic (BAME) and British, Irish and Northern European (BINE) categories (Office for National Statistics, April 2008). Changes in the proportion of BAME donations over time were analysed. The BAME donations were further assessed according to the number of donations in each ethnic group as categorised by an NHSBT-controlled document (Appendix 4) which is used by the cord blood collectors at the time of donation to record maternal and paternal donor ethnicity. Sources of data for recording ethnicity were the NHSBT Cord Bank ethnicity form, the classifications provided by the Anthony Nolan registry search data.

The transplants provided by the NHS Cord bank to patients in the UK and internationally were analysed by donor ethnicity, HLA match and TNC category. A chi-squared test was undertaken to look for differences in the number of BAME cord transplants that had been issued over the time period studied. Descriptive

statistics were used to assess differences in HLA match and cell count between BAME and BINE cord transplants.

To assess the potential unmet need among UK patients in relation to ethnicity and the likelihood of finding a potential transplant match the data provided by the Anthony Nolan registry were analysed to identify changes in the likelihood of finding a bone marrow or cord blood donor over the ten-year period overall and by BAME or BINE patients where ethnicity had been reported.

2.2 NHS Cord Bank Inventory

The NHSBT use an Oracle database called Hematos to manage the donor and product information on cord blood donations as well as the transplant information when cord blood is sent to a recipient. At the time of collection and storage of each cord blood unit questionnaires and examinations are created within Hematos to enable unique information to be stored for each cord blood donation and the donor mother. The donations are identified using ISBT 128 barcodes to provide a unique identifier which is recognised in the database. Thus, a complete picture of the cord blood characteristics and the maternal donor medical and lifestyle history is created. To meet the first aim of the research question, data points concerning date of collection and ethnicity were extracted from the database using software (Business Objects; BoBs) to provide a report. In this report unique ID, ethnicity, cell dose, date of collection and the collection site for each cord blood unit were extracted. The extracted data were then sorted by ethnic group to show the contribution to the total bank size for each group.

The categories of ethnicity found within the NHS Cord Bank are shown in Table 2.1. These are recorded against standardised ethnicity groupings listed in the maternal history questionnaire (NHSBT controlled documents INF998 and FRM2291) and indicated by the cord donor mother at the time of donation.

Table 2.1 Categories of ethnicity of cord blood donations stored in the NHS Cord Blood Bank as recorded by the donor mother according to a controlled and standardised NHSBT document completed at the time of donation.

NHS Cord Blood Bank ethnicity grouping:
Unknown
African black
Any other
Asian
African Caribbean
Black
Caucasian
Chinese
Hispanic
Indian sub-continent
Jewish
Japanese
Mediterranean Caucasian
Mid-eastern
Mixed
Mixed Caucasian and black African
Mixed Caucasian and black
Mixed Caucasian and Asian
North America, Australia and NZ
Oriental
UK North Europe
US Black
White British
Other
South America
SE Asian
SE European Caucasian

The inventory was analysed by the TNC to compare the cord donations by cell count in the BAME and BINE groups. The cord blood units (CBU) are categorised in groups A, B, C or D depending on the total nucleated cell count contained in

each CBU at point of cryopreservation, with those containing the highest range of nucleated cell counts classified as A grade. This is summarised in Table 2.2.

Table 2.2. Classification of cord blood units according to the total nucleated cell content after collection and prior to processing and storage.

CBU Grade	TNC $x10^7$ per cord blood unit
A	>= 190
B	>=135-189.9
C	>=90-134.9
D	<90

2.3 Cord blood unit (CBU) transplants provided to UK and international patients from the NHS Cord Bank Inventory

Data were extracted from NHSBT records to identify and group the ethnicity of patients for whom cord blood transplants were provided from the NHS cord bank to UK and international patients. This is shown in Tables 3.1 and 3.2 in the Results section. The data were extracted from the Hematos database and cross-referenced against an Excel spreadsheet which is maintained sequentially to record details of each cord blood to its recipient either in the UK or to an international transplant centre.

2.4 Registry searches for UK patients with HLA matched adult or cord blood donors between 2006 and 2016

Anonymised data were requested and obtained under ethical approval (Appendix 4) from the Anthony Nolan aligned registry database to determine which patient groups were eligible for a transplant but did not find a suitable match. Data were provided from this database to show the number of patients for whom a search for a potential HPC donor had been undertaken and the number of patients for whom no suitably HLA matched donor could be identified. Data fields were selected to

show the values for the year of search, ethnicity, the number of bone marrow HLA matches and the number of cord blood HLA matches.

The data were grouped to show for each ethnicity where no bone marrow or cord blood match was found, where ≤ 4 cord or bone marrow matches were found (low likelihood of progressing to transplant) and where ≥5 cord or bone marrow matches were found (greater likelihood of one of the matches being suitable for transplant on further investigation).

The data have been compared with what the NHS cord bank inventory consists of, what the HLA match was for UK patients (to determine whether an ethnically matched transplant was available) receiving cord transplant from the NHS cord bank or another bank and the ethnicity of transplant-eligible patients who were unable to find a suitable donor.

The findings from this have been used to inform the second study, in which ways to improve donation rates are sought, either through exploration of factors affecting donation rates and quality parameters or through interaction with BAME groups that are underrepresented in the inventory of the NHS cord bank. donation rates and quality parameters.

2.5 Statistical analysis

Microsoft Office Excel 2010 was used to derive graphs and descriptive statistics showing inventory composition and transplant provision from univariate data. IBM SPSS was used to analyse changes over time in the number of searches

undertaken to find available stem cell donors and the proportion of BAME donations in the inventory composition.

The hypothesis was that the number of suitably matched stem cell transplants for BAME patients had changed significantly as cord banks inventories grew and in consequence the unmet need has been improved. This could not be correlated to the NHS Cord Bank only as the searches scan all registered cord banks. It is not possible to determine the searches using the NHS Cord Bank exclusively.

2.6 Reference period for the data sets

In this retrospective analysis of the NHS cord bank inventory the data set that was analysed was cords collected and banked from 1996 when the NHS Cord Bank commenced operations until 31st December 2017.

The data set for cords that had been issued from the NHS Cord Bank for stem cell transplant in the UK and internationally covered the period from the first transplant that was issued to 31st December 2018.

The data set for analysis of ethnicity and TNC included all cord donations stored in the bank at 31st December 2017 and were visible on registries for search.

For provision of transplants the sample set included all cord donations that were visible on data registries as searchable cord donations ready for use as a stem cell transplant.

Search data provided by the Anthony Nolan included all searches carried out between 2010 and 2016 for patients in the UK to find an adult or cord blood stem cell donor matched with at least 3 of 6 HLA loci.

2.7 Study Design

Mixed method was chosen for this research. Study 1 determined whether initial targets for the NHS Cord Bank, set by NHSBT, had been met given retrospective analysis of available data. The results of study 1 were used to inform development of study 2, in which qualitative research was undertaken to explore barriers to cord donation and collection in greater depth and to determine whether practice changes could be made to address any issues identified.

3 Study 1 Results: The NHS Cord Bank Inventory and Cord Blood Transplants

This chapter presents results for the aims and objectives of the study concerning:

i) The content and composition of the NHS cord blood bank inventory regarding ethnicity and cell count.

These results are first presented as the proportion of BAME cord blood donations and BINE cord blood donations collected from the six collection sites that feed into the cord blood bank for processing and storage of the donations, where criteria for volume and cell content were met (Appendix 2). This is shown for the whole inventory and by contribution to banked donations from each collection site.

The results for BAME donations are then presented according to the categories in the ethnicity form (Appendix 3) that is completed at the time of donation by the cord blood collector and the donor mother.

Data on the nucleated cell count of the banked cord donations are presented for BAME and BINE donations in the cord bank inventory and lastly data on available births from which cord donations could be collected are described.

ii) Cord blood transplants provided for UK and international patients by the NHS cord blood bank. This is in relation to the equity of access objective for the bank and according to the UK Stem Cell Strategy.

These results are presented by donor and recipient ethnicity for domestic (UK) and international transplant provision. The self-reported donor ethnicity is presented for transplants provided to the UK and internationally.

The level of HLA match and nucleated cell count are presented for BAME and BINE donors and recipients from cord transplants provided between 1996 and 2019.

iii) Searches undertaken by the Anthony Nolan registry on behalf of the aligned registries in the UK for haematopoietic stem cell donors for UK patients across a ten-year period from 2006 to 2016.

Stem cell sources for these searches include both adult donors and cord blood donations and have been analysed for changes in availability for both BAME and BINE patients over this time period.

3.1 The NHS Cord Bank Inventory

3.1.1 The NHS Cord Blood Bank Inventory met the target recommended for BAME donations by the UK Stem Cell Strategic Forum

The composition of the NHS cord bank by donor reported ethnicity, categorised as BAME) or (BINE is shown in Figure 3.1 for cord blood donations banked between 1996, when the NHS Cord Bank commenced banking, and 31st December 2017. During this period twenty-two thousand and seven (22,007) cord blood donations were added to the NHS Cord Bank inventory. By the end of the data reference period, 31st December 2017, the proportion of BAME donations was 41.5% and the proportion of BINE donations was 57.7%. Both BAME and BINE proportions fluctuated from year to year. The average BAME proportion was 39% and the average BINE proportion was 59%. Regression analysis demonstrated a clear (highly significant) linear increase in the proportion of BAME donations in the inventory, after checking the populations were normally distributed and evenly

variable (Figure 3.1). Graphical inspection of the residuals indicated that the assumptions of normality and equal variance were satisfied.

The model explained 62.2% of the variation in the percentage of BAME donation transplants (pctBAME) and indicated a highly significant increase in pctBAME (linear regression: $t(21) = 5.88$, $P < 0.001$), with pctBAME increasing on average by 0.54% (s.e.m. = 0.09%) each year.

There was an average of 2% of donations each year where ethnicity had not been reported or recorded. The inventory size started to grow significantly from 2004 when additional collection sites opened (Table 1.3). The recommendation set by the UK Stem Cell Strategic Forum (UKSCSF) was to bank between 30 and 50% of donations from BAME donors and the target set by NHSBT was to bank 40% of BAME cord blood donations from all the cord blood donations that had been collected. This was achieved by the end of the reference period.

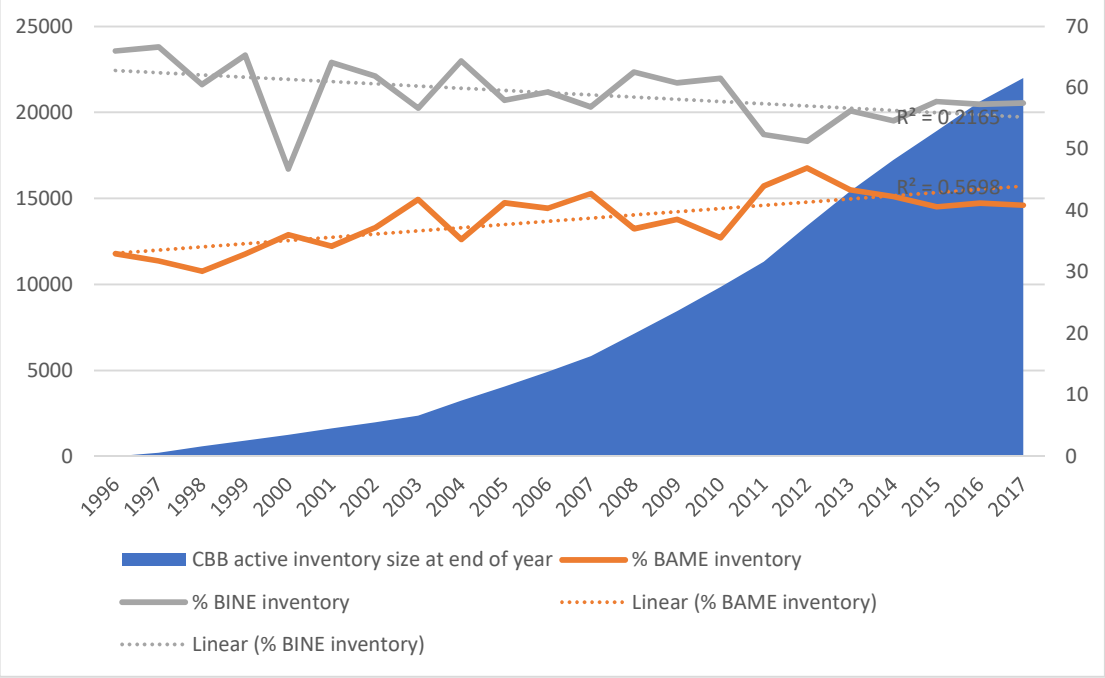

Figure 3.1. Growth of the NHS Cord Bank by year and proportions of the bank that are BAME and BINE cord blood donations by year. BAME donations increased significantly year on year ($p<0.001$)

3.1.2 The highest proportion of BAME donations are from donors of mixed ethnicity

Figure 3.2 shows the breakdown of ethnicities in the BAME cord blood donations that are stored in the NHS Cord Bank. This classification is according to controlled document FRM2291 (Appendix 3) which is used by cord collection staff when completing the maternal health questionnaire with the donor. The form has been revised since cord banking commenced to include additional sub-categories; for example the breakdown of the Asian donor category into sub-groups and tis is shown in Figure 3.2. Donors reporting their ethnicity as Hispanic or Black American were few: 2 and 3 respectively. Donors of black ethnicity accounted for 7% (n=1573) of the cord bank inventory.

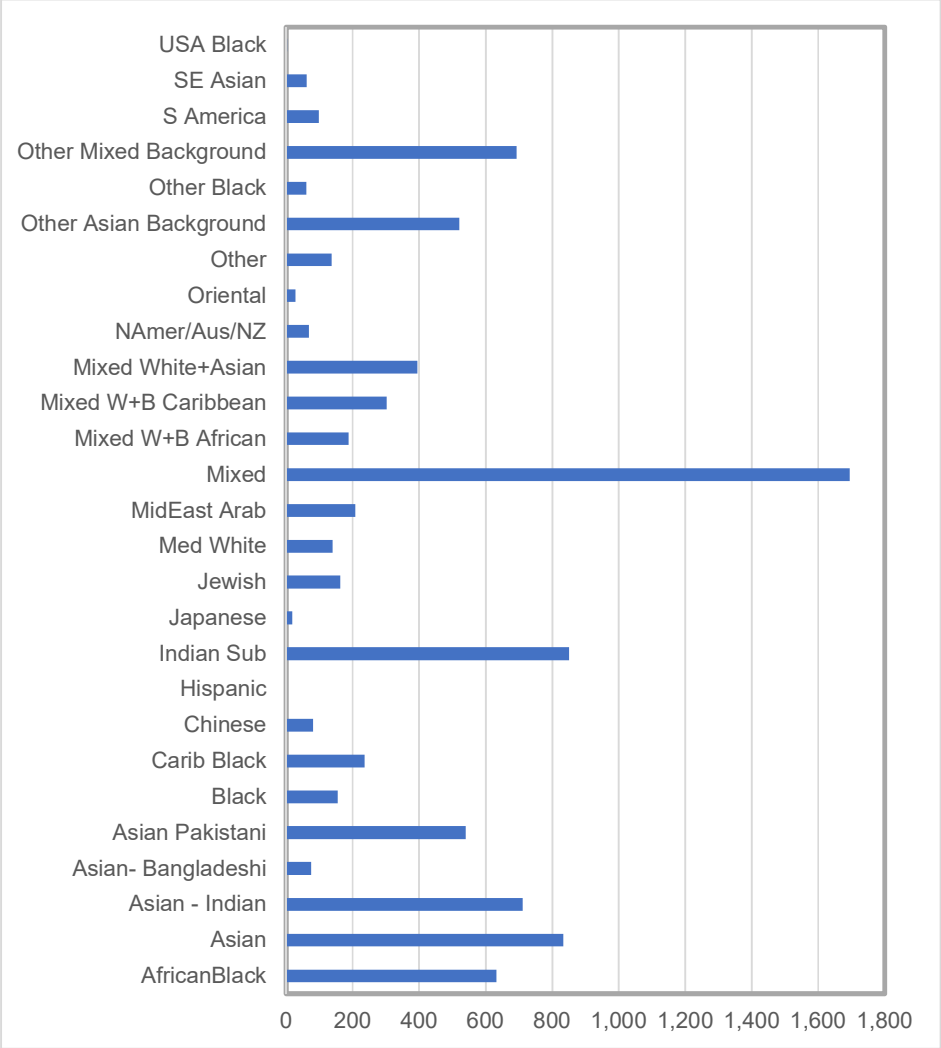

Figure 3.2. Composition of the NHS Cord Bank inventory at December 31st 2017 by donor-reported ethnicity according to standardised NHSBT coding for ethnic groups.

3.1.3 The proportion of A grade cord blood units is lower in BAME donations than BINE donations.

Figure 3.3 shows the number of cord blood donations in the inventory split by grade A, B, C and D in the BAME and BINE donations at 31st December 2017. The BINE cord blood units accounted for 12,690 cord donations; 57.7% of the total inventory, and there were 9,129 BAME cord blood units; 41.5% of the total inventory. There were an additional 188 cord blood donations in the inventory

(0.8%) where the donor ethnicity was either not disclosed (n=66) or not recorded (210).

Of the total inventory 1501 were A grade cord donations and 65% of these were from BINE donors (n=975) and 35% were A grade from BAME donors (n=526). There were 4374 B grade donations of which 63% were from BINE donations (n=2744) and 37% were from BAME donations (n=1630), the proportions by grade of cord blood unit are shown in Figure 3.3 below.

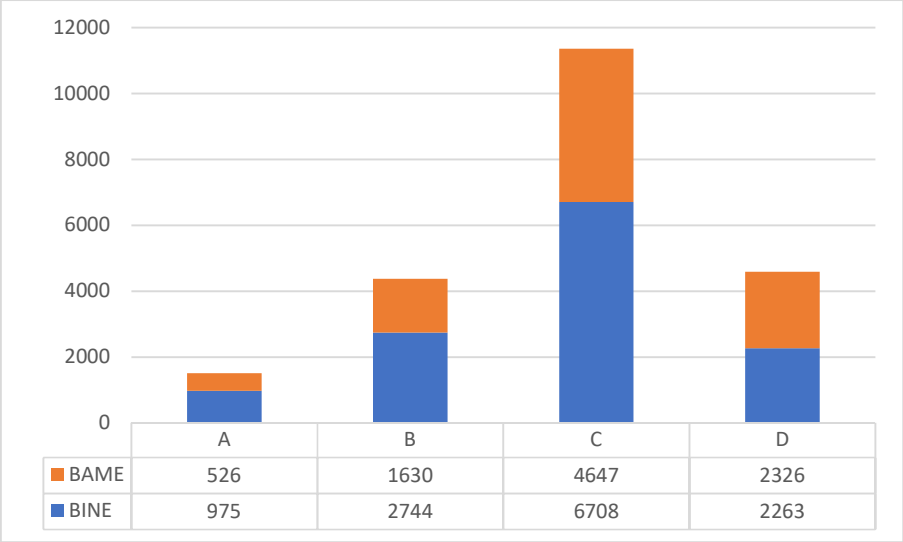

Figure 3.3 The NHS Cord Bank inventory by number of A, B, C and D grade cords for BAME and BINE donations

3.1.4 Each of the cord collection sites met the target for BAME cord blood donations that were collected and banked.

A strategic decision was made to open collection sites in areas of highest ethnic diversity around London to facilitate collection of cord blood donations from BAME donors. Data from the 2011 census shows the BAME population of the UK is 14% in England and Wales and 40% in London (UK Census, 2011). The BAME inventory proportion is 41.5%.

Figure 3.4 shows the proportion of the total inventory contributed by each of the 6 collection sites for cords added to the inventory over an eight-year period between 2010 and 2018 (n=14099). Available births at each site were roughly equal over this period and all sites operated twenty-four hours a day, seven days a week during this period. Watford General Hospital contributed 30% of all banked donations during this period, followed by St Georges Hospital at 22% of all banked donations.

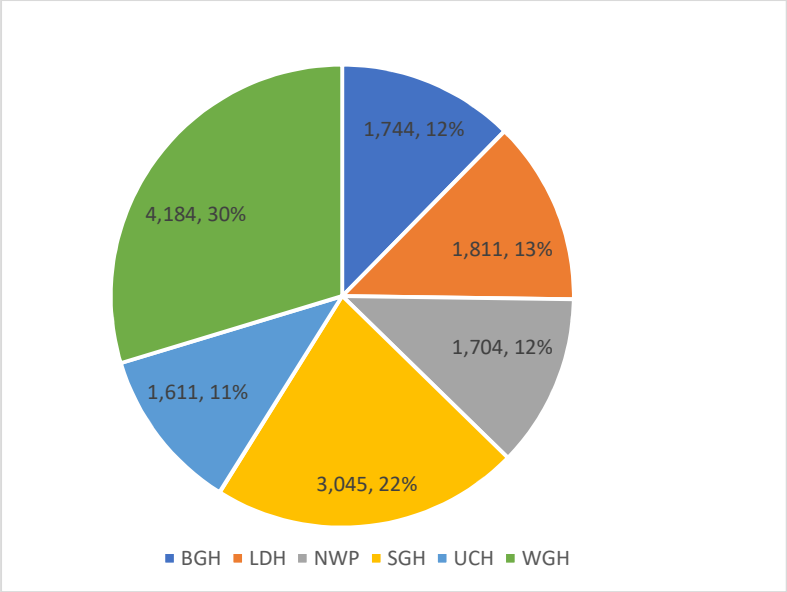

Figure 3.4. The contribution from each of the 6 collection sites for cords banked between 2010 and 2018.

Key: BGH Barnet General Hospital, NWP Northwick Park, LDH Luton and Dunstable Hospital, WGH Watford General Hospital, SGH St George's Hospital, UCH University College Hospital

3.2 NHSBT Cord Blood Transplant provision to UK and International Patients

3.2.1 The proportion of cord blood transplants to BAME patients has not risen since 2000

There were 726 cord blood units issued for cord blood stem cell transplant by the NHS Cord Blood Bank between 2000 and 2018. Of these 240 were provided to UK patients and 486 were exported to international transplant centres. The total number of transplants per annum is shown in Figure 3.5

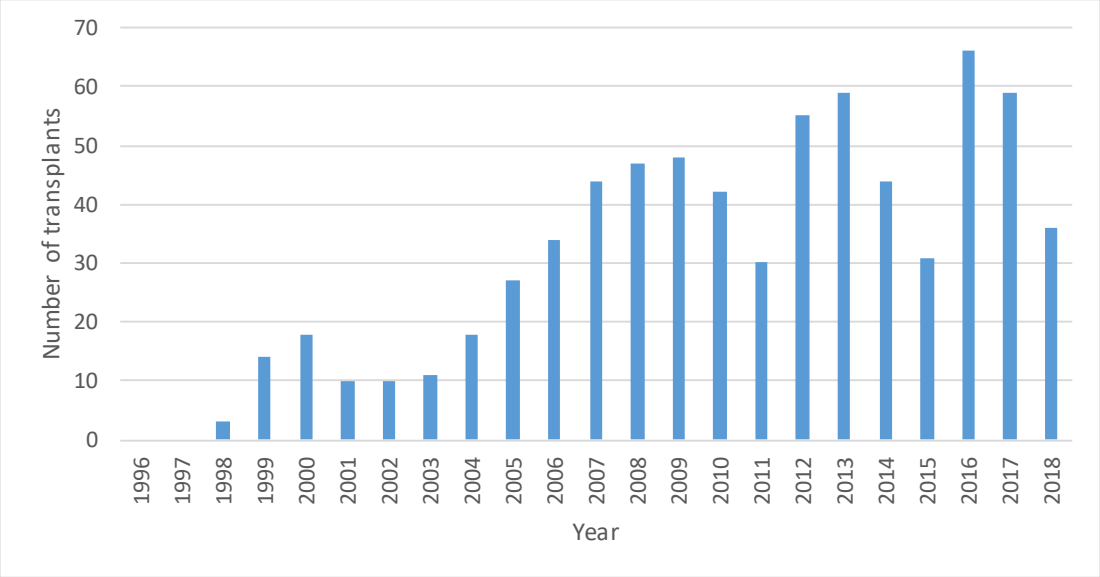

Figure 3.5 Total number of cord transplants per annum that were issued from the NHS Cord Bank from 1996 to 2018

There was no statistically significant change in the relative numbers of BAME versus BINE transplants across years or the proportion of each; 38% and 62% respectively. The cord transplants from BAME and BINE donations as a proportion of the total number of cord transplants each year is shown in Figure 3.6. The A chi-squared test of independence between the groups BAME vs. BINE and year was carried out to assess whether the relative numbers of BAME and BINE donations were independent of year. The expected counts were large enough to validate the assumptions of this analysis (no expected counts smaller than 1,

fewer than 20% smaller than 5) and the result was clearly non-significant. There was no evidence that the proportion of donations from BAME donors differed across years (chi-squared test of independence: X2 = 13.5, d.f. = 20, P = 0.853). This was also non-significant when analysed separately for UK and international transplants.

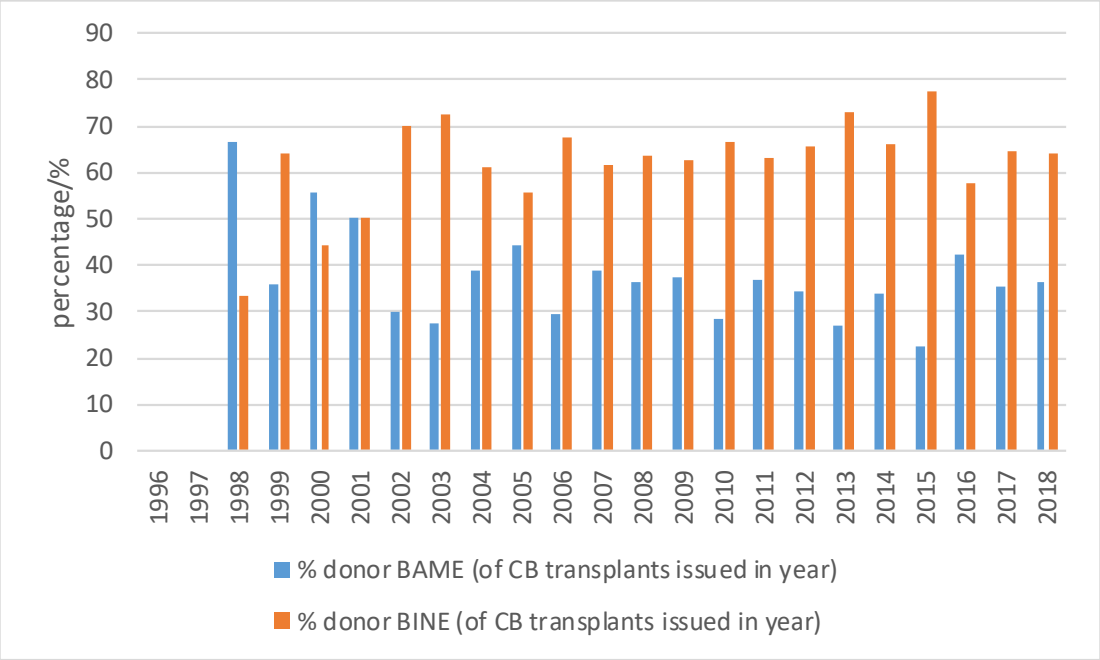

Figure 3.6 The percentage of BAME and BINE cord transplants issued each year

3.2.2 The highest proportion of BAME transplants for both UK and international patients was provided by donors of Asian or mixed ethnicity

Donations that came from donors of Asian or mixed ethnicity accounted for the greater proportion of cord blood transplants to UK patients in the BAME cord transplants, n=19 for both, and donations from these ethnicities also made up a greater proportion of the cord bank inventory than other BAME groups (6% and 8%). A similar picture was seen in cord transplants provided to international patients, donations of Asian and mixed ethnicity comprising the greater number of cord transplants issued (n=45 and 28 respectively). A breakdown of donor cord

ethnicity for cord transplants to UK and international patients is shown in Tables 3.2 and 3.3 respectively, with the proportion of the bank size for each ethnic group.

Table 3.1 NHS Cord Blood Bank transplant provision to UK patients by donor cord ethnicity and as a proportion of the inventory.

Donor cord ethnicity	Number of transplants provided (% of total transplants)	% Proportion of NHS Cord Bank
Black Caribbean	2 (0.9)	1
Asian	19 (9.3)	6
Black African	1 (0.5)	3
Caucasian N European	78 (38.0)	19
Chinese	2 (0.9)	<1
Indian	1(0.5)	5
Middle Eastern	1(0.5)	1
Mixed	19 (9.3)	8
Oriental	1 (0.5)	<1
Caucasian E/W European	81 (39.5)	>31
Total transplants	205	-

Table 3.2 Cord blood transplant provision to international patients and as a proportion of the NHS cord bank inventory

Donor cord ethnicity	Number of transplants provided (% of total transplants)	% Proportion of NHS Cord Bank
Asian	45 (18.0)	6
Black African	5 (2.0)	3
Black Caribbean	6 (2.4)	1
Caucasian	161 (64.7)	19
Jewish	2 (0.8)	<1
Mixed race	28 (11.2)	8
Indian	1 (0.4)	5
Oriental	1 (0.4)	<1
Total transplants	249	

3.2.3 A higher proportion of transplants originated from BAME donations than from BINE donations and the nucleated cell count was lower in BAME donations.

Figure 3.5 shows the proportion of A to D grade transplants provided from BAME and BINE donors. BAME cord donations comprised 54% of all transplants compared with 46% from BINE donations. The percentage of A grade transplants from BAME donations was 43% compared with 57% from BINE donations.

However, the BAME donor transplants had lower nucleated cell concentrations than the BINE donor transplants; 8.5% (n=80) compared with just under 2% (1.9%) (n=20).

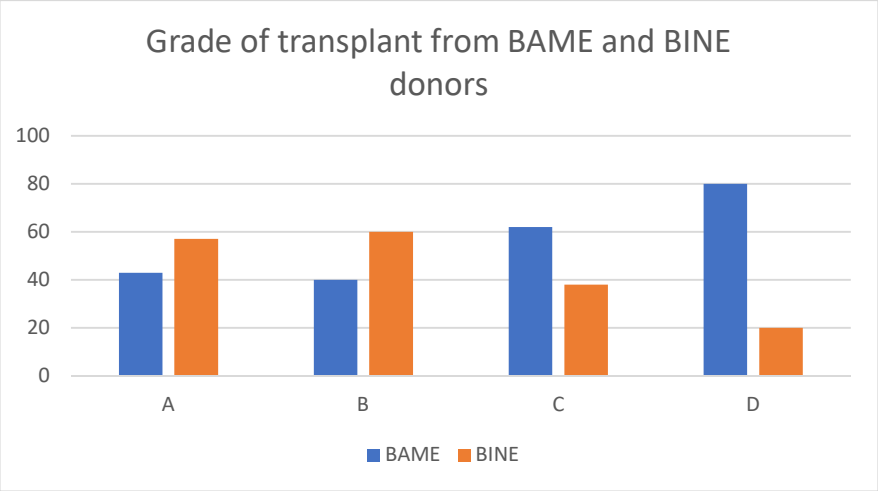

Figure 3.7 Cord blood grade for BAME and BINE transplants provided 2000-2018

3.2.4 A greater degree of HLA match with the recipient was seen in the BINE cord transplants than the BAME.

In BAME transplants issued between 2000 and 2018 from the NHS Cord Bank, 3.3% of these were a 6/6 HLA match with the recipient compared with 11% of BINE transplants. A 5/6 HLA match accounted for 22% of BAME transplants and 32% of BINE transplants. A 4/6 HLA match was provided for 33% of BAME and 35% of BINE transplants. When the nucleated cell count was considered, classified as A-D grade with A grades containing the highest cell count (Table, Introduction), a quarter of the BAME transplants (25%) that had a good HLA match with the recipient had a C or D grade TNC compared with 14% of BINE transplants with the same level of HLA match.

Table 3.3 Donor availability for UK Patients eligible for a hematopoietic stem cell transplant with an HLA match at HLA-A, B and DRB1

	BAME transplants				BINE transplants			
Column 1	HLA 3/6	HLA 4/6	HLA 5/6	HLA 6/6	HLA 3/6	HLA 4/6	HLA 5/6	HLA 6/6
A	15	66	44	7	12	78	68	18
B	3	43	28	4	2	48	46	22
C	2	31	45	13	1	15	27	17
D	0	4	13	11	0	0	2	5
Unknown	4	28	42	21				
	24	**172**	**172**	**56**	**15**	**141**	**143**	**62**

3.3.1 Cord blood donor availability has increased in for BAME and BINE patients at UK transplant centres

3.3.2

Searches for stem cell donors for UK patients eligible for a stem cell transplant and coordinated through the Anthony Nolan registry were analysed for changes over time in the availability of donors for BAME patients. A data reference period from 2011 to 2015 was selected during which data sets were more complete than in previous years.

Unknown or undeclared ethnicity data were excluded from the analysis for BAME patients. The change in donor availability between 2011 and 2015 for adult donors and cord blood donors is summarised in figure 3.6. In 2011, 1974 searches were undertaken of which 774 had full data available and were included in the analysis. In 2015, 3749 searches were undertaken of which 1436 had full data available and were included in the analysis.

In 2011 two thirds (66%) of BAME patients did not have an HLA matched adult bone marrow donor match compared with just over one third (38%) of BINE patients. By 2015 this remained about the same at 64.5% for BAME patients and had decreased slightly to 30% for BINE patients, meaning that BINE patients were twice as likely to find a suitably HLA-matched bone marrow as BAME patients. The percentage of BAME patients with more than 5 cord blood matches and at least a 3/6 HLA match increased from 68% in 2011 to 82% in 2015 and from 58% to 73% for BINE patients.

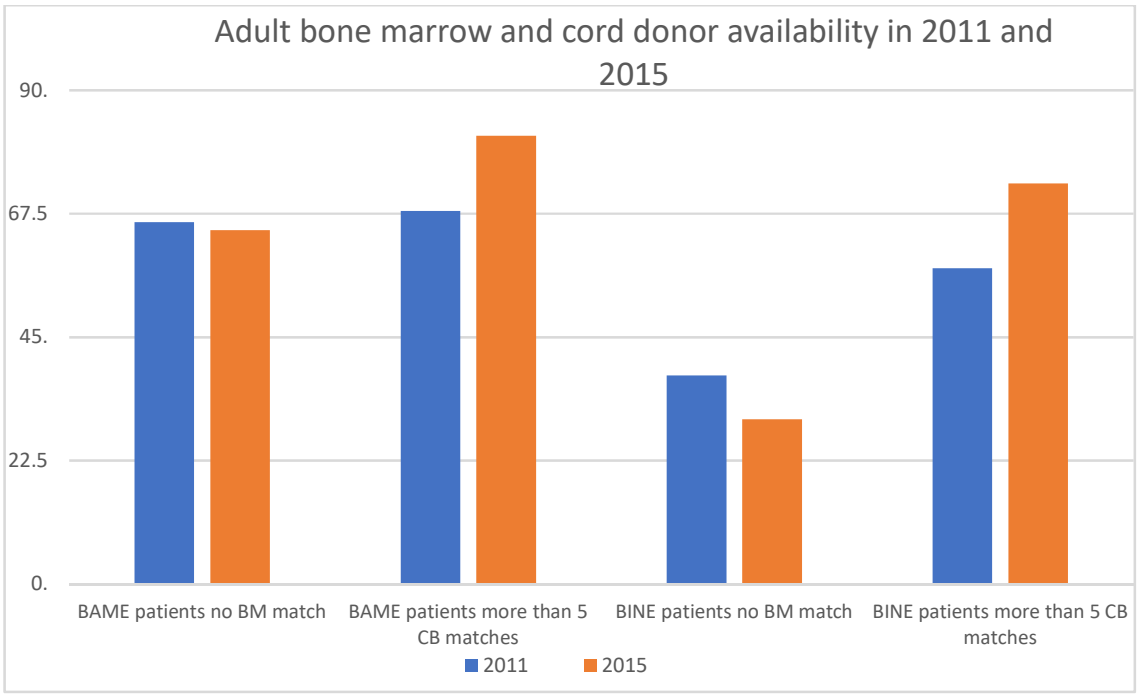

Figure 3.8 Registry data searches for bone marrow and cord blood transplants in 2011 and 2015 for BAME and BINE patients (BBMR 2016)

3.4 Summary of Study 1

1. The NHS Cord Blood Bank met the objective to bank 40% of donations from BAME donors to help address equity of access for BAME patients requiring a stem cell transplant. This group of patients has been significantly less likely to find an HLA-matched adult bone marrow donor than those of BINE ethnicity; 69% and 20% respectively (AnthonyNolan.org data). All collection sites met this target, supporting the strategy of concentrating collection sites in hospitals serving ethnically diverse populations.
2. Availability of cord blood transplants for BAME patients has increased as cord banks have been established and grown their inventory of donations but the proportion provided over time has not changed., In the experience of the NHS cord bank, the average nucleated cell count per transplant was lower in the transplants provided for BAME patients than for BINE patients. Additionally, the level of HLA match was proportionally lower in cord transplants provided to BAME patients than those to BINE patients. Both these criteria are important in predicting overall survival (Barker, 2010).
3. Search data from the Anthony Nolan aligned registry demonstrated that more cord blood donations with at least a 3/6 HLA match were available to BAME patients in 2015 than in 2011 as cord bank inventories grew. More BINE patients also had a cord transplant option available to them in 2015 than in 2011. A small increase from 2011 and 2015 was seen in bone marrow donor availability for BAME patients, suggesting that the adult stem

cell donor population had not changed significantly in terms of ethnicity over this period.

4 Study 1 Discussion

4.1 Introduction

This study was a retrospective analysis of the cord bank conducted to understand whether the initial objectives for the NHS Cord Bank were being met in terms of the quality and quantity of the bank relating to the inventory size, the percentage of cord blood donations from BAME donors and the nucleated cell counts of the CBUs.

Additionally, the cord transplants that had been issued by the bank were analysed to determine whether the proportion of BAME transplants provided had increased as the inventory size grew. The quality of the cord transplants, in terms of nucleated cell counts and level of HLA match, from BAME and BINE donations was also assessed.

To understand the wider context and implications for the bank, the searches undertaken by the Anthony Nolan Aligned Stem cell registry for suitably matched HLA cord and adult donors were analysed at two time points to establish whether availability had improved for BAME patients.

The data contribute to a clearer understanding of the NHS Cord Bank and the challenges it faces as it moves towards a self-sustaining model using the income generated from provision of cord blood transplants.

The findings of this enquiry were used to develop a qualitative study to identify and better understand barriers to cord donation with the aim of improving practices where possible to maximise the number of high quality cords that could be banked and made available as a potential cord blood transplant to all patients, with a focus on those of BAME ethnicity.

4.2 The NHS Cord Bank Inventory: size and composition by donor-reported ethnicity

4.2.1 The cord bank inventory size

By the end of the reference period, 31/12/2017, 22,007 cord blood donations had been banked and made available on stem cell registries for patients in the UK and worldwide (3.1.1). This exceeded the target of 20,000 cords recommended by the Stem Cell Strategic Forum in the refreshed 2014 version (UK Stem Cell Strategy Oversight Committee, 2014). However, when the cord banking programme commenced, all cord donations were banked regardless of the total nucleated cell count. This meant that 4589 of these donations had a cell count below the refreshed 2014 recommendation of $140x10^7$ and would be less likely to be selected for transplant than those with a higher cell count. Some of these donations, particularly those processed early in the banking programme with a cell count less than $90x10^7$, will be removed from the searchable registries and made available for research and development use. The searchable bank of cord donations that are deemed potentially suitable for clinical use that have a cell count greater than $90x10^7$ consequently reduced in number to 17,230 at the end of the reference period.

In 2010, in light of information available at the time (Querol, 2009), the Stem Cell Strategic Forum made a recommendation on the optimal cord blood inventory size based on matching donor and recipient pairs at an allelic level for HLA-A, B and DRB1 and estimated that an inventory of 50,000 cord blood units would be able to treat an additional 380 patients per annum against an estimated unmet need of 440 patients (Stem Cell Strategic Forum). This total would be split between the two UK jointly funded cord banks so that the NHSBT would bank 30,000 donations

and Anthony Nolan would bank 20,000 donations. The Forum estimated that around 40% of BAME patients would find a well-matched donor with this inventory size, given population data available at the time.

This recommendation was revised in 2014 in light of the most recent and emerging clinical data, to develop a clinical inventory of 30,000 donations and to focus on measures to achieve overall utilisation of the inventory in the region of 1% per annum by 2018. The NHSBT would bank 20,000 donations, and Anthony Nolan would bank 10,000 donations. It was further estimated that at current NHS prices an inventory of 30,000 donations, achieving 1% utilisation per annum, would generate around £4.5m per annum in income. This would allow the cord bank to become self-sufficient, using the income generated from transplant provision to support staff, infrastructure and meet consumables costs for ongoing banking of sufficient cord blood donations to improve inventory quality and to off-set inventory attrition and issue. While many of the costs of stem cell donations from adults are associated with donor work-up and stem cell collection, these processes are only undertaken once the donor has been selected to donate bone marrow or PBSC. By contrast, cord blood banking and storage costs are incurred before the selection and issue process, requiring considerable financial investment before any return is made. The estimate from the Strategic Stem Cell Forum was for a budget of c.£3 million to establish and run the cord bank during its growth phase and c.£4.5 million in income from transplant provision per annum. Given the utilisation rate is lower than predicted; 0.2% versus 1% this income figure is substantially lower.

A study by Lown (2013) suggested that a similar strategy in the USA had improved access to transplant for BAME patients, with around 60% of patients now able to

find an acceptably matched donor. The study also reported that in the UK cord transplants were more frequently used for BAME patients with 21% of BAME patients treated with a cord blood transplant compared with around 4% of white northern European patients. The results for the NHS Cord Bank showed that 50% of the transplants that were issued originated from BAME donations, suggesting that the bank has a good market share, this is supported by performance data from NHSBT (NHSBT monthly performance figures).

4.2.2 The utilisation rate and factors affecting this

The utilisation rate is the proportion of an inventory's stored donations that are issued every year and is one of the main determinants of whether a cord blood inventory is financially sustainable in the long term and so it is important to ensure that all ways in which to improve this are explored. In 2018, 50 transplants were issued from the searchable inventory of 23,109 cord donations, which equates to a utilisation rate of 0.2%, some way below the expected rate of 1% estimated in 2010. In principle, utilisation rates fall as the size of an inventory increases, but in reality this ratio is more complex, depending on factors such as the quality of the added cord blood units and any effect of changes in clinical practice for stem cell transplant. Since the cord banking programme commenced changes in selection algorithms, double cord transplants and HLA matching have affected utilisation rate

4.2.2.1 HLA matching

Since these recommendations were made, stricter HLA matching criteria have been adopted which has further reduced the number of cord blood donations available per patient (Eapen, 2017). This study on a retrospective analysis of 1586 patients receiving a single cord blood donation transplant for non-malignant disease reported data on matching at HLA-A, B, C and DRB1 and the outcomes after cord blood transplantation. 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 with 8/8. The 5-year overall survival was 79% (95% CI 74-85) after HLA matched, 76% (71-81) with a one allele mismatch, 70% (65-75) after two alleles mismatched, 62% (57-68) after three alleles mismatched, and 49% (41-57) after four or more alleles mismatched transplantations.
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). Work is being carried out within the NHS Cord Bank to ensure older cords are retyped at high level resolution to facilitate this. 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 that were mismatched at 4 or more alleles should only be considered alongside options such as haploidentical transplantation. Gragert reported that the likelihood of finding an optimal haematopoietic stem cell donor varies among racial and ethnic groups, with the highest probability among whites of European descent, at 75%, and the lowest probability among blacks of South or Central American descent, at 16% and that few patients would have an optimal cord-blood unit matched at the antigen level at

HLA-A and HLA-B and matched at high resolution at HLA-DRB1 but mismatched at one or two HLA loci are available for most patients younger than 20 and more than 80% of patients 20 years of age or older, regardless of racial and ethnic background (Gragert, 2014). This, however, needs to be taken in context of outcomes, with patients receiving a mismatch likely to do worse than patients with a fully matched cord. For cord blood transplants a degree of HLA mismatch can be mitigated by transplanting a CBU with a good TNC dose, as demonstrated in data from Avery (2010).

The data from Stevens in 2013 suggested that the present strategy for umbilical-cord blood unit selection should be reassessed to include matching at HLA C for units that are matched at HLA A, B, or DRB1 or in the presence of a single locus mismatch at HLA A, B, or DRB1 should be included to minimise mortality risks (Stevens, 2011). This may further decrease the availability of cord donations available patients and increases the requirement to maintain an inventory with good HLA diversity which is linked to ethnicity (Pidala, 2012).

4.2.2.2 Single and Double cord transplants

Although cord blood units with a high cell count are most likely to be selected for transplant, there is still potential for cords of a lower TNC to be used as one of the cords provided for a double cord transplant. Since the cord banking programme commenced the use of double cord transplants has begun and comparable outcomes to single cord transplants have been reported (Wagner Jr, 2014; Ponce, 2013). This has allowed for cord blood units with lower TNCs to be selected as one half of a cord transplant and consequently should allow for a greater utilisation

rate. This effect may have been hindered by other factors such as the increasing use of haplotype donors in place of a cord transplant.

Due to the favourable outcomes reported, transplants using two-cord blood donations have become the norm in adult patients due to the limited number of haematopoietic cells in a single cord blood donation, which has been associated with delayed haematopoietic recovery and higher mortality (Eapen, 2019). In light of information on double cord transplants in 2013 provided by Anthony Nolan it has been estimated that 59% of transplants are double cord blood; this would concur with NHS Cord Bank data suggesting about 50% of cords issued from the bank are for double cord transplant (NHS Cord bank data 2019).

4.2.2.3 Haplotype transplants

The conditioning regimen for haplotype transplants has evolved and is now a competitor for cord blood transplantation since it is now a preferred option when a suitably matched adult donor is unavailable for the patient and this is more likely in BAME patients (Ballen, 2012). Over the time period analysed a clinical trial has reported on outcomes particularly for haplotype transplants and some studies have reported comparable outcomes compared to double-cord transplants, while other studies would still recommend the use of cord blood as the primary transplant source (van Besien, 2017; Milano, 2016). Factors concerning management of medical issues associated with cord transplantation, primarily the longer period of neutropaenia, may also play into decisions on use of haplotype transplant in centres less used to cord blood transplant.

4.2.3 Inventory data Summary

A cord blood inventory expanded to the size estimated by Querol was predicted to increase the number of patients eligible to receive a haematopoietic stem cell transplant, as well as to help other patients.

Once the target inventory size of 20000 CBU stored in the NHS Cord Bank has been reached, a maintenance phase commences during which cords are added to top up those that have been issued or any that have been discarded. There is a nominal ‘expiry’ date of twenty years for cords which has now been reached by some cord blood units. Cords, if kept in stable storage conditions, should remain viable and potent (Parmar, 2014). This period has been reached since the bank commenced in 2016 (3.1.1) but many of the cords collected earlier in the banking programme are unlikely to be issued due to their TNC content and may be removed from the searchable registry. Unpublished data (paper in progress) from the cord bank suggest a small but statistically significant decline in viable CD34+ cells over time and for cords with a lower starting TNC this could be clinically significant. To increase the likelihood of maintaining or increasing the utilisation rate it would therefore be prudent to replace older cords, as well as those that have been issued, with cord donations of the highest possible quality in terms of TNC and HLA diversity.

Other cord banks globally have also estimated their target inventory size based on the number of cord blood donations needed per million of the population to serve their estimated patient population (Howard, 2008 Viswanathan, 2009 Song, 2014 Yoon, 2014)estimates are based on their population but in reality, the inventory will provide transplants for patients worldwide as well as domestically.

The number of cords collected will always exceed the amount banked due to attrition at each part of the process because of factors that mean the cord blood units do not meet quality parameters that make them suitable for clinical use. These include insufficient blood in the placenta to attempt a collection, a low TNC count or medical exclusions such as a positive virology marker. Some prospective donors may have expressed an interest in donating their cord blood but at the time of delivery they may have had a temperature spike, reached at less than 37 weeks' gestation or had twins, all of which are exclusion factors and a collection would not be attempted. There could be other barriers which prevent donation or collection which are identified when the cord collectors make contact with the potential donor. These include language barriers, refusal to donate on religious grounds, delayed clamping of the umbilical cord and needle phobia. These barriers have been explored in Study 2. As a consequence of these reasons for not being able to donate cord blood, the conversion rate from collection to a banked cord blood unit can be anywhere between 25% and 40% each month across all collection sites (NHSBT data). A reduction in the attrition rate would contribute to additional cord blood units' being banked, improving numbers in the inventory, potentially HLA diversity and hence equity of access for BAME patients awaiting a stem cell transplant.

4.2.4 Inventory composition by ethnicity

The results show that the aim; to bank between 30 and 50% of cord donations from BAME donors, was met (3.1.1). It was met from when collections first started in 1996 and continued year on year, supporting the decision to site collection sites

in areas of high ethnic diversity. Each of the cord collection sites met the target for BAME cord blood donations that were collected and banked (3.1.4).

There was a statistically significant increase in the proportion of BAME donations that had been banked over time ($p < 0.001$). This can be attributed to the addition of collection sites that collected and banked slightly higher numbers of BAME donations. There was no one collection site that banked significantly more BAME donations than another each year. There is an opportunity, however, to develop more refined data reporting on ethnicity to ensure donation rates across all ethnic groups match patient requirements. Work to reassess the unmet need among the UK population of stem cell transplant patients has recently commenced.

The inventory was made up of 59% BINE donations and 41% BAME donations at the end of the data reference period (31st December 2017). Of the BAME donations all ethnicities as described in FRM2991 (Appendix 3) were represented in varying number, with donations originating from donors of mixed ethnicity making up the greatest proportion of the BAME donations of the inventory (3.1.2). This incorporates a very wide category, including donations from donors of mixed Asian, Black and White African and Black and White Caribbbean ethnicity. This again supports the choice of geographical location for sites, reflecting the population catchment area. Census data from 2011 report a higher proportion of people of mixed ethnicity in Greater London than elsewhere in the UK; 11% versus 3% respectively. Cord donations from black donors comprised 7% of the inventory and may be underrepresented as compared with the local catchment area of the collection sites; 2011 census data report the black population of London as 13.3%. Since this is also the case on adult stem cell registries, it is important to ensure

information provided to prospective black cord blood donors addresses any queries or barriers to donation.

There were some difficulties in aligning and comparing ethnicity data due to changes in how this has been recorded since the NHS Cord Bank commenced; some of the categories have been revised on the controlled documents to include further groupings, for example a previous grouping of 'Asian' has been revised over time to include Asian Pakistani, Asian Bangladeshi, Asian Indian and Other Asian background.

4.2.4.1 Ethnicity and HLA

The genetic diversity of a cord blood inventory reflects the ethnic diversity of the cord blood donors. This is vital to ensuring the UK cord blood inventory can meet the needs of BAME patients.

The recommendation to bank genetically diverse cords was made to improve equity of access to stem cells for black, Asian and minority ethnic patients since HLA type is linked with ethnicity. Patients from ethnic minorities have long been disadvantaged in 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 (Lipton, 2011), and donors from ethnic minorities are under-represented on adult registries (BBMR data).

Data from the BBMR for 2018 illustrate this point, with 7% of adult stem cell donors added to the registry being of BAME ethnicity compared with the 40% of

BAME cord donations added to the bank. Cord banks can secure an advantage in offering a more diverse donor population than adult stem cell registries through location of collection sites to target BAME populations.

Patients of mixed ethnicity face considerable difficulty in finding a well-matched donor (NMDP Be The Match registry data, 2019). The cord bank has been successful in storing 41% of donations from mixed ethnicity groups and this will have contributed to an increase in the likelihood of patients of mixed BAME ethnicity finding a well-matched donor. Where a donor cannot be found, these patients would be more likely to be recommended for a haplotype transplant and though this treatment has more recently shown good results, the first choice of stem cell transplant would be a well-matched unrelated donor (BSBMTCT guidelines, 2019).

In the refreshed recommendations of the Stem Cell Strategy Forum in 2016 it was found that the chances of BAME patients' receiving a stem cell transplant had substantially improved since adoption of the initial recommendations from 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 of patients with haematological malignancies (Lown 2013) 21.3% of BAME patients received a cord blood transplant compared with 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 was met from the UK inventory (Lown, 2013).

Other cord banks worldwide have adopted similar approaches, focusing their efforts on collection of cords with a wide HLA diversity. In 2019 Elmoazzen

reported that the Canadian Blood Services' Cord Blood Bank (CBS' CBB) had built a high-quality and ethnically diverse cord blood inventory of 2000 units (target 10,000) since its launch in 2013. The self-reported maternal ethnicity was 58% non-Caucasian. Overall, 26% of units were classified as multi-ethnicity with Caucasian (84%) most frequently observed in combination with Asian, First Nations (predominant indigenous peoples in Canada south of the Arctic Circle), or African ethnicity. Utilisation scores that incorporate total nucleated and CD34+ cell counts in the CBS' CBB were associated with greater likelihood of utilisation than the international inventory of units ($p < 0.05$) and the utilisation rates were similar for Caucasian and non-Caucasian donations.

Classification of ethnicity was variable across organisations which made direct comparison challenging. The ethnicities recorded at the time of donation differ from those for patient ethnicity provided by transplant centres. This may not be surprising from an organisational point of view; donations of cells, tissue and organs generally will include a focus on serving a patient population. The NHS Cord Bank was partly set up to fulfil an equity of access aim for all UK patients requiring a HPC transplant. Data gathering in other areas of NHS Blood and Transplant attempt to define donor populations and target certain groups that are underrepresented in campaigns to boost donation rates (Organ Donation and Transplantation Activity Report 2018/19).

The increase in the mixed ethnicity in the UK population and consequently UK patient population presents challenges to finding a suitably HLA-matched donor and it is therefore important to maintain or increase the collection and banking rate to serve patients of mixed ethnicity. Further work is required to define which ethnic groups this term relates to. The haplotype transplant option has offered an

alternative for patients that have not previously been able to find a suitably matched donor.

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. For example, 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 (Barker, 2019). There is also a smaller donor pool since ethnic minorities have a smaller population base. Consequently, even with levels of representation comparable with Caucasians', ethnic minority patients will have a smaller selection of potential matches. 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.

4.2.5 TNC counts in the inventory

In 2014 the Stem Cell Strategic Forum recommended that as well as an inventory size of 20,000 cords for the NHS cord bank, inventory utilisation should be maximised by banking only those donations likely to contain a clinically useful dose of stem cells. This was calculated as equivalent to at least 140 x 10^7 total nucleated cells before processing, assuming a recovery of those cells after processing of about 80%.

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 (Stem Cell Strategic Forum 2014). 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 and it is essential to focus on banking cords of this quality to achieve long-term sustainability for the cord bank. This important trend was recognised by the Strategic Forum in 2010 which recommended that donations containing less than 90 x 10^7 total nucleated cells prior to processing should no longer be added to the inventory. 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 at least 140 x 10^7 TNC. Since processing recoveries have improved since 2012 the TNC cut off pre-processing of cord blood units is set at 135x10^7 at the NHSBT and Anthony Nolan.

4.2.5.1 TNC in the cord blood unit

The data show that while the number of banked cords met the objective to bank between 30-50% of donations from BAME donors, the number of A grade cords with the highest TNC counts was lower in the BAME than in the BINE donations (3.1.3). This is of significance because of an association between cell dose and outcome for patients (Barker). This is linked with degree of HLA match. In a study by Barker a degree of HLA mismatch was overcome by a higher cell dose from the cord transplant. The current recommendation for cell dose is for the transplant to contain a TNC of at least 2.5x10^7 per Kg of the patient weight in a single cord blood transplant and at least 1.5x10^7 per Kg for a double cord transplant (Hough,

2016). This can be overcome by use of a double cord transplant and the outcomes of these in terms of event free survival at five years post-transplant have proved to be as good as with single transplants (Barker, 2015; Eapen 2017).

4.3 NHSBT Cord Blood Transplant provision to UK and International Patients

The NHS Cord Bank has been storing cord donations since 1996 and first started to issue these for transplantation in 1998; with two transplants being provided in that year with a rise in provision to a peak of 66 cord transplants issued in calendar year 2016. Across the reference period to the end of 2018 a total of 726 transplants were issued (Figure 3.5) of which one third were provided to UK patients and two thirds to patients outside the UK. Over this period the proportion of transplants originating from BAME donations did not change (3.2.1). The NHS Cord Bank, however, retained a good market share during this period (Aligned Registry Report 2018). While the proportion of BAME donations has grown over the years clinical practice has changed. In 2012 875 unrelated adult stem cell transplants were performed in the UK and an analysis of 401 patients found that for every 100 unrelated adult donor transplants there were a further 30 patients for whom no well-matched unrelated adult donor could be found (Lown, 2013). This unmet demand was due to factors such as failure to find a suitably matched adult donor, patient deterioration while waiting for an adult donor to be provided or less than optimal outcomes for patients who receive a mismatched adult donation or a haploidentical donation. The banking of umbilical cord blood offers an opportunity to reduce this inequality by increasing the number of ethnically diverse stem cell transplants that are available.

4.3.1 BAME and BINE cord transplant provision from the NHS Cord Bank

Cord transplant trends have changed over the years, which has complicated interpretation of data for transplant provision from the NHS Cord Bank in terms of its own impact on equity of access for BAME patients. Haplotype transplants have adversely affected the number of cord blood transplants performed since some of the previously hard to match patients who would have had a cord transplant will have a related donor with a haplotype match. This has to be taken into account when looking at the number of cord transplants provided. Acute leukaemia is still the primary indication for cord transplant. A trial by Milano demonstrated that cord blood transplant was a more successful graft than adult haematopoietic stem cell sources, where minimal residual disease persisted in the patient at the time of transplant (Milano F, 2016).This finding has supported its selection as the graft of first choice in this particular scenario.

The data showed that the highest proportion of BAME transplants for both UK and international patients was provided from donors of Asian or mixed ethnicity (3.2.2). Cord blood units originating from mixed race donors were issued to 19 patients in the UK for transplant and 28 patients internationally. Cord transplants from Asian donors were issued to 19 patients in the UK and 45 cord units of Asian origin were sent to international patients.

It is difficult to conclude whether this is a reflection of the inventory composition or the patient population because of the way ethnicity is recorded and the lack of consistency. However, cord blood transplant is a choice for hard-to-match patients, where no other donor, including a haplotype donor, is available. To best meet the needs of patients of mixed ethnicity it should be a requirement of the

cord bank to improve the TNC of banked CBUs as much as possible to overcome any sub-optimal HLA matches (Barker, 2020).

The results showed that a higher proportion of transplants originated from BAME donations than from BINE donations, however, the TNC content was lower in the cord donations from BAME donations (3.2.3). These results suggest that the increased difficulty in finding appropriately matched cord units of sufficient cell dose may be a major obstacle to securing better outcomes in black patients. (Ballen, 2012). The mean TNC of all NHS cord transplants provided from BAME donations was $150.9x10^7$ and for BINE donations this was $179.1x10^7$. Cord blood units are graded according to their cell count after processing and this value is an important criterion* in selection of a cord blood transplant, second only to the degree of HLA match. The average cell count in the transplant provided from BAME and BINE donations would put them in the lower and higher levels respectively of a B grade cord. The TNC count is an amount parameter since it is associated with outcome (Stevens, Rubinstein, & Scaradavou, 2006; Scaradavou, 2008).

4.3.2 Relationship of donor and recipient ethnicity

A greater degree of HLA match with the recipient was seen in the BINE cord transplants than the BAME cord transplants (Table 3.3). Data on patient ethnicity were limited by several factors: Some countries do not provide this information due to their own data protection law. Some transplant centres do not provide the data as this is not a mandatory data field. The scope of ethnicity also differed for data

provided by transplant registries to the categories recorded on the NHS Cord Bank documents.

What was clear, however, was that for the data available the number of BAME and BINE transplants was similar to the number of BAME and BINE recipients. An inference could be drawn with some degree of confidence that if a BAME or BINE cord transplant is issued, it will be for a BAME or BINE patient, respectively.

4.3.3 Donor availability for UK Patients eligible for a hematopoietic stem cell transplant

Data from the Anthony Nolan Aligned Stem cell registry showed that between 2010 and 2015 cord blood donor availability has increased for BAME and BINE patients at UK transplant centres (3.3.1).

For both UK and international transplants 54% of cord transplants originated from BAME donors but the number of BAME patients still awaiting well matched transplant is not easy to assess due to incomplete data sets, difficulty in assessing patient requirements in an ethnically changing population, and with evolving clinical practice as well as a paucity of data. Search data indicate, however, that the situation for BAME patients has improved, in that more patients have gained access to more suitably matched cords or adult donors over the period analysed. Data from the Anthony Nolan aligned registry showed an increase in availability of cord blood units that were HLA matched at least 3/6 loci over the ten-year period analysed.

These data suggest that while banking of BAME donations by the NHS Cord Bank has met targets and more than half of transplant provision has been to BAME

patients, efforts should be made to bank more cord donations from ethnically diverse populations that have a high nucleated cell content not only to attain equity of access aims in terms of numbers of cord blood donations available but also with regard to the quality of the donation in terms of cell content and HLA match. This, in conjunction with the data on reasons why cords were not able to be collected and banked, led to Study 2, in which barriers to cord collection were explored with healthcare professionals involved in the NHS Cord Bank programme. There is attrition in the number of cord donations successfully captured at all stages of the cord donation, collection and banking processes (1.8.1); some of these losses may be avoidable and have been investigated in greater depth in Study 2.

In a study by Stevens of stem cell transplant patients in America, the chance of finding a match or a CBU with 1 antigen mismatch correlated with patient ethnicity (patients had the best chance of finding a good match in their own ethnic group). African-American patients were the least likely of any group to find a suitable CBU in part, because of their smaller numbers in the inventory and, in part, because of their greater HLA diversity (Stevens, Rubinstein, & Scaradavou, 2006). If this conclusion is generalisable, it would support the growth of HLA diversity within the NHS cord blood bank since cord transplants are provided internationally as well as domestically.

5 Qualitative Research Study Method

5.1 Method rationale and design

To understand the opinions, experience and challenges in the donation and collection of cord blood for the NHS Cord Blood Bank a qualitative research study was developed. This was led by the findings from Study 1 which found that while the cord bank inventory was meeting its targets of BAME donations stored, the cell content and HLA match was lower in black, Asian and other minority ethnic (BAME) cord blood transplants that had been provided to patients than in those from British, Irish and North European (BINE) donations. Consequently, there remains a need to bank cord blood units that are ethnically diverse and of high quality cell content as this affects patient outcomes (Barker, 2010). It was expected that the outcomes of this study would provide understanding to help modify or improve present practice. A qualitative method was chosen for Study 2 to allow for depth of information and a rich understanding of the barriers to cord donation disclosed by the data from Study 1 (Terry, 2017).

Previous studies have explored some of the barriers to donation (Bhandari, 2016) (Rucinski, 2010) but there has been no such study in the UK that has expressly addressed views and concerns of the healthcare professionals actively involved in consent and collection of cord blood. This was an important area to explore: to identify areas for improvement or redesign of the cord banking programme, to optimise collection and banking rates to best meet the needs of patients, as identified in Study 1.

5.2 Interviews and focus groups

Cord blood collectors, employed by NHS Blood and Transplant, and midwives, employed by the collection site NHS Trust, were invited to participate in semi-structured interviews which were chosen for the opportunities to ask participants in depth questions that could also be followed up with further probes (Braun, 2006). A focus group was held with community midwives based at one of the collection sites. A focus group was chosen due to the design being suited to speaking with lots of participants at the same time to inconvenience them the least (Sinkowitz-Cochran, 2013). There was very limited opportunity to meet community midwives due to their role's being based out in the community. The focus group was held on a team-meeting day when several community midwives were already together at the collection site and this presented an opportunity to seek views from a number of midwives at once. The interviews and focus group were undertaken at hospital maternity units where the NHS Cord Blood Bank operates to collect cord blood that has been donated altruistically by consented maternal donors. Thematic analysis was chosen to understand the data since it provides a robust method for identifying themes which could subsequently be considered for changes to practice (Braun, 2006). An inductive approach to the data was chosen which allowed the detailed observations of the participants to be gathered into more generalizable themes (Thomas, 2006) (Barnett, 2015).

5.3 Interview schedule and focus group guide

An interview schedule and a focus group guide (Appendix 17) were developed in light of data from Study 1 that allowed exploration of reasons why cord donations were not obtained. Both contained the same schedule of open, semi-structured questions that were used flexibly, to allow for the participants and focus group to reflect on issues that they felt were important.

5.4 Ethics

An application was made through the Health Research Authority (HRA) portal to seek HRA approval for this study (IRAS 230255). As the interviews and focus groups were undertaken with NHS and NHS Blood and Transplant (NHSBT) staff and concerned their area of work, HRA approval was required but NRES ethics committee approval was not. Capacity and capability at each NHS site were checked as part of the HRA approval process prior to approval being granted.

Once HRA approval (Appendix 5) had been granted, letters of access (Appendix 6) were applied for and obtained for each of the sites where interviews were undertaken with midwives through contact with the research office for the NHS Trust. Ethics approval was applied for and granted from both UWE and NHSBT for this study (Appendix 7 and 8).

5.5 Recruitment and Participants

A convenience sample of participants was recruited from the sites where the NHS Cord Blood Bank collects cord blood donations, initially through an invitation via

email (Appendix 9). This method of sampling; purposeful convenience sampling, was appropriate for the study for recruiting participants from the organisations undertaking the work of cord blood donation and collection (Etikan, 2016). Additionally, a degree of stratification was employed in participant recruitment due to the differing professional roles of the participants ((Palinkas, 2013). Inclusion criteria required participants to be healthcare professionals who were directly involved with cord blood donation and employed either by NHSBT or the NHS site at which cord donation was carried out. A total of 15 people participated in the interviews (5 cord blood collectors, 5 midwives) and focus groups, (5 community midwives at Site 4). The participants were all female with one third of BAME and two thirds of BINE ethnicity.

For the cord blood collectors, an email from the chief investigator (CI) summarising the research study was sent to the team managers at the sites. The email was forwarded to the cord blood collectors, inviting their participation and noting dates on which the CI would be on site. Consent forms and participant information sheets were attached to the email and hard copies brought to each site.

For the midwives, an initial introduction was made by email from the NHSBT local team manager to the Matron and researcher. This was followed by an approach to the matron at each of the sites to seek approval to interview midwives who were willing to participate in the study. The Matrons were sent participant information sheets and consent forms with an accompanying email summarising the research. A poster (Appendix 10) was also provided for the midwives' staff room to summarise the research and indicate when the CI would be on site. Dates were agreed for each of the sites and midwives on shift at that time were invited to participate, following the initial email.

5.6 Procedure

Participants were invited to read the information sheet (Appendix 11) to ensure they were fully informed about what taking part would involve. This included that participation was voluntary, how to withdraw, and how their data would be used and stored. Following consent (Appendix 12), data were collected from semi-structured face to face interviews. The interviews were recorded as password protected files on a telephone recording application and were subsequently transcribed verbatim (Gill, 2008). Anonymisation took place at the point of transcription using codes for the participant and site. Codes captured the site, the participant number and whether the participant was a collector or midwife; for example, the first cord collector interviewed at site 1 was coded S1C1 (Appendix 13).

5.7 Data Analysis

Thematic analysis was used to analyse the interview transcriptions and gain an in depth understanding of the data. This approach was first described by Braun and Clarke in 2006 with refinement of this approach more recently to rename it as reflexive thematic analysis (Braun & Clarke 2006, Braun and Clarke 2019).

The process of analysis was iterative, involving a cyclical process of studying the data, reference to relevant literature before returning to the data to identify and refine developing themes. An experiential inductive approach was taken, with the development of themes being led by the data rather than fitting the data into a pre-existing framework (Terry et al., 2017).

Analysis of the data commenced during transcription of the interviews to derive initial theme ideas (Appendix 14). At this point notes and reflections on the data were made with some initial ideas on themes. On completion of the transcription of the interviews, an inductive coding system was developed based on ideas and themes that recurred across sites or between interviewees. Semantic codes which identified specific surface level meanings from the transcripts were developed and collated into themes and sub themes. This facilitated organisation and cataloguing of ideas which were then examined in greater detail. Field notes were made at the time of the interview. The purpose of this was to record the conditions in interviews were conducted, any significant interruptions or other points of note which may have affected the interview process.

The six stages of analysis as described by Braun and Clarke (2006) were undertaken for thematic analysis of the data as follows:

1. The first phase of thematic analysis was familiarisation which was done initially by conducting the interviews and focus group and strengthened during transcription and subsequent readings of the interview and focus group transcripts. At this stage understanding and initial identification of interesting ideas was undertaken.
2. The data was then coded by the CI by highlighting text that seemed to be relevant in relation to the research questions to use as a resource to form initial themes.
3. The themes were developed through further familiarisation and collation of coded data into identified themes. At this stage there was repeated reading of the transcripts and further coding and tagging of text to group into themes.

4. These themes were then reviewed and checked back across the transcripts to refine them and check their reliability.
5. The themes were named to reflect the central organising concept and sub themes were also named where a specific element of a theme was identified but related to the primary theme (Appendix 15).
6. The themes were collated into a report with a discussion written separately.

The identified themes are reported in the Results section, Chapter 6.

6 Results Study 2

Ten interviews and one focus group were transcribed from secure audio files and transcribed for analysis. Theme maps were developed (Appendix 15) during analysis of the results and five themes were derived. The results for each theme are described in this chapter and discussed in Chapter 7, with conclusions, implications for the NHS Cord Bank and potential practice changes discussed in Chapter 8. Themes are ordered as barriers to donation (Themes 1 and 2) then barriers to collection (Themes 3, 4 and 5).

6.1 Theme 1: The adoption and practice of delayed clamping of the umbilical cord has become a major barrier to cord blood banking.

A key theme which was evident in the data was that delayed clamping of the umbilical cord (Chapter 7 Study 2 Discussion) after delivery has become common practice at hospital maternity suites since NICE guidance was released in December 2014 (CG190 03/12/14) and has impacted the quantity and quality of cord blood collections. As one participant reported: *"they don't cut the cord straight away like they used to"* (S2C1). This practice results in a reduction in the quantity and quality of cord blood donations because there is less blood left in the placenta after allowing the blood to flow back to the baby before clamping and cutting the umbilical cord. What was also evident was that at one time clamping was not delayed, as shown in the way participants talked about a change in practice in recent years. For example, (S2C1) commented on changes in practice since they had been in post:

> *"The placentas are worse than they used to be four years ago. They do a lot of delayed clamping now, not only on the normal birth centre like*

upstairs here and in the normal delivery suite with instrumentals they don't… If the baby is not well they don't cut the cord straight away like they used to; they try to get more blood into the baby. In the elective sections; (it used to be that) the baby is out, they clamp, they give you the placenta. Now, baby comes out, wait two minutes and even after the two minutes they milk (the cord) back to the baby so even though the placenta is big there is no blood. So, there is less blood than there used to be." (S2C1)

This view was supported by a participant who had joined the cord bank in 2010. They commented that delayed clamping "*wasn't really a thing*" early on in their post, but that it had impacted on collections significantly in the last three or four years.

"Yes, delayed clamping wasn't really a thing. I've been here 8 years in August, and it wasn't a thing so it has probably impacted I'd say probably, maybe the last three or four years maybe, a lot. And we are finding more and more mums are emphasising that they do want the delayed clamping." (S4C1)

The participant acknowledged that practice had moved on because research had demonstrated a benefit to delaying the cord clamping but seemed slightly regretful that this was at the expense of the cord banking programme:

"When I was born they just clamp it and cut it and that was it and I think, you know but research is the main thing, that's come a long way so there's obviously something to it. There's something in it. They've had to do something." (S4C1)

This turn to delayed clamping was commonly reported to be standard practice now and will have had consequences for the number of cord blood collections that can be successfully made because less blood is available in the placenta.

Participants often explained the practice of delayed clamping in relation to best practice, including it being cited in NICE guidelines (since December 2014) which has driven its adoption:

> *"Obviously now delayed clamping is in the NICE guidelines we see a lot more where they leave it longer and longer and longer."*
> *"If the baby comes out in good condition there's nothing to stop them leaving it five to ten minutes before it used to be only on the Birth Centre upstairs where you'd see it but now obviously it's best practice for a minimum of a minute but a lot of them leave it five minutes especially the newly qualified midwives because it's being taught in practice in the university."* (S3C1)

The adoption of delayed cord clamping as standard practice on delivery suites over the last few years was identified by all participants but was commented on by more of the cord blood collectors than the midwives, perhaps because they were more aware of the impact on the quality and quantity of cords that could now be collected and had seen the reduction in number of cords available over the years they had been in post.

However, the midwives were also aware of the impact on potential cord collections that adoption of delayed clamping had made. Midwife participants reported various barriers to cord blood donation for example pyrexia in labour or language barriers but attributed the number of suitable collections having decreased as due to the increase in the practice of delayed clamping:

> *"The number of suitable collections have gone down as there is more delayed cord clamping, certainly less blood in the cords as most people do delayed clamping so you're not getting the huge placenta and thick cords that are jam packed with blood."* (S3MW2)

These participants also acknowledged the reduction in blood available in the cord: "*I suspect our collections; suitable collections have gone down as there is more delayed cord clamping" (S3MW1)*. These types of narratives were common across the data, with delayed clamping adopted into routine practice at all sites.

It was evident from the data that there was variation in practice across sites and between healthcare professionals. This disparity in practice makes it even more difficult to predict whether a cord blood donation is likely to have enough blood to make a viable donation.

Cord blood collectors as a group were highly aware of documented guidance from NICE regarding delayed clamping, which recommends waiting for up to a maximum of two minutes prior to clamping the cord. This variation in practice and deviation from published NICE guidance was a source of frustration for the collectors as they felt that as well as impacting on potential collections, the length of delayed clamping was sometimes at odds with the mothers wishes:

> *We've had a couple of months where it's just generally... we've had shifts where there's been no deliveries or there's a lot of delayed clamping and I keep trying to talk to some midwives because if it's the guidelines of 2-3 minutes we have to now ask them how long they delay for. They say 10-20 minutes until it stops pulsating. Getting a bit cross sometimes, it's so frustrating. It's like the midwives are just choosing to do it without the mum asking I'm sure sometimes and I just think - stick to the guidelines. It's difficult but if the mums aren't particularly fussed about the delayed clamping, just do it for the guidelines rather than .. .til it stops. It's completely white sometimes when we get it." Bit frustrating. (S3C2)*

A collector participant was aware of the NICE guidance on delayed clamping but demonstrated within their comments that healthcare professionals opted to make their own judgements on how to apply this guidance.

> *"Yeah, if the baby is fine and there's nothing wrong with mum, if not bleeding they leave it until it's stopped pulsating until they see a placenta bleed then obviously they'll clamp and cut it but if there's nothing stopping they'll leave it. And even in theatres now they time a minute, a full minute…. It's amazing how much they get across within that one minute. Some of the surgeons milk the cord. Think there's a lot of debate between them and the*

paediatricians and the neonatologists as to whether that is best practice but they all leave it. and that's on absolutely every birth unless the baby comes out in really poor condition.

*If the baby comes out in good condition there's nothing to stop them leaving it five to ten minutes, before it used to be only on the Birth Centre upstairs where you'd see it but now obviously it's best practice for a minimum of a minute but a lot of them leave it five minutes especially the newly qualified midwives because it's being taught in practice in the university. So, we've got the guideline but it seems to be generally accepted practice as long as possible." (*S3C1)

The narrative from collectors and midwives differed in tone with collectors frustrated by lack of adherence to guidelines and the midwives rationalising variation in practice on each situation. midwives were aware of the guidance, but their views and practice were more divergent. They either felt that on a practical level it was not possible to be prescriptive about timings and that the delay in clamping would be determined on a case by case basis, or that they would clamp within the guidelines: *"It depends who it is* (attending the delivery). *Some people recommend to stop pulsating. Others say a minute*." (S4MW2). It was clear that midwives were making decisions based on a range of factors and according to context:

"They don't have active first stages so they don't give the drugs for the placenta. They can just leave it (on the birth suite) *Whereas on here we're very keen. In a way a minute is just right.*" (S3MW4)

"Mmmm, it's more you sort of assess. Depending on the baby, if the baby is poorly the priority is to cut and clamp the cord but if the child is fine, we can accommodate the delayed clamping. I think after two minutes or when it stops pulsating because there's nothing going that way." (S3MW3)

The midwives were asked about variation in practice regarding the length of time until the cord was clamped. They emphasised the practicality of the situation about clamping the cord at a precise moment.

"*Technically by the time you deliver baby, make sure baby all right, had a little look, say congrats, remember what the time is, you're not. When I first trained; you would check the anterior shoulder, but you had two midwives there. Now it's become a much more stretched out process. So you may not clamp the cord for way longer than two minutes."* (S3MW1)

"*So it depends on maternal and foetal condition and then, also who is around. How many pairs of hands you have. So, not like we sit and look at our watch and say ooh it's been two minutes we must clamp now."* (S3MW2)

It was evident from these participant responses that the midwives made decisions based on their professional opinion and ability to make autonomous decisions based on their expertise, using the NICE timings as guidance rather than a mandate. The responses from the cord collector participants supported a view that they would prefer the guidance to be followed more rigorously. Some further comments were made which alluded to the guidance and perhaps a lack of clarity: "*some people recommend stopping pulsating. Others say a minute."* They were aware that there was guidance on delayed clamping but was not sure of the detail; "*over a minute, then when it stops pulsating? I'm not 100% sure." (*S3MW3)

In summary, it was evident across the data that delayed clamping was now common practice and frequently extended beyond the guidance. This was the case even though midwives and collectors were largely aware of the benefits of clamping at two minutes as far as cord blood donation went. Social media has played a part in driving the demand for delayed cord clamping from the mothers with campaigns such as #Bloodtobaby, #waitforwhite and All4Birth, the data suggests that this has been supported by the midwives and was sometimes at odds with the mothers wish to donate cord blood. It should be stated that the NHS Cord Bank is clear that the collection of cord blood

must not impact upon the care of the mother/baby and led the UK to follow practice established by Pablo Rubenstein in NY with collection taking place outside the delivery room. Emphasizing that the decision when to clamp is made by the obstetric team and that the cord blood collectors were handed the "waste product of delivery".

6.2 Theme 2: From no training to training as ineffective**: '***You can tell them about it till you're blue in the face'*

A theme was constructed from the data concerning the training provided to the healthcare professionals involved in the cord bank programme. The formal training package that was implemented in 2006 did not seem to have reduced or removed the number of damaged placentas despite this being a key reason for it's use. There was a sense of frustration amongst the cord collector participants that despite repeated attempts the training was not working.

> *"Even with the training pack, doctors in this hospital and a couple at site 3, it doesn't matter how many times, how important it is, they just don't care in terms of clamping placenta. I take a picture of bad placentas. I'll show you some examples."* (S2C1)
>
> *"The training? I think we've still got a file so if new ones come in we go through what we do. There are a few that I don't know. You can tell them about it till you're blue in the face. There's a particular midwife I don't know why she does it but we all told her at least clamp it. Then you get given a placenta and there's no clamps on it."* (S3C2)

Some collector participants felt that this was due to a lack of engagement with the programme, particularly where this was apparent from senior management.

> *"We went round to all the individual midwives but I'm not going to be able to go and train the matron of this place. She's not going to give me five*

minutes to talk her through how to handle a placenta and that's really the issue. So you can get a few midwives in the sense that obviously some people just don't understand it and when you explain they're very good but if you really want things to change it has to come from above and I don't know if it will. I hope it will." C1S1

Many of the participants did not refer to or remember the official, documented training package and reported that informal, verbal training was what they had encountered: *"So they're always around (cord collectors), and part of it, so they will answer questions and things as you go".* (S3MW1) and ***"****No, just briefly told us what we are doing for us to inform the women." (S3MW3)*

There was a sense from some participants that this was preferable; "*There was no formal training. Especially for new staff, they'll explain, you mainly pick it up as you go along."(S3MW3).* One of the participants explained:

"When you come to the delivery suite that's part of the process. You meet collectors. When you say hello to people and what you do, and I think it's something that happens spontaneously: Oh I'm a cord blood collector, oh how does that work? It's not done routinely and it's y'know not something you need hours of training for.. This is what we do, everybody knows it. Not like when I started training and only just take the placenta for cosmetic companies."(S3MW2)

The data supported a feeling that the collector participants were driving awareness and training of the doctors on the delivery suites through their own efforts:

"*When they do their induction if they'll be involved they'll be spoken to and quite often I know they try to pop along to some of the doctors meeting but that's all off their own back, all off collectors backs. There is no actual training I don't think."(S3MW1)*

"Double clamping; told not to. That's what we used to do. Well, I never had specific advice but they (Collectors) take them quite quickly, I wouldn't say midwives reminded me but the cord blood collectors do." (S3MW4)

Whereas the midwife participants felt that the doctors should be trained as part of their induction to mitigate some of the issues with damaged or unsuitable placentas that were experienced: *"It's not incorporated into their induction."(S3MW2)*

"Tell the doctors. Lot of them are just start clamping away and needles to get blood gases so to just highlight that with the doctors." (S4MW1)

This theme has a significant impact on collections because time has already been invested by the cord collectors in providing information to the donors and taking consent from them before the point of donation. When the placenta and cord arrive with the collector and have been damaged or rendered unusable by placing too many clamps on the cord it is not only an inefficient process but demoralising for the collectors.

6.3 Theme 3: The relationship between healthcare professionals on the delivery suite plays a major role in collection of cord blood donations.

The importance of the relationship between midwives and cord blood collectors in accessing cord blood donors was highlighted across many of the interviews. This was evident in interviews with cord collectors: "*If you get to know the people you're working with, be part of the team, that works."* (S4C1) and with midwives: "*Participation in the team makes all the difference for getting the numbers of collections."* (S3MW2). The data from the cord collectors evidenced the need to be friendly, visible and helpful to facilitate good communication and cord collection. They stressed the importance of being part of the delivery suite team and felt that

developing good relationships with the midwives was key to obtaining access to good quality donated placentas:

> *"Be as friendly and helpful with the midwives as possible. Get them on your side."* (S3C2)

> *"I mean we're friends with most. Well, I am friends with a lot of the midwives. I think the closer you are with the midwives, the more time you spend on the floor, the better. Being here prompts them and reminds them that you're here. If they're not seeing you, they get distracted. They've got a million and one other things to do. Don't bug the midwife too much. Get the right balance; be friendly but don't bug them. Don't constantly ask them; how's this, that and the other. Just be here. Don't sit in the office. Be on the floor."* (S3C1)

These participants presented a picture of the busy midwife who had a myriad of important responsibilities and for whom cord blood donations were not necessarily always at the forefront of their mind. Therefore, cord collectors worked hard to engage them and build bridges to enable cord donations. There was also evidence that the midwives acted in a gatekeeper role and that the cord collectors were being granted access to the potential donors and placentas by the midwives. "*Had the midwife let me in sooner I could've spoken to her."* (S1C1). Therefore, collectors worked to get midwives 'on side' to enable access to donors:

> "*Yeah, we do rely on them* (the midwives) … *unless you're quite proactive and unless you're outside the door or there's a midwife that's particularly supportive it'll be just thrown away."* (S1C1)
>
> *"You have to know when to approach the midwives because without their permission you can't go in the room. You have to know the midwife who will let you go in immediately, who you have to be nice to first before you can ask, engage them in conversation how are you, how's it going, y'know all of this - not just can I go in the room? Have to butter them up a little bit and*

*make them sort of comfortable around you and even though I've been here however many years around still some of them won't let you go in…you have to know who you're talking to and how to pitch it." (*S3C1)

The collectors respected midwives and worked to nurture strong relationship with them, while midwives emphasis was on the importance of working relationships with collectors.

In turn, midwives reported their appreciation of collectors being visible and active as a part of the team. This was important as a constant reminder of the cord banking programme: ***"****The girls are always available when you deliver." (S3MW3).* Further participant comments supported this view that good communication across teams meant that access to cord donors and donations would be more likely.

"*I think the reason that the service works here is down to the collectors and the integration. They're visible and look after the team and it's very much the culture that when you get a placenta you ring them." (*S3MW1)

"*Having them as part of the team. Collectors are part of the team. They'll be around at handovers, talk with midwives, social events they would be invited. Rather than them and us…they are happy to help, happy to be around and we also want to help… I think we do try to get good placentas*." (S3MW2)

The midwives noted the benefit of having the cord collectors on site; that it made their jobs a little easier by relieving them of some tasks. This support from collectors would make them more likely to engage in helping to achieve the aim of accessing potential cord blood donors. The data from the collectors regarding being helpful was supported by the midwives' comments that a mutually beneficial relationship between the midwives and the cord blood collectors was important:

"*Plus they do our blood gases, take samples. So there is actually direct benefit for us for our working to have them around. They are supportive."* (S3MW1)

> **"***They do a lot, it's actually beneficial for us helping them out because they will do a lot of our work for us…The fact that it's their job and they go and check who's been consented, they go and talk to the ladies, they do all the paperwork means it's not a real extra job for us."* (S3MW2)

As well as noting the benefit of the collectors being constantly present and willing to help, the midwife participants acknowledged that collectors were aware that building relationships would facilitate access to donations *"*[I think the collectors work on] *Developing good relations with the midwives because then they get more collections. Being part of the team."* (S3MW4)

> **"***And also I think it's very much the fact that's it's no more work for us* [as midwives]*…They'll* [collectors] *come, say I'm going to consent woman for bloods, do you want me to take any other? Thinking about making our lives easier and thinking it's really good having them around. Even like when they say do you want a cup of tea (*laughs*). Because they're with us all the time. I mean certain of them will answer the phone, come and find us, point people in the right direction."(*S3MW1)

The impact of the culture at sites on cord donation and collections, with regard to a sometimes hidden or silent hierarchy and how all healthcare professionals interacted with each other in a department was evident in the data. The sites where the whole team communicated on the same level were viewed as more successful for cord blood donation than other sites. "*We're really lucky here; all the same, not the same at all sites. All the doctors, midwives, everybody's on board with us. Some hospitals' doctors don't speak to us, some sites it's quite divided whereas here it's not."* (S4C1) By contrast, at sites with a hierarchical culture there was a distinct impact on staff:

> *"At that site we are part of a team, here we are not. Sometimes they* [midwives] *don't give us placentas. Atmosphere between midwives. There is a scale of levels: doctors, nurses, matrons, midwives. We are right in the bottom by the cleaners. This hospital very much. All talk on the same level (*at the other site*)."* (S2C1)

Additionally, it was evident from the data that engagement was needed from senior management through to the 'shop floor' to ensure support for the cord blood programme and that where this was not in place, the collectors felt it was harder to resolve issues and obtain good donations.

> *"Don't know how you get the doctors motivated. If there is an issue (at another site) you would tell (the manager) or everyone and talk, they might not listen but can have that approach. Here it is very difficult. Even people from this team find it difficult."* (S2C1)

This notion of the importance of engagement was echoed by another participant who felt strongly that the site and the cord banking programme were all part of the NHS and should collectively uphold its values:

> "*They shouldn't view us as guests. We are the NHS, we will respect their decisions as they care for mums, we won't tread on their toes but they have a responsibility as an NHS worker to support voluntary blood donation and even if they don't support voluntary blood donation they should be supporting the mothers wishes*." (S1C1)

The participant went on to highlight difficulties with senior staff engagement at the site, suggesting that this should have been addressed.

> "*So, you know, when you go the senior management they don't care, they've actually said to me 'why are you telling me it's been damaged?' I've tried talking to the midwives, this particular midwife doesn't particularly care but they take no responsibility for it. It's quite worrying really because they don't really even really see it as mums choice so even if you want to make the argument that it's not their responsibility to support blood donation*

which is quite a bad view but even if you go with that argument, with women that have signed up to donate they do not view it as her placenta they do not view it as her choice to donate and their responsibility to support that choice they just see it as, right I've delivered it so I'll handle it however I want…somebody senior does need to say this is a voluntary blood donation; you should be supporting NHS blood donation" (S1C1)

There had been several attempts to integrate the cord banking team into the maternity unit since opening the site but these had not proven successful, for example, allowing cord blood collectors access into theatres to collect placentas donated after a caesarean section. The collector felt that there was a fundamental problem with engagement with the programme by the senior staff on the unit and in the collectors experience they found that the midwives they liaised with were "*either really good or really bad*.". (S1C1)

In summary, the relationship between collector and midwife was a key element in obtaining cord donations and access to potential donors. Factors affecting this relationship were the collectors' visibility and constant availability on the delivery suite, as well as their willingness to help the midwives with additional tasks. The culture on the unit and commitment to the cord banking programme from doctors and senior management were also important in determining the success of the programme and where there was lack of engagement and a strong sense of hierarchy amongst staff this seemed to be both detrimental to the morale of the cord collectors as well as the amount of cord donations.

6.4 Theme 4: Language was understood by both midwives and collectors to be a major barrier to cord blood donations without viable solutions.

" Language is a big one. A barrier. "(S4MW1)

Participants, both midwives and cord collectors reported that language was a significant barrier to taking consent and donation, resulting in many lost cord blood donations:

> *"I have language barriers all the time! It is my daily life! I mean if you look on here as an example some days are worse. Erm, so Thursday got one Bulgarian, one Pashto, two Pashto – so three because of language exclusion. We lose a fair amount; two or three a day." (S1C1)*

One participant (S3C2) thought this had increased in the last six months and accepted that these donations would be lost. The participant was told second-hand that the participant could not speak English rather than being able to ascertain this herself, so this comment was made with a degree of scepticism.

> *"Funny, I do notice quite recently there's a lot more ladies we can't do because of no English so I just think it seems to be more. I don't know if we've got more immigrants coming over that can't speak English. But recently I seem to have quite a lot. I've been told they can't speak any English. There's been an increase in that, recently I think. So we obviously miss out on those ones."* (S3C2)

This was revisited later when the participant commented on language possibly being used as a means to deny access to potential donations and was supported by other participant comments:

> *"If it's handed over to me, I'll always check with another midwife when the night or day shift comes in. I do check that it's true that mum definitely doesn't speak English because it's happened a few times when handed over to me. I think we should all double check sometimes that that is the case." (S3C2)*

> "*You can be told by one midwife that mum doesn't speak any English it's handed over to you not to approach her coz she's got no English but then the midwife changes and the next midwife might say to you actually she*

does if her husband is not around she is talking quite good English. So maybe not take the first time as gospel. It's sometimes a lot of these ladies from certain cultures they won't speak when the husband is around. I don't know if it's like they're not allowed to, but they can actually speak quite good English but not when the husband is there. Sometimes when you establish that, and you try to pick your moment and talk to her." (S3C1)

This data suggested that some midwives were not supportive of the cord blood programme and possibly felt that this was an easy way to avoid interacting with the collector and also that some cultural barriers presented themselves using language as the primary obstacle. If the collector had an opportunity to speak with the women individually at a later time it would sometimes become clear that they spoke good English, sufficient to understand the information and consent process, as well as the health questionnaire (1.7.2.1)

Midwife participants as well as cord blood collectors felt that language was a significant barrier to cord blood donation: *I would say that's one of our main reasons; that and the temperature would be our main reasons for non-collections." (S3MW4)* and commented on the reason why it was a barrier: *"They can't answer all their questions to accurately complete the questionnaire, then they can't donate. (S3MW1)*

Participants mentioned colleagues who were able to speak other languages but felt they were not easily accessible or that there was no defined procedure in place for them to act as interpreters.

"We don't (access these donors*) is the short answer. Most of the time we can't because we don't hire interpreters and because we can't do the health screen through the partner for obvious reasons erm, we assess the ladies language if we feel we can go on and communicate with her in English putting things in simple terms so she understands things like that then we*

will obviously continue but if we can't then we won't and we don't really, we used to when we started to have people in the office; managers, that spoke certain languages; they used to either do home visits or come to the hospital but because of staffing numbers, it's not their fault, they're not hired as interpreters, they tend not to do that and there was a big push to, that I don't really like, for us to take our personal mobile in so I don't do that because…"(S1C1)

*There's no SOP or anything for this as well, so you know a proper procedure where we can do it over the phone and that would certainly increase things. For example, today I've got (looks at list) oh, that's a bad day but I've only got one language exclusion but I mean that's Romanian and (*another collector*) could've done that but…" (S1C1)*

The participants from the cord blood collectors group felt that the system of contacting another team member who could speak the relevant language was not a robust system as it relied on their availability at a particular time when they might be engaged in their own role or on leave. These participants thought that it was futile to commence the collection process when they could not guarantee completion of the health questionnaire and consent process.

The data suggested a sense of having given up on trying to obtain donations where language had been a barrier despite systems such as interpreters being available. *"I know that they don't have time to do home visits so it's pointless me collecting it knowing it's going to be wasted." (S2C1)*

The collector noted that a few of her colleagues spoke other languages but the that only viable solution to offering these women the opportunity to donate their cord blood would be to use an interpretation service such as Language Line. The participant felt that this would be an expensive option and possibly of limited value since we were routinely able to collect from a wide range of ethnicities.

> *"Unless you're prepared to pay a lot of money to use language line like the midwives have to. Yes, that's what they do, and it is costly for the NHS. Only that really (getting sufficient BAME collections) or y'know thankfully there are a few of us, not myself personally, who do speak other languages, like Polish or Spanish." (S3C2)*

This was echoed by a participant comment that whilst many donations are missed from certain groups where language is a barrier, they were able to communicate with most people.

> *"The ones we miss are a lot of Tamal and south Asian countries but we don't use interpreters, I mean most of the people we can talk to them." (S2C1)*

Some participants did not talk about language barriers but there was a sense that this was a barrier that could not be overcome and consequently not discussed as something that could be affected. One of the midwife participants (MW1S4) commented that they would not want to use an interpreter during labour, as they felt that they were able to communicate sufficiently: *"Like these women that I've cared for, they have enough English to understand enough of it. I'm not using a translator in labour. We are getting by. They know enough" (S3MW4)*
They suggested that Google Translate or providing written information in a range of languages could be used for answering the health questionnaire.

In summary, language was recognised to make a significant impact on the number of potential cord blood donations but was accepted with little challenge as a barrier that could not be removed. This may be due in part to a feeling that enough BAME donations were otherwise collected or that interpreters or interpretation services were not viable due to expense or availability.

Additionally, language was sometimes used as a reason to prevent access to donors, either due to some midwives beliefs around the cord blood banking programme or for cultural reasons where potential donors did not feel able to speak English in front of their partners. This called for great sensitivity on the part of the cord blood collectors to navigate their way around cultural beliefs.

6.5 Theme 5 – Information and misinformation

Another key theme that emerged from the data found that information sources for potential donors could be misleading and off-putting, despite a willingness to donate. This theme had several sub themes which all linked back to the central organising concept of information or, more frequently, misinformation, which ranged from misconceptions about delayed cord clamping to private blood banking, sample requirements and religious and cultural reasons.

"*Will I get it back?"*

Some of the participants reported confusion from potential donors about the type of banking that was being offered. Some of these donors where suspicious of private banking but were happy to donate when they understood that the NHS cord bank was an altruistic cord blood bank.

> *"sometimes there is confusion over private collectors and us, so sometimes they think we are going in and asking for money and obviously when we make clear we're not it's like oh yeah I'll do it to the point some of them will actually stop you talking to them 'no I don't want to do it'. Then the midwife will explain we're not private collectors, its NHS then we go back, and they want to donate." (S4C1)*

One participant thought that for some donors the motivation for donating their cord blood was knowing that there was a reasonable likelihood that their babies cord blood would remain in the bank for their use in future if not used for an unrelated

transplant. This presumed a background knowledge of public and private banking and utilisation rates. The option to 'use' the public bank as free private storage was implied in this case but not something that was frequently commented on. Several participants reported a reluctance to have blood samples taken which called for explanation and persuasion by the cord blood collectors.

> *"We get questions about the blood tests that we take. So for example I've just seen a lady now that's thinking about whether she wants to donate and it's not necessarily the fact that she doesn't like needles but they think four tubes of blood is a lot and hard to reassure that it's 17ml blood, just over a tablespoon but people can't imagine that, they think it'll make them anaemic. So those are generally the questions."*(S1C1)

> "*Sometimes, mums don't want to have the bloods taken. You say that we need the samples…. And you explain to them that we need to test the mums blood and that the cord blood is safe to give to somebody who is extremely poorly. And they get that but then they say they don't like the samples. They ask can you take it from the cannula and obvs we can't but if we could, we would! You can come and get them at the same time but it would not be an extra needle so then sometimes that does sway them. They think well, ok then if I've got to have blood samples taken anyway. So that kind of swings them. But then other mums they just don't want to be bothered. They just want to focus on their baby, their mindset is not to do anything else but to focus on having their baby and I get that."(S4C1)*

Several participants talked about cultural and religious reasons influencing would be donors' decisions to donate or not. It was clear that the collectors were willing to put in a lot of time to allay fears or clear up misconceptions the donors had and were great communicators, able to adapt their approach depending on who they were speaking to.

"You approach the lady and she'll say no I can't do it because I'm religious and we say we do have a lot of people from the Jewish community who do donate... speak to the rabbi, have a think about it. We tend to give them the usual chat about what we do and how we do it and why we do it etc"
We give them the paper information that we have here. Usually they'll say well I'll check with the rabbi or whoever it is go back and then more often than not it's yes I'll go ahead and donate. There's a small amount of ladies that are like, I can't do it." (S4C1)
Obviously Jehovah's Witnesses do not do it so we don't approach…..but the other ladies it's just that they think they can't do it. There was one last week I went to see, a Jewish lady and she said I can't do it coz I'm Jewish. ….Yeah, you can do it. So she was like Oh, all right I Can do it." (S4C1)

Some participants reported cultural reasons for reluctance to donate their cord blood. This seemed in some cases to be due to misinformation about what would happen to their cord blood.

"I think more cultural: Are you going to clone my baby and things like that? Where are these cells going to go? Somebody once told me that they Didn't know who the cells where going to go to and that puts them off. If that person is a bad person…"(S3C1)

Some of the participants felt that there may be some suspicion or superstition attached to not wanting to donate, particularly amongst donors of BAME ethnicity.

"Sometimes, especially with ethnic minority ladies, they're not quite familiar with it so if you have explained reasons and how they collect it and how it can benefit another child they're usually 'ok'. I sometime tell them, don't know if it's right or wrong, I tend to say sickle cell is more prominent in Afro Caribbean then you just explain after that the placenta is no use so we usually just get rid of it. Could save someone's life. It's a waste product that could help someone else. (S3C)
If they're not interested in it they aren't fully well informed, not because of staff, it's just simply because of the environment and what's happening. people are quite superstitious about it as well; they feel like it's that

connection with the baby so they're just a bit more sort of not sure what you use that product for." (S3MW4)

There was also a sense from some of the participants that they would not want to explore reasons too much for fear of offending potential donors:

"Some of the donor mums don't like the idea. They think we're going to do weird and wonderful things with their cells, think we're gonna clone. A lot of dads; a lot of dads actually, they say no on behalf of their partners and obviously you can't then sort of, that's him speaking on her behalf is what I find very odd but obviously within some cultures it's a standard thing, but not many, not many. Maybe one once a month you'll get someone who doesn't like the idea or doesn't want to do it. Don't know if I'm allowed to say this; A lot of black Caribbean, people from black Caribbean areas don't like the idea, at all. Always you can get a vibe, you get a vibe off people, you can always tell and I think primarily it's that kind of people from that kind of ethnicity and even if you try.."(S3C1)

Social media and the internet were regarded by collectors and midwives as a common route to obtaining information. *"New parents get their information online" (S2C1)* ***"****Media mostly" (S4MW3), "Internet, friends" CMWFG* and ***"****We discuss the birth plan and then they (cord collectors) come and explain the benefit and women read about it on the internet." (S3MW3)*

The cord bank website however was rarely mentioned, other than one participant (S2C1) who felt quite strongly that that the NHS cord bank website would benefit from additional information and content particularly in relation to the websites of private cord banks. This participant felt that better publicity would boost donation rates and commented that the website should be improved to give potential donors more information to enable an informed choice to be made.

"If you type cord blood bank on the internet you get all these amazing things from private banks. Our website is now worse. More we could do with the number of donor mums in the first place." (S2C1)

"I think if you look on baby forums and things on fb a lot of them are saying you've got to leave it 'til it's white. I mean That's not gonna happen on all of them, but I think perhaps when they see these things on line it's a lot of influence. People post things on fb, even if you're not searching for it. I mean I'm not pregnant, I don't want a baby, at the moment but I still see these articles that other people have shared and I think definitely within NCT they get the message across that you can't do both because you can't delay it and you can't donate."(S3C1)

Private antenatal classes were cited by some participants as a source of misinformation, particularly regarding delayed clamping of the cord. Both cord collector and midwife participants during interviews and the focus group talked about private antenatal classes as a source of misinformation particularly about delayed clamping of the cord. They reported quite negatively about these classes feeling that the wrong information was given which painted the cord bank in a negative light.

"NCT told them that if they sign with us, the midwives will cut the cord very early and they won't be able to have delayed clamping. So some parents get mixed information not from us, from an outside source. Saying like delayed clamping is the best thing and if you don't do delayed clamping the baby will be very sick and that If you sign (for cord banking) they will cut the cord very quickly and then the baby will be ill so there is misinformation from parents." (S2C1)

"It's taught in NCT (delayed clamping). NCT, I've heard, that they're telling them they can't do both and can't donate their cord blood. I do think they're told the longer the better rather than 1 or 2 minutes. We hear it a lot. We tell them that's not true. I remember last year someone had sent their consent

in the post (p27) then we got a call saying they'd declined, they want to withdraw their consent because they think, they were under the impression, think they spoke to someone in the office, and we got a message that if they did what we did then the midwife would not delay the cord clamping for them". (S3C1)

"A lot of people do NCT, about 40%. I would say the majority that don't come to NHS go to NCT so the ones that don't come here and see the midwives they are going there." CMWFG

"I think sometimes we are portrayed as bad guys by NCT. Lie on your back and they'll make you do this. So wrong (laughs). People that teach NCT are not midwives so sometimes I wonder if it's based on their own experience. I don't know where it comes from. You do hear some negative stuff has come from them." CMWFG

Participants who were interviewed reported that donors were willing to donate as long as they could delay clamping of the cord: "*They always say yes that's fine but can I still do delayed clamping?"(S3C1)* and participants from the community midwives focus group (CMWFG) *"I think most women would be happy to if they knew it wasn't going to affect the delayed clamping I think a lot of people would be happy." CMWFG*

Other potential donors may have sought or found information about alternative uses for their placenta and decided against cord donation in favour of these uses. Private cord banking was mentioned by some participants, although was not seen as a problem since advertising form private banks was discouraged at maternity units where the cord blood banking programme is active.

Some participants mentioned that a minority of potential donors chose encapsulation of the placenta, a process in which a small amount of placenta is made into a tablet or drink by a private company:

> *"They drink it or make tablets. They only take quite a small part of the placenta. The women believe it's high in stem cell and protein and prevents postnatal depression".* (S3MW3)

Other participants spoke about the disappointment for some potential donors when they were not able to donate due to the exclusion criteria. The participants were not always clear of the rationale for these criteria:

> *"I would say about 90% maybe 80% (would like to donate their cord blood). I think more women want to but so many are told they can't. Sepsis is one of those things but lots of the women are really disappointed: Twins, they're really disappointed. But from our point of view, that pre-term 36 plus 5 that you can't take because they're not 37 (*weeks gestation*) and we see it and we are like 'such a juicy cord'. Such a shame. Erm, no-one's told me why not. We just know we don't."(S4MW1)*

Although some participants reported that not many questions were asked about what happens to the donations, "*Most of the time there's not many questions about what it goes to treat. Occasionally we get ones where they ask if it's worldwide. However, I suppose this is the only other question we get – can they have their blood back? (C1S1)* some participants were unclear about what happens to the cord donation *"I think lack of understanding about what happens afterwards and then I struggle to answer that question because I wasn't really sure"* (S3MW4)

The theme centred around information sources and the impact that this can have on donors and donation. Misinformation or lack of information lead to preventable delays and inefficiency in the donation process as collectors and midwives need to spend additional time providing the correct information. Lack of understanding

about what happens following cord donation could also affect donation rates if a compelling answer is not provided to the potential donor.

The themes are discussed in Chapter 7, with implications for, and changes to, practice considered in Chapter 8. Each of the five themes had a central organizing concept that was consistent across sites and participants, with sub-themes evident for some of them.

7 Discussion Study 2

Five themes emerged from the data, the first two identified significant barriers to cord blood collection and themes 3, 4 and 5 identified barriers to cord blood donation: i) delayed clamping of the umbilical cord, ii) training of healthcare professionals involved in cord blood donation, iii) the relationship between midwives and cord blood collectors, iv) language v information). These barriers were noted by all participants, however evident their different perspectives depending on their professional role.

7.1 Delayed clamping of the umbilical cord

The practice of delayed clamping (1.7.2.2), evident at all collection sites (6.1), has greatly influenced the number of successful cord blood collections. A decline in the number of cold blood collections has been seen in the monthly collection figures for the cord bank over the past few years and delayed clamping was a major reason for this, as demonstrated in the Participant data. This situation is not unique to the NHS Cord Bank and has been seen at others. A study by Allan (2016) at the Canadian Cord Bank found that in 367 cord collections delayed cord clamping diminished the volume and TNC count of collected CBUs, which increased the time expected to create an inventory. Similarly, a study by Ciubotariu showed that a delay of more than 60 seconds, as recommended by NICE, significantly reduces the likelihood of collecting a clinically useful cord blood unit (Allan, 2016, Ciubotariu 2018). Several participants commented on the difference in practice over the last few years and the data supported the view that

delayed clamping of the cord had become standard practice over the last few years.

Delayed cord clamping was initially recommended for pre-term infants to reduce the likelihood of anaemia (Mercer, et al., 2006) and was expanded to include term infants following a number of studies that assessed the benefits of a delay in clamping the cord (Garofalo & Abenhaim, 2012).

NICE introduced guidance in 2015 (NICE guidance, QS105 Statement 6) and the Royal College of Obstetricians and Gynaecologists issued their statement in 2013. Both of these recommended not clamping the umbilical cord before one minute unless there was concern about the integrity of the cord or the baby's heartbeat. The American College of Obstetricians and Gynaecologists issued committee opinion in January 2017 recommending a delay of at least 30-60 seconds after birth, noting that this would increase haemoglobin levels at birth, improve iron stores in the first several months of life which may have a beneficial effect on developmental outcomes. There is a small additional risk of jaundice requiring phototherapy associated with delayed clamping and this has been seen at some of the collection sites (reported by NHSBT cord collectors). The benefits of delayed cord clamping have been strongly stated sometimes without compelling evidence. Conditions such as autism, behavioural and developmental delays have been linked to immediate clamping of the umbilical cord (Mercer, 2018) (Dorling,2018) but a Cochrane review by Rabe, last updated in 2019, did not find evidence to support the conclusions of these studies (Rabe, 2019). Delayed clamping has been adopted across the maternity units with NHS cord collection sites in the last

five years with varying degrees of interpretation compared to the NICE and RCOG guidance as demonstrated in this study (6.1).

7.1.1 Variation in Practice

Research has been undertaken to assess the effect of timed delays on clamping and some studies have shown a minimal influence on cell count with delays of up to one minute (Ciubotariu, et al., 2018), while other studies have found that cord banking is feasible with delayed clamping practices (Frändberg, et al., 2016). The NICE (QS105, 2015) and RCOG guidance (Scientific impact paper no 14, Feb 2015) suggest a delay in clamping of up to 2 minutes and not before 1 minute. This guideline was poorly adhered to across the collection sites and resulted in a significant decrease in available collections. Participant cord blood collectors wanted adherence to the guidance whereas the midwives and doctors regarded the guidance, inviting exercise of professional opinion and judgement in each birth to allow for variation in practice. A Cochrane review in 2012 demonstrated that delayed cord clamping in preterm infants can lead to improved circulatory stability, less need for blood transfusion, reduced incidence of necrotising enterocolitis and a lower risk of intravascular haemolysis (Rabe, 2012).

The participants had differing views on delayed cord clamping. While the cord collectors understood that delayed clamping delivered benefits to the baby, they felt frustration that this practice varied between healthcare professionals, generally inclined to a longer delay which resulted in failed collections because the volume of blood left in the cord was not suitable for banking.

The midwife participants were convinced of the benefits to babies' health of delayed clamping and applied the guidance according to their professional

judgement rather than strict adherence to the NICE guidelines. Of the midwife participants interviewed, some reported little benefit in delaying clamping beyond 1-2 mins (6.1) yet in practice the number of cords collected would suggest this delay is often longer enough to mean the difference between a collected and discarded cord donation. There is however, correlation between the initial size of placenta and amount of blood that would be initially available and so it cannot be assumed that all failed collections where the blood volume is too low for clinical banking can be linked to delayed clamping in excess of the guidance.

7.1.2 Conflicting views and professional decisions

The NHS Cord Blood Bank takes a position not to interfere in any way with a birth plan, recognising that the safety of mother and baby are paramount. This is not in dispute but does put cord blood collectors in a difficult position where they feel unable to comment on delayed clamping for fear of suggesting anything that might be seen to compromise the health of the baby.

Participants reported variable delays in clamping. This may have been popularised by the “Wait for white” campaign (https://waitforwhite.com), which has high visibility on internet search for ‘delayed cord clamping’.

Some conflict was suggested by cord collector participants between the midwives’ beliefs concerning delayed cord clamping and the prospective donors’ wish to donate their cord blood to the bank.

7.2 Training of healthcare professionals involved in cord blood donation

The midwives and collectors were asked about training that they had received because some of the cords that are eligible for collection are lost. Causes of loss could be avoided if effective training of midwives and doctors were consistently applied at all collection sites. Across sites collectors found it was difficult to reach all the doctors and midwives involved in cord collection either due to availability, rapid staff turnover or lack of engagement. At some sites engagement with the cord banking programme was evident at senior management level, which adversely affected engagement across the delivery suite (6.2). At other sites the lack of engagement was individual. The collectors at all sites felt that where the training package had been delivered, it was not having a positive effect on the number of damaged placentas they received. It should be noted that the damaged placentas may or may not have been delivered by healthcare professionals who had received the training package. None of the midwives who were interviewed was aware of a specific training package, but this may be because they had worked with the cord bank collectors prior to introduction of any formal training materials. Both collectors and midwives felt that the information they offered or received verbally was of greater value than the written information. Amongst the midwives the rationale for exclusion criteria was not well understood. Some of the midwives challenged some of the criteria, whereas the collectors were more inclined to accept the criteria and did not raise them as barriers to donation during interview. Criteria such as twin births and gestational age at delivery are in place to prevent attempted collection of cord blood donations that would not be clinically suitable due to the low blood volume available. The rationale for these criteria needs to be clearly explained to equip healthcare providers and prospective donors with information that supports decisions on whether cord blood donations

can be made. A review by Peberdy in 2016 found that across nine papers relating to collection and storage of cord blood, there was insufficient focus placed on healthcare professionals knowledge of cord banking and that this knowledge influences their practice (Peberdy, 2016).

7.3 Relationship between cord blood collectors and midwives

A strong theme emerged from the participant data that demonstrated the importance of the relationship between healthcare professionals involved in cord donation and collection in maximizing access to donors (6.3). At all the NHS Cord Bank collection sites, the cord collectors are employed by NHSBT and hold honorary contracts with the hospital Trusts. Other cord banks use a different model in which midwives are contracted by the Cord Bank to undertake cord collections and this appears to result in a high staff turnover compared to the NHS Cord Bank model (verbal reports at WMDA Cord Working Group). The NHS Cord Bank model has been successful in embedding a team of cord collectors at each of the delivery suites where cord collections take place which promotes team working through continuity of staffing allowing good working relationships to be built up over time. Several participants reported very positive working relationships although for the cord collectors this was dependent on their visibility and willingness to perform tasks for the midwives. It was clear from the participants responses that good, productive working relationships worked best at sites where all healthcare professionals valued each other's roles. This was found in a paper by Gluyas in which good team work was found to lead to improved patient safety (Gluyas 2015). Hierarchical cultures in other medical specialities have been linked with damaging behaviours and impacts on patient safety (Green, 2017; Reynard, 2009). Efforts to integrate into the team had not been successful at one of the

interview sites (site 2), leading to lower staff morale as reported by a participant at site 2. This is identified as an area for improvement through additional engagement with senior staff at the site.

7.4 Language

The use of interpreters or language interpretation services had not been pursued at any of the collection sites. Some participants who had a second language felt that they were able to speak to most prospective donors so there was less incentive to try interpretation services. However, non-collection data that is routinely recorded at each collection site suggests that many donations are being lost due to language barriers.

There was an acceptance by the participants that interpretation services were difficult to access as well as expensive when resources are limited and may be inadequate to taking fully informed consent and health history. The published guidance on consent, from the HTA states that: “Consent is valid only if proper communication takes place and the person has a reasonable understanding of what is being explained to them” with “Particular consideration given to the needs of individuals and families whose first language is not English.” and that “Where appropriate, information should be available in a variety of languages and formats such as video, audio or Braille, and in line with other legislation, such as the Equality Act 2010.” (HTA Code of Conduct Code A: Guiding principles and the fundamental principle of consent 3 April 2017)

Although data from Study 1 showed that the target is being met in terms of the proportion of BAME donations banked, it is still unclear whether the diversity of the cord bank inventory is sufficient to meet the needs of all patients awaiting a stem cell transplant. This is due in part to patient data on ethnicity being incomplete and inconsistently coded. Language as a barrier to donation has not been explored fully and its remedy could permit many more donations to be collected. The data from Study 1 suggest that while 40% of cord donations are sent to treat BAME patients, the TNC and HLA match is worse than that for the cord donations sent to treat BINE patients. This would imply that more can be done to ensure high quality, diverse donations are stored and made available the better to meet the unmet need. Adding these missed donations could add to the HLA diversity of the cord bank inventory and consequently access to a transplant for patients who are otherwise unable to find a suitable match. However, more than 40% of donations are routinely banked from BAME groups; a target set early in the cord bank strategy which the Strategic Stem Cell Forum estimated would achieve equity of access to transplants for BAME groups.

Some studies have been published which assess the effect of language barriers on informed consent, mostly in emergency care settings, and conclude the difficulties in provision of appropriate information, especially if untrained interpreters are used, (Schenker, 2007) (Hunt & Voogd, 2007).

In a cord donation setting there is greater opportunity for planning and provision of information prior to donation than in an emergency situation, which supports consideration of language services to remove this barrier and open up access to donors who do not speak English as a first language and provide an equal opportunity to donate their cord blood

7.5 Information

The data from the interviews identified several areas where misunderstanding or lack of awareness resulted either in missed collection or additional discussion to allay or explain prospective donors' concerns. These areas included private banking, cultural or religious beliefs and custom that could preclude donation, exclusion criteria being poorly understood by donors and the uses of cord blood. Additionally, it was reported by some participants that midwives based at hospitals with a cord collection site thought the programme was for research and development and placed less value on this, resulting sometimes in lack of communication or access to donors.

All the collectors interviewed placed a higher value on the verbal information that they provided to prospective donors than on any of the written information. Their focus was on the women they spoke to at the delivery unit, where questions can arise that have not been addressed in the written information. For example, the amount of blood sample required for testing was enough of a concern for some women to deter them from donating. When it was explained that the samples could be taken at the same time as other samples the midwives would take anyway, most women were happy to proceed with a donation. Other women needed the difference between private and public cord banks clarified before consenting to donate, which the collectors felt was easier to explain verbally. This has been seen in other studies that have sought to assess women's understanding of private and public cord banks (Peberdy 2018). However, the majority of women with whom they discussed donating their cord blood were well informed on the cord banking programme. This would indicate that the information provided in leaflets and at antenatal sessions at the collection sites reaches the

women who go on to attend the delivery suite. They were also aware that the cord blood could be used to help save a life, but there were mixed messages on how much additional information might be valued by the donors in terms of what cord blood is used for. Some midwives thought that the donors were content to donate if they knew it could help save a life, whereas other midwives thought donors would like to be notified if their cord blood was used but were not interested in more detail regarding its possible uses.

Timing of the provision of the information emerged as a theme with the community midwives. They felt that a later stage in pregnancy was about the right time as this is when the birth plan is discussed and any queries concerning delayed clamping could be addressed then (Peberdy, 2018). The perceived incompatibility of delayed clamping and cord blood donation was a common theme in the interviews and if this could be addressed at the right time in antenatal care, it could reduce the number of objections to donation at the delivery suite and reduce the time needed by the collectors to explain that delaying clamping would not preclude an attempt at collection of any remaining cord blood. Rationale for exclusion criteria, particularly twin births and gestation prior to thirty-seven weeks, seemed to be poorly understood, which led to queries from some women who wanted to donate their cord but fell within these criteria, which the midwives were unable fully to answer.

The 2018 study by Peberdy reviewed international literature on parents' knowledge of cord banking and found that knowledge of cord blood varied greatly, with many participants unable correctly to identify uses. The review otherwise identified that parents were generally aware of the options for storing cord blood

and had a positive attitude to donation. This review identified the parents' view but not healthcare professionals' knowledge and information and did not include UK public banks.

Information sources for parents on cord blood was found to be varied, fragmented and inconsistent. Health professionals were identified as the preferred source of information on cord blood banking for parents. The review by Peberdy identified papers that suggested healthcare professionals were the best choice to provide information on cord blood banking for parents. It is consequently important for healthcare professionals involved in cord blood banking to be well informed, with access to accurate and current information, to enable parents to make fully informed choices.

Participant data confirmed private antenatal classes as a source of misinformation on delayed clamping: firstly in that cord donation was not compatible with delayed clamping; secondly that cord clamping should be left as long as possible to maximise the perceived health benefits to the baby; and thirdly that if pregnant women signed up for cord donation, the midwives would clamp the cord immediately.

7.4.1 Private banking

Reasons given for private cord blood banking included insurance for their baby in that the cord blood might be needed in future, and they might then regret not having stored their baby's cord blood (Ballen, 2015).

The option to bank privately, sometimes known as family banking, was raised by the participants but was not viewed as a significant factor in missed donation. At

the collection sites private banks are discouraged from routinely visiting but some mums will arrange to have their cords privately banked or to have the placenta encapsulated, for example. Private banks focus more on advances in therapeutic uses rather than storing for disease treatment (Reimann, 2009) which may increase interest in private storage but has not yet been identified as an issue at the NHS Cord Bank collection sites.

One of the sub-themes on information was the view of some donors, as reported by cord collector participants, that they could bank their cord blood as an alternative to private banking as they understood that there was a reasonable likelihood of their cord blood's remaining stored in the bank. This view was corroborated by feedback from medical staff on the delivery suite following a cord bank training session at one of the NHS Cord Bank collection sites (Registrar training session 2018) and while not a barrier to donation, should be clarified in information that is provided to donors.

7.4.2 Culture and religion

Although religious or cultural belief and custom accounted for some missed cord collections, they were not perceived by the collectors or midwives to be a major barrier to donation. All interviewees had encountered refusals to donate on cultural or religious grounds. Some of the collectors did not feel comfortable or that it was within their remit to explore the reasons for refusal, perhaps feeling that it would be tactless or impertinent to do so. This would be an area for further research to elucidate the reasons for refusal reported as being cultural. At one of the sites the potential /prospective donors were sometimes unclear whether their religion allowed donation of their cord blood. Those who had time to check with their

religious leader, who duly assured them their religion permitted donation, were then able to proceed. Some studies have sought to understand parents or public awareness and knowledge of cord blood donation and banking (Peberdy, 2018) (Jawdat, 2018) but few studies have addressed religious perspectives, although there a number of publications that investigate religious and cultural barriers in blood and organ donation (Joshi 2017, Spratling 2019). In 2012 Jordens (Jordens 2012) sought opinion from expert commentators in six world religions (Catholicism, Anglicanism, Islam, Judaism, Hinduism and Buddhism). Their commentary suggested unanimous support for cord blood banking, with a moral preference for public banking. None of the commentators suggested any religious significance in cord or its blood prohibiting donation.

Most of the interviewees reported that some refusals were probably due to cultural beliefs and that if the collector felt able to explore this further, if they were able to highlight some of the uses, for example, altruistic, even lifesaving, uses of cord blood that might have some resonance with the prospective donor, then this would sometimes result in a donation. A study by Neelotpol in 2016 found that tailoring information to cultural relevance increased the likelihood of samples' being donated for research purposes in a cohort of pregnant women of South Asian origin (Neelotpol, 2016). Among all interviewees at the various sites it was felt that information provided verbally with opportunity to answer questions at the time, was more valuable than, or certainly a necessary addition to, the written information. The interaction with women prior to their decision to donate was seen as an enjoyable part of the collector's role, which they valued, and this contributed to their opinion that providing verbal information was important.

Lack of awareness was the only barrier to cord blood donation identified in a study by Grossman (Grossman, 2005). Most women surveyed (88%) indicated that they definitely or probably would donate cord blood. The study concluded that strategies to increase the proportion of African-American blood and cord blood donations might include educating potential /prospective donors in the process and benefits of donation to particular patient populations and engaging church leadership in supporting blood and cord blood donation.

Results from a study by Bhandari cited nervousness and lack of information on donation and the utility of the product as commonly found reasons for not donating (Bhandari, 2011). Additionally, irrespective of age or level of education, women relied on healthcare providers for information regarding UCB donation. These results suggest that dedicated personnel focused on disseminating information, obtaining consent, and collecting the UCB product at major hospitals can enrich cord blood banks especially with minority cords. Sustained and focused efforts could improve upon a relatively high wastage rate and ensure a robust supply of UCB products at local public banks (Jordens, 2014).

Several studies have reported on the views of mothers and cord banking (Perberdy, 2018 Jordens 2014, Jawdat, 2018). The majority found a favourable attitude to altruistic cord donation. This would concur with cord bank data which found that few refusals were encountered. For those potential /prospective donors that did refuse, this was frequently due to needle phobia, and this has been seen in other studies of blood donation. Other forms of refusal were occasioned by misconceptions from incomplete or incorrect information.

Some studies have assessed donor mothers' understanding of cord banking options (Rucinski, 2010) (Peberdy L, 2018) but this is the first study to attempt understanding of barriers to donation from the point of view of healthcare professionals directly involved in the cord banking programme in the UK. At a point where the NHS cord bank is going from a period of DH-funded inventory growth to an unfunded maintenance period it was important to maximise efficiency and quality of banked CBUs wherever possible.

Results of a study by Bhandari (2017) suggest that dedicated personnel focused on disseminating information, obtaining consent and collecting the UCB product at major hospitals can enrich cord blood banks, especially with minority cords. Sustained and focused efforts could improve upon a relatively high wastage rate and ensure a robust supply of UCB products at local public banks.

A review by Peberdy in 2018 concluded that cord blood banking is complex and often poorly understood by parents and health professionals, with significant gaps in parents' knowledge and awareness of cord blood banking identified. The study suggested further research should focus on identifying the information expectant parents would like to receive to assist them in making an informed choice in cord blood banking as well as identifying barriers to health professionals' provision of this evidence-based information.

Several studies have reported on the views of mothers on cord banking (Sugarman J, 1998) (Jordens CF, 2014) (Rucinski, 2010) (Shin S, 2011). The majority found a favourable attitude to altruistic cord donation and this concurs with cord bank data which found that few refusals were encountered (NHS Cord Bank data). Amongst the potential donors that did refuse, this was frequently due

to needle phobia, other refusals were caused by misconceptions from incomplete or incorrect information relating to medical exclusions, religion and culture.

The unavoidable reasons for not collecting a cord blood donation, the exclusion criteria, were not discussed as a barrier by the collectors. It is likely that the criteria are understood and accepted by the collectors and consequently not questioned remove this or put at the end. Conversely, midwives at all sites where interviews took place discussed the criteria as barriers to donation. The rationale did not seem to be well understood and some reasons were queried because the midwives regarded some of the cords that did not fit inclusion criteria as 'good' and, in their view, not to be wasted. While the midwives felt that many cords were lost due to transient pyrexia during labour, they also felt that it was better to apply one rule rather than risk collecting from a donor with a genuine infection. It was felt by the midwives that information should be provided during antenatal care to avoid disappointment for some women, particularly those who had twins and were not clear on the rationale for excluding their donation.

7.6 Summary

The themes identified in Study 2 have provided opportunities for changes in practice, primarily relating to clarification of information, improved training packages and sustained engagement with doctors and midwives to promote teamwork and commitment to the cord banking programme. Interventions to overcome Some of the barriers to cord donation and collection explored in this study may not be economically viable when balanced against the additional

number of cord donations that could be collected. It is likely that there may be small gains from addressing each of the barriers and collectively these will lead to a higher number of cords being donated that are clinically suitable with a high cell content and HLA diversity.

Reflexivity

As a Cord Bank manager in my substantive post I was aware that when I was interviewing my colleagues I needed to remain neutral and to listen from the perspective of a researcher without adding my own views and reactions. I may have been biased in terms of selecting practice changes to meet objectives associated with the operations of the cord bank. Following a transparent process by which interviews were recorded and transcribed verbatim and the use of interview schedules helped to avoid any bias of this sort. It was difficult for me to be entirely objective as an employee of the Cord Bank and I used the semi-structure of the interview questions to try to maintain a consistent and neutral position as a researcher.

I devised the interview and focus group questions based on data that had been analysed in the first part of the study and referred to research papers on cord banking practice particularly on challenges to donation and collection to further ensure that a rigorous research process was followed.

As a researcher I acknowledged that the participants who were recruited from the Cord Bank or associated with the Cord Banking programme might have a strong

commitment to a particular issue or agenda, or want to raise particular concerns which may not relate to the main purpose of the discussion. I discussed with my Director of Studies how I might handle this situation if it arose, which was to emphasise the purpose of the research prior to the interview or focus group and through the questions used. Additionally, I also emphasised my role as an impartial student and researcher and the anonymity of each participants views. This strategy seemed to be successful in keeping participants engaged in responding to the research questions without deviating into other unrelated areas (see also 8.21.1 Limitations of the Study).

8 Implications and Conclusions

8.1 Implications for practice

Study 1 explored the NHS Cord inventory from commencement of the banking programme in 1996 to its status at the end of the growth phase (of the inventory). The content of the cord bank inventory was analysed with regard to the cell content and ethnic composition of cord donations stored and the provision of transplants to ethnic minority patients and the quality of the cord blood unit in terms of the cell content and HLA match. The results were used to determine gaps in the inventory areas where there was potential for service improvement.
While the cord bank was shown to be ethnically diverse (Chapter 3.1), there was a disparity in the quality of cord transplants provided to BAME and BINE patients in terms of HLA match and cell dose. This would indicate a need to continue banking cord donations with a high cell count from an ethnically diverse population, if these patients still require readily available, suitably matched donors and cord donations. In response to these findings, planned removal of CBUs with a low TNC from the inventory would be examined first to ensure that this does not adversely affect the diversity of the bank and that any further increase in the minimum TNC for banking (Appendix 2) does not decrease the number of donations from BAME donors.

Searches for patients requiring a stem cell transplant from either bone marrow or cord blood were analysed for a change in available, suitable donations over a period of ten years as cord donations grew in number and diversity and it was shown that the number of available adult donors and cord donations had increased for BAME patients awaiting a stem cell transplant. This was one step towards understanding the unmet need of patients awaiting a haematopoietic

stem-cell transplant and work has commenced in recent months to review the unmet need of patients to access a suitably matched donor. The data available to date have been incomplete and inconsistently recorded with regard to ethnicity. A working group derived from the refreshed Strategic Stem Cell Forum has been formed to address this and undertake an analysis of the current status of patients awaiting a stem-cell transplant, separating out data fields to a greater level of granularity, for example distinguishing between patients with a related donor, fully matched or haplotype and those for whom an unrelated donor is the only option, as well as the total number of potential donors or cord donations available. One of the problems identified during analysis of the data was the disparity in classification between the ethnic background of the patient and donor and the lack of data for patients, which made analysis by patient ethnicity statistically unfeasible. Discussion at the Stem Cell Strategic Forum and at the NHSBT has begun to address this and bring consistency to reporting of ethnic background. Additionally, there has been a focus on language and terminology at the NHSBT, with alternative ways of describing ethnicity being sought. The terms BAME and BINE have been previously used as a broad classification adopted in measuring donation rates but are not helpful in showing the complexity of background or in understanding the needs of patients of a particular ethnic group. Furthermore, the NHSBT has had a renewed focus on equality, diversity and inclusion this year and feedback from several fora has indicated that the terms BAME and BINE are neither useful nor liked for the assumed generalisation that they imply. In response to the data from Study 1 we are now developing a way of monitoring provision of transplants from different ethnicities to give a more granular way of demonstrating inventory use in relation to ethnicity and HLA match. These data will be used to

inform decision on whether to target collection of cord blood from specific ethnic groups.

Cord blood collections have become fewer in all cord banks since delayed cord clamping became routine practice. At the same time, as clinical practice has evolved, the requirement to bank cords of higher cell content has increased. Consequently understanding practice in delayed cord clamping has been of significance. Furthermore, further research is planned at the NHS Cord Bank collection sites to understand the donor's voice and how their opinions on delayed clamping can help to shape the information that is provided.

Since this work was undertaken a leaflet on delayed clamping has been drafted in conjunction with the Anthony Nolan cord bank. A joint publication was preferred to ensure a consistent message is given from the public cord banks in the UK. Once finalised with approval from each hospital Trust where there is a collection site, the leaflet will be provided with other antenatal information at scanning clinics and antenatal classes. Leaflet INF317 was updated in response to the participant data on delayed clamping (Chapter 6.1) to include a statement on delayed clamping: *Cord blood collection does not affect your obstetric care or birth plan e.g those who have opted for delayed clamping".* Additionally, the NHS Cord Banks' frequently asked questions (INF825) that cord collectors put to potential /prospective donors have been updated to include a statement on delayed clamping; *"Some birth plans may yield less blood e.g. physiological third stage; however, this does not always mean that we cannot make a successful collection, as this often depends on the concentration of stem cells within the blood. We can still attempt a collection after delayed clamping if you have consented to donate your cord blood and tissue.".*

Taking forward the comments from several participants on language barriers (Chapter 6.4), cord collectors have further been consulted to consider the operational practicalities and changes to procedure that would be required if interpreters were to be used. Challenges remain with implementing interpretation services, due in part to coordinating availability of interpreters with the timing of deliveries and the short duration of the donor's stay. It has been agreed that provision of written information in other languages to supplement the verbal information that some cord collectors are able to provide in other languages will be taken forward as a first step to opening access to cord donation for prospective donors where language is a barrier.

The written training package was not being effectively delivered (Chapter 6.2) and since this work changes have been implemented to facilitate delivery of training. A short video has been made that shows where clips should be attached to the umbilical cord and how to handle the placenta. This has been shown at training sessions, handovers and induction sessions for new staff. The use of tablets to deliver this training is being investigated, which would allow more immediate delivery of training on the delivery suites than waiting for training sessions and would also facilitate rapid refresher training for staff when needed. In response to the comments about damaged placentas and lack of engagement with medical staff at some sites, I have to date delivered three sessions on the cord blood banking programme during training sessions for medical staff on delivery suites. This has generated useful feedback and discussion, particularly on delayed clamping, as well as highlighting the value of the programme in providing life-saving stem cell transplants.

8.2 Strengths and Limitations of the study

8.2.1 Limitations

This study was undertaken as student research towards a professional doctorate and was conducted with clear advice to participants that this was the case. However, it should be noted that in the interviewer's professional capacity as manager of the cord bank may have had some influence on the interviewees, particularly but not exclusively for those employed by the NHS Cord Blood Bank. The study was undertaken prior to the launch of a consultation which led to a reduction in the number of collection sites and staff employed by the cord bank. The proposed changes had not been announced at the time of the study but it is highly likely that all staff would be expecting changes to be made during the following year as it had been public knowledge that funding from the Department of Health to enlarge the cord bank inventory would cease in 2018 and changes to the cord bank operating model would be likely to follow. Consequently, although it was emphasised that the interviews were confidential, anonymised and part of a student research study, collectors may have felt that it was important to present a positive picture if they thought that there might have been a threat to their site or role on the horizon. The semi-structured format of the interviews allowed some control of the topics that were covered, and this kept the scope to challenges and opinion on donation and collection. All the interviewees were forthcoming and open about their role and the challenges.

Research has been conducted previously to explore the donor mother's understanding, opinions and beliefs about cord blood banking (Busby, 2010). In this study the donor was not perceived by collection staff, or indeed quantitatively

implicated on audit of the non-collection data, as a barrier to collection of cord bloods. The process of donation and engagement with potential /prospective donors starts further back than the point at which reasons for non-collection are recorded, which is generally at the delivery suite at or around the time of birth. At all collection sites cord collectors attend ante-natal information sessions for women to explain the cord-banking programme and how interested women might get involved. The cord bank office subsequently receives expressions of interest by post, email or telephone call. Some women will consent to donation prior to delivery, while others will consent on arrival at the delivery suite if they are at a suitably early stage of labour. All collectors reported during interview that they rarely encountered a direct objection to donation from any of the women they spoke to during antenatal sessions or at the delivery suite. Consequently, at the sites where the NHS cord blood bank collects, most women arrive with an awareness of the option to donate their placenta and cord blood to a public cord bank. While refusal to donate has not been an issue at NHS Cord Bank collection sites, some of the issues discussed with collectors and midwives raised questions about the opinions of potential /prospective donors, which will be explored in a follow-up study.

8.2.2 Strengths

This was a comprehensive audit of the NHS Cord Blood Bank at the end of its growth phase which has not been previously undertaken and has enabled areas for practice changes to be identified supported by the data. The provision from BAME and BINE donors to BAME and BINE patients from the NHS cord bank was analysed and this data contributes to understanding future inventory requirements.

This work was the only research from a UK public cord bank to explore barriers and motivations around the cord banking programme from healthcare professionals who are directly involved. This has enabled practice changes to maximise collection efficiencies and address gaps in information and training.

8.4 Conclusions

The COVID-19 pandemic in 2020 has seen an upsurge in interest in cord blood transplant, primarily to ensure a suitable donation would be available if the adult donor were unable to donate due to COVID-19. This need has supported the continuation of cord blood banking to ensure that high quality cord donations are available.

This study has highlighted that while the NHS Cord Bank has been successful in meeting its objectives, inequalities remain for BAME patients undergoing stem cell transplantation. Study 2 was helpful in exploring the barriers to cord donation and consequently identifying changes in practice that could remove them and consequently improve banking rates and equity of access.

Difficulties remain in assessing the unmet need. There are gaps in data and differences in the way ethnicity is recorded, but since their identification work has commenced to bridge them. The issue of the unmet need is further complicated by changes in ethnic diversity and, inconsequence, changes in the patient population in the UK over time.

Since study 2 was undertaken several changes in practice, directly or indirectly linked to findings, have been made to improve practice and donation rates. These

changes have been subject to procedures at the NHSBT to ensure that any and all changes are made in strict accordance with quality assurance systems and do not breach regulatory or accreditation requirements. Measurement of donation rates concerning practice changes has been hindered by changes to/in the operating model of the Cord Bank in quarter 3 of 2018 which made direct comparison of donation rates before and after the changes to the operating model unfeasible. After October 2018, the number of collection sites was reduced from six to five with a further loss of a collection site in 2019. Additionally, the operating hours for the collection sites changed from 24/7 to weekday shifts between 8am and 8pm. A reduction in the number of cord collectors was also seen due to the reduction in hours and collection sites. Expectations of a period of stability during which assessment of practice changes could be made have not been met this year either since cord collections were suspended in March 2020 due to COVID-19 restrictions. The continuing restrictions have severely affected the number of cord donations able to be banked and consequently, when restrictions ease, there will be a desire to make up numbers of banked CBUs with those of the highest quality in terms of cell count and ethnic diversity. It is expected that the findings of Studies 1 and 2 that have driven and contributed to practice changes will enable this.

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In creating one life why not save another?

NHS Blood and Transplant

Donate your cord blood to the NHS Cord Blood Bank

Appendix 1

What is cord blood?

Cord blood is the blood that remains in the placenta and umbilical cord after your baby is born.

It is rich in stem cells, which can help to cure many life threatening diseases. Following the birth of your baby, the placenta and umbilical cord are usually thrown away along with these life-saving stem cells.

Stem cells have the ability to make new blood cells:

- Red cells to carry oxygen around the body
- White cells to fight infection
- Platelets which are needed to help blood clot.

At 10 days old, Alessia was taken to hospital with a severe skin complaint. When she didn't respond to antibiotics, further tests revealed that she was suffering from Omenn's SCID, a rare life-threatening immune deficiency.

A stem cell transplant was Alessia's only hope for survival and so the search for a stem cell donor began. The best match for Alessia was found in a cord blood donation, which was given nine years previously. The cord blood transplant was successful and Alessia is now a healthy, happy and active little girl.

What is it used for?

Cord blood can be used to treat patients who are suffering from life-threatening diseases, including;

- Blood disorders, such as leukaemia and sickle cell anaemia
- Some immune disorders
- Metabolic disorders, such as Hurlers syndrome.

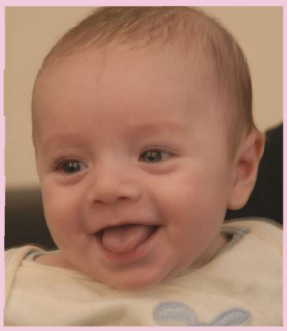
The stem cells found in cord blood restore the function of the patient's immune and blood producing systems. It is an alternative to using bone marrow, with the advantage of being immediately available when required.

For the transplant to be a success, stem cells taken from the cord blood must match the patient's tissue type as closely as possible. So, for patients to have the best chance of a 'match' we need to store as many cord blood donations as possible, and we can't do this without you.

"We hope that one day our decision will save someone's life..."

Bilal's Mum, Laura, was very keen to donate her baby's cord blood after seeing our leaflet in her Hospital's 'Booking In' pack.

"I discussed donating our baby's cord blood with my husband and we both knew immediately that it was something we wanted to do. We hope that one day our decision to donate Bilal's cord will save someone's life or help with research into finding a cure for illnesses that some children face."



Why donate to the NHS Cord Blood Bank?

By donating your cord blood to us after the birth of your baby, you are making a voluntary donation that could save the life of any patient who is in need of a cord blood transplant, in the UK or anywhere in the world.

The NHS Cord Blood Bank was set up in 1996 to collect, process, store and supply cord blood. Our work is for the sole purpose of providing a life-saving product from something that is normally thrown away.

We are a public cord blood bank, are part of the NHS and it is **FREE** for you to donate your cord blood to us. Private cord blood banks are also available, where you store your cord blood for your own family's use, but you have to pay for this service.

"The decision to donate (to the NHS Cord Blood Bank) was easy "

Where can I donate?

Nurun donated the cord blood from her baby daughter Shakira, to the NHS Cord Blood Bank.

"The decision to donate was easy and I definitely made the right choice. It's not as if I wanted to do anything else with it and it would just have been thrown away."

How can I donate my cord blood?

You can only donate your cord blood in hospitals where we have dedicated staff that are trained to collect cord blood.

We have deliberately targeted our resources so that we collect from hospitals with the widest ethnic mix. This combined with hospitals that have high delivery rates give us the greatest variety of tissue types for patients. These tissue types are inherited and are different in different ethnic groups.

Currently these are:

- Barnet General Hospital
- Luton and Dunstable Hospital
- Northwick Park Hospital
- St George's Hospital
- University College Hospital
- Watford General Hospital

Our staff work throughout the day and night, although there may be some occasions when our staff are not available and sadly at these times you will not be able to donate.

Cord blood can only be donated at the hospitals listed above where we have a Third Party Agreement in place. Our specialist staff are responsible for the collection of cord blood, allowing the midwives and doctors to concentrate on the care of you and your baby.

Donating your cord blood will not compromise your obstetric care.

"Thankfully, his consultant found a cord blood match..."

Harvey was diagnosed with Hurler's syndrome when he was nine months old. It is a rare, life threatening disease and occurs when the body fails to produce a particular enzyme. Without a cord blood transplant Harvey would not have survived.

Thankfully, a good match was found and within weeks he received his life-saving cord blood transplant. Harvey now has lots of fun attending nursery.

If you are interested in donating your cord blood, you can register your interest in the following ways:

- Complete the attached form and send it back to us using the freepost address (no stamp is required).

Trish and her husband, Jaynta, decided to donate the cord blood from both of their children, Maya (10 months) and Kai (two years old).

"We had contemplated storing the cord blood at a private cord blood bank but knowing that it was unlikely that our children would ever need it, we decided it would be better

to donate it to he NHS Cord Blood Bank, where it was more likely to be used.“

By completing the attached Consent for Collection Form you can give permission for the NHS Cord Blood Bank to collect and process, and place your cord blood in short-term storage. Following a successful collection we will interview you in hospital to complete the full consent process and to take a blood sample.

- Visit our website **www.nhsbt.nhs.uk/cordblood** and complete the on-line form. Call us on **0800 783 5870** during office hours (answer phone service available evenings and weekends).

As of April 2007 a new legislation came into effect (The EU Directive for Tissue and Cells), which states that consent for the use and testing of your cord blood must be obtained prior to the birth of your baby (which includes active labour).

This ensures that you have had plenty of time to ask us any questions you have relating to the collection, testing and storage of your cord blood. We call this ‘informed’ consent, as we encourage you to make an informed decision about donating your cord blood to the NHS Cord Blood Bank.

Without your consent before your baby is born we are not able to collect your cord blood and your placenta will be thrown away.

Don’t forget! Register today.

What happens next?

The procedures we use to collect cord blood are safe and risk free for both you and your baby. Cord blood collection does not affect your obstetric care or birth plan e.g those who have opted for delayed clamping. This is because the collection of cord blood is made from the placenta after the baby is born. Once your baby has been born, the umbilical cord is clamped and cut.

When the midwives have checked the cord and placenta to make sure everything is OK they will pass it to a member of our team who will do the collection in a dedicated room nearby. The donation is labelled with a unique donation number and information about you and the cord blood donation will be entered onto the NHS Blood and Transplant database. The donation will be evaluated to ensure it contains sufficient cells and that it is suitable for clinical use. If it is suitable it will be processed and stored and made available for any patient anywhere in the world. Donations that are not suitable for clinical use will be disposed of according to UK regulations or, if you have given consent, used for ethically approved research.

Following your donation we will come to visit you to complete the consent process while you are still in hospital. We will ask some routine questions and take a blood sample from you. **No blood is ever required from your baby under any circumstances.**
Your blood sample will be tested, as is done for blood donors, for HIV, hepatitis, syphilis and some other blood borne infections. We have to do these tests to ensure that the cord blood is safe for transplantation. In the unlikely event that any test result is positive, one of our doctors will contact you to offer appropriate advice.

We may contact your GP at around 6 weeks or telephone you 12 weeks after the birth of your baby to check you and your baby are well.

"Thanks to the donated unit of cord blood, Hollie survived"

A GP noticed that something was drastically wrong with six month old Hollie during a routine doctor's appointment for her mum. Hollie was taken to hospital and diagnosed with a potentially fatal disease, Infantile Acute Lymphoblastic Leukaemia.

A cord blood transplant was urgently needed to help Hollie fight the disease and luckily a match was found. Thanks to the donated unit of cord blood Hollie survived and she is now an energetic, bubbly little girl who loves to be outdoors riding her pony, Tiggy.

Consent for collection form

2. Donate your cord blood

NHS Cord Blood Bank, NHSBT Colindale, Charcot Road, London, NW9 5BG

Freephone 0800 783 5870 www.nhsbt.nhs.uk/cordblood

cordblood.donation@nhsbt.nhs.uk

You are being asked to allow the NHS Cord Blood Bank to collect your cord blood. This is the blood that remains in your placenta (afterbirth) and umbilical cord following the birth of your baby. Your cord blood is usually thrown away but, as it is rich in stem cells, it can be stored and used to treat patients with life-threatening illnesses such as leukaemia, thalassemia, sickle cell anaemia and other blood disorders.

If you give your permission, we will collect the cord blood from the delivered placenta before it is discarded. If we obtain a suitable collection, we will

evaluate the number of cells present, and process the donation to place in short-term storage.

A member of our team will come and see you before you leave hospital to:

- Complete a medical and lifestyle donor screen.
- Obtain your consent for long-term storage, testing and use of cells.
- Obtain a small sample of blood from you (no blood is ever required from your baby).
- Answer any questions you may have.

MOISTEN HERE, FOLD AND SEAL TO FORM AN ENVELOPE

If you are interested in donating your cord blood, please complete this form and return it to us. No stamp is required. Without a completed form, we are not able to collect your cord blood.

PLEASE PRINT

Name

House number and street

Town Postcode

Home telephone number

Mobile

Email

Your baby's due date Your date of birth

Delivery hospital

MOISTENHERE,FOLDANDSEALTOFORMANENVELOPE

MOISTENHERE,FOLDANDSEALTOFORMANENVELOPE

3. Consent for Cord Blood Collection

I voluntarily give permission for the NHS Cord Blood Bank to collect, evaluate and process my cord blood, umbilical cord placental tissue, and place it in short term storage. I understand that following the successful collection of my cord blood, umbilical cord and placental

tissue, I will be required to give an additional blood sample and I will be interviewed by a member of the NHS Cord Blood Bank staff to discuss giving informed consent for testing, use and long term storage. I understand that I do not have to donate and I can withdraw my consent at any time. If I refuse consent it will not prejudice my treatment.

I agree to NHS Blood and Transplant (NHSBT) holding my personal details in their donor database and processing this information as necessary for the proper administration of NHSBT.

Signature: Date:

CONSENT REAFFIRMATION (To be completed by CBB Staff)

Consent given for cord tissue collection? Yes No

Name: Signature: Date: Time:

FRM2331/8 Effective: 03/04/2018

Do something amazing

Donate your cord blood to
the NHS Cord Blood Bank

FOLD HER

Appendix 2

DAT 962

1. Criteria for assessing Cord Blood Units in Colindale Evaluation Centre.

CBU should be shipped to Filton for processing and cryopreservation if the following criteria are met:-

- Volume excluding anticoagulant 60ml
- Total nucleated cell count 135 x 10^7 /unit.
- Donor mother has given documented consent
- Haemoglobin 8 g/dL
- Platelet count 100x10^9/L
- Nucleated Cell Count 8x10^9/L (if nucleated cell count > 50 x10^9/L review blood film)

Cord blood units which are not suitable for transplantation may be suitable for research and development based on the following criteria:

- Volume >40 ml
- NEGATIVE for all mandatory infectious disease makers (See MPD668)
- Donor mother has given documented consent for research and development.

THE NHS CORD BLOOD BANK WILL DISTRIBUTE THESE R&D CORD BLOOD UNITS TO THE APPROPRIATE R&D LABORATORIES WHERE THE RELEVANT ETHICAL APPROVAL EXISTS.

Table 1. List of criteria and normal ranges of cord blood donations.

Description	Minimum Range	Maximum Range	Note
Donation Corrected Nucleated Cell Count (x10^6/mL)	9.5	30.7	3
Donation Corrected Haemoglobin (g/dL)	13.2	19.2	3
Donation Corrected Platelet Count ((x10^6/mL)	147	413	3

4. Criteria for Assessing CBU After Processing in Filton Processing Facility

CBU are assessed post-processing as described in SOP2824 and according to the following criteria.

- Parameters in Table 2.
- Freezing curve is acceptable. The freeze profile used should be 'LCBB' (defined in SOP2103). The cooling rate should be between 1–2.5°C/min between -10 °C and -40 °C with the end point at -50 °C.
- Bacteriology screening result states 'No Bacterial or Fungal Growth Detected'
- NEGATIVE for mandatory infectious disease makers in accordance with MPD668

Table 2. List of criteria and normal ranges post processing.

Description	Minimum Range	Maximum Range	Note
Critical Quality Attributes			
Nucleated Cell Recovery (%)	60	100	2
Total Nucleated Cell Count (x10^7)	>90.00		2
Total CD34 Count (x10^6)	>1.25		1
Volume Reduced CD34 Viability (%)	85	100	1
Volume Reduced CD45 Viability (%)	85	100	1
Bacterial/fungal contamination	No growth		1
Fresh CFU	Growth		1
Other Parameters			
Volume Reduced Haematocrit (%)	10	45	2
Mononuclear Cell Recovery (%)	60	100	2
Lymphocyte Recovery (%)	60	100	2
RBC Recovery (%)	7.5	50	2
Volume Reduced Volume (mL)	19	22	1
Final Product Weight (g)	< 33.2g		2

Notes (1): Products that don't meet these parameters are not suitable for clinical use. Refer to the processing facility director or designee for review and authority to discard. (2) Products that don't meet these parameters should be referred to the processing facility director or designee to agree the fate of the donation. (3) The minimum and maximum ranges shown are for indication only. Blood counts that fall outside the range indicated are not a contra-indicator to transplant but may indicate underlying disease.

5. QC Criteria for Assessing CBU Post Thaw Prior to Release for Transplant

CBU are assessed for QC release criteria as described in SOP1714 and SOP1715 using contiguous line sample frozen and stored with CBU. Samples also assessed according to the following criteria.

- Parameters in Table 3
- Parameters from section 2 met in full at banking
- Criteria set out in SOP1714 and SOP1715 are met
- Medical release criteria met and CBU authorised for release by medical authority in accordance with SOP4990

Table 3. List of criteria and normal ranges post thaw.

Description	Minimum Range	Maximum Range	Note
Critical Quality Attributes			
Nucleated Cell Recovery (%)	60	100	2

Post Thaw CD34 Viability (%)	70	100	2
Post Thaw CD45 Viability (%)	40	100	2
Post Thaw CFU	Growth		1
Other Parameters			
CBU Identity	Verified against listed HLA and confirmed maternal link		1
Time CBU subjected to non-cryogenic temperatures during transfer (sec per event)	-	60	3

Notes: (1) Products that don't meet these parameters cannot be released for clinical application. Notify processing facility director or designee. TC must be informed of QC release criteria failure. (2) Products that don't meet these parameters do not meet criteria for clinical release. Notify processing facility director or designee. TC must be informed of QC release criteria failure. Authority to release under concession in extenuating circumstances must be authorised by processing facility director or designee, medical authority and receiving facility. (3) Products that don't meet these parameters may still be suitable for clinical use. Further viability/potency assessment is required to determine clinical suitability. Release must be authorised by head of laboratory or designee.

6. Reasons for Discarding Cord Blood Units

Cord blood units that are not suitable for transplantation or research and development should be disposed of as clinical waste. Cord Blood Donations are discarded if they fail to meet clinical criteria listed above or for the following reasons:

PROCESSING ERRORS

- Buffy coat volume <19ml or >22ml
- Final product volume >28ml (>33.2g)
- Processing protocol not OK
- Failure to cool the buffy coat to 4°C before the addition of DMSO
- DMSO added to cells in less time than quoted in SOP
- Failure to continually mix the cells whilst adding the cryoprotectant
- Faulty heat seal
- Faulty SCD weld
- Machine failure, mechanical or electrical
- Delay >15 minutes between addition of DMSO and cryopreservation
- CRF profile gradient of <1 or >2.5°C/min

FAILURE TO OBTAIN CONSENT

- Failure to obtain informed maternal consent
- Donor mother excluded for medical reasons Language exclusion

LABELLING ERROR

- Missing or incorrectly labelled cord or maternal samples or documentation
- Missing address labels on collection sheets

MISCELLANEOUS

- Damaged bags
- Missing samples for required tests
- Missing results
- Positive bacterial/fungal screening results
- Unable to obtain mothers samples

mother's Donation Number	Cord Blood Donation Number
Are the parents related? ☐ YES ☐ NO	How?
Sex of baby ☐ MALE ☐ FEMALE	Additional languages spoken by mother, other than English

motHEr'S BirtHplaCE (please record country of birth)	fatHEr'S BirtHplaCE (please record country of birth)
Mother _____	Father _____
Maternal Grandmother _____	Paternal Grandmother _____
Maternal Grandfather _____	Paternal Grandfather _____

motHEr'S EtHNiC BaCKGroUND

White

☐ A1 UK/other Northern Europe
☐ A1B Southern Europe
☐ A1D Jewish
☐ A1G Mediterranean
☐ A1E Americas/Australia/ New Zealand
☐ A1F Other _____

Black

☐ A2A Africa
☐ A2B America
☐ A2J Caribbean
☐ A2C Other _____

Asian & Middle Eastern

☐ A1C Middle East
☐ A5F Pakistan
☐ A3M China
☐ A5A Nepal/Burma/ Thailand/Indonesia
☐ A5H India
☐ A5G Bangladesh
☐ A5B Japan
☐ A5I Other _____

Other

☐ A6A South America
☐ A6 Other _____
☐ A4 Hispanic

Mixed

Please indicate mother's & father's ethnicity

Mother _____ Father _____

fatHEr'S EtHNiC BaCKGroUND

White

☐ A1 UK/other Northern Europe A1E
☐ A1B Southern EuropeNew
☐ A1D Jewish A1F
☐ A1G Mediterranean
☐ Americas/Australia/ Zealand
☐ Other_____

Black

☐ A2A Africa A2J Caribbean
☐ A2B America A2C Other
☐ _____

Asian & Middle Eastern

☐ A1C Middle East
☐ A5F Pakistan
☐ A3M China
☐ A5H India
☐ A5G Bangladesh
☐ A5B Japan
A5A Nepal/Burma/
A5I Other _____ Thailand/Indonesia

Other

☐ A6A South America
☐ A6 Other _____
☐ A4 Hispanic

Mixed

Please indicate mother's & father's ethnicity

Mother _____ Father _____

form completed by (please print name)	**Date**

Appendix 3 (FRM4991)

Who are the researchers and what is the research about?

I am researching beliefs and views about cord blood banking and whether they may have any effect on altruistic donation of umbilical cord blood. I hope that the findings can be used to guide the information provided to healthcare professionals and donors about cord blood banking.

My name is Alex Ross and I am a biomedical sciences postgraduate student in the Department of Health and Social Sciences, University of the West of England, Bristol. I am completing this research for my Professional Doctorate thesis.

What types of data are being collected?

I am collecting data using a focus group discussion. A focus group is simply a group discussion 'focused' on a particular topic or theme - in this case, beliefs and opinions about the collection and uses of umbilical cord blood that is donated to a public bank. I am interested in your views and opinions on the topic of cord blood banking and would like the focus group to be a lively discussion; there are no right or wrong answers to the questions you will be asked to discuss!

Who can participate?

Anyone over the age of 18 who is interested in taking part and employed as a midwife at one of the NHS cord blood collection sites, employed by NHSBT as a cord blood collector or attends a community group.

What will participation in the focus group involve?

This particular focus group will involve as many participants as are available up to 5 in total and one moderator (me) and will be audio-recorded. It will last for whatever time you can spare. You will be asked to sign a consent form before participating. In the group, you will be asked to talk about issues relating to cord blood banking. The questions will relate to your perspectives and views on this and to your own individual experiences and practices related to cord blood banking.

When will this take place?

I will be at Site X on: **Monday 19th March between 11am and 3pm**
I will check your availability on the day and hold the discussions at your convenience.
The finding s from my research will be fed back to you once the analysis is complete.

Thank you for reading this.

Appendix 10

Exploring the Unmet need in Cord Blood Banking Interviews

Participant Information Sheet

Who are the researchers and what is the research about?

Thank you for your interest in this research about cord blood banking. I am researching beliefs and views about cord blood banking and whether this may have an effect on altruistic donation of umbilical cord blood. My name is Alex Ross and I am a biomedical sciences postgraduate student in the Department of Health and Social Sciences, University of the West of England, Bristol. I am completing this research for my Professional Doctorate thesis. My research is supervised by Dr Rachel Gillibrand (see below for her contact details).

What does participation involve?

You are invited to participate in a qualitative interview – a qualitative interview is a 'conversation with a purpose'; you will be asked to answer questions in your own words. The questions will cover your experience of cord blood banking, either as a healthcare professional or as someone who has donated cord blood or knows someone who has donated cord blood. During the interview we will be talking about the uses of cord blood and any experience with cord blood collection, donation and banking that you have. The interview will be audio recorded and I will transcribe (type-up) the interview for the purposes of analysis. On the day of the interview, I will ask you to read and sign a consent form. You will also be asked to complete a short demographic questionnaire. This is for me to gain a sense of who is taking part in the research. I will discuss what is going to happen in the interview and you will be given an opportunity to ask any questions that you might have. You will be given another opportunity to ask questions at the end of the interview.

Who can participate?

Anyone over the age of 18 who is interested in taking part and is an NHSBT employed cord blood collector.

How will the data be used?

Your interview data will be anonymised (i.e., any information that can identify you will be removed) and analysed for my research project. This means extracts from your interview may be quoted in my dissertation and in any publications and presentations arising from the research. The demographic data for all of the participants will be compiled into a table and included in my dissertation and in any publications or presentations arising from the research. The information you provide will be treated confidentially and personally identifiable details will be stored separately from the data.

The personal information collected in this research project (e.g., the interview audio recording and transcript, and the demographic form) will be processed by the University in accordance with the terms and conditions of the 1998 Data Protection Act. We will hold your data securely and not make it available to any third party unless permitted or required to do so by law. Your personal information will be used/processed as described on this participant information sheet.

What are the benefits of taking part?

You will get the opportunity to participate in a research project on an important issue related to patient's treatment options where cord blood transplantation is a potential treatment.

How do I withdraw from the research?

If you decide you want to withdraw from the research please contact me via email at Alexandra.Ross2@live.uwe.ac.uk Please note that there are certain points beyond which it will be impossible to withdraw from the research – for instance, when I have submitted my dissertation. Therefore, I strongly encourage you to contact me within a month of participation if you wish to withdraw your data. I'd like to emphasise that participation in this research is voluntary and all information provided is anonymous where possible.

Are there any risks involved?

We don't anticipate any particular risks to you with participating in this research; however, there is always the potential for research participation to raise uncomfortable and distressing issues. For this reason we have provided information about resources which are available to you. If you feel distressed as a result of participating in the focus group, and you are an NHSBT employee, the Employee Assistance Programme provides support https://healthassuredeap.co.uk/home/.

If you have any questions about this research please contact my research supervisor:
Dr R. Gillibrand, Department of Health and Social Sciences, Frenchay Campus, Coldharbour Lane, Bristol BS16 1QY
Email: rachel.gillibrand@uwe.ac.uk

This research has been approved by the Health and Applied Sciences Faculty Research Ethics Committee (FREC)

V1 01/12/17 IRAS 23025

Appendix 11

7. Exploring the Unmet Need in Cord Blood Banking

8. Consent Form

Thank you for agreeing to take part in this research on cord blood banking.
My name is Alex Ross and I am a biomedical sciences postgraduate student in the Department of Health and Social Sciences, University of the West of England, Bristol. I am collecting this data for my Professional Doctorate thesis. My research is supervised by Dr R. Gillibrand. She can be contacted at the Department of Health and Social Sciences, University of the West of England, Frenchay Campus, Coldharbour Lane, Bristol BS16 1QY [Tel: (0117) 3281234; Email: rachel.gillibrand@uwe.ac.uk if you have any queries about the research.
Before we begin, I would like to emphasize that:
- your participation is entirely voluntary
- you are free to refuse to answer any question
- you are free to withdraw at any time [within the limits specified on the information sheet].
You are also the 'expert'. There are no right or wrong answers and I am interested in everything you have to say.

Please sign this form to show that you have read the contents of this form and of the participant information sheet and you consent to participate in the research:
_____ (Signed)
_____ (Printed)
_____ (Date)
Please return the signed copy of this form to me.

This research has been approved by the Health and Applied Sciences Faculty Research Ethics Committee (FREC)

V1 01/12/17 IRAS 230255

Appendix 12

Interview Transcript
SCC1 19th March 2018

Interviewer: So why don't you start by telling me about when you started with the cord bank
S3C1: I joined Sep 2014. My first job. Stumbled on it by accident. Been here ever since. So most shifts I work alone, on lates. Doing a night.
Interviewer: And what sort of training did you have when you first came in?
S3C1: When I first started, erm I got trained with girls on a couple of early shifts and then I think maybe after two weeks I was going alone so they showed me what to do. How to consent people, how to do the collections, erm, along with those two and Edward I got sent on a venepuncture course coz I couldn't take blood previously so I think like a month or two they managed to get me on so I went to Cambridge to Newmarket for a day, learned how to do that then the other guys on the team helped me get all my required observed practices done to get all that and then yeah I was flying solo.
Interviewer: Great, ok. You must have had a fair bit of practice at getting the collections. Have you seen it change much over the time, even in the time?
S3C1: Yeah definitely, obviously now delayed clamping is in the NICE guidelines we see a lot more where they leave it longer and longer and longer.
If the baby comes out in good condition there's nothing to stop them leaving it 5-10 mins before it used to be only on the Birth Centre upstairs where you'd see it but now obviously it's best practice for a minimum of a minute but a lot if them leave it 5 mins especially the newly qualified midwives because it's being taught in practice in the university.
Interviewer: Ok, to leave as long as possible?
S3C1: Yeah if the baby is fine and there's nothing wrong with mum, if not bleeding they leave it until it's stopped pulsating until they see a placenta bleed then obviously they'll clamp and cut it but if there's nothing stopping they'll leave it. And even in theatres now they time a minute a full minute just leave the baby time a minute it's amazing how much they get across within that one minute. Some of the surgeons milk the cord. Think there's a lot of debate between them and the paediatricians and the neonatologists as to whether that is best practice but they all leave it. Theatre when you start when the baby is born they've got the minute timer on so the listen for the beeps to tell them it's a minute ….and that's on absolutely every birth unless the baby comes out in really poor condition.
Interviewer: Right, so that's in theatre
S3C1: Yeah
And then everywhere else, so we've got the guideline but it seems to be generally accepted practice as long as possible.
Interviewer: And are there any reasons for leaving it for longer and longer

S3C1: I think, I mean I'm not. I think it's just that it's part of the circulating volume and to make sure the baby gets as much iron as possible; I think is the general consensus and they leave it still it stops pulsating. They think, once sort of enough blood has gone through and stops pulsating anyway then clots.
Interviewer: Do you get any mums asking you about,
S3C1: Nearly everybody

Interviewer: Do they?
S3C1: They always say yes that's fine but can I still do delayed clamping?
It's taught in NCT. NCT, I 've heard, that they're telling them they can't do both and can't donate their cord blood. We hear it a lot. We tell them that's not true. I remember Lat year someone had out their consent in the post then we got a call saying they'd declined they want to withdraw their consent because they think, they were under the impression, think they spoke to someone in the office, and we got a message that if they did what we did then the midwife would not delay the cord clamping for them. Which is obviously untrue I certainly stress when I do my mini consent… I don't know about my other colleagues; you'd have to ask them but I stress we don't interfere. It's just you and the midwife. We're only present in theatre, were not present in the rooms we're not hanging around bearing over them WE let then now they've consented. They do what they need to do and then. We often have it when the midwives come out and say. I'm really sorry, you can have a look but there's not much left
Interviewer: Do you think the mums ask for do you think they're aware of the NICE guidelines because if it's one or two minutes
S3C1: I think they get taught, told about it I NCT classes They get told about it in their antenatal classes. I do think they're told the longer the better rather than 1 or 2 minutes.
Interviewer: It affects us but we've still got a chance, haven't we?
S3C1: Yeah we do have a chance but I think it depends on size of placenta to begin with but if it's more on the smaller size 1 or 2 mins makes a massive difference I think. I think if you look on baby forums and things on fb a lot of them are saying you've got to leave it 'til it's white. I mean That's not gonna happen on all of them but I think perhaps when they see these things online it's a lot of influence. People post things on fb, even if you're not searching for it. I mean I'm not pregnant, I don't want a baby, at the moment but I still see these articles that other people have shared and I think definitely within NCT they get the message across that you can't do both because you can't delay it and you can't donate.
Interviewer: So you're finding you're having to spend quite a bit of time addressing that without making any influence on anybody's birth plan?
S3C1: I think I have to convince them that it's fine and you can do what you want and express your wishes to your midwife and do best for you and your baby and as long as everything's safe but you end up having to reassure mum that they can do both

Interviewer: Yes, and are there any other, moving on from the dc a little bit, reasons or barriers that you have come across in your time as a collector to collecting either from other colleagues or HCPs or the donor mums?
S3C1: Some of the donor mums don't like the idea. They think we're going to do weird and wonderful things with their cells, think we're gonna clone. A lot of dads; a lot of dads actually, they say no on behalf of their partners and obviously you can't then sort of, that's him speaking on her behalf is what I find very odd but obviously within some cultures it's a standard thing, but not many, not many. Maybe one once a month you'll get someone who doesn't like the idea or doesn't want to do it. Don't know if I'm allowed to say this; A lot of black Caribbean, people from black Caribbean areas don't like the idea, at all. Always you can get a vibe, you get a vibe off people, you can always tell and I think primarily it's that kind of people from that kind of ethnicity and even if you try..
Interviewer: Why do you think that might be?

S3C1: I don't know, I honestly don't know. We're not allowed to ask but I don't know
Interviewer: Do you think it's religious or cultural? Or more wondering what's going to happen?
S3C1: I think more cultural: Are you going to clone my baby and things like that? Where are these cells going to go? Somebody once told me that they Didn't know who the cells where going to go to and that puts them off. If that person is a bad person…
Interviewer: ok. Do you think our information that we give then upfront; the written info is enough? Or is it not enough of an issue?
S3C1: Honestly I don't think the written info upfront makes it. I think it's the way you give the speech to the person. I will happily admit to targeting and adjusting my speech. Obviously I'm not going to explain that we can help treat blood-based disorders more I'd say it more to a black person than a white person just because of the obvs like the whole sickle cell situation. It's more y'know that's the kind of thing that they would want to know more about and I say a lot more about ethnicity to a black person than I would a white person. Y'know we'll give it somebody who's from the same sort of ethnicity as you are gets more of an effect out of a black person than a white person I think it's more about knowing the collector themselves knowing the audience. You've got to judge the person you've got to judge whether or not they're going to say yes or no and you've got to pitch it to what you think will trigger in their brain as it being a good thing.
INTERVIEWER: You're absolutely right. Any advice to other collectors?
S3C1: I think that is really key. You can't give the same speech to everybody you have to be aware of the person that you're talking to if they are looking at their partner. If they seem keen, if there's something you say and they pull a funny face you have to be watching them and then you can sort of elaborate as necessary on the areas they might need more reassurance or want more information about that you can then give and say be happy to say do you have any questions or is there anything you're sort of thinking about.
INTERVIEWER: Ok, that's interesting. Communication skills being key.
S3C1: And again with the midwife you have to know when to approach the midwives because without their permission you can't go in the room. You have to know the midwife who will let you go in immediately, who you have to be nice to first before you can ask, engage them in conversation how are you, how's it going, y'know all of this - not just can I go in the room. Have to butter them up a little bit and make them sort of comfortable around you and even though I've been here however many years around so many years still some of them won't let you go in so you sort of have to know that's fine just come to me I'm her y'know. You have to know who you're talking to and how to pitch it.
INTERVIEWER: Would you say there is much resistance or is that a minority.
S3C1: Very much a minority here. I mean we're friends with most. Well, I am friends with a lot of the mw. Like, going on holidays/hen do/weddings of a lot of the mw here. We y know I think the closer you are with the midwives the more time you spend on the floor the better. I go into my office to do my temp check to do my collections and to fill in my paperwork and every other min of the shift I'm out r. here
INTERVIEWER: That has certainly come through. Yes, they all sung your praised very much and said that is really key to you being very much in the team. Really seems to help.
S3C1: Oh, massively. You don't know what's happening when you're in the room. Being here prompts them and reminds them that you're here. If they're not seeing you they got

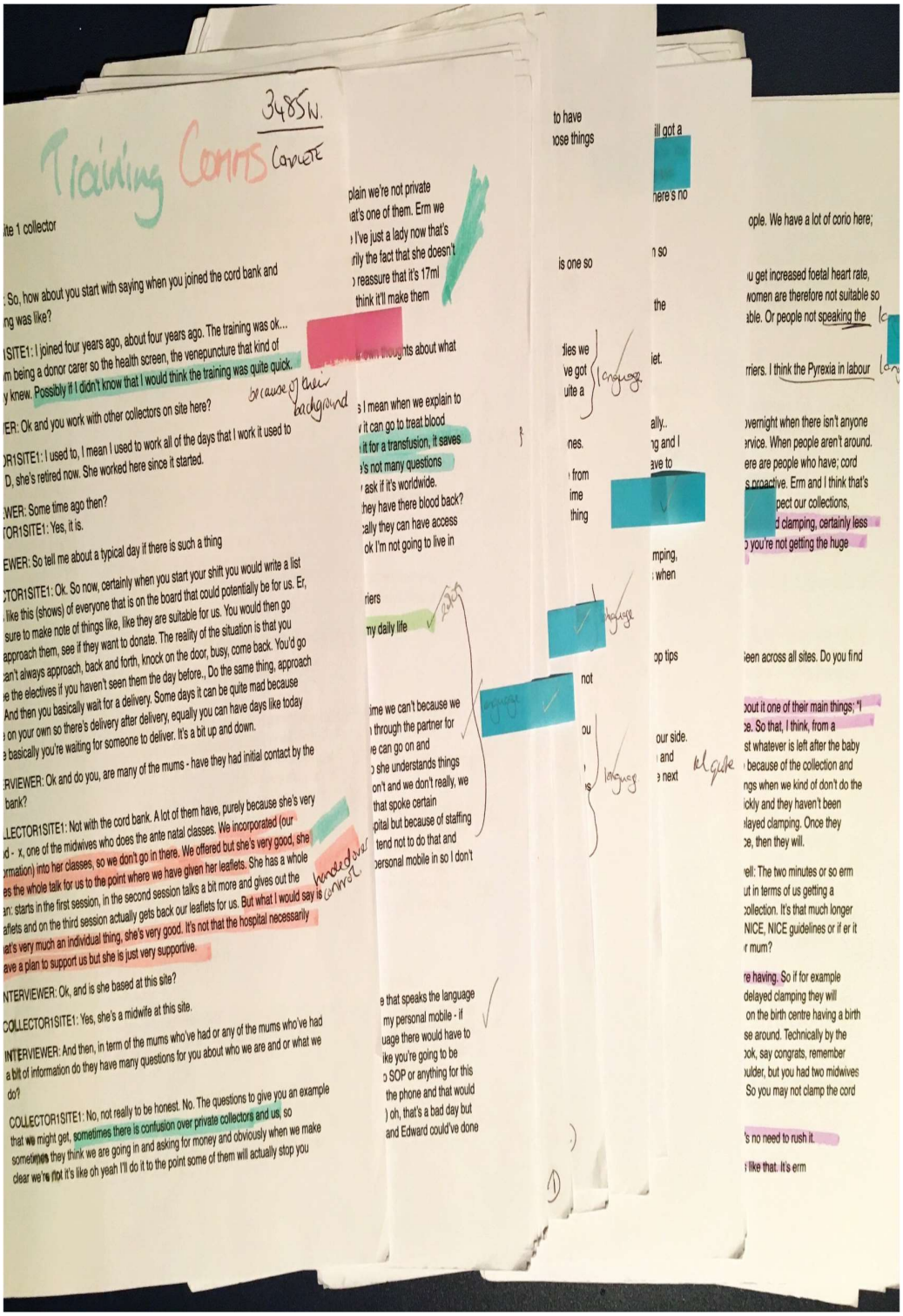
distracted. They've got a million and one other things to do. It's always better and especially because we've got central monitoring I can interpret the CTG, I know what's happening. If you can learn how to interpret the CTG you can tell that a midwife, you know how often she's contracting. I can see if a trace looks like she's pushing or she's fully. I can see if she's not contracting enough so chances are she will need synto before she pushes so therefore I've got a bit more time., you can plan your shift better. If she's a primip she's prob going to need a full hour of pushing, if it barely looks like she's contracting they'll give her syntocin it might take up to two hours, you can go and do other things, get other things done.
INTERVIEWER: And then are you there outside as soon as…
S3C1: As soon as she's delivers yeah. If she's in a room at this end I'll just pop round but they know I'll be there waiting patiently. I spend my life waiting. That's what they say – are you waiting?
[Interrupted by MW]
INTERVIEWER: So, you've got two more mins. Also talking to the mums and the information they get, is there any because this site is particularly good at getting collections. And it'd be nice if there was any advice that you'd offer to other Sites, other collectors or other mw on how to get the max number and quality,
S3C1: Be here, learn the physiology of what's going on so you can be aware. Also that means you don't bug the mw too much. Get the right balance be friendly but don't bug them., Don't constantly ask them; how's this that and the other. Learn it yourself. Yes occasionally you have to ask but learn it yourself so you can just do it. Just be here. Don't sit in the office. Be on the floor. You know and be aware of what's going on. If a multip comes in and pushes the baby out, and you've been in the office for 30 mins she could've been in, delivered, the placentas out and she could and be half way up to the postnatal ward and you wouldn't have a clue because you're not there and you're not paying attention, and if the midwife's busy or she's new then you have to then you'll just miss it. If you're here you can get it immediately you can ask the midwife. We've got the training programme in place. Soon as a midwife rotates to the delivery suite for first time train them, don't train on the postnatal ward because they'll forget and then physically showing them and
INTERVIEWER: So there's not much of an issue with damaged placenta?

S3C1: The occasional doctor gets a bit rough and puts their hand in but I have a way. I'm like – you've ruined another one of my placentas, you're breaking my heart here. Just try and be a little bit nicer, a little bit more gentle. And if she's bleeding mums the priority, mum's always the priority. Just take a little bit more time.
INTERVIEWER: And has that worked?
S3C1: Now the doctors apologise to us. They'll pull it out and like I'm so sorry it's got a whole in it. So sorry, it just snapped. We're there in theatre so they see us around.
INTERVIEWER: Is it the same cohort or is there a big turnover of doctors?
S3C1: Yes, every 6 months we have new registrars.
INTERVIEWER: So you have the same conversation?
S3C1: Yep, soon as they start. When there's a lull, just catch them
INTERVIEWER: Last thing I was going to ask about, was the info that you get back from the cord bank. What would you like, if anything, about what happens to the cords once they've been collected? Do you get enough information?

S3C1: I think we do. I think it would be nice to know if it's successful. We get the list of where it goes but it would be nice to know if it's successful. Obviously, we won't get it at the same time. If the transplant was a successful transplant, that might be nice to know, yes we know they go but are they actually working?
INTERVIEWER: That's something we can definitely look at. We get outcome data but it comes through about 18 months behind real time. Just the way it all works but we do get outcome data. The vast majority of our cords do engraft. They've obviously gone through a lot, collection, evaluation, processing before they're put into the bank. They've had quite a journey but there's so many checks along the way that we wouldn't be sending anything out unless we're sure of its quality. Then there's a load of other factors to do with the patient's treatment. We don't unfortunately get much personalised information about the transplants. That's very hard to get hold of. Particularly as we do send quite a lot of ours abroad but that's definitely something we could provide a little more on. Do you think that would also be useful for the midwives and the mums?
S3C1: I think the mums like to know where they go.
INTERVIEWER: Do you think they're quite well aware?

S3C1: Not really. I think they'd be quite keen to know where it went.
INTERVIEWER: Ok, thanks ever so much for your time
S3C1: Sorry I had to rush you; it's been busy all morning. Thank you.

Appendix 13



Initial development of theme map and codes

Appendix 14

Themes	Potential improvements
Practice is variable across sites and within sites	Could be too soon for pregnant women to take on board Cost and time of resource to implement and sustain this.
There is awareness of the guidelines, but these are not adhered to in practice	
There is a general perception from pregnant women that the longer the delay the better for the baby	Regulatory risk around controlled documents provided if they are not version controlled. Clarify the information that is provided during antenatal care.
Social media campaigns can have significant influence during ante-natal care, for example the 'Wait to white' campaign	Easy to implement within current quality management system No additional resource required Clarify the information that is provided during antenatal care.
Perception for pregnant women is that delayed clamping and cord blood donation are not compatible	Clarify the information that is provided during antenatal care. May only reach a limited number of women and those who already attend NHS ante-natal classes
Perception from collectors and midwives that some private ante-natal classes are a source of misinformation	Engage with private ante-natal classes. May only reach a limited number of women and those who already attend NHS ante-natal classes
Themes	Potential improvements
Collectors found it difficult to deliver standard training package to all healthcare professionals.	Improve training package
Collectors felt the training package was of limited use, reflected in the number of damaged placentas increasing.	Provide training in a different format
None of the midwives mentioned receiving a specific training package.	Provide training in a different format
Word of mouth and engagement with the cord blood collectors was deemed more valuable	Provide training in a different format
Rationale for exclusion criteria was not well understood.	Clarify reasons for exclusion criteria

Theme	Potential improvement
Requirement for blood samples was a barrier to donation for some women.	Clarify requirement in written information. Take samples at same time as midwife and from cannula where possible.
Some confusion reported over public versus private banking	Revise information and FAQ to clarify common queries
Verbal information generally viewed as more useful than written information	Provide information in different formats
Uses of cord blood and specific information on cord bloods used for transplant would help engagement with midwives	Provide information on a regular basis on the uses of cord blood
Theme	Potential improvement
Language was viewed as a significant barrier to donation at some sites	Provide information in a range of languages Employ multi-lingual collectors Employ translators at collection sites
Interpreters are not used in the delivery room or by the cord bank	
At least 40% BAME donations banked despite language barriers	
Themes	Potential improvements
Private banking was notable when it occurred but infrequent compared to other barriers to donation.	Continue to collect data and monitor.
Themes	Potential improvements
Rationale for exclusion criteria was not well understood by the midwives.	Add information to training sessions
The exclusion criteria for collection account for a significant proportion of available births, with pyrexia accounting for the greatest proportion.	Review criteria for suitability
There is a perception from the midwives that some 'good' cords are missed due to the criteria for gestational age.	Add information to training sessions
Clear information on exclusion criteria during ante natal care would be useful in managing expectations for some women.	Review and revise written information provided during ante-natal care.

Appendix 15

Donating Cord Blood, Umbilical Cord and Placental Tissue

Frequently Asked Questions

NHS Blood and Transplant

NHS Cord Blood Bank
Charcot Road, Colindale
NW9 5BG

This document provides answers to questions most frequently asked by donors and may help you decide if you want to donate your baby's umbilical cord, placental tissue and cord blood. If you choose to help us and agree to donate to the NHS Cord Blood Bank please sign the consent form provided.

Where can I donate my cord blood to the NHS cord blood bank?

We can only collect from; Barnet General Hospital, Luton & Dunstable Hospital, Watford General Hospital, St George's Hospital and University College Hospital. Collection is not always possible, and many donations are not suitable to be banked for clinical use when they are evaluated, and so you should never transfer to one of these hospitals just for the chance to donate.

What is cord blood?

Cord blood is the blood that remains in your placenta and umbilical cord after you give birth. It is normally thrown away as clinical waste but, as it is rich in stem cells, it can be stored and used to treat patients. Stem cells are special cells that can either remain a stem cell or specialise into other specialised cells, such as a muscle, skin, liver, nerve or blood cells. They can divide to renew damaged cells, and in doing so act as a repair system for the body. Cord blood is rich in haematopoietic stem cells that can make new red and white blood cells, and platelets which are needed to help blood clot. Cord blood, cord and placental tissue also contain other stem cells such as mesenchymal stem cells which can repair other tissue in the body. It is possible we could use your donations to make new biological therapies by selecting certain cells and allowing them to grow and multiply under laboratory conditions.

Why is cord blood important?

The stem cells found in cord blood can be used to treat a variety of diseases including:

- Blood cancers, such as leukaemia and lymphoma
- Some immune disorders, such as Aplastic Anaemia and Severe Combined Immunodeficiency (SCID)
- Metabolic disorders, such as Duncan's Syndrome (also known as X-linked lymphoproliferative disease – a disease which often leads to death from bone marrow failure, irreversible hepatitis, and malignant lymphoma in boys) and Hurler's Syndrome

(a lysosomal storage disease which causes developmental deformities, vision problems, organ damage and death)

These stem cells can be given to patients as a cord blood transplant and are essentially an alternative to bone marrow transplantation. The cells can be stored frozen for many years and have the advantage of being immediately available when required for a patient.

Why do you need to collect cord blood?

We aim to store 20,000 cord blood units, this will complement a UK public bank of 30,000 cord blood units in collaboration with another UK cord blood bank held by the Anthony Nolan charity. A public bank of this size would allow the UK to provide life-saving cord blood transplants for a large number of patients who currently can't find a donor and reduce the need to import cord blood from banks overseas.

How do I give consent?

Without your consent we are unable to collect your cord blood, cord and placental tissue following the birth of your baby. The consent process is regulated by the Human Tissue Authority to ensure it has been done properly. We will talk through the process with you where you will have an opportunity to ask questions at any time during the consent process. If you decide to donate your baby's umbilical cord, placenta and cord blood you will need to sign the consent form. Even if you have signed the consent form you can still change your mind and withdraw consent at any time before or after your baby is born. If you change your mind after donating your cord blood the cord blood collection, remaining samples and any paperwork bearing your personal identification data will be discarded. Where the donation has been used already it may not be possible to withdraw consent for the use of the cells and you will be informed if this is the case.

Am I eligible to donate my cord blood and tissue?

Most mothers are able to donate their cord blood and tissue, but we will need to ask a few questions about your lifestyle and medical history to confirm that the donation would be safe for any patient.

Do I need to change my birth plan if I wish to donate my cord blood and tissue?

No. We do not interfere with your choice of birth plan or the actual delivery of your baby which will be supervised by your attending midwife/doctor. The safe delivery of your baby is the absolute priority and any consideration of collecting your cord blood will only be carried out once this is achieved. If you have consented to cord blood donation we will attempt to make a collection regardless of method of delivery. Some birth plans may yield less blood e.g. physiological third stage, however, this does not always mean that we cannot make a successful collection, as this often depends on the concentration of stem cells within the blood. We can still attempt a collection after delayed clamping if you have consented to donate your cord blood and tissue.

How is my cord blood collected and what will happen to it?

Once your baby has been born, the umbilical cord is clamped and cut. When the midwives have checked the cord and placenta to make sure everything is OK they will pass it to a member of our team who will do the collection in a dedicated room nearby. This dedicated NHSBT collector will collect the blood using a specially designed sterile collection kit. The donation is labelled with a unique donation number and information about you and the cord blood donation will be entered onto the NHS Blood and Transplant database. The donation will then be sent to the NHS Cord Blood Bank

laboratories where it will be evaluated and, if it is suitable for clinical use processed. If the donation is not suitable for clinical use, it will either be disposed of according to UK regulations or, if you have given consent for research, we will use it for ethically approved research. It is possible your donations (cord blood, cord and placental tissue) could be sent abroad to researchers in other countries.

Is all cord blood collected and stored?

We can't guarantee that your cord blood will be collected and stored. It may not be collected because the collection staff may not be available to make the collection, or there may be a medical or technical reason why the cord can't be collected.
If a collection is made they frequently do not contain enough cells for clinical use and these won't be processed or stored. In addition, some cord blood donations with lower cell counts are used for research, quality control purposes so we can monitor the quality of our processes and to make sure they are fit for purpose or alternatively to validate new procedures.

Will donating cord blood affect my baby or me?

No. The safe delivery of your baby takes priority. We have worked with midwives and doctors since 1996 to develop procedures that are entirely safe for you and your baby and do not interfere with the birth in any way. We use dedicated collection staff so that your midwife is free to concentrate on taking care of you and your baby both during and after delivery.

What tests are performed on the blood samples taken from me?

Following your donation we need to take a blood sample from you. Although we don't require blood samples from your baby we may occasionally detect your baby has low platelets (a blood factor important in clotting) by testing directly on the cord blood at our laboratory. As it is not always routinely carried out on all new-borns in hospitals, we will inform your maternity team accordingly if this is the case. In the same way that blood from blood donors is checked for infections, we must check your blood to confirm the cord blood is safe for transplantation. In the unlikely event that any test proves positive, you will be informed and offered appropriate advice. In exceptional circumstances, for instance if your baby is at risk, your GP, obstetrician or baby's doctor may be informed. As for blood donors the requirement for testing will not affect your ability to obtain life assurance, health insurance or a mortgage.

We may also use your blood to develop rare blood panel tests or other diagnostic purposes.

What tests are performed on my cord blood?

We will test your blood only to make sure it is safe to be transplanted into any patient. Specifically, we will test for blood borne diseases including viruses and other diseases, such as sickle cell and hepatitis. We will also carry out haematology tests to count the stem cells to make sure there are sufficient for clinical use. In addition, we will tissue type (termed HLA type) your blood and the cord blood donation. The HLA type is used by transplant centres to match donations with patients. Where the transplant patient has a good HLA match with the cord blood donation there is a much better chance the transplant will be successful. The maternal HLA type can also help with matching the donation to a patient.

If your donations are used for research it is possible that other genetic (DNA) tests could be performed.

Is my personal information, including my test results, kept confidential?

Yes. We'll store your information on our cord blood donor database, where it will be given a unique donation number. We'll then refer to this donor number when reporting to other institutions such as transplant centres, without identifying either you or your baby. Your personal information will not be shared with a third party unless you give express consent we can do so. All information provided to NHSBT is used in accordance with the General Data Protection Regulation (GDPR) and all other relevant privacy and data protection laws. To find out more about your privacy rights please visit our website **www.nhsbt.nhs.uk** or call us on **0300 123 23 23**.

Will you contact me again?

Possibly, we may contact you again after 6 or 12 weeks just to make sure you and your baby are well and that there are no reasons why we shouldn't transplant your cord blood. The interview is by telephone and will only take a few minutes. If a patient needs your cord blood we will endeavour to contact, you or your GP before the cord blood is released to the transplant doctors caring for the patient. Again, this is only to make sure that you and your baby are still well and that there are no reasons why your cord blood should not be used.

Does it cost me any money? Do I get paid?

No, there is no cost to you in donating your cord blood to the NHS Cord Blood Bank. Your donation will be on a voluntary basis only and we are not able to offer any payment to mothers for donating their cord blood. This includes your donations for research, cell line or new therapy creation.

How long is my cord blood stored for?

Cord blood donations are stored below -190°C where we can keep them indefinitely. Cord blood donations over 15 years old have been successfully used for transplants.

Will my cord blood be available to my own family should it be needed in the future?

We operate our cord blood bank as a public resource making donations available for any patient anywhere in the world and do not store cord blood for private family use. In the extremely unlikely event a member of your family requires a cord blood transplant in the future, a search will be made of public cord blood registries around the world to identify the best cord blood unit available. It is possible that your donation may be available, but the transplant centre may prefer to use another donation from a different individual.

How does the NHS Cord Blood Bank differ from private banking?

The NHS Cord Blood Bank is publicly, or government funded and only collects cord blood from public hospitals. The potentially life saving product is then stored for any patient that needs a transplant anywhere in the world. There is no charge to the donor, but the product is not stored specifically for that person or their family.

There are several commercial cord blood banks that charge a fee to collect and store cord blood for private family use only. If you wish to use one of these companies, you need to contact them directly. To fully understand the potential of private storage we would advise you to research the claimed benefits thoroughly and seek out independent advice from institutions such as the EU and/or various medical bodies representing doctors and professional medical opinion.

The Human Tissue Authority has produced a parental guide on cord blood banking available at: **https://www.hta.gov.uk/guidance-public/cord-blood-banking-guide-parents**.

Why does the NHS Cord Blood Bank only collect cord blood and tissue in certain hospitals?

The NHS Cord Blood Bank is funded entirely by the Department of Health and funding constraints mean we are only able to collect at a few hospitals in and around London. These have been chosen to have a high birth rate and a diverse population. London has the highest incidence of Black and Minority Ethnic communities in the UK and, having the collection centres close together in one city reduces the infrastructure costs.

Will my cord blood or tissue be used for research?

We endeavour to store every cord blood donation to the NHS Cord Blood Bank for clinical use. However, donations will frequently, through no fault of your own, not meet the very high specifications required to ensure it is suitable for transplantation or use in a clinical trial. If this is the case and you have given specific consent for research, the donation may be used for ethically approved research purposes instead and consequently will not be wasted. Provision of cord blood, cord or placental tissue for research is governed by our approvals under the National Research Ethics Committee to protect your safety, rights, wellbeing and dignity.

Traditionally patients requiring a transplant to treat blood diseases such as leukaemia have been treated using bone marrow cells from a relative or a nonrelated donor. Research has revealed that the stem cells found in cord blood can be just as effective in treating these patients as bone marrow stem cells. Research is now being carried out to see how and why these cells are so effective, how to improve their effectiveness and the range of potential treatments for which they may be suitable.

Other research being done includes studies on the way different types of cells are made or work in the body. This research can lead to better prevention or treatment of diseases such as blood diseases, cancer, and heart disease. This work may involve growing cells in the laboratory for prolonged periods of time as so-called cell lines and may involve the storage and testing of DNA. It is possible animals could be used in this research. Tests may be done on other components of your donated cells, tissue or blood. All research will always be done on an anonymised basis.

It is also possible NHS Cord Blood Bank could provide your research donations to private/commercial companies in the UK or abroad. We also recover the cost of collecting and supplying these materials that you have so kindly donated for research, to these companies.

Cord blood or tissue will under no circumstances be released for use in cosmetics safety or related testing, nor other consumer (non-biomedical) product related research.

Why is my cord tissue needed?

Your cord tissue is a valuable source of Mesenchymal Stromal/Stem Cells (MSC)! These are an amazing kind of cell that can differentiate into a variety of cell types, including osteoblasts (bone cells), chondrocytes (cartilage cells), myocytes (muscle cells) and adipocytes (fat cells which give rise to marrow adipose tissue). These cells also can have a profound effect on the immune system. NHSBT, many companies and researchers are trying to produce new novel therapies by perfecting the growing of MSCs in laboratories

to get enough of them in a pure form to use in clinical trials. If researchers can use your donated cord tissue to grow enough Mesenchymal Cells we can use them to treat many diseases. For example, we may be able to use MSCs as a cell therapy for primary sclerosing cholangitis (PSC), a liver disease for which there is currently no treatment. Like most liver diseases, PSC involves inflammation that leads to liver damage. In the absence of effective treatment, damage from the disease means that patients often need liver transplants. It is believed MSCs could be a better treatment by dampening down the immune response that is at the root of the problem in PSC.

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For further information, queries or complaints, contact the NHS Cord Blood Bank as detailed below.

NHS Cord Blood Bank is part of NHS Blood and Transplant, a special health authority within the NHS.

Freephone 0800 783 5870 E-mail: cordblood.donation@nhsbt.nhs.uk

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Appendix 16

Focus Groups with Midwives and Interviews with Cord Blood Collectors

Objective

- Hear their views
- How the programme is working for them
- Advice for other collectors/midwives

General information to provide at the start of the interview/focus group

- Timescale; no more than one hour
- Right to withdraw consent
- Confidentiality, recorded securely then anonymised at point of transcript
- Feedback available once research is completed

Questions

1. How has your week at work been so far?
2. Why do you think we do this?
3. What has been your experience of the process, at which points have you been involved?
4. What are your feelings about it?
5. Do you think that had any effect on the process?
6. Have you found any language barriers?
7. What are your thoughts on private banking?
8. What advice would you give to a new collector?
9. What advice would you give to the collectors/midwives?
10. Have I asked you the right questions to understand your thoughts, experience?
11. I'm going to xxxxxx next, have you got any advice or questions for them?

Appendix 17

Official journal of the CORD BLOOD ASSOCIATION

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CORD BLOOD BANK MANAGEMENT, ADMINISTRATION, AND SUSTAINABILITY

018

Demonstrating Equity of Access from the National Health Service Cord Blood Bank

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ABSTRACT 17

Introduction

The National Health Service (NHS) Cord Bank was established in 1996 to build an inventory of altruistically donated cord blood units to provide equity of access to all patients eligible for a stem cell transplant. Fixed cord blood collection sites were selected in areas of high black and minority ethnic (BAME) populations, and a performance indicator was set to routinely bank 40%–50% of cord blood units from BAME donors.

Objectives

The primary aim of this study was to bank at least 40% of donations from BAME donors at each of the six collection sites. To analyze the total nucleated cell count (TNC) of banked BAME donations. The study also aimed to monitor the provision of cord blood transplants to BAME patients.

Methods

Data are input to National Health Service - Blood and Transplant-specific software from the point of collection through banking to transplantation to ensure a robust audit trail. This data was extracted using a database query and analyzed for both banked cord blood units and for cord units provided for transplant. Data relating to the self-reported donor ethnicity and collection site were extracted and analyzed as a proportion of the whole bank, as a contribution of BAME donors from each collection site, and to ascertain the proportion of BAME donations with a high TNC.

Results

Banking of at least 40% BAME donations was routinely met. Representation from all groups listed on our donor screen was demonstrated in the collected and banked cord donations. Non-BAME donations comprise the greater proportion of high TNC cord units. Provision of cord blood transplants to BAME patients comprises at least 50% of all transplants provided by the NHS cord blood bank.

Discussion

The initial strategy to select collection sites in areas of high BAME birth rates has been successful in building an inventory with a high proportion of BAME donations. The value of this has been borne out by the provision of cord transplants to more than 50% BAME patients. Further work to understand any link between the volume and TNC of collected cord blood with ethnicity and subsequently to improve the efficiency of collections from BAME donations is needed to improve the suitability for transplant of an HLA matched cord. Further work to establish the number of patients unable to find a suitably matched stem cell transplant with sufficient cell dose is being undertaken.

Appendix 18

Demonstrating Equity of Access in the NHS Cord Blood Bank

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NHS Cord Blood Bank, *University of the West of England

Introduction

The NHS Cord Bank was established in 1996 to build an inventory of altruistically donated cord blood units to provide equity of access to all patients eligible for a stem cell transplant. When cord banks were established the likelihood of finding an adult bone marrow donor was lower for patients of black and other minority ethnic (BAME) background than for a Caucasian patient[1]. At the point of collection, the ethnic background reported by the donor is the only parameter available to provide an indication of HLA diversity, prior to HLA typing being completed.

Fixed cord blood collection sites were selected in areas of high black and minority ethnic (BAME) populations, and a performance indicator was set to routinely bank 40%–50% of cord blood units from BAME donors.

One of the primary selection factors for a cord transplant is the total nucleated cell count, yet within BAME cord donations it has been reported that the total nucleated cell count is typically lower than Caucasian cord donations[2]. As cord banks strive to bank cord donations with the highest cell counts it is important to monitor and maintain banking of BAME cord donations.

Methods and Objectives

The objectives of this study were:

i) to assess the composition of the total bank by donor reported ethnicity.
ii) to assess the composition according to total nucleated cell count.
iii) to monitor the provision of cord blood transplants to BAME patients.

Data are input to secure NHSBT-specific software from the point of collection through banking to transplantation to ensure a robust audit trail. This data was extracted using a database query and analysed for both banked cord blood units and for cord units provided for transplant. Data relating to the self-reported donor ethnicity and collection site were extracted and analysed as a proportion of the whole bank (Fig 1) and as a proportion of the bank where the total nucleated cell count was above (Fig 2.) or below (Fig 3.) $90x10^7$.

Cord transplant provision was analysed by recipient ethnicity (Fig 4.) for all transplants provided by the NHS Cord Bank from 1998 to 2017.

Results

As an overall proportion of the cord bank, banking of at least 40% BAME donations was routinely met. Representation from all groups listed on our donor screen was demonstrated in the collected and banked cord donations.

For banked cord donations with a TNC less than $90x10^7$, 48% were from BAME donations compared to 39% of banked cord donations with a TNC greater than $90x10^7$. Non-BAME (Caucasian) donations contributed 61% of donations where the TNC is greater than $90x10^7$ and 52% where the TNC is less than $90x10^7$.

Provision of cord blood transplants to patients from BAME donors comprises 40% of all transplants provided by the NHS cord blood bank. The average post process TNC provided for BAME patients was $150.9x10^7$ and for non-BAME (Caucasian) patients the average TNC provided was $179.1x10^7$ (Table 1).

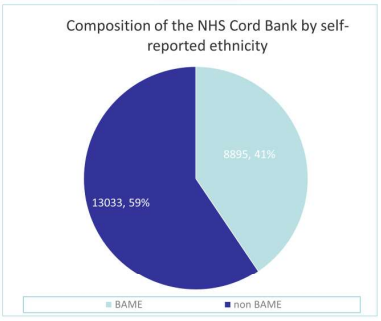

Fig 1. Composition of the NHS Cord Bank by donor reported ethnicity, total bank size across all categories of total nucleated cell (TNC) count

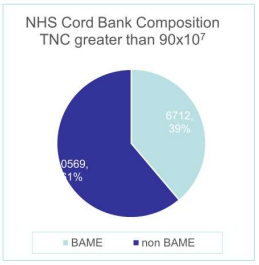

Fig 2. Composition of the cord bank for cords with a total nucleated cell count greater than $90x10^7$

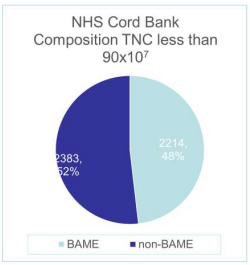

Fig 3.Composition of the cord bank for cords with a total nucleated cell count greater than $90x10^7$

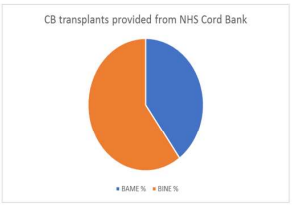

Fig 4. Cord transplants provided by donor ethnicity

Cord transplant recipient	Average post process TNC x10^7 provided
BAME	150.9
non-BAME	179.1

Table 1. Post process TNC x 10^7 provided to BAME and non-BAME recipients (patients).

Discussion

The initial strategy to select collection sites in areas of high BAME birth rates has been successful in building an inventory with a high proportion of BAME donations. The value of this has been borne out by the provision of cord transplants to BAME patients. Further work to understand links between the volume and TNC of collected cord blood with ethnicity and subsequently to improve the efficiency of collections from BAME donations is needed to improve the suitability for transplant of an HLA matched cord. This will be considered alongside the requirement to continually improve the quality of cord banks, where total nucleated cell count is used as a measure of quality. Further work to establish the number of patients unable to find a suitably matched stem cell transplant with sufficient cell dose is being undertaken.

References

1.J Pidala *et al* Race/ethnicity affects the probability of finding an HLA-A, -B, -C and -DRB1 allele-matched unrelated donor and likelihood of subsequent transplant utilization. *Bone Marrow Transplantation*, 2012

2. Akyurekli C *et al*, Impact of ethnicity on human umbilical cord blood banking: a systematic review. Transfusion. 2014 Aug;54(8):2122-7

No relationships to disclose

Appendix 19