

# **Related Haematopoietic Progenitor Cell Donor Care: The Influence of Current Guidance, and Pathways to Improvement**

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College London (UCL), for the Degree of Doctor of  
Medicine (Research)

## Authorship declaration

I, Chloe Anthias, confirm that the work presented in this thesis is my own. Where information has been derived from other sources, I confirm that this has been indicated in the thesis.

Signature

Dr Chloe Anthias

25<sup>th</sup> August 2016

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## ABSTRACT

Historically, relatively little regulation has been in place to safeguard the health and well-being of related HPC donors (RDs), and retrospective studies have suggested an increased incidence of adverse events in comparison to unrelated donors. Although in recent years, FACT-JACIE Standards have introduced specific requirements aiming to address this gap, accreditation is not mandatory in many countries, and the influence of such changes has never been evaluated.

This thesis provides insight into current procedures for managing RDs in transplant centres internationally, examines the impact of regulatory guidance to date, and explores potential pathways to improvement.

Studies in this thesis provide a detailed analysis of RD care pathways in the USA and Europe, and I am able to clearly demonstrate the potential for regulation to drive change in this field. Improvements are shown over time in aspects of care that have been addressed by regulatory standards, and management of RDs in accredited centres is shown to be more consistent with accepted best practice than that in non-accredited centres. These studies also reveal heterogeneity in donor care at each stage of the pathway with the result that RDs who would be deemed suitable by some transplant centres would be deferred by others.

In an effort to align care standards for RDs, I assessed the feasibility of alternative care pathways and showed considerable logistical and financial difficulties for care models where the entire RD pathway is managed outside the transplant centre setting. However I was able to establish a model of RD follow-up by an unrelated donor registry, which was evaluated through a successful pilot study.

After I demonstrated enthusiasm for clear guidelines and medical criteria in related donor care, I led the development of national RD care guidelines and including an online tool for comprehensive RD medical suitability criteria.

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## MANUSCRIPTS PUBLISHED

Anthias C. et al. The impact of improved JACIE standards on the care of related BM and PBSC donors. (2014). *Bone Marrow Transplantation* 50(2), 244–247.

Anthias C. et al. Related hematopoietic cell donor care: is there a role for unrelated donor registries? (2015).. *Bone Marrow Transplantation* 50(5), 637–641.

Anthias C et al. Significant improvements in the practice patterns of adult related donor care in US transplantation centers. (2015). *Biology of Blood and Marrow Transplantation* doi: 10.1016/j.bbmt.2015.11.008

Anthias C et al. EBMT transplant centers with FACT-JACIE accreditation have significantly better compliance with related donor care standards. (2015) *Biology of Blood and Marrow Transplantation*, 1–26. doi: 10.1016/j.bbmt.2015.11.009

Anthias C. et al. Harvests from bone marrow donors who weigh less than their recipients are associated with a significantly increased probability of a suboptimal harvest yield. (2016) *Transfusion*. doi: 10.1111/trf.13509

## MANUSCRIPTS SUBMITTED OR IN PREPARATION

Anthias C. et al. Variations in practice in UK transplant centres: results of a related donor care survey. Submitted to *Bone Marrow Transplantation*, March 2016.

Anthias C et al. Management of Related Haematopoietic Progenitor Cell donors. Guidelines from the British Committee for Standards in Haematology and the BSBMT. In pre-submission consultation.

## PRESENTATIONS

### INVITED TALKS

*February 2016, TANDEM Annual Meeting, Honolulu*

Improving practice patterns in adult related donor care

*November 2015, NMDP Council Meeting, Minneapolis*

Looking after the family: How can we improve adult related donor care pathways?

*November 2014, Scottish National Apheresis Education Meeting, Glasgow*

Related donor care: How can we improve current variations in practice?

### ORAL ABSTRACT PRESENTATIONS

*November 2014, World Marrow Donor Association Fall Meeting, Minneapolis*

**Anthias C** et al. Factors influencing the yield from bone marrow harvests

*April 2014, EBMT Annual Meeting, Milan*

**Anthias C** et al. Related HPC donor safety and management has been enhanced by adherence to improved JACIE Standards

### POSTER PRESENTATIONS

*April 2015, EBMT Annual Meeting, Istanbul*

**Anthias C.** et al, Significant improvements in the practice patterns of related donor care in US transplant centers

*April 2015, EBMT Annual Meeting, Istanbul*

**Anthias C.** et al, JACIE accreditation significantly improves compliance with international recommendations for related donor care in EBMT transplant centers

*December 2014, American Society of Haematology (ASH) Annual Meeting, San Francisco*

**Anthias C.** et al, Longer procedure duration and large volume harvests reduce the likelihood of achieving requested cell dose from unrelated bone marrow donors.

*May 2014, International Donor Registry Conference (IDRC), London*

**Anthias C.** et al. Impact of JACIE standards on related HPC donor care

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## GLOSSARY

Term	Definition
Adverse event	Any unintended or unfavorable sign, symptom, abnormality, or condition temporally associated with an intervention that may or may not have a causal relationship with the intervention, medical treatment, or procedure. An adverse reaction is a type of adverse event.
Adverse reaction	A noxious and unintended response suspected or demonstrated to be caused by the collection or infusion of a cellular therapy product or by the product itself.
Anthony Nolan	A UK charity that is the largest unrelated HPC donor registry in the UK, and carries out research in the field of HPC transplantation.
Apheresis	A procedure using a cell separator to separate the blood of a donor into its component parts, the desired component is removed, and the remaining components are returned to the donor.
BM	Bone marrow
BSBMT	The British Society of Blood and Marrow Transplantation.
CD34	A cell surface glycoprotein, expressed by 1-2% of normal bone marrow mononuclear cells, that is defined by a specific monoclonal antibody (anti-CD34) using the standardised cluster of differentiation (CD) terminology.
Centre for International Blood and Marrow Transplant Research (CIBMTR)	This organisation is a research collaboration between the National Marrow Donor Program and the Medical College of Wisconsin that facilitates observational and interventional research in the field of blood and marrow transplantation.
Collection centre	A facility affiliated with an unrelated donor registry, equipped to carry out collection of haematopoietic progenitor cells, In most cases, the same centre will be responsible for medical assessment of donors to determine suitability to donate.
Conditioning	The administration of chemotherapy, radiotherapy or immunotherapy to modulate the recipient haematopoietic system prior to haematopoietic progenitor cell infusion to allow engraftment +/- to control disease in the recipient.
Cord blood unit	Cord blood, which is rich in HPCs can be collected from placental and umbilical cord blood vessels after the umbilical cord has been clamped. Cord blood units are then cryopreserved and stored in a cord blood bank.

Donor	A person who is the source of cells organs or tissue for a transplant or transfusion of a cellular therapy product. For the purpose of this thesis, a donor is an individual providing haematopoietic progenitor cells or lymphocytes for allogeneic transplantation.
Donor advocate	An individual distinct from the recipient's main physician whose obligation is to protect the interests, well-being, and safety of the donor. The donor advocate may help the donor to understand the procedures, and the potential risks and benefits of donation.
Donor lymphocyte infusion	The process of giving lymphocytes, to a recipient who has already received an allogeneic hematopoietic progenitor cell transplant from the same donor. Typical indications for DLI include correction of mixed chimerism, or treatment/prevention of relapse. Lymphocytes may be stored from the original donation, or collected during a subsequent apheresis procedure.
EBMT	The European Group for Blood and Marrow Transplantation.
Europdonor	The unrelated HPC donor registry in the Netherlands.
Foundation for the Accreditation of Cellular Therapy (FACT)	An organisation founded by the ISCT and the American Society of Blood and Marrow Transplantation (ASBMT) to provide inspection and accreditation in the field of cellular therapy. FACT produces international standards in the field, in collaboration with JACIE.
Granulocyte colony stimulating factor (GCSF)	A haematopoietic cytokine glycoprotein which regulates production, differentiation and functional activation of neutrophils. GCSF can be administered at higher pharmacological doses to stimulate production of HPCs and their subsequent release into the circulation.
Graft versus host disease (GvHD)	A reaction that occurs when cells from the transplanted donor immune system recognise the genetically disparate host tissues as foreign and mount a response against them.
Haematopoietic progenitor cell (HPC)	A multipotent cell capable of self-renewal and of differentiation into any of the hematopoietic lineages.
Haploidentical donor	A related donor who shares a single HLA haplotype with the intended recipient.
Haplo-identical donor	An HPC donor who matches the intended recipient at a single haplotype. Since haplotypes are inherited in a mendelian fashion, individuals will inherit one haplotype from each of their parents. Thus any parents or offspring of an individual will be potential haploidentical donors, and any siblings have a 50% chance of being haploidentical.
HLA	The system that encodes the cell surface proteins that are responsible for recognition of 'self'.
HPC mobilisation	The process of administering GCSF (or an alternative mobilisation agent) to stimulate production of excess HPCs and their release into the peripheral circulation.

HPC transplantation	Haematopoietic progenitor cell transplantation, which comprises transplantation of the recipients own HPCs (autograft) or donor HPCs (allograft). Allogeneic transplantation includes the use of an HLA matched or mismatched family donor, a volunteer unrelated donor or an umbilical cord blood unit
Human Tissue Authority (HTA)	The competent authority responsible for regulation of human cells, tissues and organs in the UK.
ISCT	International Society for Cellular Therapy
Joint Accreditation Committee of ISCT-EBMT (JACIE)	A collaborative global organisation which provides inspection-based accreditation in HPC transplantation against established international standards. The standards are produced in collaboration with FACT.
National Marrow Donor Program (NMDP)	The largest unrelated HPC donor registry in the United States of America.
Peripheral blood stem cells (PBSC)	Haematopoietic progenitor cells that have been mobilised into the peripheral circulation and collected by apheresis.
Related donor (RD)	A tissue donor who is a blood relative of the transplant recipient. For the purposes of this thesis this term refers to a related HPC donor unless otherwise specified.
Swiss Blood Stem Cells (SBSC)	The unrelated donor registry in Switzerland.
Transplant centre	A unit (usually within a hospital) capable of carrying out haematopoietic stem cell transplantation. For the purposes of this thesis, this term refers to centres that carry out allogeneic HPC transplantation.
HLA Typing	The process of establishing the HLA phenotype, for the purpose of determining a match for allogeneic transplantation
Verification Typing	HLA typing performed on a second independent sample from a patient or donor to confirm identity and verify concordance with the initial HLA typing result.
Volunteer Unrelated Donor	A haematopoietic progenitor cell donor who is not related to the intended transplant recipient and has been identified through an unrelated donor registry.
The World Marrow Donor Association (WMDA)	A global organisation providing accreditation for unrelated donor registries and a forum for global collaboration to improve the care of haematopoietic progenitor cell donors.
Worldwide Network for Blood & Marrow Transplantation (WBMT)	An international organisation aiming to promote excellence in HPC donation, transplantation and cellular therapy. WBMT undertakes global activity surveys and develops consensus guidelines in the field.

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## THESIS AIMS

### PRIMARY AIMS

To provide an in-depth analysis of current practice patterns in related donor care, in the UK and worldwide, focusing in particular on the influence of regulatory standards and consensus recommendations in the field.

To explore alternative models of related donor care and test the acceptability to transplant teams, the logistics and financial impact, and the acceptability to donors.

### SECONDARY AIMS

To investigate the influence of donor characteristics on the safety and efficacy of HPC donation in the related donor setting.

To explore the experience of related donors and to determine areas in which current care pathways could be improved.

To use the results of the studies in this thesis as a basis for development of national peer-reviewed guidelines for the management of related HPC donors.

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## THESIS OVERVIEW

Chapter 1 provides an overview of current knowledge regarding related donor care pathways. The factors known to influence the safety of HPC donation are described and the legislation and guidance in this field is discussed.

Chapter 2 describes the methodology behind the studies described in chapters 3,4 5, 6 and 7.

Chapter 3 details the findings of a study of 207 RDs who donated in a single centre between 2004 and 2013, and examines the impact of changes to regulatory guidance during this time period on the management of these donors. The influence of donor characteristics on the incidence of SARs is also described.

Chapter 4 provides a detailed analysis of related donor care in UK transplant centres, with a survey that examines compliance with FACT-JACIE Standards and consensus recommendations. The views of UK transplant physicians regarding current care pathways and potential initiatives for improvement are also discussed.

Chapter 5 builds on the findings of Chapter 4 describing a study that provides an international perspective on related donor care. Comparison with an earlier study in the USA allows interpretation of the influence of regulatory changes in that region, while in Europe differences between care in accredited and non-accredited centres are examined.

Chapter 6 provides an analysis of the feasibility of alternative pathways of RD care, where aspects of the care pathway are provided by an organisation other than the recipient's transplant centre.

Chapter 7 reports a retrospective study of 53 related donors, examining donor experience in the setting of a transplant centre where FACT-JACIE Standards and international recommendations have been adopted.

Chapter 8 describes the development of national guidelines for related donor management, based on the results of the studies outlined in earlier chapters of this thesis.

Chapter 9 summarises the findings of this thesis and describes some of challenges encountered, and future plans to expand on this work.

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## CHAPTER 1. BACKGROUND

### 1.1 INTRODUCTION

#### 1.1.1 HISTORY OF HAEMATOPOIETIC PROGENITOR CELL TRANSPLANTATION

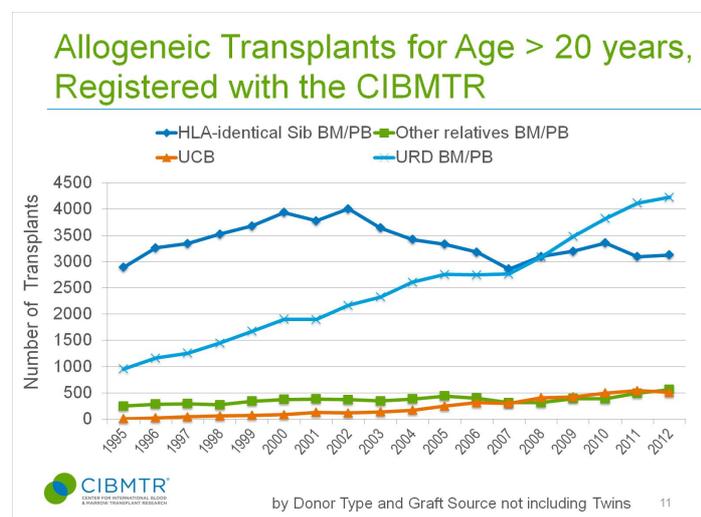
Allogeneic haematopoietic progenitor cell (HPC) transplants in humans were first successfully reported in 1957 by Thomas *et al* who treated leukaemic patients with lethal doses of chemotherapy or irradiation followed by an infusion of bone marrow (BM) (Thomas *et al*, 1957). At this early time, the only successful transplants were seen in recipients of BM from an identical twin donor, and were followed by a brief remission period before patients succumbed to their original disease (Copelan, 2006; Thomas *et al*, 1959). Subsequent discovery and characterisation of antibodies reacting with antigens on the cell surface of leukocytes led to the understanding of the importance of matching donors and recipients at specific HLA loci in HPC transplantation (Dausset, 1958). Development of early serological typing techniques in the 1960s enabled identification of matched sibling donor-recipient pairs, which resulted, for the first time, in prolonged successful engraftment and remission in patients receiving HCTs for aplastic anaemia and advanced leukaemia (Buckner *et al*, 1970).

The 1970s saw HPC transplantation become established as a treatment option for previously incurable patients with matched sibling donors, and rapidly led to efforts to increase knowledge around HLA, and to improve serological typing techniques. These efforts resulted in the first successful unrelated donor transplant in 1973, (Copelan, 2006; O'Reilly *et al*, 1977), and to the set up of the first unrelated donor stem cell registries shortly afterwards (Cleaver, 1993).

To meet the needs of the two thirds of patients with such diseases who lack a matched sibling donor, unrelated donor registers have rapidly expanded, and there are now over

25 million unrelated donors listed internationally (source [www.bmdw.org](http://www.bmdw.org), accessed 14<sup>th</sup> October 2015). Despite this, there remain patients for whom an acceptable unrelated donor cannot be found, and thus over the last 20 years investigators have explored the use of alternative donor stem cell sources. Following successful results from HPC transplants using umbilical cord blood, cord blood banks were established worldwide. However, despite several advantages of this cell source, the use of cord blood has been limited by expense and relatively low HPC doses. More recently, attention has turned to the use of mismatched related donors. Since HLA haplotypes are inherited in a medelian fashion, only one in four siblings will match both haplotypes, but one in two will be haploidentical (sharing a single haplotype), as will both an individual's parents, and any offspring. Advances in outcomes for recipients of haplo-identical transplants have been greeted with much enthusiasm, and some countries have seen a rapid rise in utilisation of this donor source.

Figure 1.1 Trends in donor source for recipients of Allogeneic HPC transplant aged >20 years in the USA. CIBMTR summary slides (Pasquini & Zhu)



While the above progress has changed the landscape of transplantation dramatically and has led to a continued rise in the number of patients receiving an allogeneic HPC transplant, a matched sibling remains the ideal donor for most patients.

### 1.1.2 PATIENT ACCESS TO ALLOGENEIC HPC TRANSPLANTATION

In addition to the increase in available donors, another major reason for the continued increase in patients undergoing allogeneic HPC transplantation lies in the development of reduced intensity transplant conditioning regimens. In the initial years of HPC transplantation, it was believed that engraftment of a donor haematopoietic system could only occur if that of the recipient had been completely ablated. Since myeloablation requires the use of very high doses of irradiation or chemotherapy conditioning prior to stem cell infusion, the associated toxicity precluded this treatment in older or less fit patients. The subsequent discovery that engraftment was possible, providing sufficient immunosuppressive therapy was administered without the need for complete myeloablation, led to development of less toxic conditioning regimens, opening up transplant as an option for older patients and those with comorbidities. Accordingly, many transplant centres will now accept patients into their early 70s for this procedure, providing they are otherwise fit, which has resulted in a parallel increase in the age of HLA-matched siblings undergoing donation.

### 1.1.3 PRINCIPLES OF HPC TRANSPLANTATION

For patients receiving an allogeneic HPC transplant for non-malignant haematological disease the purpose of this treatment is to replace a non-functioning haematopoietic system with a healthy system. In these patients, the aim of the pre-transplant conditioning is purely to allow sustained engraftment of the donor stem cells, and, since there is no advantage to a genetic disparity between the donor and recipient, the HLA match should ideally be as close as possible.

For patients receiving HPC transplantation for malignant disease, this treatment serves two functions. Firstly, it allows delivery of very high intensity anti-tumour chemo/radiotherapy, which would be lethal if not followed by a stem cell infusion. Secondly, the engraftment of a genetically disparate donor haematopoietic system confers a graft-versus-tumour effect which is crucial in maintaining disease remission in

these high-risk patients. For patients receiving reduced intensity conditioned transplants, this latter effect provides the majority of the treatment efficacy.

When it became apparent in the early 1990s that the graft-versus-tumour effect is mediated by T cells, researchers investigated methods of enhancing this effect using therapeutic lymphocyte infusions. These were initially used as treatment for patients with relapsed disease, and more recently, for patients where evidence of recipient haematopoiesis remains after reduced intensity transplants. Donor lymphocytes infusions are now administered to almost 10% of patients receiving reduced intensity transplants, and consequently the number of donors undergoing more than one donation procedure is increasing.

#### 1.1.4 COMPLICATIONS OF HPC TRANSPLANTATION

Despite the multitude of advances in transplantation over the last 30 years, the long-term overall survival of adults transplanted for malignancy is still as low as approximately 50%. Outcomes in children and patients with non-malignant disease are somewhat better, but all patients remain at risk of a number of severe complications with the potential for long-term morbidity.

##### *1.1.4.1 Disease relapse*

Relapse of primary disease remains the major cause of treatment failure. In selected patients, further treatment aiming to enhance the graft-versus-tumour effect can be successfully initiated.

##### *1.1.4.2 Graft-versus-host-disease*

Graft-versus-host disease (GvHD) occurs when donor-derived T cells initiate immune responses against unshared recipient tissue antigens. The risk of GvHD is thus dependent on genetic disparity between the donor and recipient, and is greatest in

recipients of HLA mismatched transplants. GvHD can be classified according to National Institute of Health (NIH) criteria depending on distinct clinical features and the timing of onset. In brief, GvHD is a multisystem disease which can occur at any time post transplant and has a clinical picture, ranging from mild symptoms requiring no treatment, to severe disease requiring multiple immunosuppressive agents and causing severe morbidity or mortality.

#### *1.1.4.3 Infectious complications*

All recipients of HPC transplants will develop profound immune suppression as a result of the conditioning treatment and GvHD prophylaxis. Immune reconstitution occurs over a period of a year or more and is further delayed in patients with chronic GvHD. During this time patients remain at risk of infection from a wide range of organisms including bacteria, fungi, and viruses.

#### *1.1.4.4 Organ toxicity and late effects*

Many patients will have already undergone intensive treatment for their primary disease before reaching the point of HPC transplantation. The cumulative effects of this previous treatment, the pre-transplant conditioning and post-transplant complications can lead to long-term organ dysfunction and also confers an increased risk of secondary malignancies.

### **1.1.5 FACTORS KNOWN TO INFLUENCE TRANSPLANT OUTCOME**

The incidence of the complications described above is, to an extent, dependent on several known patient and donor factors.

#### *1.1.5.1 Patient factors*

##### *1.1.5.1.1 Disease*

The nature of the primary disease and, for malignant disease, its inherent susceptibility to the graft-versus-tumour effect, is arguably the most important factor in determining

transplant outcome. Several groups have been able to show stepwise reduction in overall survival following allogeneic transplantation in recipients with good risk, intermediate risk and poor risk markers of disease (Cornelissen *et al*, 2007; Koreth *et al*, 2009)

#### *1.1.5.1.2 Comorbidities*

Although the advent of reduced intensity conditioning has expanded the pool of patients that can undergo this therapy, outcomes for patients with pre-existing medical issues, or organ dysfunction acquired during primary treatment for their disease, are nevertheless inferior to those of fitter patients. Research in this area has led to development of a specific co-morbidity index for patients undergoing HPC transplantation to aid clinician decision-making regarding the relative risks and benefits of this procedure and to allow adjustment for this risk factor in transplant trials.

#### *1.1.5.2 Donor factors*

##### *1.1.5.2.1 HLA matching*

HLA matching is the most important determinant of transplant outcome with higher rates of GvHD seen in UD versus matched sibling transplant and in mismatched (<10/10) versus matched (10/10) unrelated donor transplants (Shaw, 2008; Lee *et al*, 2007).

##### *1.1.5.2.2 Cytomegalovirus (CMV)*

CMV serostatus is the second most important donor factor, with recipients of a graft from a CMV matched donor demonstrating significantly more favourable outcomes than those who are CMV mismatched (Ljungman *et al*, 2014).

##### *1.1.5.2.3 Donor age*

In the unrelated donor context a survival advantage has been shown for recipients of HPC transplants from younger donors (<30 years) (Bertani *et al*, 2014; Kollman *et al*,

2001). This finding has led to debate regarding the optimal donor for a patient with an elderly HLA matched sibling; whether the sibling or a well matched young unrelated donor should be used (Ringdén *et al*, 2014).

## 1.2 COLLECTION OF HPCs AND THE RELATED DONOR PATHWAY

### 1.2.1 COLLECTION OF HPCs

#### 1.2.1.1 Bone marrow

As described, the earliest stem cell transplants were all conducted using BM as the cell source. The procedure for harvesting BM involves extraction of marrow directly from bilateral posterior iliac crests under general anaesthetic. To avoid haemodilution of the product, operators must make multiple small volume aspirations, re-siting the harvest needle between each one (Bacigalupo *et al*, 1992; Batinić *et al*, 1990). Some centres perform a midway cell count to ensure marrow quality and to guide the required harvest volume (Wang *et al*, 2011), however generally no more than 20mls/kg donor weight is harvested, to prevent anaemia. It is usually possible to complete this procedure within 30-45 minutes and, depending on centre practice, BM donors are either discharged the same or the following day. The harvested marrow is heparinised and filtered before being infused to the patient. Achievement of a harvest containing a high concentration of HPCs requires considerable operator expertise and there are concerns that centre experience is diminishing (Remberger *et al*, 2015) over time.

#### 1.2.1.2 Peripheral blood stem cells

While BM is rich in the HPCs required for transplantation, these cells are present in low concentration in the peripheral blood. In order to collect HPCs from the peripheral blood a two-stage process is necessary. Firstly HPCs are ‘mobilised’ using granulocyte colony stimulating factor (G-CSF) injections for 4-5 days, and then collected from the peripheral blood using leukapheresis. This procedure entails connecting the donor to a

cell separator using bilateral peripheral cannulae, or a central venous catheter (CVC) for the small minority with inadequate venous access. Blood from the donor is circulated through the apheresis circuit, and mononuclear cells are removed by centrifugation, and the remaining blood components are returned to the donor. The apheresis circuit is primed using ACD anticoagulant. This procedure typically takes approximately 4 hours. In 80-90% of healthy adult donors a single collection is necessary to collect adequate HPCs for an allogeneic transplant while the other 10-20% of donors will return the following day for a second collection.

### 1.2.2 MOBILISATION OF HPCs

GCSF is a haematopoietic cytokine glycoprotein, endogenously produced by monocytes, fibroblasts, and endothelial cells. Under normal circumstances GCSF regulates the production, differentiation, and functional activation of neutrophils. In the early 1990s two chemically different recombinant GCSFs lenograstim and filgrastim were launched, and are now routinely used in treatment of a variety of haematological conditions. When given at high pharmacological doses, GCSF stimulates the development of primitive HPCs, which are then released into the peripheral blood (Pamphilon *et al.*, 2008). The summary of product characteristics of lenograstim and filgrastim recommend doses of 10mcg/kg/day for mobilisation of allogeneic HPC donors for 4-5 days with leukapheresis on the fifth day. Once daily and split twice daily doses are both common administration schedules, although there is no convincing evidence of an improvement in yield using 5mcg/12hours versus 10mcg/24hours (Anderlini *et al.*, 2000; Martino *et al.*, 2015).

More recently, other mobilisation agents have been developed. Three biosimilar GCSFs are now approved for all the registered indications of their originator filgrastim, including stem cell mobilisation. Plerixafor, a CXCR4 antagonist, was developed to enhance HPC mobilisation in patients who failed autologous HPC collection using standard mobilisation procedures. Neither biosimilar GCSF nor plerixafor have been extensively studied in healthy donors and are not used by unrelated donor registries.

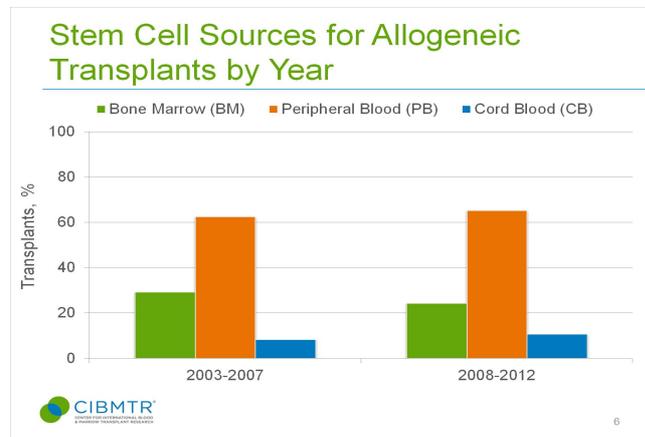
### 1.2.3 COLLECTION OF DONOR LYMPHOCYTES

Collection of lymphocytes for therapeutic T cell infusion is also performed using the leukapheresis procedure. Since adequate numbers of lymphocytes are present in the peripheral blood, no prior mobilisation is necessary and a single apheresis procedure suffices for multiple doses of therapeutic T cells.

### 1.2.4 TRENDS IN THE SOURCE OF HPCs

Over the last twenty years there has been a significant shift from BM to PBSC as the requested cell source in both related and unrelated donors (Passweg *et al*, 2013). Studies have consistently demonstrated faster hematopoietic recovery in recipients of PBSC (Anasetti *et al*, 2012; Bensinger *et al*, 2001) as well as lower rates of graft failure (Blaise *et al*, 2000; Pavletic *et al*, 1997; Champlin *et al*, 2000) due to an increased number of haematopoietic stem cells infused. HPC source also influences other transplant outcomes, with evidence of a reduced incidence of relapse in patients with advanced haematological malignancies using PBSC (Champlin *et al*, 2000). However, this occurs at the expense of higher rates of chronic GvHD than recipients of BM. Other groups have shown more favourable outcomes, including a survival advantage, in paediatric patients who receive BM rather than PBSC (Eapen *et al*, 2004). These effects have been attributed to a difference in product cell composition between the two sources, with PBSC containing a ten times greater number of T cells, monocytes and NK cells (Ottinger *et al*, 1996) than BM. For these reasons the preferred cell source varies between different patient groups.

Figure 1.2 Changes in source of HPCs between eras. CIBMTR summary slides (Pasquini & Zhu)



### 1.2.5 FACTORS INFLUENCING THE STEM CELL YIELD FROM HEALTHY DONORS

The total nucleated cell count (TNC) has traditionally been used to calculate the yield of bone marrow grafts and is still used for this purpose today. The TNC is divided by the patient's weight to give a TNC dose received per kilogram. Doses of  $3-5 \times 10^8$  TNC/kg recipient weight are generally considered optimal, while cell doses of  $< 2 \times 10^8$  are widely considered to be inadequate. Higher cell doses have been associated with faster neutrophil engraftment and improved graft function, as well as improved survival in some studies (Bittencourt *et al*, 2002; Spitzer *et al*, 1994; Barrett *et al*, 2000). The factors that have been shown to influence BM harvest yield are summarised in Table 1.1.

Table 1.1 Factors known to influence BM harvest yield

Factors	Effect	References
<b>Donor factors</b>		
Donor weight	Increase TNC yield and increased quality of harvest in some studies	(Kao <i>et al</i> , 2009; Wang <i>et al</i> , 2011)
Donor BMI	Higher BMI associated with higher CD34 yield	(Favre <i>et al</i> , 2003)
<b>Procedure factors</b>		
Aspiration techniques	Multiple small aspirations (<5mls) are superior to larger volume aspirations	(Spitzer <i>et al</i> , 1994; Bacigalupo <i>et al</i> , 1992; Batinić <i>et al</i> , 1990)
BM stimulation with GCSF	Improves TNC yield per kg donor weight	(Ji <i>et al</i> , 2002)
Operator expertise	Difference in quality between collection centres. Difference in quality between operators	(Remberger <i>et al</i> , 2015)
Harvest volume	Inversely associated with BM harvest quality	(Wang <i>et al</i> , 2011)

PBSC HPC calculations are always based on CD34+ cell dose. CD34 is a transmembrane glycoprotein that is expressed on undifferentiated haematopoietic progenitor cells but is lost as maturation occurs and therefore provides a robust measurement of the HPC content. Determination of the CD34 cell dose is performed using immunophenotyping. Typically,  $4 \times 10^6$ /kg recipient weight is considered optimal, although engraftment will usually occur with  $>1 \times 10^6$ /kg.

Table 1.2 Factors known to influence PBSC harvest yield

	Effect	References
<b>Donor factors</b>		
Female gender	Lower CD34 yield in some studies	(Martino <i>et al</i> , 2006; Billen <i>et al</i> , 2014; Fischer <i>et al</i> , 2005; Wang <i>et al</i> , 2013)
Donor weight	Higher weight associated with higher yield	(Ings <i>et al</i> , 2006; Billen <i>et al</i> , 2014)
Donor BMI	Higher BMI associated with higher yield in some but not all studies	(Favre <i>et al</i> , 2003)
Donor age	Lower CD34 yield in older donors	(Martino <i>et al</i> , 2006; la Rubia <i>et al</i> , 2001; Lysák <i>et al</i> , 2010; Rinaldi <i>et al</i> , 2012)
<b>Procedure factors</b>		
Once versus twice daily GCSF dosing	No difference in the majority of studies providing the same total daily dose used.	(Anderlini <i>et al</i> , 2000; Martino <i>et al</i> , 2015)
Filgrastim versus lenograstim	Higher in vitro efficacy with lenograstim in early studies. Subsequent studies suggest equal efficacy.	(Ings <i>et al</i> , 2006; Martino <i>et al</i> , 2006)

## 1.3 THE PATHWAY OF DONOR CARE

### 1.3.1 RELATED DONORS

Potential related donors are always identified by their sick relatives, who put them in touch with the healthcare worker(s) responsible for arranging tissue typing within the transplant centre or referring hospital. Due to the fact that most countries do not have a central organisation accountable for related donor management, this work has traditionally been undertaken by the same transplant centre caring for their intended recipient, and often by the same medical professionals.

After being identified as an HLA match, related donors undergo a formal donor medical evaluation, the aim of which is to identify any medical condition that might pose a risk to the donor during donation (medical suitability) and to identify any conditions that

might pose a risk to their intended recipient (medical eligibility). Typically this evaluation occurs within a few weeks of the planned donation, with consent for the procedure taken at the same appointment. Since transplant teams in many centres are limited to a small number of physicians, this has historically led to a physician frequently being simultaneously responsible for the care of a RD and their intended recipient.

RDs donate by apheresis or bone marrow at the transplant centre caring for their recipient and the harvested cells are infused fresh the day of or day following the donation.

This donor pathway has developed independently in each transplant centre with protocols largely determined at a local level. As a result, little is known about the process each donor undergoes and how this varies between centres nationally and internationally.

*Figure 1.3 The related donor care pathway*



### 1.3.2 UNRELATED DONORS

Volunteer unrelated donors are recruited to donor registries through a variety of methods, including national blood donation programmes, university organisations, patient appeals, and specific campaigns to improve registry diversity. At the point of recruitment, all donors are provided with information about the stem cell donation process, and are required to complete a health questionnaire and to provide a saliva or blood sample for HLA typing.

Potential donors will then be contacted, often many years later, when they have been identified as a possible match for a specific patient. At this point further information is provided to the donor, a detailed health questionnaire is completed, and, if the donor is considered fit and willing to proceed, a blood sample is arranged for verification typing. Once finally selected by a transplant centre, the unrelated donor then undergoes a formal evaluation in an affiliated collection centre of the donor registry by an experienced physician using defined medical suitability and eligibility criteria.

Donors who are deemed to be suitable undergo donation in the registry collection centre, and are subsequently followed up by the collection centre or registry. Any requests from the transplant centre for subsequent donations are formally reviewed by the registry.

At each stage of this process the donor is protected by anonymity, and procedures are in place to prevent coercion of the volunteer unrelated donor.

*Figure 1.4 The unrelated donor care pathway*



### 1.3.3 STUDIES EXAMINING RD CARE PATHWAYS

Although very few studies have specifically focused on procedures for RD care, three groups have drawn attention to differences between care pathways for related and unrelated donors. In particular these have concentrated on determining the degree of uniformity of care in the related donor context.

The first study investigating the pathway for management of RDs was conducted by the European Group for Blood and Marrow Transplantation (EBMT) Nurses Group/Late Effects working party (Clare *et al*, 2010). The study population consisted of 63 nurses, delegates at the 2005 EBMT annual meeting, who completed questionnaires regarding the counselling, consent and follow-up of RDs at their centres. Their results showed significant variation in several areas. They demonstrated variation in donor counselling procedures, with only 32% of centres stating that RDs were consented by a professional who was not involved in the care of their recipient, and also highlighted that the donor's HLA results would be first disclosed to their recipient in 11% of centres. In 48% of centres donors were provided with national or international written information regarding the donation procedure, while in the remaining centres only locally produced information was used. This information was relayed by a variety of methods, including written and face-to face communication in 36%, and verbal information alone in 27% centres. The authors identified a donor follow-up programme in 60% of responding centres, however the study did not examine the extent of this follow-up.

This study was useful in outlining the variation in procedures between centres, but had several limitations. Firstly, the survey population were self-selected, and were not a population who were necessarily best placed to answer questions about related donor care at their centre. Secondly, there was regional bias with 34% of respondents working in UK centres. Thirdly, although the scope of the survey was broad, and encompassed several stages of the RD care pathway, these areas were not studied in depth.

In 2007, a larger study of RD care examining US centre practice was conducted by the Donor Health and Safety Working Committee of the Center for International Blood and Marrow Transplant Research (CIBMTR) (O'Donnell *et al*, 2010). The authors invited all 222 directors of US transplant programs to participate in a survey which largely focused on determining whether practices protected donors from the potential for conflict of interest. They received 98 evaluable responses and reported that in >70% centres, the same physician caring for the donor had either simultaneous responsibility

for, or might be involved in the care of, the recipient, and that 5% of centres had no written criteria for related donors. This study drew attention to a major issue in the donor care pathway- the routine practice in many centres for donor and recipient care to overlap. As a direct result of this study, changes to FACT-JACIE standards were made, described in section 1.8.

A third study examining the pathway of related donor care was published by an Italian group (Coluccia *et al*, 2012). The authors retrospectively analysed the notes of 500 related donors undergoing PBSC collection in Italy between 2005 and 2009. They showed that the donor eligibility criteria, collections and follow-up were managed differently in each of the nine centres studied. They found that in 4/9 centres donors and recipients were managed by the same physician, and that only 26% of donors underwent thorough screening according to Italian Bone Marrow Donor Registry standards. They also described unsuitable pre-apheresis peripheral blood parameters in 39% of the apheresis procedures. This study added to the evidence for routine overlap of donor and recipient care and also raised the issue that related donors do not undergo the stringent screening procedures of UDs to ensure suitability.

## 1.4 THE SAFETY AND WELLBEING OF HPC DONORS

### 1.4.1 COMMON SIDE EFFECTS OF DONATION

Almost all BM and PBSC donors will report some side effects associated with donation. These side effects have been extremely well characterised in prospective studies of healthy unrelated donors.

#### 1.4.1.1 Bone marrow

Post-procedure collection site pain is the most commonly reported event in BM donors, and is experienced by over 80% of donors (Favre *et al*, 2003; Bredeson *et al*, 2004; Pulsipher *et al*, 2010). Fatigue is the second most common symptom in most studies and is reported by 50-80% donors. Approximately one third report throat pain related to anaesthesia and less commonly other post-anaesthesia symptoms such as headache

(Miller *et al*, 2008). Although over 50% of BM donors will have mild on-going side effects at one week post-donation, these subside quite rapidly, with >80% reporting full recovery at one month. A small percentage of donors (<1%) develop long-standing pain following bone marrow donation (Pulsipher *et al*, 2013; Nishimori *et al*, 2002).

#### 1.4.1.2 PBSC donation

The common short-term side effects of GCSF can be divided into those caused by GCSF and those due to the apheresis procedure.

The side effects of GCSF mobilisation are well documented in patients, unrelated and related stem cell donors. Bone pain is experienced by >90% of donors, which typically starts 24-48 hours following administration of GCSF and peaks on day five (the day of the first apheresis procedure). Over 50% of donors report this pain as mild and interventions other than simple analgesia are very rarely required (Miller *et al*, 2008; Hölig *et al*, 2009). 40-70% of donors experience fatigue at some point during mobilisation and collection, and myalgia and insomnia are both reported in approximately half of healthy donors. Less common symptoms include nausea and anorexia, which are reported by approximately a quarter of donors. In prospective studies using Common Terminology Criteria for Adverse Events (CTCAE) the majority of symptoms are reported as mild (grade 1) (Pulsipher *et al*, 2010; Hölig, 2013).

The most common side effects of the apheresis procedure are symptomatic hypocalcaemia, hypovolaemia and bruising, or nerve injury related to venepuncture (Pulsipher *et al*, 2009). Following completion of the harvest procedure, the side effects experienced by PBSC donors tend to resolve quickly with only 10% of donors complaining of on-going symptoms at 1 week post-donation. While the largest studies have been performed in unrelated donors, symptoms in related donors appear to be comparable (Rinaldi *et al*, 2012).

#### 1.4.1.3 Comparison of the PBSC and BM donation experience

In studies comparing experience of the two donation routes, the main difference is timing, with PBSC donors experiencing peak discomfort on day 5 (the day of the first harvest) compared to 1-2 days after collection for BM donors. PBSC donors reported a median time to recovery of 1 week compared to a median time to recovery of 3 weeks for BM donors. Overall, the latter report more days of restricted activity due to pain/fatigue (Pulsipher *et al*, 2013; Favre *et al*, 2003; Bredeson *et al*, 2004; Siddiq *et al*, 2009).

### 1.4.2 SERIOUS ADVERSE REACTIONS

Serious adverse reactions are defined as an unintended response, that is fatal, life threatening, disabling, incapacitating or which results in, or prolongs, hospitalisation or morbidity (FACT-JACIE, 2012). Due to the absence of mandatory adverse event reporting in related donors, the majority of evidence regarding rates of SARs is derived from studies in unrelated donors.

#### 1.4.2.1 SARs in BM donors

The serious risks of bone marrow donation include bone and soft tissue trauma at the site of aspiration, risks of anaesthesia, and hypovolaemia or anaemia following large volume aspiration. Recent reviews by the NMDP examining the incidence of SARs in normal adult donors suggest that these occur in 1-2% cases (Miller *et al*, 2008; Pulsipher *et al*, 2014).

#### 1.4.2.2 SARs in PBSC donors

Large prospective and retrospective studies estimate that SARs occur in 0.5-0.6% unrelated PBSC donors (Miller *et al*, 2008; Pulsipher *et al*, 2014; Halter *et al*, 2009). These include splenic rupture, cardiovascular complications, thrombotic events, anaphylaxis and events relating to CVC placement. GCSF may also unmask or

exacerbate autoimmune conditions (Parkkali *et al*, 1996; Nasilowska-Adamska *et al*, 2010).

#### 1.4.2.3 Fatal adverse events

Fatalities in one bone marrow and four PBSC donors within 30 days of donation were described in a retrospective EBMT study of 36,317 family donations between 1993 and 2005 (Halter *et al*, 2009). Causes included a pulmonary embolus, a subarachnoid haemorrhage in a donor on aspirin, and two deaths from cardiac arrests without further information. Additional fatalities reported have included a sickle crisis in a PBSC donor, and others due to respiratory or cardiac arrests (Horowitz & Confer, 2005). The above deaths exclusively occurred in related donors, and to date, one UD death has been reported to the WMDA, caused by a haemothorax secondary to traumatic subclavian line insertion.

### 1.4.3 LONG TERM CONSEQUENCES OF DONATION

Following theoretical concerns about short-term growth factor therapy leading to leukaemia in donors, several large studies have been performed comparing the incidence of malignancies in donors who have received GCSF with either bone marrow donors or age/sex matched populations. These studies have reported a reassuring lack of evidence for an increased incidence of haematological, malignant or other diseases (Pulsipher *et al*, 2014; Shaw *et al*, 2015; la Rubia *et al*, 2008; Hölig *et al*, 2009).

### 1.4.4 QUANTIFYING THE RISK OF DONATION IN RDS

Far fewer publications have investigated adverse events in related donors, than those examining unrelated donors, and those that have done so have used diverse criteria and have largely reported retrospectively. Existing data suggest that related donors have an increased risk of adverse events compared to unrelated donors; particularly

striking is the fact that fatal adverse events have almost exclusively occurred in the related donor setting.

Defining risk factors associated with adverse events in related donors is especially difficult, and the retrospective nature of most investigations has complicated assessment of the causal relationship between reported events and the donation procedure.

## 1.5 THE PSYCHOLOGICAL ASPECTS OF DONATING TO A RELATIVE

While few studies have specifically evaluated the physical adverse events associated with donation in the related donor context, even fewer have concentrated on psychological outcomes.

Studies in unrelated donors generally report positive psychological reactions, with donors reporting satisfaction and a greater sense of self-worth as a result of donation, although donors who experienced more side effects derived less psychological benefit (Butterworth *et al*, 1993).

While donation can also be a positive experience for related HPC donors, a significant proportion report some psychological difficulty with the donation process, particularly if their recipient dies or develops GvHD (Switzer *et al*, 1998; van Walraven *et al*, 2010a; Wolcott *et al*, 1986). One study in BM donors reported significantly higher scores on the Beck Depression Inventory (a self-reported measure of depression) in donors whose sibling died, compared to those whose siblings remained alive (Chang *et al*, 1998). Others have described guilt, a feeling of responsibility and on-going distress or anxiety regarding the recipient's health (Pillay *et al*, 2012). These negative psychological impacts of HPC donation may manifest years after donation (Switzer *et al*, 1998).

Investigations have universally shown very low ambivalence to donation, reporting that donors described donation as a 'natural choice' or one that required very little consideration (Christopher, 2000; Pillay *et al*, 2012). Despite this, there are suggestions that relatives nonetheless experience anxiety about the donation procedure, as well as about the outcome for the recipient. One study demonstrated a significant reduction in high anxiety levels immediately following donation (Fortanier *et al*, 2002).

The nature of the relationship with the transplant recipient appears to be an important factor in RD experience, with a better relationship resulting in fewer negative psychological sequelae (Labott & Pfammatter, 2014). Likewise, a more positive experience has been reported in the presence of good emotional support from family, friends and hospital staff (Pillay *et al.*, 2012).

Table 1.3 Studies examining the psychological consequences of donation.

Study population	Objectives	Results	Authors
28 adult sibling donors	The influence of the donor–recipient relationship on related donor reactions to stem cell donation	Donors reported very little ambivalence about donating. A better relationship with the recipient resulted in fewer negative emotional consequences if the recipient’s health declined.	(Labott & Pfammatt er, 2014)
44 adult sibling donors	The effects of bereavement on adult sibling bone marrow donors’ psychological well-being and reactions to donation.	High self-esteem and happiness in adult related donors pre-donation. Reduction in the feeling of having helped during the first year post-donation. Donors whose recipient had died ultimately reported higher self-esteem, happiness and satisfaction which authors suggested was due to continuing concern for medical issues of their sibling in those who were still alive.	(Switzer <i>et al</i> , 1998)
64 adult sibling donors	Comparison of anxiety and pain in sibling donors donation BM or PBSC	Levels of anxiety before the collection procedure were fairly high in both groups of donors. Levels of anxiety fell immediately following donation suggesting the major anxiety was around the procedure itself. In both groups of donors, the great majority of donors felt, after having completed the collection procedure, that it had been an ‘easy’ process for them.	(Fortanier <i>et al</i> , 2002)
12 sibling donors	Psychological consequences of donating bone marrow to a relative	Deep personal satisfaction that they were able to donate, and little or no reluctance. Stressful aspects related to unanticipated pain and negative transplant outcome.	(Christopher, 2000)
18 adult sibling donors	Psychological adjustment of adult bone marrow transplant donors whose recipient survives.	High self-esteem and high life satisfaction among BM donors whose recipient survived but 10-20% experienced some psychological difficulty. Reported a link between the donor’s psychological status and the recipient’s health, suggesting that negative changes in recipient health might result in negative impacts on the donor.	(Wolcott <i>et al</i> , 1986)
22 adult sibling donors	Psychosocial impact of PBSC donation before, during and after donation, and to gain insight into donors’ experiences of the preparation for, and procedures associated with donation.	Low ambivalence pre-donation, 68% reported that the decision required little consideration. Pre-donation donors described joy at being a match, but anxiety about the donation and outcome. During the donation process, donors reported satisfaction at being able to help but anxiety regarding the outcome. Post-donation donors felt glad they had donated but described guilt, responsibility, decreased mood and ongoing distress and anxiety about the recipient’s health. 55% stated that they were closer to their sibling recipient after donation.	(Pillay <i>et al</i> , 2012)

77 related and unrelated adult donors	To determine whether related donors experience more distress than UDs	Related donors report significantly more acute physical pain than unrelated donors	(Chang <i>et al</i> , 1998)
22 adult sibling PBSC donors	Analyse how family PBSC donors cope when confronted with this particular risk context quality of life (pain and anxiety) before, during and after donation	Donors felt responsible for the recipients' state of health, more so among female than male donors. Donors tended to underestimate the risks which the authors reported was due to pressure exerted by the family and the physicians at the time when the choice of procedure had to be made underestimate the involved.	(Munzenberger & Fortanier, 1999)
14 sibling donors aged 9-28	Psychological experiences of sibling stem cell donors	Donors reported feeling concerned about donation and a need for more information about the process, outcomes and complications. They also reported guilt about poor recipient outcomes.	(Wiener <i>et al</i> , 2008)
13 parental related donors	Explore the experience of parents with a dual role of donating and caring for their children	All parents felt inadequately informed about the effects for themselves as a donor, and felt they had no choice in the decision to donate	(van Walraven <i>et al</i> , 2010a)
15 paediatric sibling donors	Explore the psychosocial experience of sibling donors of successful and unsuccessful hematopoietic stem cell transplants	Sibling donors whose recipients had an unsuccessful outcome reported greater negative impacts and feelings of guilt, compared with those whose recipients had a successful outcome. Both groups reported that informed consent involved "no choice" and that psychological aspects of the procedure outweighed physical aspects.	(MacLeod <i>et al</i> , 2003)
21 donor and 23 non-donor paediatric siblings of paediatric HCT survivors	Examine the psychosocial consequences of BM transplantation in donor and non-donor siblings Sibling perceptions of BM transplant process	Self-report measures indicated significantly more anxiety and lower self-esteem for non-donors than donors. Teacher-rated scales showed significantly more adaptive skills for donors and significantly more school problems for non-donors. A third of siblings in each group reported moderate levels of post-traumatic stress reaction. Donors reported lack of choice regarding the decision to donate.	(Packman, 2004)
15 paediatric patients and their families	To explore psychosocial issues and coping in patients, and donor and non donor siblings	The authors reported increased behavioural issues in donor siblings compared to non-donor siblings	(PotMees <i>et al</i> , 1987)
36 paediatric sibling donors	Psychological perspectives of paediatric sibling donors and their parents	Sibling donors reported increased self-esteem post donation and increased closeness to their sibling, however some expressed anger about donation and concerns regarding the long-term effects on their own health.	(Ritchie <i>et al</i> , 2005; Massoud <i>et al</i> , 2014)

## 1.6. RISKS TO THE TRANSPLANT RECIPIENT

HPC products carry the same risk of transmission as blood products, but include the additional risk of cellular pathogen transfer. Recipient acquisition of infections from HPC products including bacteria, viruses, fungal disease and parasites to recipients of allogeneic stem cells is well documented. Table 1.4 describes infections reported in blood, organ and HPC transplantation and those that are believed to represent a risk but where transmission is not yet documented.

*Table 1.4 Infections with the potential for transmission via haematopoietic cell transplantation*

<b>Reported in HPC transplantation</b>	<b>Reported in blood transfusion or solid organ transplantation but not HPC transplant</b>	<b>No reported cases but theoretical risk exists</b>
Cytomegalovirus (Ljungman, 2014) EBV HIV Hepatitis B Hepatitis C (Shuhart <i>et al</i> , 1996) HTLV1/2( Miyoshi <i>et al</i> , 1995; Ljungman <i>et al</i> , 1994) Parvovirus (Heegaard & Laub Petersen, 2000) HHV6 (Strenger <i>et al</i> , 2014) Malaria( Dharmasena & Gordon-Smith, 1986; Lefrère <i>et al</i> , 1996; O'Donnell <i>et al</i> , 1998) Toxoplasmosis Cryptosporidiosis (Collier <i>et al</i> , 1984) Brucellosis (Naparstek <i>et al</i> , 1982; Ertem <i>et al</i> , 2000) Leishmaniasis Babesia Fungal disease Familial Mediterranean fever(Petropoulou <i>et al</i> , 2010)	<b>Blood</b> Hepatitis E Creutzfeldt-jakob disease  <b>Solid organ</b> Swine flu (Griffiths, 2010) Strongyloides( Roseman <i>et al</i> , 2013; Abanyie <i>et al</i> , 2015) Schistosomiasis (Ahmed <i>et al</i> , 2007)  <b>Blood and solid organ</b> West nile virus (Winston <i>et al</i> , 2014; Stanley <i>et al</i> , 2009) Rabies (Kusne & Smilack, 2005) Dengue fever (Saigal <i>et al</i> , 2013; VWM Chuang, 2008) Trypansomal cruzi (Gomez-P <i>et al</i> , 2014)	Chikigunya virus Ebola

Malignant cells can be transferred during HPC donation and may lead to disease in the recipient, either through engraftment of HPCs causing haematological cancer, or via transfer of solid organ malignant cells causing metastases in the recipient. Case reports of donor-transmitted malignancies following HPC transplantation are currently limited to haematological cancers. However, reports of solid organ cancer transmission and development of donor-derived malignancies in recipients of organ transplants have occurred (shown in Table 1.5).

*Table 1.5 Malignancies transmitted by haematopoietic cell transplantation*

<b>Reported in HPC transplantation</b>	<b>Reported in solid organ transplantation but not HPC transplant</b>	<b>Donor derived malignancies identified</b>
AML(Niederwieser <i>et al</i> , 1990) CML(Baron <i>et al</i> , 2003) T cell lymphoma (Berg <i>et al</i> , 2001) Follicular lymphoma (Hart <i>et al</i> , 2007) Chronic lymphocytic leukaemia (Flandrin-Gresta <i>et al</i> , 2010; Ferrand <i>et al</i> , 2012)	Glioblastoma multiforme (Frank <i>et al</i> , 1998) Choriocarcinoma (Braun-Parvez <i>et al</i> , 2010) Melanoma (MacKie <i>et al</i> , 2003; Kim <i>et al</i> , 2009) Pancreatic carcinoma (Gerstenkorn & Thomusch, 2003) Lung cancer (Lipshutz <i>et al</i> , 2003) Sarcoma (Garrido & Matesanz, 2008) Prostate cancer (Loh <i>et al</i> , 1997) Hepatocellular carcinoma (Ison <i>et al</i> , 2009)	Small cell lung cancer (Nair <i>et al</i> , 2007) Ovarian cancer (Lipshutz <i>et al</i> , 2009) Bladder cancer (Ferreira <i>et al</i> , 2010)

As shown in Table 1.6, all inherited diseases that originate from HPCs can potentially be transmitted during HPC transplantation, as can passive transfer of autoimmune disease.

Table 1.6 Autoimmune diseases transmitted by HPC transplantation

<b>Disease</b>
Myasthenia gravis (Smith <i>et al</i> , 1983)
Atopy/allergy (Storek <i>et al</i> , 2011; Bellou <i>et al</i> , 1997)
Thyrotoxicosis (Thomson <i>et al</i> , 1995)
Immune thrombocytopenia (Minchinton <i>et al</i> , 1982)
Psoriasis (Daikeler <i>et al</i> , 1999; Li <i>et al</i> , 2015)
Sarcoid
Antiphospholipid syndrome (Ritchie <i>et al</i> , 2005; Massoud <i>et al</i> , 2014)
Type 1 Diabetes mellitus (Mellouli <i>et al</i> , 2009; Lampeter <i>et al</i> , 1998)
Coeliac disease (Bargetzi, 1997)
Systemic lupus erythmatosus (Autoantibodies without disease)

## 1.7 THE HEALTH AND WELL-BEING OF PAEDIATRIC DONORS

### 1.7.1 ETHICAL CONSIDERATIONS OF DONATION IN CHILDREN

Donation of HPCs carries a degree of risk, and is of no direct medical benefit to the donor. The accepted justification for permitting minor siblings to donate is that the donor will benefit from the greater likelihood of survival and reduced suffering of their sibling. This justification is supported by results of some studies, describing psychosocial benefits experienced by paediatric sibling donors, including increased self-esteem, pride, and worth of life and independence (Wiener *et al*, 2008; Packman *et al*, 2010; MacLeod *et al*,; van Walraven *et al*, 2013). However, in some of these studies (as with adult donors), the donation experience was linked to recipient transplant outcome and some donors of unsuccessful transplants report negative experiences (van Walraven *et al*, 2013).

Children have been permitted to serve as stem cell donors for >30 years, and expert ethical bodies have repeatedly concluded that it is appropriate to continue to allow them to do so (American Academy of Pediatrics, 2010; Bitan *et al*, 2015). Based on ensuring benefit and limiting harm, donation is only considered justifiable provided there is a strong positive link (or an anticipated strong positive link in very young

children) and a reasonable chance of a successful transplant outcome (Pentz *et al*, 2008).

### 1.7.2 THE SAFETY OF DONATION IN CHILDREN

While PBSC has overtaken BM as the requested cell source in unrelated donor transplantation and adult sibling donor allografts, BM collection remains the most common procedure for paediatric donors (Passweg *et al*, 2014). This is partly due to the fact that their intended recipient will usually also be a child, and many centres continue to prefer BM in this patient population. Secondly, due to historical concerns about the leukaemogenic potential of growth factors, and licensing restrictions in some countries, as well as technical challenges of the apheresis procedure in young children, PBSC products are less commonly collected from paediatric donors (Passweg *et al*, 2014).

### 1.7.3 BM HARVESTING IN CHILDREN

BM harvesting has been performed in children for >30 years and appears to have an excellent safety profile, with the risk of life-threatening events of less than 0.5% (Buckner *et al*, 1984). The EBMT paediatric diseases working party (Styczynski *et al*, 2012) conducted a study in 313 BM donors reporting a very low incidence of adverse events. The greatest risk in very small donors is causing anaemia requiring allogeneic transfusion, which is widely regarded as an inappropriate intervention in this population. Providing that the maximum aspirated volume does not exceed 20mls/kg donor weight, allogeneic blood products are very rarely required (Styczynski *et al*, 2012).

There are no regulations regarding a minimum donor age or weight in paediatric donors, and centre practice has not been widely studied. If BM harvests are undertaken in very young donors (e.g. <6 months old) donating to an older sibling, it is likely that allogeneic transfusion would be required to obtain an adequate yield for engraftment.

#### 1.7.4 PBSC HARVESTING IN CHILDREN

A retrospective analysis conducted by The Paediatric Blood and Marrow Transplant Consortium examined the safety and efficacy of PBSC donation by 201 paediatric sibling donors, aged 8 months to 17 years (Pulsipher *et al*, 2004). This study demonstrated few side effects during mobilisation, with <15% donors experiencing growth factor induced pain, which in no cases exceeded CTCAE grade 2. However, 92% of donors <20kgs required priming of the apheresis circuit with allogeneic blood, and although 80% of 13-16 year olds were collected using peripheral access, this was only possible in a third of 7-12 year olds. Further analyses corroborate the finding that children report fewer side effects during GCSF mobilisation than adults. The Spanish cooperative group studied 61 paediatric donors and found significantly fewer side effects in paediatric donors compared to an adult cohort (41% vs. 71%) (la Rubia *et al*, 2001). A further study (Kawano *et al*, 1999) found that while children <10 years experienced less discomfort than those 10-19 years, the older age group did not experience more symptoms than one would expect in an adult cohort. The PBSC Transplantation Study group of Japan described side effects in 57 donors between the age of 9 months and 24 years. Again, the reported side effect profile compared favourably to studies using adult cohorts; bone pain was described in only 17.5% and headache in 5.3% donors during GCSF therapy (Watanabe *et al*, 2002).

Although there are insufficient data to estimate a precise risk of SARs in paediatric donors undergoing PBSC harvesting, the above studies are reassuring and serious events do not appear to occur more frequently than in adult PBSC donors. The aforementioned EBMT paediatric diseases working party study (Styczynski *et al*, 2012) included 140 PBSC donors, and reported the only serious adverse event in a donor who developed a pneumothorax following insertion of a central venous catheter.

There are a lack of long-term follow-up data in normal paediatric donors, and thus the long-term safety of GCSF in this donor population cannot be confirmed, however, experience with GCSF therapy in paediatric patients and adult donors are encouraging.

In particular, no malignancies in patients with cyclic or idiopathic neutropenia have been reported to the severe chronic neutropenia international registry.

### 1.7.5 THE EFFICACY OF PBSC DONATION IN CHILDREN

A number of studies have included donors <18 years in assessments of PBSC yield following GCSF and concluded favourable efficacy in younger donors. In 2002 a Japanese group published a study examining factors associated with successful mobilisation with GCSF in PBSC donor and found a negative correlation between stem cell yield and age (Shimizu *et al*, 2002). These findings were echoed in a more recent Italian multi-centre study (Bertani *et al*, 2014), which investigated donor variables correlating with HPC mobilisation in 360 donors aged 13+ treated with GCSF. Again, younger age was associated with better mobilisation following GCSF. The report from the Paediatric Blood and Marrow Transplant Consortium detailing PBSC donations in 201 paediatric siblings (Pulsipher *et al*, 2004) recorded good yields in all age groups. In 2006, a study (Ings *et al*, 2006) examining the factors associated with successful mobilisation in 400 donors aged 12+ receiving lenograstim was published, reporting that poor mobilisation occurred exclusively in donors aged 54 years or older.

## 1.8 LEGISLATION AND GUIDANCE IN RD STEM CELL DONATION

### 1.8.1 NATIONAL UK LEGISLATION

The Human Tissue Act 2004 sets out a legal framework for the storage and use of tissue from the living, and for the removal, storage and use of tissue and organs from the dead, and covers England, Wales and Northern Ireland. In Scotland there is separate legislation -The Human Tissue (Scotland) Act 2006. The fundamental principle of this legislation is informed consent.

Following introduction of the Act, the Human Tissue Authority (HTA) was established to provide regulation for activities concerning the Act. The HTA produces nine codes of

practice designed to provide professionals with practical guidance on the human tissue legislation. Code of Practice 6 (HTA, 2014) covers donation of allogeneic bone marrow and PBSC for transplantation, and includes principles relating to consent and communication for donation.

Under the Human Tissue Act, donation of bone marrow and PBSC both by adults with capacity and children competent to give consent may be approved locally. The HT Act England and Wales, defines children as less than 18 years of age, however donation of bone marrow and PBSC by children competent to give consent can be approved locally. The competence of potential donors <18 years should be determined locally and children competent to give consent are considered 'Gillick-competent' and may consent. In the Gillick case, the court held that a child was considered competent to give valid consent to a proposed intervention if they had sufficient intelligence and understanding to enable them to fully understand what was involved. Under the provisions of the HT (Scotland) Act, children are defined as being less than 16 years of age, therefore those over 16 may consent to donation in the same way as older adults.

Consent for the first and each repeat donation must be obtained before harvesting bone marrow or PBSC from a donor for transplantation and the HTA requires that informed consent must cover the following:

- 1) Details about the donation procedure, the long- and short-term risks and that a further collection of stem cells or lymphocytes might be requested
- 2) The chances of the transplant being successful and any possible side effects or complications for both donor and recipient
- 3) The right to withdraw consent at any time and the implications for both donor and recipient of the withdrawal of consent
- 4) The fact that donation is an entirely voluntary act and that the donor (and where applicable the person consenting on their behalf) must be free of any kind of coercion or pressure
- 5) The fact that it is an offence to seek or receive payment or reward for providing tissue, including bone marrow or PBSC for transplantation

## 1.8.2 CONSENT OF MINORS

Donations of bone marrow from children who are not competent to give consent, or from adults lacking capacity, must be approved by the HTA. HTA regulations require that all cases of minors who are not competent to consent are reviewed by an independent assessor, who interviews the donor and submits a report to the HTA. The assessor must be satisfied that the best interests of the potential donor have been properly considered and that the HTA's codes of practice have been appropriately implemented. In particular, the assessor's responsibilities are to:

- Conduct separate interviews with the donor, the person giving consent, and the recipient
- Ensure, where appropriate, that the child has received all necessary information in a way they are most able to understand
- Ensure that consent is obtained with no duress, coercion and no evidence of an offer of reward

Legally, parents can consent on behalf of their child, however, it is recognised that a conflict of interest exists for parents of a child donating to their sibling. If the child objects, the independent assessor will explore the reasons behind this and, in exceptional circumstances, the decision may be referred to a court.

## 1.8.3 INTERNATIONAL GUIDANCE

### *1.8.3.1 World Health Organisation*

The World Health Organisation first produced guiding principles on human cell, tissue and organ transplantation in 1991. Covering the whole field of transplantation these are intended to provide an ethical framework for the acquisition and transplantation of human cells, tissues and organs for therapeutic purposes. The principles relevant to HPC donation include:

- Live donors should be informed of the probable risks, benefits and consequences of donation and consent should be free from undue influence or coercion.
- Selection criteria for donors should be scrupulously applied and monitored.
- Payment other than reimbursement of expenses is prohibited.
- Psychosocial evaluation is needed to guard against coercion of the donor or the commercialism.
- The national health authority should ensure that the evaluation is carried out by an appropriately qualified, independent party.
- Specific measures should be in place to protect minors or those lacking competence and, wherever possible, assent should be obtained before donation.
- Follow-up should be well organised. The long-term outcomes of cell, tissue and organ donation and transplantation should be assessed for the living donor as well as the recipient in order to document benefit and harm.

#### *1.8.3.2 FACT-JACIE Standards*

In 1996, the Foundation for the Accreditation of Cellular Therapy (FACT), was established by the International Society for Cellular Therapy (ISCT) and the American Society for Blood and Marrow Transplantation (ASBMT) to provide standards and accreditation in HPC transplantation in North America. Two years later, JACIE was founded by European Group for Blood and Marrow Transplantation (EBMT) and ISCT, to meet the same objectives in Europe. The two organisations collaborate and jointly produce FACT-JACIE Standards for the provision of quality medical and laboratory practice in HPC transplantation. The Standards consist of evidence-based requirements developed by consensus within committees consisting of clinicians, scientists and quality experts including international leaders in cell therapy, cord blood banking and HPC donor registries. Prior to publication the Standards undergo public and legal consultation.

Transplant and cell processing programmes apply for FACT or JACIE accreditation, which is required for reimbursement of transplant costs in the UK, but is voluntary in many other European countries.

JACIE adopted the first edition of FACT Standards in 1999, and subsequently the joint 2<sup>nd</sup> Edition Standards were produced in 2002. Since the first edition, recommendations and requirements regarding the evaluation of allogeneic HPC donors have been included, and have become more extensive over time, as awareness around related donor health and well-being has increased. A summary of the Standards pertaining to related donor care and the notable changes between editions are summarised in Table 1.6. The Standards define that the term ‘shall’ indicates that the standard is to be complied with at all times while the term ‘should’ refers to activity that is recommended or advised, but for which there may be effective alternatives. Several of the studies described in this thesis refer to FACT-JACIE Standards. At the time these studies were undertaken, 5<sup>th</sup> Edition Standards were in use, and are referred to as the ‘current’ standards in these studies.

*Table 1.7 Summary of FACT-JACIE Standards pertaining to the care of related donors and changes through the last three editions*

3 <sup>rd</sup> Edition Oct 2006	4 <sup>th</sup> Edition Oct 2008	5 <sup>th</sup> Edition March 2012
<b>Training</b>		
Physicians should be knowledgeable in BM harvest and apheresis procedures	Physicians shall be trained and competent in BM harvest and apheresis procedures	
		Specific training and competency annually in donor informed consent
<b>Policies and procedures</b>		
There shall be written criteria for allogeneic donor selection, evaluation, and management		
The Collection Facility shall establish and maintain policies and procedures shall address:		
Donor and recipient confidentiality.		
Donor consent.		
Donor treatment.		
Donor screening.		
Management of donors, including pediatric donors if applicable		
There shall be a policy covering the creation, regular review, and retention of donor records.		
<b>Donor Evaluation</b>		
		Allogeneic donor suitability should be evaluated by a physician who is not the physician of the recipient.
The donor shall be evaluated for potential risks of the collection procedure. The risks of donation shall be documented, including:		
Possible need for central venous access.		
Mobilisation therapy for collection of HPC, Apheresis.		
Anesthesia for collection of HPC, Marrow.		
	Donors shall be evaluated for risk factors for disease transmission by medical history, physical examination, examination of relevant medical records, and laboratory testing.	
The medical history for allogeneic donors shall include at least the following:		
Vaccination history. Travel history. Blood transfusion history.		
Questions to identify persons at high risk for transmission of communicable disease		
Questions to identify persons at risk of transmitting inherited conditions.		
Questions to identify persons at risk of transmitting a hematological or immunological disease.		
Questions to identify a past history of malignant disease.		
Within thirty (30) days prior to collection, all HPC donors shall be tested for Human immunodeficiency virus, type 1. Human immunodeficiency virus, type 2. Hepatitis B virus. Hepatitis C virus. Treponema pallidum (syphilis)		
Any abnormal findings shall be reported to the prospective donor		
The use of an ineligible allogeneic donor shall require documentation of the rationale for his/her selection and suitability by the transplant physician, urgent medical need documentation, and the documented informed consent of the donor and the recipient.		

<b>Consent</b>		
		Sufficient information regarding the donation process shall be provided to the potential allogeneic donor prior to HLA typing.
The donor shall have an opportunity to ask questions.		
The donor shall have the right to refuse to donate.	The donor shall have the right to refuse to donate and be informed of the potential consequences to recipient of such refusal.	
Informed consent from the donor shall be obtained and documented by a licensed physician or other health care provider familiar with the collection procedure.		
		Informed consent from allogeneic donors should be performed by licensed physicians or other healthcare providers other than the potential recipients' primary physicians.
The collection procedure shall be explained in terms the donor can understand, and shall include the following information at a minimum: The risks and benefits of the procedure. Tests and procedures performed to protect the health of the donor and the recipient. The rights of the donor to review the results of such tests. Alternative collection methods.		
<b>Minors</b>		
		Written criteria shall include criteria for the selection of minor allogeneic donors.
There shall be a process to address age specific issues including informed consent, donor size, and venous access. Specific consent is required for the use of growth factors, if utilised, in a minor, allogeneic donor. For minor donors assent should also be obtained in an age appropriate manner		
In the case of a minor donor, informed consent shall be obtained from the donor's parents or legal guardian in accordance with applicable laws		
		There should be a donor advocate available to represent minor allogeneic donors and allogeneic donors who are mentally incapacitated.
<b>Follow-up</b>		
There shall be a policy for follow-up of donors that includes routine management and the management of donation-associated adverse events.		

### *1.8.3.3 WMDA recommendations for family donor care management*

In 2010, the Ethics Working Group and the Clinical Working Group of the WMDA formed a subcommittee, which established consensus recommendations for family donor care (van Walraven *et al*, 2010b).

These included that:

- Counselling, including written information covering all aspects of BM/PBSC donation should be available for each family member before HLA testing. This should cover the option for the donor to choose not to donate.
- TCs should establish procedures to ensure that donors are appropriately counselled regarding their right to refuse typing or donation.
- The practitioner (for example, independent advocate, physician) counselling the donor should have a documented donor advocacy role and should not be involved in the recipient's care.
- Systems should be in place to evaluate clinical risk to the donor against defined criteria and to document decisions made.
- Systems should be in place both for adverse event reporting and for long-term follow-up of related as well as unrelated donors.

### *1.8.3.4 WBMT recommendations for standardised reporting of donor outcomes*

In 2013, consensus recommendations were published (Halter *et al*, 2013) regarding the standardised assessment of donor outcome, recommending identical follow-up for related and unrelated donors.

These guidelines include that:

- All consenting donors who start the donation procedure for allogeneic HSC or other therapeutic cells from peripheral blood or BM shall be registered and followed for 10 years after the last donation procedure.

- A minimum data set including survival status, development of haematological or non-haematological malignancy or autoimmune disease should be collected.

#### 1.8.4 REGULATION OF UNRELATED DONOR CARE

The World Marrow Donor Association (WMDA) was founded in 1994 with the purpose of establishing a global network facilitating the provision of quality hematopoietic stem cell products and preserving the health and safety of the volunteer unrelated donors providing such products. WMDA provides accreditation for donor registries, which are required to conform to WMDA Standards, covering all aspects of unrelated donor care from donor recruitment, consent, medical assessment, collection, and donor follow-up.

The WMDA donor suitability working committee produces criteria for acceptance of unrelated donors, these take a conservative approach to preserving donor health, recommending deferral of any donors with issues that may represent a risk to their health during donation.

WMDA member organisations are also obligated to report to a central Serious Events and Adverse Effects Registry, using standardised criteria. All events are reviewed by a committee with specific expertise in donor health, and any concerning incidents are then disseminated through registry networks to physicians involved in unrelated donor assessment, and addressed through changes to the WMDA medical suitability criteria. Although the WMDA collaborates with other organisations within the transplant field, there are no clear channels through which such information is communicated to the physicians who evaluate related HPC donors.

#### 1.8.5 REGULATION OF SOLID ORGAN DONATION FROM RELATED DONORS

Regulations regarding the donation of solid organs from related donors are far more comprehensive than those in HPC transplantation. This occurs in part because of a clear need to prevent organ trafficking, which is not an issue in HPC transplantation,

and also a difference (or perceived difference) in donor risk since HPCs are by definition self-renewable.

While HPC donation from competent adults does not require approval, all living solid organ donations from living donors must be approved by the HTA, with a report submitted by an Independent Assessor (as is the case for minors or donors lacking capacity in the context of HPC donation).

A second regulatory framework for solid organ donation also exists, the EU Organ Donor Directive, which sets minimum standards that must be met by all member states aiming to reduce variation in donor care standards between EU countries. The HTA is also the competent authority for implementation of this framework, which is entrenched into UK law through the Quality and Safety of Organs intended for Transplantation Regulations 2012. These regulations encompass both procurement and transplantation activities. In contrast to HPC donation, these regulations specifically require central reporting of serious adverse events or reactions (which are reported to NHSBT acting on behalf of the HTA) and requires arrangements for donor follow-up.

Since 2000, UK Guidelines for Living Donor Kidney Transplantation have been produced by a joint working party of the British Transplantation Society and the Renal Association. These comprehensive evidence-based guidelines include the ethical and medico-legal aspects of donor selection, donor evaluation, medical deferral criteria, and the management of complications. This includes clear recommendations for:

- Separate teams managing the donor and recipient
- Psychological evaluation and support must be available if required
- Long term follow-up for all donors

In addition there are several international sources of consensus guidelines on managing related organ donors. These include comprehensive international guidelines by The Ethics Committee of the Transplantation Society (TTS) with consensus statements on the care of live renal donors (The Consensus Statement of the

Amsterdam Forum on the Care of the Live Kidney Donor, 2004) and on live Lung, Liver, Pancreas, and Intestine Donors (Pruett *et al*, 2006).

## 1.9 CONCLUSION

Over the last 30 years HPC transplantation has developed as a treatment modality offering the chance of long-term cure to an increasing number of patients with haematological disease. Although other donor options are now available, fully matched siblings offer the best results and recent advances have also resulted in increasing numbers of mismatched transplants using other relatives. Compared to both the unrelated HPC donor and related solid organ donor field there is a relative lack of regulation to protect the health and interests of related HPC donors. Several recent studies have drawn attention to the increased occurrence of serious health events among related HPC donors, but the lack of a process for centralised SAR reporting makes it difficult to determine the precise incidence of such events. In addition, with retrospective analyses and small donor cohorts forming the majority of available evidence, it is difficult to establish a causative relationship between specific medical issues or donor characteristics and adverse events.

Furthermore, concerns have been raised that current procedures may not sufficiently protect RDs from a potential conflict of interest, and it is also clear that we currently know very little about the pathway of RD care in transplant centres. This thesis will explore current pathways of RD care focusing on procedures at each stage of the donor care pathway and will endeavour to look for solutions to concerns that have been raised thus far.

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## CHAPTER 2. MATERIALS AND METHODS

### 2.1 INTRODUCTION

This chapter describes the methodology behind the five studies that are detailed in subsequent chapters of this thesis. These include a retrospective study examining the impact of JACIE accreditation on RD care, a study of RD care provision in UK transplant centres, a study of RD care provision in the USA and Europe, a study of related donor experience in a single UK centre and a prospective study exploring provision of RD care in a UD registry setting.

### 2.2 A RETROSPECTIVE STUDY OF THE IMPACT OF JACIE ACCREDITATION ON RELATED DONOR CARE

#### 2.2.1 IDENTIFICATION OF THE STUDY POPULATION

All sequential evaluations of adult potential RDs occurring between 1<sup>st</sup> January 2004 and 31<sup>st</sup> December 2013 at the Royal Marsden Hospital were retrospectively analysed. This included the evaluations that resulted in donor deferral, as well as those resulting in allogeneic donation.

The details of all recipients of related donor allogeneic HPC transplants during the study period were obtained from the hospital's ProMISe database. Using the patient electronic records, the details of all related donors who had proceeded to HPC donation were acquired. I then retrieved the details of all patients who had undergone HLA typing from January 2003 to December 2013 from the Anthony Nolan SOLAR database. I reviewed the results of the 879 relatives of all 485 patients who had undergone HLA typing, to identify patients who had a fully matched donor but who did not proceed to transplant with this donor. I was thus able to identify any relatives who

had been evaluated and deferred. Details of any subsequent therapeutic T cell collections were not collected.

### 2.2.2 DATA COLLECTION

The data regarding the medical evaluation of the study cohort were collected from the hospital's electronic patient records. All records from the study period included a detailed summary of the evaluation and description of the consenting process from the assessing physician. All blood results, donor medical observations, investigations and consent forms were available electronically and were reviewed. Data regarding the apheresis procedure(s) or bone marrow procedure were also reviewed using electronic medical records.

During the study period The Royal Marsden quality team prospectively collected information regarding donors who were contacted and offered follow-up. This team provided information regarding donors who were offered follow-up, and, where donors had participated, data from the follow-up questionnaires were collected from the electronic medical records.

The presence of adverse events was determined by reviewing donor medical records for any events occurring from the start of mobilisation until 30 days post-donation. Any adverse events requiring admission to hospital, modification of the mobilisation regimen or the apheresis procedure were classed as severe. Data regarding well-recognised side effects of donation such as bone pain and citrate toxicity, that required only standard interventions, were not recorded.

The electronic medical records of the recipients of these donors were examined and data regarding HPC dose infused, and engraftment data and recipient demographics were collected.

### 2.2.3 ASSESSMENT OF DONOR SUITABILITY STATUS IN ADULT DONORS

Using the details of the donor demographics, results of investigations, and the medical summary recorded by the evaluating physician, I was able to retrospectively assess whether all adult donors in this study would have been accepted as unrelated donors. This assessment was performed using the Anthony Nolan medical suitability criteria, available at <http://med-guidelines.org.uk>, accessed on 12<sup>th</sup> November 2013.

#### 2.2.4 ASSESSMENT OF THE IMPACT OF JACIE STANDARDS ON DONOR MANAGEMENT

During the time-period studied, changes to FACT-JACIE Standards regarding the care of related donors were introduced at two time points. In April 2011, the 4<sup>th</sup> FACT-JACIE Standards (FACT-JACIE, 2011) introduced a requirement for “a policy for follow-up of allogeneic donors that includes routine management and the management of donation-associated adverse events”. In March 2012, the 5<sup>th</sup> edition of the Standards came into effect and introduced the stipulation that allogeneic donors should be assessed by a “licensed health care professional who is not the primary transplant physician overseeing care of the recipient”. The impact of each change was assessed by comparing donor care before and after the introduction of the relevant standard.

#### 2.2.5 STEM CELL COLLECTION PROCEDURES

Apheresis donors were mobilised with lenograstim (glycosylated GCSF; Chugai Pharma, London UK) with a dose of 10 µg/kg/day administered subcutaneously ± 10% for 4 consecutive days. Where less than 90% of the CD34+ target yield was achieved with the first procedure on day 5, a further dose of GCSF was administered and a subsequent collection performed on day 6.

The standard procedure for bone marrow harvests entailed aspiration from bilateral posterior iliac crests under general anaesthetic. Multiple-side-hole needles were used, with the exception of small paediatric donors in whom these were considered

unsuitable. All harvests were performed by Consultant-level Haematologists who had undertaken specific credentialing, and had extensive experience in this procedure.

## 2.2.6 STATISTICAL ANALYSES

The relationship between era of transplant (pre-and post introduction of 4<sup>th</sup> JACIE Standards) and the existence of donor follow-up, and between era (pre and post-introduction of 5<sup>th</sup> JACIE Standards) and independent donor consent were examined using the chi-squared test.

To analyse factors associated with adverse events, continuous donor characteristics were categorised and relationships between donor characteristics and the occurrence of severe adverse events, or achievement of requested harvest yield were examined using chi-squared, or Fisher's exact test where appropriate.

The relationship between continuous donor variables and CD34+ yield as a continuous outcome was determined using linear regression analysis. The relationship between categorical donor variables and CD34+ yield as a continuous outcome was examined using the Mann-Whitney-U test. Only first HPC donations were considered in evaluations of HPC yield achieved.

## 2.3 A STUDY OF RELATED DONOR CARE IN THE UK AND TRANSPLANT PHYSICIAN OPINIONS

### 2.3.1 DEVELOPMENT OF THE SURVEY

A 47-question survey was developed to address the study objectives (see Appendix 1), using multiple-choice questions where possible to increase likelihood of response. Questions aiming to determine compliance with regulatory standards were phrased using language identical to the regulation concerned. The draft survey was piloted by five healthcare workers in the field of HPC transplantation to ensure comprehensibility

and to identify ambiguities. The final survey was then reviewed by the BSBMT clinical trials committee who approved the study.

### 2.3.2 DATA COLLECTION

The study population consisted of programme directors of all 28 UK transplant centres performing adult allogeneic HPC transplants and one apheresis centre managing adult related donors. Since it was anticipated that the centre director might not always be fully cognisant with their centre's donor care policies, the invitation letter requested that the survey be forwarded to the physician responsible for donor care in their centre.

In order to maximise the response rate, the survey was administered by email via the BSBMT. The study population were sent an invitation requesting completion of the internet-based questionnaire via a secure hyperlink ([surveymonkey.com](https://www.surveymonkey.com)). Following the initial email invitation in April 2014, non-responders received three further email reminders, and the study closed on 31st July 2014. Where more than one response was received from a centre, the most complete was used for analysis. The survey allowed participants to skip questions they were unwilling/unable to answer.

Data regarding centre transplant volumes (number of allografts per year) were obtained from the BSBMT, this data refers to transplant volumes in 2012.

### 2.3.3 STATISTICAL ANALYSES

Due to the small number of transplant centres in the UK, this study was not powered to generate statistically significant differences between transplant centres, and analyses were therefore largely descriptive. Centre volume (defined as the total number of allografts performed per year) was categorised (<10, 11-20, 31-50, 51-70, and >70) and relationships between centre volume and response rate or adherence to standards were examined using the chi-squared test.

## 2.4 A STUDY OF RELATED DONOR CARE IN THE US AND EUROPE

### 2.4.1 DEVELOPMENT OF THE SURVEY

This study was designed to examine RD care in two distinct geographical regions: the US and Europe. A single survey was developed to study both regions, but with differing primary objectives. In the US, where an earlier survey of donor care had been previously undertaken, the primary objective was to determine whether improvements had occurred following international donor care initiatives. In EBMT transplant centres, the primary objective was to determine whether appreciable differences in care were present between JACIE accredited and non-accredited centres.

In order to allow comparison between eras, the 38-item survey (see Appendix 1) I developed for this study contained some questions with wording identical to the earlier US survey, as well as new questions to address areas of care that had not been previously examined in either region.

The survey included questions examining all aspects of RD care, but with a particular focus on those areas which have been addressed by consensus guidelines, or where regulatory bodies have made recommendations or stipulations.

The areas of care studied included:

- The information supplied to RDs prior to HLA typing
- The presence and method of RD health assessment prior to HLA typing
- Assessment of RD willingness prior to HLA typing
- The person to whom donor HLA results are first disclosed
- The existence of a written RD care policy
- The presence of written eligibility criteria for acceptance of RDs
- The existence of a process for credentialing physicians performing BM harvests

- The involvement of the RDs consenting physician in the care of the recipient.
- The presence and duration of a RD follow-up programme

The draft survey questions and all procedures were reviewed by the CIBMTR Donor Health and Safety Working Committee, including statistical review. The survey was then tested by 10 transplant physicians from the US and Europe, to identify ambiguities and to ensure that the terminology used was appropriate for both regions. The study was approved by the NMDP Institutional Review Board and by the Donor Outcomes Committee of the EBMT.

#### 2.4.2 STUDY POPULATION

The study population consisted of programme directors of EBMT and CIBMTR allogeneic transplant member centres, who were contacted via email using CIBMTR and EBMT mailing lists for programme directors. CIBMTR centres that were recorded as purely paediatric centres were excluded, but this information was not available for EBMT centres. All centres were contacted simultaneously with an initial invitation sent in August 2014 via the CIBMTR requesting completion of the internet-based questionnaire via a secure hyperlink ([surveymonkey.com](https://www.surveymonkey.com)), or, to forward the survey to the appropriate donor care physician in the centre. Entry into a draw for a free Tandem meeting registration was offered as an incentive to increase the response rate. Non-responders received a further three email reminders prior to closure of recruitment on 31<sup>st</sup> November 2014.

The invitation to this study specified that the study referred to the care of adult related stem cell donors only, and the survey terminated if respondents answered ‘no’ to the first question “Does your centre perform allogeneic HPC transplants from adult (>18 years old) related donors?”.

Where >1 response was received from a centre, the most complete was used for analysis. The survey allowed participants to skip questions they were unwilling or unable to answer.

## 2.4.2 STATISTICAL ANALYSES

For analysis of response rates, EBMT centres were categorised by centre volume, defined as the number of first allografts performed per year (<10, 11-25, 26-50, 51-75, >75) using data collected from the most recent EBMT activity survey (Passweg *et al*, 2013). Centres were also grouped according to their geographical location (Eastern Europe, Northern Europe, Southern Europe, Western Europe, Non-European nations).

For analysis of response rates US centres were grouped by size in the analysis, defined as the number of allografts per year, as reported to CIBMTR (2011-2012). Centres were also grouped according to their geographic location by US regions including: New England (ME, NH, VT, MA, RI, CT), Mid-Atlantic (NY, NJ, PA), South Atlantic (DE, MD, DC, VA, WV, NC, SC, GA, FL), East North Central (OH, IN, IL, MI, WI), East South Central (KY, TN, AL, MS), West North Central (MN, IA, MO, ND, SD, NE, KS), West South Central (AR, LA, OK, TX), Mountain (MT, ID, WY, CO, NM, AZ, UT, NV); and Pacific (WA, OR, CA, AK, HI). Relationships between these categorical centre variables and survey response rates were analysed using Chi-squared or Fisher's exact test where appropriate.

For the purpose of analysing adherence to the international recommendations listed above, EBMT centres were grouped into two centre volume categories (above and below the median 23 allografts per year) and were categorised by the presence or absence of JACIE accreditation. US transplant centres were grouped into two centre volume categories (above and below the median 25 related donor allografts per year).

## 2.5 A PROSPECTIVE STUDY EXPLORING THE FEASIBILITY OF UD REGISTRY INVOLVEMENT IN RD CARE

### 2.5.1 OVERVIEW

This study explores the potential role(s) of an UD registry in related HPC donor care. In conjunction with the Anthony Nolan donor provision and follow-up teams, and physicians from three large transplant centres, I devised three models of RD care and explored the feasibility of each, before setting up a prospective pilot study of the most feasible.

### 2.5.2 DEVELOPMENT OF POTENTIAL DONOR CARE PATHWAYS FOR PILOT STUDY

I used the thoughts expressed at an EBMT annual meeting 2013 session debating the potential role for UD registries in the management of related donors at (outlined in detail in Chapter 6) as a basis for determining where input from an UD donor registry would be more helpful in RD care. I considered each of these advantages and disadvantages in the context of the UK healthcare system and transplant centre set-ups.

I next contacted donor physicians from three European registries where the registry has successfully assumed responsibility for some aspects of RD care in recent years. I obtained details of these models from the teams responsible, and analysed the advantages and disadvantages of implementing these models in the UK.

I used this data to formulate three potential related donor pathways with options ranging from the registry conducting the whole care pathway to the registry providing one aspect of donor care. Briefly, these included the following:

Model 1) A pathway where the registry provided all aspects of care following identification of a suitable related donor

Model 2) A pathway with donor evaluation performed in the transplant centre by an independent external physician and donor follow-up performed by the registry with other aspects of care unchanged

Model 3) A pathway with donor follow-up performed by the registry, and all other aspects of care managed by current procedures within the transplant centre

These models are discussed in detail in Chapter 6.

I worked with staff within the Operations, Quality and Finance teams of the Anthony Nolan to define each step of each pathway and determine the changes in procedures required by the registry. I obtained internal approval for pilot studies for each proposed model. Standard operating procedures and donor information and consent forms provided at each stage of the pathway for unrelated Anthony Nolan donors were reviewed and altered where necessary to be fit for purpose in RDs.

I next discussed these pathways with three large UK transplant centres and modified the models to best accommodate transplant centre needs. For Model 1, I also discussed the processes involved in this pathway with the clinical Haematology team at the largest affiliated collection centre, The London Clinic.

### 2.5.3 COST ANALYSIS

As part of assessment of the feasibility of these three pathways of donor care I had devised, I conducted a cost analysis to determine whether a) funds would be required for a pilot study and b) whether these models would require additional resourcing for related donor care if implemented on a national scale in the future.

In order to conduct a cost analysis I examined each proposed model of donor care that I intended to pilot, from the point of request for donor work up to donor follow-up to

determine where proposed changes in procedures from current transplant centre based care would influence the cost care provision.

I interviewed the managers of Anthony Nolan Donor Provision, Medical and Donor Follow-up teams and obtained estimates for the number of hours work required per donor. Costs for each team member per hour were then obtained from the Anthony Nolan human resources department allowing calculation of registry manpower costs for each donor. I obtained the costs for the aspects of the donor care performed by the affiliated collection centre from the pricing agreement between Anthony Nolan and the largest affiliated collection centre. This included the donor medical procedure, donor investigations, and charges for the harvest procedure. I calculated the likelihood of a one-day or two-day PBSC collection in related donors using data I obtained from the study outlined in Chapter 3, and thus calculated an overall apheresis cost per donor. The travel, accommodation and employment reimbursement costs that are provided by the registry for unrelated donors were not included in this model, as these are not usually covered in the related donor context.

In order to provide transplant centres with a comparison, I also calculated typical costs for provision of related donor care within the transplant centre setting. I obtained these costs by interviewing team members within a large transplant centre, The Royal Marsden - one of the centres invited to participate in this study. I obtained estimates for the number of hours work per donor provided by the nursing, medical, data management and apheresis teams. I obtained costs per hour for each staff member from The Royal Marsden clinical trials team.

#### 2.5.4 SET UP OF PILOT STUDIES

After defining work flows and cost calculations for these three models of donor care, I contacted three large UK transplant centres, The Royal Marsden, King's College Hospital, and Nottingham University Hospital. These were selected for two reasons. Firstly, as large transplant centres, these use the highest number of RDs. Secondly,

these centres all use the Anthony Nolan Graft Identification and Advisory service and strong links exist between Anthony Nolan and these organisations.

Following discussions with transplant centres confirming initial interest, proposals (see Appendix 1) were sent to The Royal Marsden and King's College Hospital outlining Model 1 'Provision of Related Donor care in a UD registry setting from the point of donor identification' and Model 2 'Evaluation of Related Donors within a transplant centre by an external physician'. A proposal regarding the Model 3 'follow-up of related donors by Anthony Nolan' was sent to Nottingham University Hospital (see Appendix 1).

As detailed in Chapter 6, the proposed pilot studies for Model 1 and Model 2 were not finally approved by either centre for logistical and financial reasons. Following acceptance of the pilot study for Model 3 by the Anthony Nolan Institutional Review Board and by Nottingham University Hospital, recruitment to the study commenced on 1/10/14 for a thirteen-month period to 1/11/15.

### 2.5.5 ASSESSMENT OF FEASIBILITY

In order to determine the future potential of this care model I wanted to evaluate the pathway from 3 perspectives; those of the related donors who undertook follow-up at Anthony Nolan, the transplant team at Nottingham University Hospital, and the Anthony Nolan donor follow-up team. Since the follow-up of these donors is on-going to 10 years post-donation, it was not possible to complete an evaluation of the whole follow-up process, for discussion in this thesis, but an initial evaluation to 'troubleshoot' problems was conducted.

Related donors were given the opportunity to feed back on the donation process and the initial contact from the Anthony Nolan donor follow-up team during completion of the Day 7 medical questionnaire. This questionnaire contained identical questions to

the version sent to all Anthony Nolan unrelated donors, allowing some descriptive comparisons between the two groups.

At the mid-point and end-point of study recruitment, I conducted an interview with the Anthony Nolan donor follow-up manager responsible for the related donors on the pilot study, to determine any problems with the process and consider modifications that would be necessary if this follow-up model was to be offered nationally. Initial acceptability of the pathway to the transplant centre was evaluated by email.

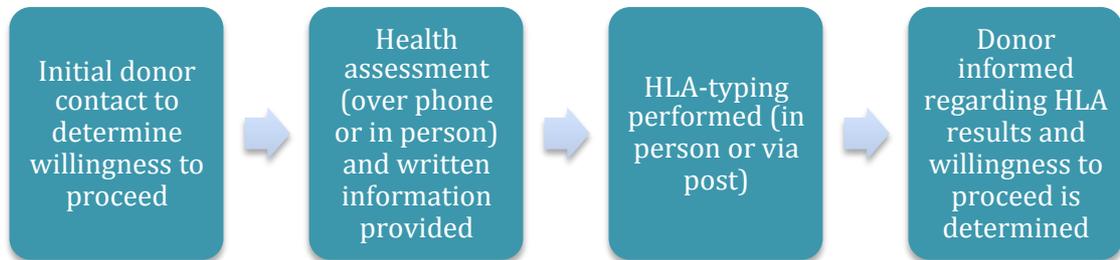
## 2.6 A STUDY EXAMINING THE EXPERIENCE OF RELATED DONORS

### 2.6.2 THE DONOR CARE PATHWAY

The process for donor care in the centre studied, The Royal Marsden, is summarised in Figures 2.1 and 2.2. Donors are initially identified by their relatives who pass the details of potential donors to a transplant clinical nurse specialist who acts as donor coordinator throughout the process. Donors are contacted by telephone and the details of the donation procedure are discussed. Willingness to donate is determined and a health assessment is conducted, either by email, phone or in person. Written information about donation is also supplied at this point.

Blood for HLA typing is drawn at the hospital or via the GP depending on the donor's location. The donor is informed of the HLA results by telephone or email and donors are again asked to confirm willingness to proceed and consent to inform the recipient of their matching status is taken.

Figure 2.1 Process for identification of matched related donors at The Royal Marsden



Donors visit The Royal Marsden for evaluation and consent, which is conducted by a transplant physician who is not responsible for the care of the recipient. Donors are assessed using modified Anthony Nolan suitability criteria for unrelated donors. Donors are offered a choice of donation route.

GCSF administration is arranged at the hospital, or via the GP for the first injection, following which donors may administer their own subsequent doses if desired. Donors attend The Royal Marsden for donation. A follow-up phone call is made by the donor coordinator or an apheresis nurse within 7 days of donation to ensure the donor is recovering as expected. Donors then receive annual follow-up questionnaires for 10 years post-donation, according to the WBMT recommended minimum data set (Halter *et al*, 2013). A summary of the recommendations that this pathway meets is provided in Table 2.1

Figure 2.2 Process for the donation and follow-up of related donors at The Royal Marsden



*Table 2.1 Summary of the recommendations with which the donor pathway complies*

<b>Recommendation</b>	<b>Source of recommendation</b>
Information is provided prior to HLA typing	FACT-JACIE
Willingness is determined prior to HLA typing	WMDA subgroup recommendations
HLA typing results are first disclosed to the potential donor	FACT-JACIE WMDA subgroup recommendations
Donor evaluation is conducted by a physician not involved in recipient care	FACT-JACIE WMDA subgroup recommendations
Donors are offered a choice of donation routes	WMDA subgroup recommendations
The risks and benefits of the procedure are discussed	FACT-JACIE
Policies for related donor care include donor evaluation, BM and PBSC harvesting from donors	FACT-JACIE
Written eligibility criteria are used to assess related donors	FACT-JACIE
Donors are followed up to 10 years post-donation	FACT-JACIE WBMT WHO guiding principles

### 2.6.3 SURVEY DEVELOPMENT AND ADMINISTRATION

A 20-item questionnaire was created to evaluate the emotional support and information provided at each stage of the donation process, and the physical and psychological effects of donation. Questions were also asked to allow identification of any logistical difficulties experienced by donors, and their thoughts on ways to improve the pathway were sought.

The following domains were addressed:

- 1) Care before the donor medical evaluation (6 items)
- 2) The donor evaluation and donation procedure (9 items)
- 3) Post donation care (5 items)

The study questionnaire and letter of invitation was reviewed by the Royal Marsden Audit committee, HPC Transplant Consultants and Clinical Nurse Specialists.

The study population consisted of all adult (>16 year old) related donors who had undergone stem cell donation under the adult RD pathway at The Royal Marsden between 1<sup>st</sup> January 2009 and 31<sup>st</sup> December 2014. The survey was administered by post, using the last recorded address in the donor medical records. Donors received a letter outlining the study aims and inviting them to participate along with a printed copy of the survey questionnaire and a return envelope. The invitation also contained a link to an internet-based version of the same questionnaire via a secure hyperlink (smartsurvey.com) with a unique identifier to allow donors the choice of response methods. Following the initial invitation on 14<sup>th</sup> April 2014, non-responders received 1 further reminder, sent in an identical manner six weeks after the first invitation. The study closed to recruitment on 1<sup>st</sup> August 2015.

Details regarding donor demographics, donation dates and participation in follow-up were obtained from the hospital electronic patient records.

#### 2.6.4 STATISTICAL ANALYSES

Continuous donor characteristics were categorised for the purpose of analysis. Age above or below the median 50 years at the time of donation, era of transplant (pre and post 2012) and the relationship between these variables and donor sex to responses rates and to selected questions about donor experience were examined using chi-squared. Elsewhere descriptive analyses were applied.

## CHAPTER 3. A RETROSPECTIVE STUDY EXAMINING THE IMPACT OF JACIE ACCREDITATION ON RD CARE

*A paper based on the findings of this study was published in the journal Bone Marrow Transplantation in November 2014, entitled “The impact of improved JACIE standards on the care of related BM and PBSC donors” (Appendix 2)*

### 3.1 INTRODUCTION

In the introduction to this thesis I described some of the studies conducted by large unrelated donor registries, which have demonstrated a reassuringly low incidence of short-term adverse events (Pulsipher *et al*, 2009; 2014) and a lack of evidence for long-term effects of donation in this population (Shaw *et al*, 2015).

There are far fewer data on which to base estimates of adverse events in related donors, however, studies to date suggest that these donors are at greater risk than UD during BM and PBSC donation (Halter *et al*, 2009; Wiersum-Osselton *et al*, 2013; Kodera *et al*, 2013). In addition, surveys performed in Europe and the United States have outlined concerns regarding the potential for a conflict of interest when a single physician is simultaneously responsible for a related donor and their intended recipient. Differences between the care received by UD and RDs was also noted, including the absence of organised follow-up in the RD setting (Clare *et al*, 2010; O'Donnell *et al*, 2010).

As a result of such studies, changes have been made to FACT-JACIE Standards aiming to promote the interests of related donors. In April 2011, the 4<sup>th</sup> Standards (FACT-JACIE, 2011) introduced a requirement for “a policy for follow-up of allogeneic donors that includes routine management and the management of donation-associated adverse events”. This was followed by a further recommendation in the 5<sup>th</sup> edition (March 2012) (FACT-JACIE, 2012) that allogeneic donors should be assessed by a

“licensed health care professional who is not the primary transplant physician overseeing care of the recipient”

Other organisations with an interest in donor health and safety have offered consensus recommendations in this field. The most comprehensive of these were produced by the Ethics Working Group and the Clinical Working Group of the WMDA (van Walraven *et al*, 2010b) and focus on donor counselling prior to HLA typing, consenting procedures (including the importance of independent consent, and offering donors a choice of donation route), and donor follow-up. In 2013, a Worldwide Network for Blood and Marrow Transplantation (WBMT) consensus statement was published outlining the importance of standardised global follow-up for both RD and UD, with a recommended minimum data set to be collected at a minimum of 1, 5 and 10 years post-donation (Halter *et al*, 2013).

To date, the impact of these efforts to improve related donor safety and to standardise care, has not been evaluated.

Due to a lack of national or international medical suitability for related donors, screening procedures for RDs are likely to be less thorough than those undertaken for UDs internationally. One study (Coluccia *et al*, 2012) showed that just 26% of 500 RDs donating in Italy were screened in accordance with national UD protocols, and a large prospective study in Japan (Kodera *et al*, 2013) showed a 5 times greater risk of SAEs in RDs who did not meet national UD criteria.

Most experts feel that RDs who undergo fully informed consent should be permitted to proceed with conditions for which an UD would be deferred, providing that the increased risk is felt to be minimal; but defining which conditions should be accepted is very difficult. The question of an upper age limit for RDs in the absence of medical issues is particularly challenging. Most transplant centres accept donors above the UD upper limit of 55-60, but WMDA Standards for evaluation of UDs (Lown *et al*, 2014) were developed for donors under the age of 55-60, and the optimal approach to older

donors is unclear, i.e. whether additional screening procedures are warranted (Niederwieser *et al*, 2004).

A second concern when considering the use of older haematopoietic progenitor cell (HPC) donors is the quality of stem cells harvested. Older age (>55) correlated with lower CD34+ yields in some studies (Lysák *et al*, 2010; Richa *et al*, 2009; Vasu *et al*, 2008) but despite this, adequate engraftment occurred, and medically fit older donors usually harvest adequate CD34+ cells to allow transplantation to proceed (de Lavallade *et al*, 2009; Richa *et al*, 2009; Vasu *et al*, 2008).

To address these questions, I carried out a single centre retrospective study of related donors who underwent donation before and after introduction of these JACIE Standards. The primary objectives of the study were:

- 1) To determine whether donors' follow-up became more prevalent following the introduction of 4<sup>th</sup> FACT-JACIE Standards in April 2011 requiring "a policy for follow-up of donors that includes routine management and the management of donation-associated adverse events"
- 2) To determine whether consenting procedure changed following introduction of the 5<sup>th</sup> FACT-JACIE Standards in March 2012 recommending that allogeneic donors should be assessed by a "licensed health care professional who is not the primary transplant physician overseeing care of the recipient".

Secondary objectives included:

- 1) To evaluate whether serious adverse events were more likely to occur in donors who would not have been accepted as unrelated donors.
- 2) To evaluate whether age alone was associated with an increased likelihood of serious adverse events in otherwise healthy donors.
- 3) To assess whether donors >60 years old were less likely to achieve an optimal harvest.

## 3.2 METHODS AND MATERIALS

This was a retrospective study of all adult and paediatric allogeneic donors donating from January 2004 to December 2013 at the Royal Marsden Hospital. Donor health history, details of the harvest and yield, and adverse event and follow-up data were collected from the donor electronic medical records. The full material and methods can be found in Chapter 2.

## 3.3 RESULTS

### 3.3.1 DONOR AND PATIENT CHARACTERISTICS

221 related donor transplants occurred during the study period. Five of these were excluded from the analyses, four because frozen HPCs were used which had been collected prior to the study period, and one because sibling cord blood was used. The data regarding the remaining 216 donations from 207 related donors were collected and analysed (9 siblings donated twice during the study period). 204 donors were fully matched siblings, one was a fully matched mother, one a fully matched cousin, and one was a haplo-identical son.

Table 3.1 describes the donor characteristics. The median RD age at donation was 43.5 years (range 22 months-74 years). 181 PBSC harvests were performed, of which two were classed as mobilisation failures and were followed by an emergency bone marrow harvest. 37 BM harvests were performed. 30 (14.5%) donors were paediatric (<16 years), of whom all donated bone marrow.

Table 3.1. Characteristics of the 207 related donors and 216 donations studied

Donor characteristics	N (%)
<b>Gender</b>	
Male	117 (57)
Female	90 (43)
<b>Age at 1<sup>st</sup> donation</b>	
Median (range)	43.5 (1-74)
<16	30 (15)
16-40	65 (31)
40-60	87 (42)
>60	25 (12)
<b>Stem cell source</b>	
PBSC	181 (84)
BM	37* (16)
<b>PBSC apheresis procedures</b>	
1	104 (57)
2	77 (43)
<b>PBSC target &gt;4x10<sup>6</sup> /kg reached</b>	
Yes	129 (71)
No	52 (29)
<b>Year of donation</b>	
2004	1
2005	21
2006	20
2007	25
2008	27
2009	23
2010	33
2011	24
2012	30
2013	14
<b>Deferrable adult donor</b>	
Yes	53 (30)
No	124 (70)
<b>CVC insertion for PBSC collection</b>	
Yes	4 (2)
No	177 (98)
<b>Overseas donor</b>	
Yes	55 (27)
No	152 (73)

\*two BM harvests were performed as 'rescue' procedures following poor PBSC mobilisation

Table 3.2. Characteristics of the transplant recipients

<b>Recipient characteristics</b>	<b>N = 207</b>
Age at transplant	48.1 (2-74)
Days to engraftment	15 (7-31)
<b>Alive at last FU</b>	
Yes	123 (58%)
No	89 (42%)

### 3.3.2 THE EFFECT OF CHANGES TO FACT-JACIE STANDARDS ON DONOR CARE

I was able to show significant improvements following changes to FACT-JACIE Standards. Prior to the introduction of a specific recommendation to separate donor and recipient consent in 2012, the same physician consented both the donor and their recipient in 34/173 (20%) cases, compared to 0/43 cases occurring after this event ( $p=0.003$ ). Despite this, on review of the patient records, I found that although the consenting procedure had been separated, in 26% of these 43 cases, the physician consenting the donor had nevertheless been responsible for the care of their intended recipient within the last month.

I examined donor follow-up before and after the introduction of a specific FACT-JACIE requirement for donor follow-up in April 2011. I again found significant improvements, with follow-up beyond 1 week post-donation having been attempted in 37% of donors before this time point, compared 58% of donors after this point ( $p=0.007$ ).

Although insufficient details were available retrospectively to determine compliance with all the consensus recommendations published by WMDA (WMDA, 2013), I was able to analyse the reports of the consent discussions, and found that discussions had become more extensive over time, specifically regarding discussion of both potential routes of donation for adult donors. After guidelines recommending that donors be

offered a choice of donation route were published in 2010, 80% adult donors were offered this choice, compared to 33% prior to 2010 ( $p < 0.001$ ).

### 3.3.3 RETROSPECTIVE EVALUATION OF ADULT RDS USING ANTHONY NOLAN DONOR SUITABILITY CRITERIA

On retrospective review of all adult RDS using national (Anthony Nolan) medical suitability criteria (available at <http://med-guidelines.org.uk>, accessed 12<sup>th</sup> November 2013), I found that 53 of 177 adults (30%) would have been deferred as unrelated donors. The reasons for deferral are outlined in Table 3.3. Age over 60 years was the most common reason (29 donors, 55% deferrals) and of these donors, 19 would have been deferred for age alone, while the other 10 had a second deferrable condition (most commonly uncontrolled hypertension).

*Table 3.3. Deferral conditions for 53 deferrable donors on retrospective assessment using Anthony Nolan medical suitability criteria*

<b>Reason would have been deferred</b>	<b>Number of donors</b>
Age >60	29*
Uncontrolled Hypertension	16
Diabetes on treatment	5
BMI >40	2
Other **	12

\*19 of these donors were also deferrable for a second reason other than age

\*\*Sickle trait undergoing PBSC donation; Gout three weeks pre-PBSC donation; endometrial cancer; gene repair defect msh2; previous intravenous drug user; central nervous system symptoms following head injury; multinodular goitre awaiting surgery; severe chronic back pain and paraesthesia; SVT pre-ablation; ischaemic heart disease

### 3.3.4 SERIOUS ADVERSE EVENTS

The serious adverse events reported in this donor cohort are described in Table 3.4. All SAE occurred in donors undergoing their first donation. Five adults (2.7%) and one paediatric donor (3.2%) developed SAEs. A 67-year-old male donor developed severe gout two weeks post donation, which did not respond to treatment. He then developed

hypotensive episodes, which resulted in admission to hospital three weeks post-donation. A 62-year-old female with no previous cardiac history developed chest discomfort towards the end of her first apheresis procedure. Her ECG showed new T wave inversion, but her chest discomfort settled and cardiac enzymes were negative. The apheresis procedure was prematurely terminated, but the yield was nevertheless satisfactory ( $8.5 \times 10^6$  CD34+ cells/kg recipient weight). She was referred to her GP for follow-up cardiac investigations, the results of which were not available.

In the third case, a 62-year-old male donor developed severe chest pain during mobilisation. On day 3 of mobilisation, he attended for review and was admitted for pain control and observation. Although the pain was not felt to be cardiac in nature, due to the severity of his symptoms the dose of GCSF was halved for subsequent doses. He went on to collect a satisfactory harvest ( $5.7 \times 10^6$  CD34 cells/kg recipient weight).

The fourth SAE occurred in a 60-year-old male, who developed chest pain during mobilisation, which was relatively mild and was not reported to the transplant centre. He then described the same pain on arrival for apheresis and was found to have new ischaemic ECG changes in the anterior leads and a borderline troponin rise. He underwent PBSC harvest and was given aspirin and a statin but collected a CD34+ dose of  $1.56 \times 10^6$ /kg recipient weight on the first day. He was not given further GCSF and the following day his ECG had normalised and he underwent a second apheresis procedure. He subsequently underwent extensive cardiac investigations, which were unremarkable.

The fifth SAE occurred in a 55-year-old man with no previous medical history who complained of pain in his right foot on arrival for apheresis. Examination was consistent with gout. He was harvested but symptoms continued to deteriorate over the next two days, such that he was unable to mobilise and could not return home by plane. His symptoms settled over a period of several months.

One paediatric donor aged 22 months, received an allogeneic red cell transfusion following bone marrow harvest due to a post procedure haemoglobin 62g/L. This was the sole severe adverse event amongst paediatric donors.

*Table 3.4. Procedure related serious adverse events in five adult donors*

<b>Donor age</b>	<b>Donor Sex</b>	<b>Year of donation</b>	<b>Donation route</b>	<b>Deferrable donor</b>	<b>Deferrable Condition</b>	<b>SAE</b>
67	M	2012	PBSC	Yes	Age, hypertension	Gout + hypotensive collapse 3 weeks post-donation
62	F	2011	PBSC	Yes	Age	Ischemic ECG changes during donation
62	M	2008	PBSC	Yes	Age	Chest pain requiring modification of GCSF dose during mobilisation
60	M	2005	PBSC	Yes	Age	Chest pain with ischemic ECG changes during apheresis
55	M	2009	PBSC	No	NA	Severe gout during donation

I analysed the donor characteristics associated with SAEs in these adults and found that 10.3% donors who were >60 years developed SAEs compared to just 1.3% of those aged 60 or less (p=0.020). I also found that adults who would have been deferred due to donor health risks, had they been assessed according to Anthony Nolan donor suitability criteria, were more likely to develop SAEs. 8% of these deferrable adults developed SAE compared to 0.7% of donors who would not have been deferred for risks to donor health.

Table 3.5 Factors influencing the incidence of severe adverse events

<b>Donor characteristic</b>	<b>Severe adverse events N (%)</b>	<b>p</b>
<b>Donor sex</b>		
Male	3 (2.9)	0.824
Female	2 (2.4)	
<b>Adult donor aged &gt;60 Adult donor aged 60 or less</b>		
Adult donor aged >60	3 (10.3)	0.02
Adult donor aged 60 or less	2 (1.3)	
<b>Year of donation</b>		
Pre 2010	3 (2.9)	0.824
2010 or later	2 (2.4)	
<b>Deferrable for donor health reasons</b>		
Yes	4 (7.5)	0.018
No	1 (0.7)	

### 3.3.5 THE IMPACT OF DONOR CHARACTERISTICS ON HPC YIELD AND ENGRAFTMENT

#### 3.3.5.1 PBSC donations

A median yield  $4.83 \times 10^6$  CD34+/kg recipient weight (range 0.15-54) was harvested from PBSC donors. Engraftment occurred at a median 14 days in these recipients. There were no cases of primary graft failure, however 3 patients died of infection within 28 days of transplant without engrafting.

As shown in Figure 3.1, a significant reduction in CD34+ yield was associated with increasing donor age. Of note, this resulted in an effect on engraftment, recipients with a donor >60 years were more likely to take longer than the median 14 days to engraft than donors in other age groups ( $p=0.039$ ).

Figure 3.1 the relationship between donor age and CD34+ yield achieved at PBSC harvest.

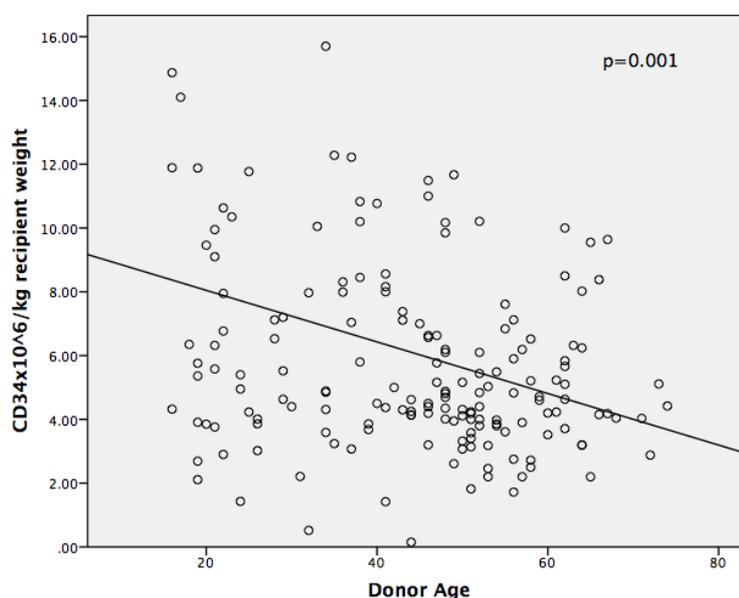
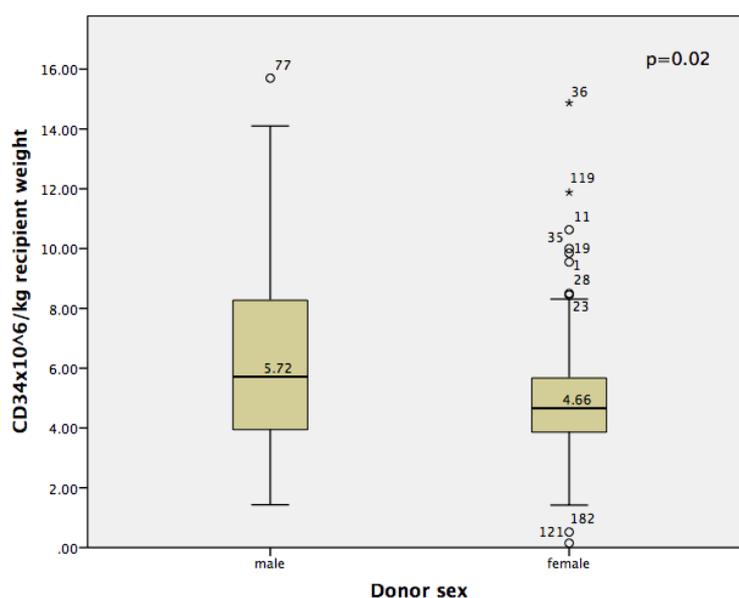


Table 3.6 The relationship between donor or recipient characteristics and recipient engraftment

Characteristic	Number of recipients taking >14 days to engraft	p
<b>Donor age</b>		
16-39	27 (48%)	0.029
40-60	54 (62%)	
>60	19 (79%)	
<b>Donor sex</b>		
M	58 (62%)	0.586
F	42 (58%)	
<b>Patient age</b>		
<16	5 (42%)	0.14
16-39	24 (53%)	
40-60	54 (61%)	
>60	17 (77%)	

Although first PBSC harvests from male and female donors were equally likely to achieve the requested cell dose ( $>4 \times 10^6/\text{kg}$ ), harvest from male donors had a significantly higher yield than those from female donors (median 5.72 versus 4.66;  $p=0.02$ ).

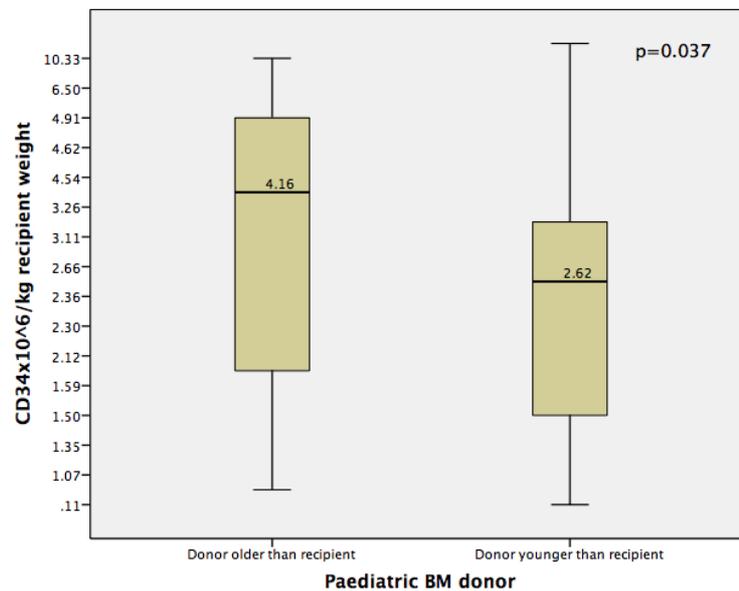
Figure 3.2 Box plot showing CD34+ cell yield in male and female donors



### 3.3.5.2 Bone marrow donations

Bone marrow donors harvested a median  $2.66 \times 10^6/\text{kg}$  CD34+ cells, and engraftment was seen at a median 20 days post-transplant in recipients of BM. Harvests from paediatric donors who were donating to an older sibling were significantly less likely to achieve the target CD34+ cell dose of  $4 \times 10^6/\text{kg}$  recipient weight (18% versus 53%;  $p=0.031$ ). I noted similar findings examining HPC yield as a continuous variable; a median of  $4.16 \times 10^6$  CD34+/ $\text{kg}$  was seen in paediatric donors to a younger sibling compared to  $2.6216 \times 10^6$  CD34+/ $\text{kg}$  from paediatric donors donating to an older sibling ( $p=0.037$ ).

Figure 3.3 Box plot showing the relationship between donor recipient age discrepancy and HPC yield.



### 3.3.6 DONOR FOLLOW-UP

85 donors (41%) were offered follow-up beyond one week post-donation, achieving in total 95 donor follow-up years. Follow-up was undertaken using medical questionnaires to collect the minimum data set recommended by WBMT (Halter *et al*, 2013) in 54 donors, and were returned by 30 donors (56%) with a significant difference seen in response rate, depending on recipient health status. Only 31% of donors whose recipient had died returned their follow-up questionnaires, compared to 66% of donors whose recipient was alive at time of follow-up (p=0.020).

27 donors had been offered clinic appointments at 3-9 months post donation, which 23 (85%) attended. GPs had been asked to provide follow-up for a further 4 donors.

There was no record of an attempt to contact the remaining 124 RDs beyond one week post-donation, of whom 11 were living overseas and had no permanent address recorded by the hospital. I was, however, able to collect follow-up medical data from 19 of the donors, who had either failed to return medical questionnaires or had not been offered follow-up, from reports from medical evaluation prior to subsequent lymphocyte donations, which occurred 2-60 months following their initial donation.

In total, as detailed in Table 3.7, six donors described new medical issues at follow-up, none of which were felt to be donation related.

*Table 3.7. Medical issues identified at follow-up*

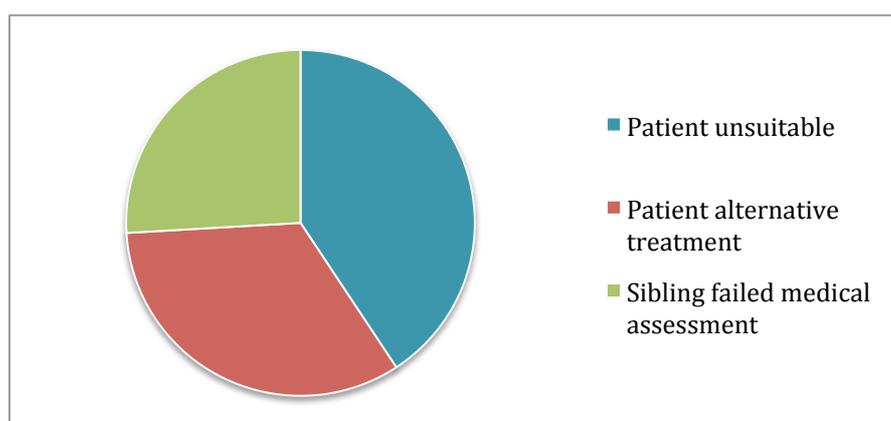
<b>Donor sex</b>	<b>Donor Age</b>	<b>Deferrable donor</b>	<b>Reason would have deferred</b>	<b>Donation route</b>	<b>Event</b>
M	66	Yes	Age	PBSC	Required further hypertensive meds
M	45	Yes	Hypertension	PBSC	Macular degeneration
F	57	Yes	Multinodular goitre	PBSC	Neutropenia and rheumatoid arthritis
M	50	Yes	Gout 3 weeks pre-donation	PBSC	Gout 5 months post-donation
F	74	Yes	Age	PBSC	Hypertension diagnosed 6 months post donation
F	21	No	NA	PBSC	On-going tiredness 2 years post donation

### 3.3.7 MATCHED DONORS WHO DID NOT PROCEED TO DONATION

Over the period studied, 28 patients had at least one fully HLA matched sibling identified, but did not proceed to transplant with this donor. In 11 patients this occurred because the patient developed progressive disease or became subsequently unsuitable for allograft, due to clinical deterioration. Nine patients were considered for matched sibling allograft but finally determined to be more suitable for alternative

treatment strategies. In one case a matched sibling donor was identified after having samples sent for HLA typing to the UK from the potential donor's home abroad, but subsequently declined to donate due to the personal financial burden of travelling from abroad.

*Figure 3.4 The reasons for failing to proceed with sibling transplants in 28 patients with matched sibling donors*



A further seven HLA-matched siblings were scheduled for donation but subsequently failed at the point of donor medical assessment. Of note, these cases all occurred in the latter part of the study period, between 2011-2013. The reasons for deferral are described in Table 3.8. Six donors were failed for medical reasons and one for failure to commit to abstaining from high-risk sexual practices. Interestingly, 5/6 of these siblings failed medical evaluation due to abnormal haematological indices. In three of these cases, two with eosinophilia and one with polycythemia, it was felt that the donor could potentially have been used if further investigations could be undertaken to exclude a primary haematological diagnosis. However, these donors all lived overseas, and were unable to remain in the UK for sufficient time to allow such investigations to be completed. In each of these cases the decision was made to use a previously identified well matched UD instead.

*Table 3.8 Details of 6 related donors who were failed at the time of donor medical*

<b>Reason for failing donor medical</b>	<b>Patient outcome</b>
Anaemia+ eosinophilia	UD HSCT
Polycythaemia with microcytosis	Foreign self-employed donor decision not to await investigation UD HSCT
Eosinophilia + weight loss	UD HSCT
BMI 43+ polycythaemia	Transplant delayed. Cord HSCT
High risk behaviour	UD HSCT
High platelets. JAK2 positive on further testing	UD HSCT
Uncontrolled Hypertension	Matched younger sibling used

### 3.4 CONCLUSIONS

Following the introduction of requirements for donor follow-up in 2011 and separation of donor and recipient consent in 2012, my results show significant improvements in these areas. However, although donors were not consented by the physician consenting their intended recipient after 2012, I found that the donor's physician had been responsible for the recipient's care in a quarter of cases within the last month. This finding suggests that some potential for conflict of interest remains.

To completely avoid a potential conflict of interest, the recipient and donor should ideally be cared for by separate teams. Although historically transplant physicians have provided donor care in the majority of centres, there is no reason that they should be uniquely able to do so. Stem cell donor evaluation should be performed by a clinician with the skills to identify occult medical conditions that may present a risk to the donor or recipient, however, a general physician or non-transplant haematologist should be equally well placed to conduct such an assessment. The important thing is that this donor assessor should undergo specific training in donor health, and should evaluate the donor independently.

In this study, I found a similar incidence of SAEs to those reported previously (Wiersum-Osselton *et al*, 2013) but importantly, I was able to identify predictive factors here. I found that donors who did not meet Anthony Nolan medical suitability criteria for reasons of donor risk, were more likely to experience SAEs. This was also true of donors aged over 60 years.

The problem with this finding lies in the fact that deferral of all donors who did not meet the Anthony Nolan deferral criteria would have resulted in deferral of 28.6% of these adult donors, thereby depriving their recipients of the optimally matched donor. If age were not included as a deferral criterion, this high deferral rate would have fallen to 18.4% of adults. Whilst it would be overly conservative to consider deferring all donors over the age of 60 on the basis of these results, my results suggest that consideration should be given to enhance screening procedures undergone by donors in this age group. In both this study and other reports, cardiovascular complications constitute the majority of SAEs and additional cardiac assessment may therefore be warranted.

Perhaps understandably, donors whose recipient had died were less likely to respond to follow-up questionnaires. This raises the question of whether donors may find it more acceptable to be followed up by an organisation separate to the centre where their relative was treated, or whether they are simply less willing to engage in follow-up due to negative connotations about the donation episode.

This study had some notable limitations. Firstly, since the data were collected retrospectively, it is possible that additional adverse events other than those detailed occurred, but were not recorded in the donor record or were not reported by the donor to the transplant centre. Secondly, the donor health information was collected from the report by the assessing physician, and since a number of different physicians were responsible for donor evaluation over this period, it is possible that some donors had medical conditions that were missed in these reports.

In conclusion, this study importantly demonstrates that FACT-JACIE, as a regulatory body, can drive change in the field of related donor care. The identification of donor

characteristics associated with increased likelihood of adverse events adds to current evidence in this area and should act as a basis for development of additional screening strategies in these donors, and for fully informing donors of additional risks posed. Ultimately, risk stratification and screening of older donors and those who do not meet UD medical suitability criteria should serve to reduce rates of SAEs in related donors.

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## CHAPTER 4. A STUDY OF RELATED DONOR CARE IN THE UK, AND TRANSPLANT PHYSICIAN OPINIONS

*A paper based on the findings of this study was submitted to the British Journal of Haematology entitled “Variations in practice in UK transplant centres: results of a related donor care survey”.*

### 4.1. INTRODUCTION

In the previous chapter I retrospectively assessed the changes resulting from the introduction of two FACT-JACIE standards directly addressing donor care, in a single UK transplant centre. I was able to show that practice had improved following as a result of regulatory standards, but that a potential for conflict of interest remained. I also showed that this centre had been unable to fully comply with the requirement for donor follow-up.

There are no published studies exploring the management of RDs UK wide. A survey of RD care (Clare *et al*, 2010), conducted at the EBMT Annual Meeting in 2007, was completed by 22 UK nurses, comprising 34% of total survey respondents. The results of UK centres in this study were reported in aggregate with those of other nations, and showed variation in a) the way that donors were informed regarding the donation procedures, b) consenting procedure and c) follow-up policies. A weakness of this study was that the survey was completed by nurses who were not necessarily well versed in their centre’s procedures for managing related donors.

Experts who have reported on the few studies performed to date examining related donor care have suggested two potential avenues towards improvement in this field. The first relates to standardisation of care within transplant centres through introduction of consensus guidelines for donor care procedures, along with specific medical criteria against which to evaluate donors. Some parties have suggested that these could be best implemented using existing regulatory frameworks to ensure compliance. The

second option that has been proposed is that related donor management (or parts of the care pathway) could be performed by a separate organisation to the transplant centre, thus removing the problem of conflicted priorities for a transplant clinician assessing the donor while being involved in the care of their intended recipient. This idea was explored in detail in a debate session during the EBMT annual meeting 2013, where the perceived advantages and disadvantages of UD registry involvement in the care of RDs were discussed. Overall, the transplant physicians and donor care experts present at that debate expressed enthusiasm for exploring alternative models of related donor care. However, these experts were a group of self-selected clinicians who likely attended this session due to a pre-existing interest in donor welfare and these opinions cannot be generalised to the transplant community as a whole.

Before starting to consider the optimal approach to donor care in the UK, a vital first step was to comprehensively define current UK care pathways, and to engage the physicians who are currently providing this care in discussion regarding alternative models of donor care. I hypothesised that logistical and financial difficulties within transplant centres may result in incomplete compliance with some mandatory FACT-JACIE Standards, and that the lack of defined criteria for RD care may lead to variation between centres regarding donor evaluation procedures and regarding the medical conditions with which RDs are accepted. To explore these hypotheses I undertook a UK-wide survey of related donor care.

The primary objectives of this study were:

- To determine compliance with recommendations including:
  - a) mandatory FACT-JACIE Standards
  - b) consensus recommendations on donor care
    - i) WBMT recommendations for standardised donor outcome reporting
    - ii) WMDA subgroup recommendations for family donor care management
- To detect variations in RD evaluation procedures.

The secondary objectives were:

- To define how donor care in the UK is carried out for the whole pathway from initial contact with the donor through to follow-up procedures.
- To investigate the views of UK physicians involved in RD care regarding current care pathways and attitudes to potential development of national guidance and alternative care pathways.

## 4.2. METHODS AND MATERIALS

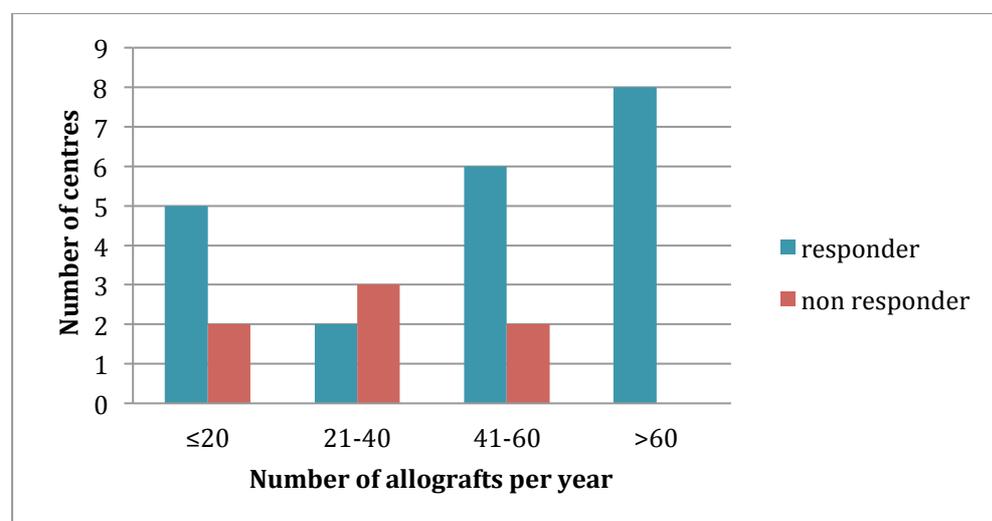
A 47-item survey was sent to transplant directors of all UK transplant centres performing allogeneic stem cell transplants in adults. The survey was administered via a secure hyperlink (surveymonkey.com) from April to July 2014, with invitations sent via the BSBMT. A full description of the materials and methods employed can be found in chapter 2.

## 4.3. RESULTS

### 4.3.1 RESPONSE RATE

26 responses were received from 29 invited transplant centres. Duplicate responses were received from three centres, and one centre was excluded after answering 'no' to the first question "Does your centre assess/manage adult related donors?" This left a total of 22 responses for analysis; a response rate of 76%. No statistically significant difference was seen in response rate by centre size, however all eight of the highest volume transplant centres (those performing >60 allografts per year) responded. The median number of allografts performed was 49 per year (range 4-92) and overall the responding centres performed 82% of the total UK allografts per year (BSBMT data, 2012).

Figure 4.1 The effect of centre volume on the response rate



Of note, 19 of the 22 centres (86%) were JACIE accredited, and a further one centre had undergone first time inspection but not yet received accreditation.

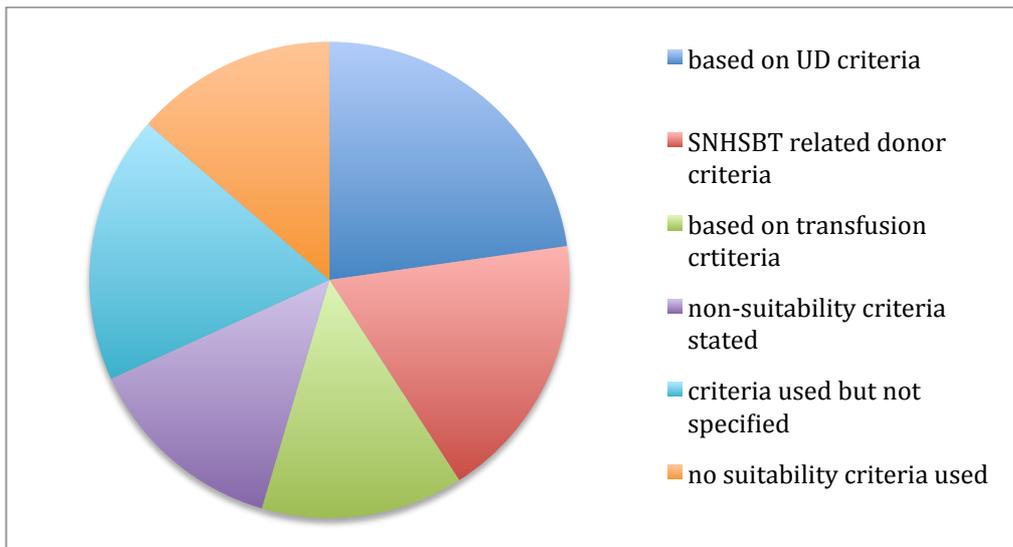
#### 4.3.2 COMPLIANCE WITH FACT-JACIE STANDARDS

I found very good compliance with the recommendations and requirements of FACT-JACIE Standards in UK centres. 21 of the 22 respondents (96%) surveyed stated that their centre had a written policy for RD care. Accreditation status influenced the likelihood of centres having a defined policy for RD care. Of the two centres that were not JACIE accredited nor had undergone first time inspection, 1 centre (50%) did not have a policy for RD care, while all 19 centres with accreditation or on the pathway to accreditation had an RD care policy ( $p=0.005$ ).

19 respondents (86%) stated that defined medical suitability are used for evaluation of related donors in their centre. Of these 15 respondents stated the origins of their suitability criteria. Four centres used the Scottish NHSBT related donor criteria, four used criteria based on UK UD criteria, and one centre on US (NMDP) criteria, and three centres based their criteria on UK blood transfusion service criteria. The remaining three centres either stated HTA or BSBMT as the source of their criteria,

neither of which produce guidelines for determining donor medical fitness to proceed. Two accredited centres and one non-accredited centre lacked defined medical suitability criteria for adult related donors.

Figure 4.2 The origins of medical suitability criteria for related donors in UK transplant centres



*Table 4.1. UK transplant centre compliance with regulatory standards and consensus guidelines in related donor care*

<b>Guideline or standard</b>	<b>N (%)</b>
Existence of a written policy for RD care	21 (95%)
Medical suitability criteria exist	19 (86%)
<b>Information supplied to donors prior to HLA typing</b>	
Verbal only	3 (14%)
Local written information	14 (64%)
National written information	5 (23%)
<b>RD health assessment prior to HLA typing</b>	
By written health questionnaire	4 (18%)
Health questionnaire over phone	5 (23%)
Verbal discussion with open-ended questions	4 (18%)
No assessment	8 (36%)
Willingness to donate is verified pre-HLA typing	21 (96%)
<b>Donor consent and evaluation is undertaken by</b>	
The same transplant physician managing the recipient	1 (5%)
A different transplant physician	10 (45%)
A physician from a different team	9 (41%)
A physician from a different organisation	2 (9%)
Donor follow-up is performed	
To one week	21 (96%)
To one month	17 (77%)
To 1 year	7 (32%)
To 5 years	5 (23%)
To 10 years	3 (14%)
There is a process for credentialing physicians performing BM harvests	
Yes	18 (82%)
No	2 (9%)

All respondents confirmed that their centres comply with the requirement to provide RDs with information about donation prior to HLA typing. In 3 (14%) centres information about donation was communicated verbally at this point, while the other 19 (86%)

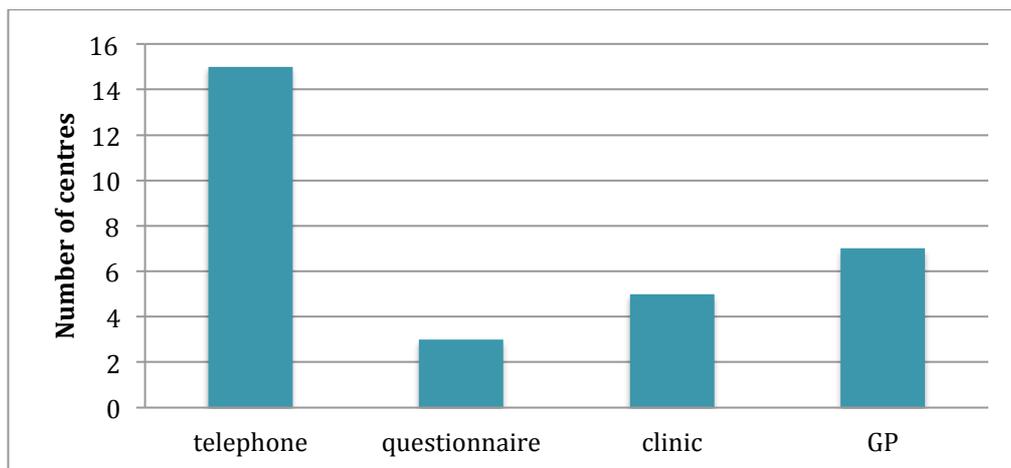
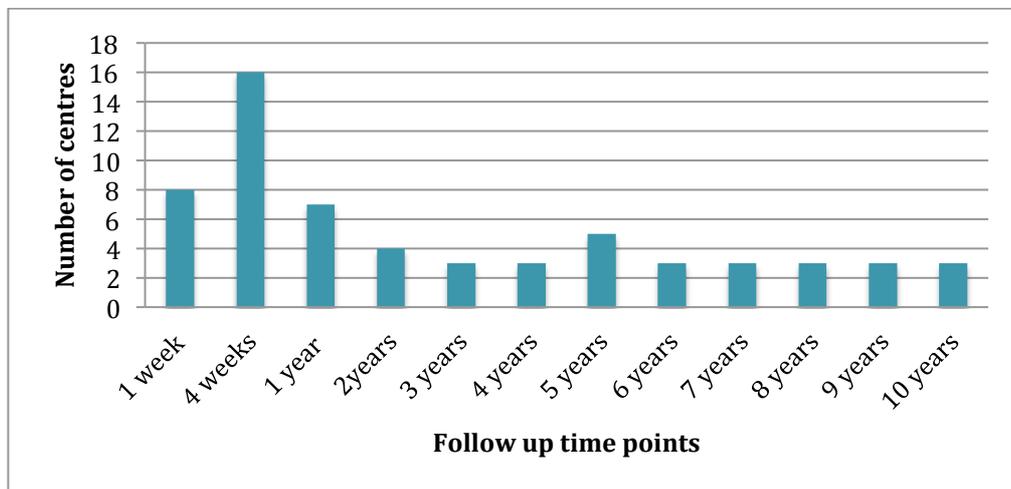
provided written information. In 5 (26%) centres this written information was nationally produced, with four centres supplying donors with the information booklet produced by Lymphoma and Leukaemia Research 'donating stem cells' (Bloodwise, 2012) and one centre supplying approved written information produced by SNBTS (Douglas, 2014). The other 14 centres produced their own local written information for donors.

Respondents stated that RDs are consented by transplant physicians in 50% centres, by a physician from a separate team in 41% centres and by a physician from another organisation in 9% centres. Only one respondent indicated that their centre was unable to meet the JACIE recommendation to separate donor and recipient care, by stating that the same physician would be simultaneously responsible for the care of the recipient.

18 of the 20 centres that perform BM harvests on RDs comply with FACT-JACIE Standards in having a process for specific training of physicians performing BM harvests.

The responses regarding donor follow-up procedures were varied. 21 (96%) centres performed short-term donor follow-up at either one week or four weeks post donation, however only 5 (23%) centres performed follow-up to 5 years and only 3 (14%) centres continued to 10 years. As shown in Figure 4.3, donor follow-up was undertaken by a variety of methods, the most common being telephone calls. Of note, only three centres used written donor follow-up questionnaires, all of which were centres where one of the transplant physicians is concurrently employed by a UK UD registry. 23% of centres report data to EBMT using donor outcome forms, a further 36% were familiar with these forms but these were not used in their centre, and the remaining 36% of respondents were not familiar with this option for reporting donor data.

Figure 4.3 Practice patterns of related donor follow-up: a) The time-points at which follow-up is provided at UK centres b) The methods of donor follow-up employed in UK centres



### 4.3.3 ADHERENCE TO CONSENSUS RECOMMENDATIONS

When I examined aspects of care that have not been addressed in FACT-JACIE Standards, but where published consensus criteria have aimed to harmonise practice, I found consistency in some areas. This included that 21 (96%) centres stated compliance with the consensus recommendation to verify donor willingness to donate before performing HLA typing, and 18 (82%) centres adhered to the recommendation

that donors should be informed of their HLA matching status before the recipient, (van Walraven *et al*, 2010b) while one centre informed the recipient first, and two stated ‘no consistent practice’.

Regarding other recommendations, compliance was more varied. Perhaps most notably, 36% of respondents stated that their centre did not perform any assessment of donor health prior to HLA-typing of a potential donor. In centres where a health assessment was completed, this took the form of a formal questionnaire completed either over the phone or in person in 9 centres (43%) while in 4 (19%) this consisted of a verbal discussion with open-ended questions.

#### 4.3.4 ASSESSING THE MEDICAL SUITABILITY OF RELATED DONORS

As shown in Table 4.2, I found considerable diversity regarding whether transplant centres would accept donors with specified health parameters that are known to influence either donor or recipient risk. Regarding donor risk, 12 (57%) stated that their centre had a limit for donor blood pressure, and 9 (43%) for donor BMI. Regarding recipient risk, 12 (57%) had a policy regarding previous allogeneic blood transfusion and 14 (67%) had a policy regarding previous tattoos. Age, which could be considered as both a donor and recipient risk factor, had an upper limit for acceptance in 9 (43%) centres.

While routine full blood counts and basic biochemistry tests were performed by all centres, other investigations performed as standard by UD registries were not universally undertaken. ECGs are performed in all donors by 67%, Chest Xrays by 33% of centres, and 43% of centres perform urinalysis in all donors.

Table 4.2 Medical assessment of related donors in UK transplant centres

Policies regarding donor care	N (%)
<b>Donor suitability/eligibility criteria include policies for:</b>	
Age	5 (23)
BP	12 (55)
BMI	9 (41)
Min weight	7 (32)
Tattoos	14 (64)
Allogeneic blood	12 (55)
<b>Related donors are accepted with the following conditions:</b>	13 (59)
Diabetes mellitus on insulin	10 (45)
Asthma on tablet medication	11 (50)
Previous IHD	2 (9)
Previous systemic AI disease	
Full blood count	21(100)
Renal and electrolytes	21(100)
Bone profile	18 (86)
Thyroid function	12 (57)
Liver function tests	21(100)
LDH	13 (62)
ESR	5 (24)
Serum Protein Electrophoresis	10 (48)
Pregnancy test (pre-menopausal females)	21 (100)

Table 4.3 The investigations performed as part of the related donor evaluation in UK transplant centres

Investigation	Performed in all donors	Performed where clinically indicated	Never performed
CXR	7	14	0
ECG	14	7	0
Abdominal US	0	19	2
Haemoglobinopathy screen	2	18	1
Urinalysis	10	9	2
ECHO	0	20	1
Bone marrow aspiration	0	15	6

I found similar discrepancies between the answers regarding whether RDs would be permitted to proceed with specific medical conditions, with many centres allowing relatives who would be refused as UDs to proceed with donation. Most notably, 52% of centres stated that they would accept RDs with a history of IHD and 62% would accept donors taking insulin for diabetes mellitus.

#### 4.3.5 POLICIES REGARDING THE DONATION PROCEDURE

All centres surveyed had apheresis facilities on site, but 3 centres did not have facilities for BM harvesting. RD BM harvests are performed by transplant physicians in 96% of centres, and in 73% of centres these physicians have simultaneous responsibility for the transplant recipient. Collection of autologous blood unit(s) prior to BM harvest was undertaken by only two centres (9%) which in one centre collected units are routinely returned. 63% of centres routinely give oral iron to BM donors. Donors are routinely kept overnight following BM harvest in 84% of centres, and in 43% of centres the donor will be cared for on the same ward as their recipient.

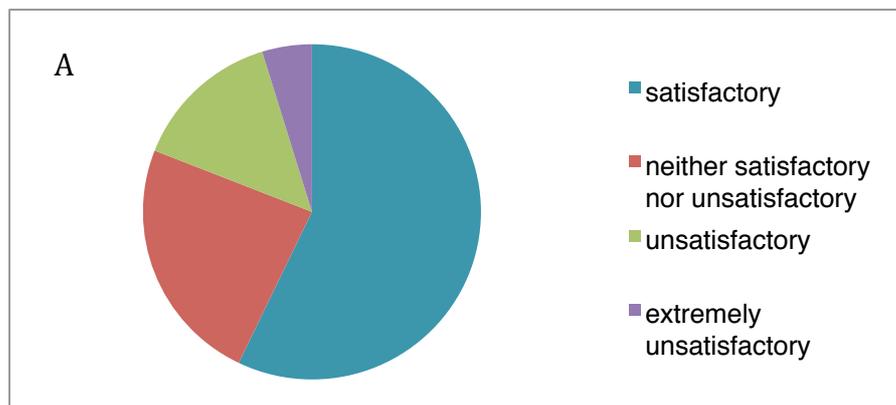
Transplant physicians were responsible for the apheresis procedure in 16 centres (73%). 89% of centres use Granocyte® (lenograstim) or Neupogen® (filgrastim) to mobilise RDs. Two centres (9%) use a biosimilar GCSF, and, notably, 5 respondents (23%) stated that their centre had used off-label plerixafor to mobilise RDs. 50% of centres allow donors to give the first dose of GCSF and 59% allow donors to give subsequent doses. In the remaining centres GCSF is administered either by the transplant centre or by the donor's GP. In 96% of centres donors are asked to contact the transplant team if they develop any issues during mobilisation, while in the remaining centre, donors contact the apheresis team.

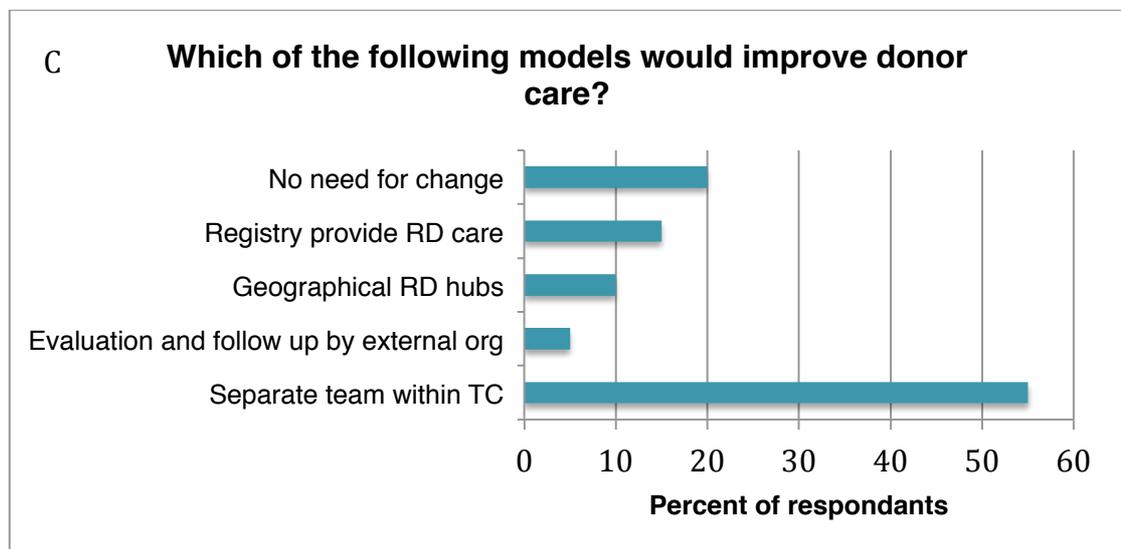
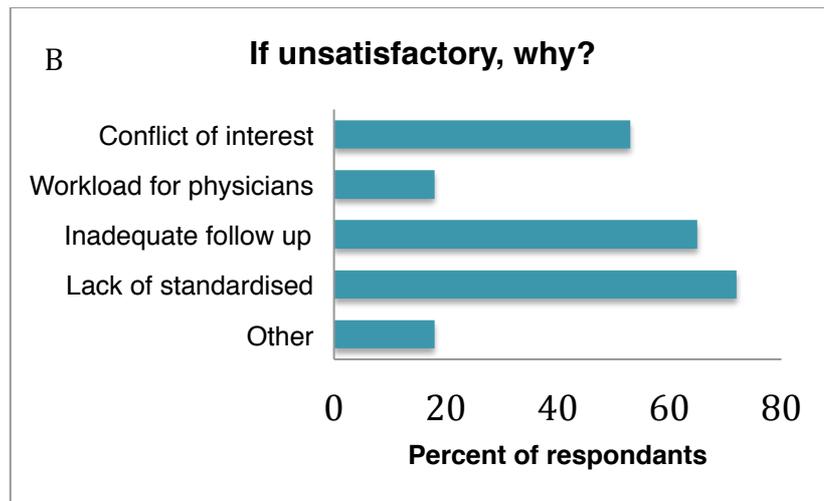
Regarding policies for donation limits for RDs, I found that only 5 centres (23%) have a policy for subsequent donations, while 59% have a limit for the number of apheresis procedures a donor may undergo at their initial donation and 14 (67%) have specified limits for the volume of BM collected at harvest. Where details of these policies were stated, limits were consistent with national UD policies in nearly all cases.

### 4.3.6 VIEWS OF UK PHYSICIANS RESPONSIBLE FOR RD CARE

As shown in Figure 4.4A, 57% of physicians described UK RD care as satisfactory. The most commonly stated reasons for considering care to be unsatisfactory were lack of standardised guidelines (72%) and inadequate donor follow-up (65%). 67% of respondents felt that national RD suitability criteria would improve donor health and 81% responded that guidelines for the whole donation process would improve care. As shown in Figure 4.4C, mixed opinions were reported regarding the optimal model for RD care in the UK, but notably, only 27% of respondents thought that RD care should be performed by a separate organisation to the recipient's transplant centre.

*Figure 4.4. The views of responding physicians in UK transplant centres regarding current practice in related donor care: A) Overall opinion; B) Reasons for finding care unsatisfactory; C) Views on alternative care pathways*





## 4.4 CONCLUSIONS

The results of this study provide a unique in-depth analysis of RD care which, with a response rate of >75%, is representative of current UK practice. I was able to show near universal consistency in practice in areas where clear FACT-JACIE Standards exist. This included the presence of policies for RD care, provision of information to potential RDs prior to HLA typing, and measures to prevent the same physician being simultaneously responsible for an RD and their intended recipient. I showed that international consensus recommendations in RD care have not been so widely adopted

in the UK, particularly regarding assessment of donor health prior to HLA typing and regarding length of donor follow-up.

I found distinct differences between transplant centres in both the suitability criteria and the investigations employed during evaluation of potential RDs, and crucially, I was able to show that this leads to RDs who would be accepted by some centres being deferred by others.

The major limitation of this study was that despite a very satisfactory response rate, the low number of respondents limits the possibility to explore the relationship between practice and centre characteristics, and for this reason, the analysis I performed is purely descriptive. Secondly, although I was able to demonstrate diverse practice in the medical conditions with which relatives would be permitted to proceed, I was unable to investigate this in depth. For example, accepting a donor with a history of ischaemic heart disease who has undergone a curative intervention and who undertakes informed consent regarding this specific risk, is very different to accepting a donor who has had a recent myocardial infarct, or a donor with whom an increased donation-associated risk has not been discussed. Thirdly, although I requested that transplant directors forward the survey to the person in their centre responsible for donor care, there was no guarantee that this person was familiar with every aspect of their centre's procedures.

Discrepancies between centres in their approach to acceptance of RDs is not surprising given the lack of specific RD suitability criteria. While clear medical criteria have been published for UD, it is not possible to directly apply these to RDs. Although some experts would argue that it is not right to allow RDs to undergo more risk than a UD, many others feel that the risk/benefit ratio is different for an RD who often has a potential psychological benefit to gain from a successful transplant outcome. There is a general agreement that it is not right to expose any donor to a known substantial health risk, but there are grey areas, where the risks are theoretical or inadequately defined. In the UD setting these grey areas rightly lead to deferral, but in the RD setting

flexibility may be appropriate. For example, using a protocol exception system to gain specific consent regarding potential increased risk in such cases.

The most notable areas in which consensus guidelines are not adhered to are assessment of RD health prior to HLA typing, and RD follow-up. Although donors are counselled before HLA typing in all centres, and willingness to proceed is verified in all but one centre, 36% of centres do not undertake a health assessment at this time. Assessment of potential RD health prior to HLA typing is necessary, both to prevent delays to the transplant recipient by reducing deferrals at the point of donor medical, and by reducing potential distress or guilt to the RD by being cancelled after they are known to be HLA-matched. Likewise, there is a strong rationale for long-term donor follow-up, which was only performed in 3 centres, which is particularly important given my finding that >20% of centres have used off-label plerixafor in RD mobilisation. I suspect that logistical issues are responsible for the failure to develop follow-up systems in UK transplant centres, however, these can potentially be conducted with minimal resource implications if standardised questionnaires are used to collect a minimum data set. This finding raises the question of whether this particular aspect of care could be provided by another organisation e.g. a UD donor registry. Finally, I was able to show enthusiasm for development of national guidelines for RD care and national suitability criteria.

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## CHAPTER 5: AN INTERNATIONAL PERSPECTIVE ON RELATED DONOR CARE

*Two papers based on the findings of this study were published in the journal Biology of Blood and Marrow Transplantation in December 2015, entitled “EBMT transplant centres with FACT-JACIE accreditation have significantly better compliance with related donor care standards” and “Significant improvements in the practice patterns of adult related donor care in US transplant centres” (see Appendix 2)*

### 5.1 INTRODUCTION

In the previous chapter of this thesis I described current UK related donor care practice and demonstrated variation in both how care is delivered, and regarding the medical conditions with which relatives are permitted to proceed as donors. In order to consider how further initiatives in this field might result in greater uniformity, it was necessary to establish care patterns in other nations economically comparable to the UK.

Three studies described in the introduction have directly addressed this topic. Their methods and major findings are summarised in Table 5.1

Table 5.1 Investigations examining the pathway of related donor care

	US	Italy	Europe
<b>Year of study</b>	2007	2005-2009	2005
<b>Study design</b>	Prospective survey	Retrospective review of donor notes	Prospective survey
<b>Study population</b>	US transplant centre directors	9 centres, with 352 RD notes analysed	63 Nurses attending EBMT annual meeting
<b>Consenting procedures</b>	>70% centres the same physician consenting the donor had either simultaneous responsibility for, or might be involved in the care of, the recipient	All centres undertook written consent. 91% were offered information about both BM and PBSC procedures	75% indicated RDs were consented by a physician who was involved in recipient care
<b>Disclosure of HLA results</b>	Not studied	Not studied	11% centres donor HLA results were first disclosed to the intended recipient
<b>Screening of RDs</b>	>70% centres the physician providing donor clearance had either simultaneous responsibility for, or might be involved in the care of, the recipient	Only 26% donors underwent thorough screening according to Italian Bone Marrow Donor Registry standards	Not studied
<b>Donor follow-up</b>	Not studied	8/9 provided follow-up to one month post-donation. 5/9 provided follow-up beyond 1 year.	60% respondents stated their centre provided follow-up but this was limited follow-up in 10% and duration of follow-up was not described.
<b>Other findings</b>	5% centres lacked written policies for management of RDs	23% of donors were offered psychological assessment	Information for related donors was from local sources in >50% and was relayed by transplant team in 84% cases

As a result of these studies, guidelines and regulations aimed at improving the safety and wellbeing of related donors were published, but the impact of these efforts had not been evaluated. This chapter details two studies, conducted in parallel, to explore in detail pathways of related donor care internationally, and to assess the influence of regulatory change.

### 5.1.1 OBJECTIVES OF THE STUDY OF RD CARE IN US TRANSPLANT CENTRES

The study published by O'Donnell et al in 2010 focused on the potential conflict of interest that exists when a single healthcare professional is responsible for the care of both a related donor and their recipient. This publication had practice- changing consequences and directly led to changes in FACT-JACIE standards.

By examining current practice in the USA, I would be provided with an opportunity to directly assess the effect of these changes on healthcare provision of RD care by asking transplant directors identical questions to the earlier study and comparing responses between eras. I therefore proposed a repeat study, but with a broader scope, to examine the whole donor care pathway. The proposal was accepted by the donor health and safety working committee of the CIBMTR.

The objectives of this study were:

- To determine whether a greater proportion of centres now ensure separation of related donor care compared to reports from the 2007 survey conducted by O'Donnell et al.
- To evaluate compliance with regulatory standards and international consensus recommendations.
- To explore practice patterns in areas of care that are hypothesised to differ from unrelated donor paradigms.

### 5.1.2 OBJECTIVES OF THE STUDY OF RELATED DONOR CARE IN EBMT MEMBER TRANSPLANT CENTRES

As described in Chapter 3, I found key differences in provision of care following the introduction of FACT-JACIE requirements in specific areas. These findings led me to the hypothesis that adult RD care in Europe is more likely to conform to FACT-JACIE Standards and international guidelines in centres with JACIE accreditation, compared to those that have not gone through the accreditation process. To test this hypothesis I decided to undertake a study of RD care in EBMT centres addressing all the areas of care that has been studied in the 2005 survey by the EBMT Nurses Group/Late Effects working party. In addition I aimed to examine other aspects of care where clear standards exist in the UD setting, but which have not yet been considered by regulatory bodies in RD care.

The objectives of this survey in EBMT member transplant centres were:

- To compare provision of related donor care between JACIE accredited and non-accredited transplant centres.
- To evaluate compliance with regulatory standards and international consensus recommendations.
- To explore practice patterns in areas of care where clear UD standards exist, but which are not yet embedded in regulatory guidance for RDs.
- To determine, where possible, changes in care since the 2005 survey (Clare *et al*, 2010).

## 5.2 METHODS AND MATERIALS

A 38-item survey developed to examine related donor care practice (see Appendix 1) was administered as an internet-based questionnaire. I worked with the authors of the earlier US study (O'Donnell *et al*, 2010) to ensure identical language was used to the

earlier survey. Invitations were sent by email to transplant directors of all CIBMTR and EBMT member centres. UK centres were excluded, these having been evaluated in the study described in Chapter 4. The full materials and methods are described in Chapter 2.

## 5.3 RESULTS OF THE STUDY IN US TRANSPLANT CENTRES

### 5.3.1 RESPONSE RATE

Excluding 3 duplicates, 73 responses from 139 eligible centres in the US were received, a response rate of 53%. All respondents answered ‘yes’ to the question ‘does your centre assess/manage adult related donors?’.

Centre transplant volume (defined as the number of allografts per year) significantly impacted the likelihood of a response, with similar patterns observed to those reported in the 2007 survey (shown in Figure 5.1); 67% of non-responding centres performed less than 30 allografts per year, compared to 22% of responding centres ( $p < 0.0001$ ). Since non-responding centres tended to have small transplant volumes, centres who responded to the survey had performed >80% of total allogeneic HCTs and 79% of total related donor HPC transplants reported to NMDP (2011-2012).

*Figure 5.1 Survey response rate by centre volume (number of allogeneic hematopoietic cell transplants performed each year) (Anthias et al, 2015a)*

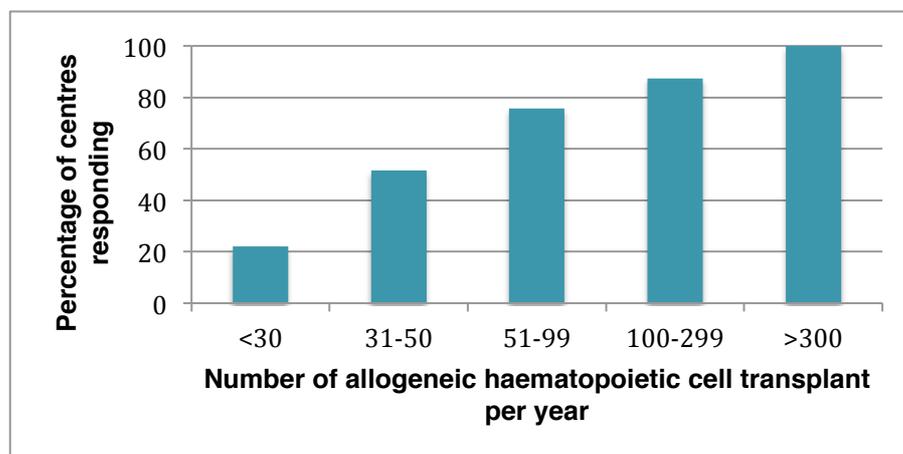
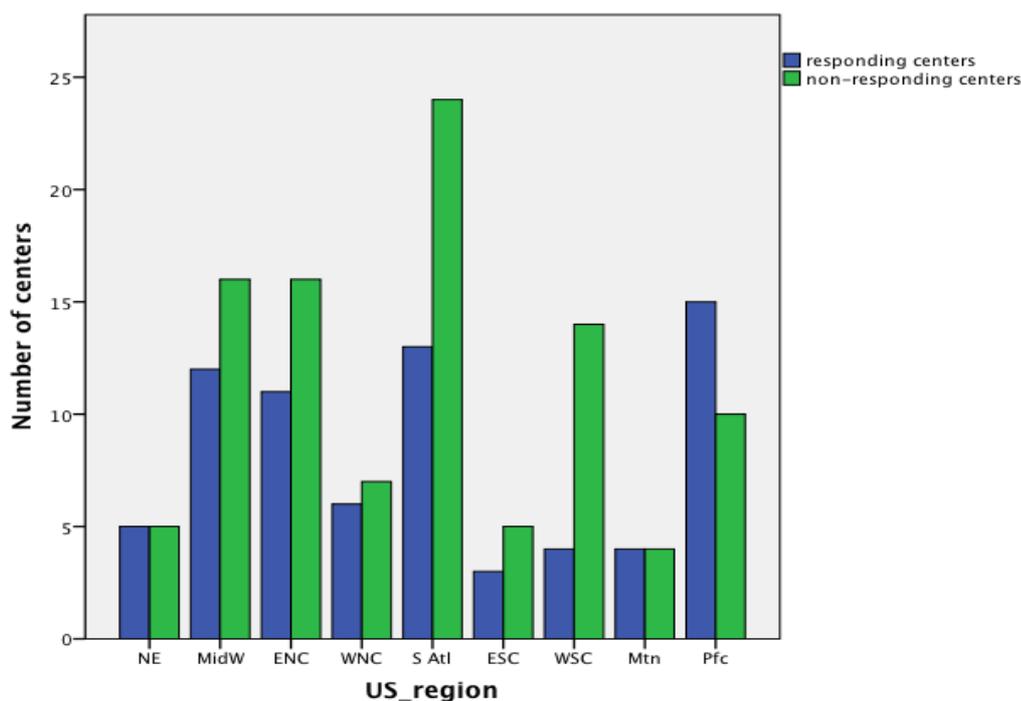


Figure 5.2 Distribution of responding and non-responding transplant centres by geographic region: NE indicates, New England; Mid-Atl, Mid-Atlantic; S-Atl, South Atlantic; ENC, East North Central; ESC, East South Central; West North Central; WSC, West South Central; Mtn, Mountain and Pac, Pacific. (Anthias et al, 2015a)



FACT accredited centres were more likely to respond; 70/109 (64%) accredited versus 3/30 (10%) non-accredited centres responded ( $P<0.001$ ). 70 (96%) responding centres were FACT accredited, one further centre had undergone first time inspection, and the remaining centres were working towards accreditation. A response rate of 59% was seen in NMDP-affiliated centres but no responses were received from non-NMDP centres. As shown in Figure 5.2, the response rate did not vary significantly between US regions, with a similar pattern to the earlier survey.

Table 5.2 Characteristics of responding centres

<b>Responding centres (N = 73)</b>	
Median related donor allografts per year (range)	25 (1-167)
<b>Related donor allografts per year, n (%)</b>	
<10	12 (16)
11-40	45 (62)
41-70	9 (12)
71 or more	7 (10)
Median total allografts per year (range)	63 (1-397)
<b>Total allografts per year, n (%)</b>	
<30	16 (22)
31-50	15 (21)
51-99	25 (34)
100-299	14 (19)
300 or more	3 (4)
NMDP-affiliated transplantation centre n (%)	73 (100)
FACT accredited centre, n (%)	70 (96)

### 5.3.1.3 Comparison of US centre responses with 2007 survey

I compared responses regarding provision of donor care between my study and the earlier study conducted in 2007 (O'Donnell *et al*, 2010). All 73 respondents to the 2014 survey indicated that their centre had a written donor care policy, which had been lacking in 5% of centres in the earlier study.

I found that transplant physicians remained responsible for donor clearance in 77% of centres, a very similar figure to the earlier survey (shown in Figure 5.3). However, there had been a major improvement in separation of donor and recipient care between the two eras (shown in Figure 5.4), with 62% of respondents now indicating that their centre ensures separation of recipient and donor care, an increase from 23% in the previous survey. In just 7% of centres the physician responsible for donor clearance

routinely currently has responsibility for the transplant recipient (reduced from 32% centres in 2007), and in 30% of centres the physician responsible for donor clearance may be involved in the care of the transplant recipient (a reduction from 42% centres in 2007);  $p < 0.0001$ .

Figure 5.3 Professional background of the provider responsible for donor clearance in US transplant centres (Anthias et al, 2015a)

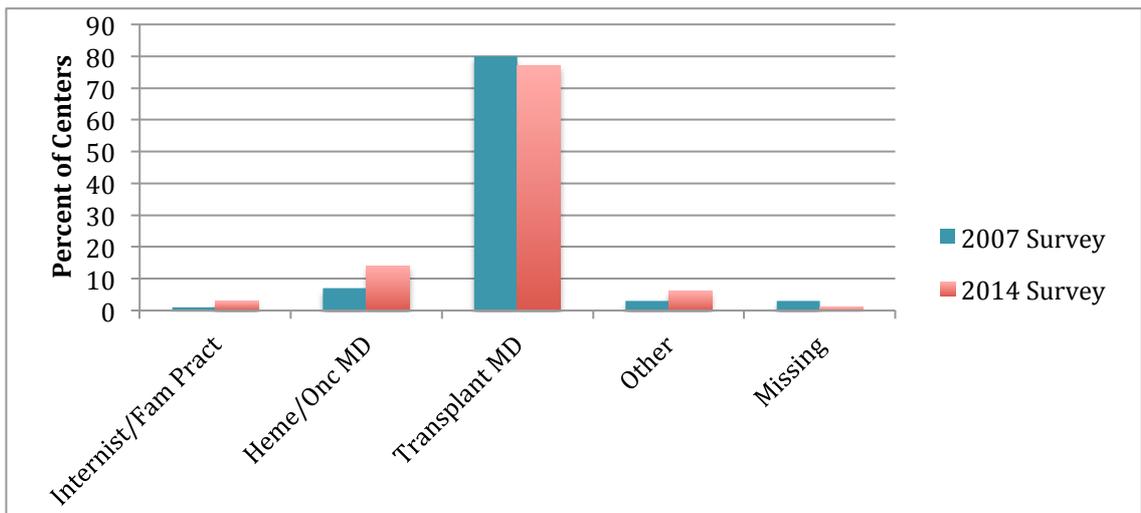
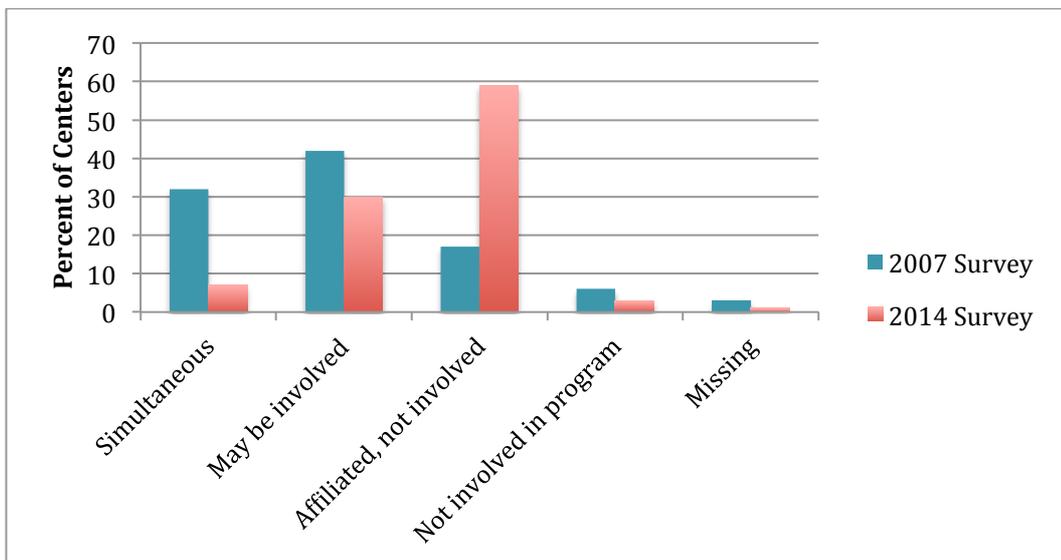


Figure 5.4 Involvement of the physician providing donor clearance in the care of the recipient in US transplant centres (Anthias et al, 2015a)

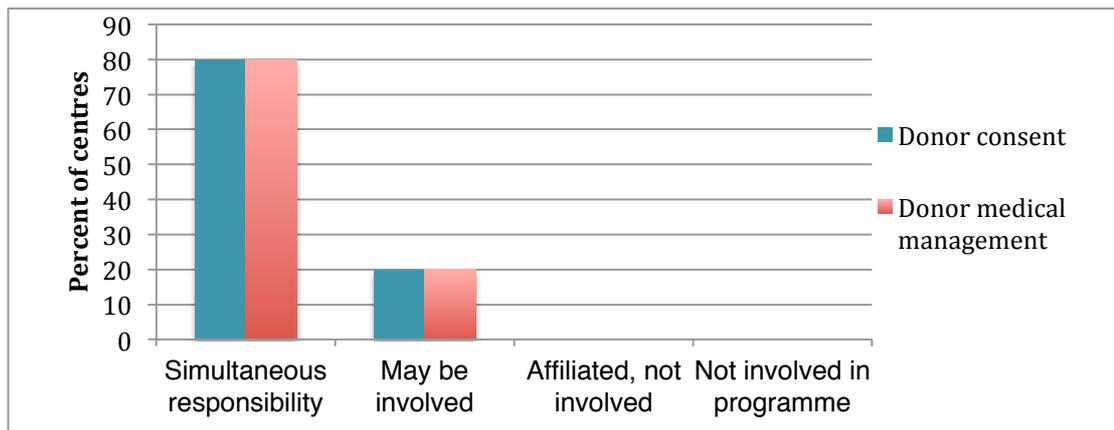


The five respondents who stated that the physician providing donor clearance in their centre would always be simultaneously responsible for the recipient were asked additional questions about the use of a donor advocate and provision of donor care at other points.

In four (80%) of these centres, both donor consent and donor medical management were also performed by the physician with simultaneous responsibility for the recipient, while one respondent stated that this physician may have responsibility for the recipient.

Four (80%) of these centres stated that related donors would always have a specific donor advocate, distinct from the transplant recipient’s primary treating physician, to fully inform and protect the interests of the donor.

*Figure 5.5 Involvement of the physician providing donor consent and donor medical management in the care of the recipient in US transplant centres*



### 5.3.2 COMPLIANCE WITH REGULATORY STANDARDS AND CONSENSUS RECOMMENDATIONS IN ASPECTS OF RD CARE NOT ADDRESSED IN THE 2007 SURVEY

#### *5.3.2.1 Care of potential donors prior to HLA typing*

I observed considerable variation in the management of RDs during the early stages of donor care (shown in Table 5.2). In almost half of centres RDs were informed about the donation process through a verbal discussion, without receiving written information. Despite specific information for RDs being freely available from the NMDP, this was used by only 7% of centres, with a further 45% producing local written information for donors. Verification that the donor was theoretically willing to undertake donation was not determined in 25% of centres before drawing blood for HLA typing. Furthermore, in 30% of centres an assessment of donor health was not undertaken prior to determining RD matching status, and only a small proportion of centres (17%) conduct a formal health history questionnaire at this point.

Disclosure of donor HLA typing results was not performed in accordance with recommendations in the majority of centres, with 25% centres informing the potential recipient about their donor's HLA matching status before the donor themselves. In 17% of centres these results were disclosed to a referring physician, 19% of respondents stated that their centre had no consistent practice, and only 39% indicated that the donor would always be the first informed.

*Table 5.3 Responses regarding the care of related donors prior to HLA typing in US transplant centres*

<b>Response</b>	<b>Number of centres</b>	<b>Source of recommendation</b>
<b>Healthcare provider making initial contact prior to HLA typing:</b>		
Transplant physician	6 (8%)	Nil
Other Physician	4 (5%)	
Transplant Specialist Nurse	45 (62%)	
Other nurse	8 (11%)	
Non-clinical Admin	10 (14%)	
<b>Information supplied to donors pre-HLA typing:</b>		
Verbal only	35 (48%)	5 <sup>th</sup> Edition FACT-JACIE Standards requirement
Local written information	33 (45%)	
National written information	5 (7%)	
<b>RD health assessment pre-HLA typing</b>		
By written health questionnaire	5 (7%)	Family donor care management
Health questionnaire over phone	7 (10%)	
Verbal discussion open ended questions	39 (53%)	
No assessment	22 (30%)	
Willingness to donate is verified pre-HLA typing	55 (75%)	Family donor care management
<b>Individual to whom donor HLA results are first disclosed:</b>		
Donor	28 (39%)	5 <sup>th</sup> Edition FACT-JACIE Family donor care management
Recipient	18 (25%)	
Referring physician	12 (17%)	
No consistent practice	14 (19%)	

### *5.3.2.2 Donor care policies and harvesting procedures*

As demonstrated in Table 5.3, the policies required for compliance with current (5<sup>th</sup> edition) FACT-JACIE Standards were almost universally in existence in responding centres. In addition to a written RD care policy in all centres, 67 respondents (92%) stated that defined criteria are used to assess adult RDs in their centre. These were

based on NMDP suitability criteria for unrelated donors in 59% of centres and on WMDA criteria in 4%.

84% of respondents from centres where BM harvests are performed on related donors stated compliance with FACT-JACIE standards by having a process for credentialing the physicians performing these procedures.

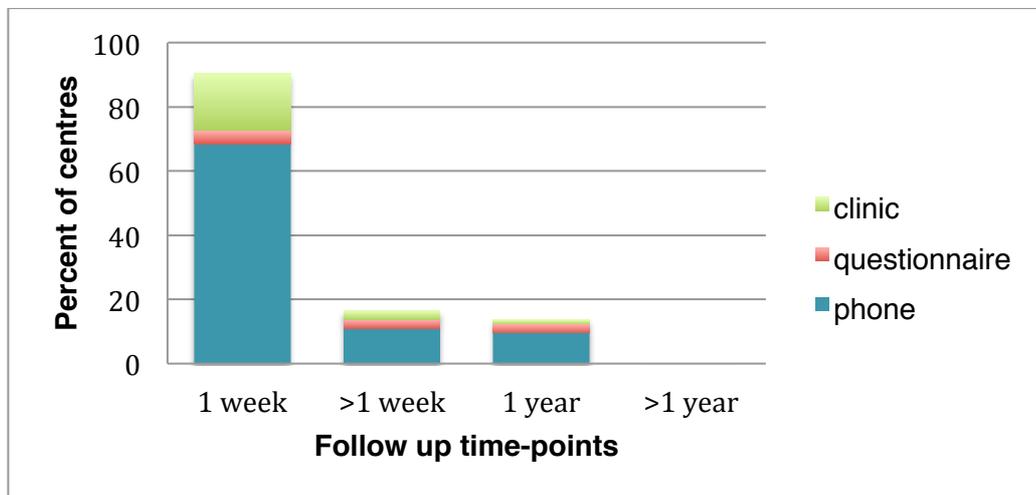
*Table 5.4 Responses regarding policies in related donor care in US transplant centres*

	<b>Number of centres</b>
Existence of a written policy for RD care	73 (100%)
Written eligibility criteria exist for acceptance of RDs	67 (92%)
A health history questionnaire forms part of the donor assessment	65 (89%)
There is a process for credentialing physicians performing BM harvests	61 (84%)

### *5.3.2.3 Donor follow-up*

Despite explicit FACT-JACIE requirements for a follow-up policy for RDs and international consensus recommendations, I found that long-term donor follow-up in US centres is non-existent. As shown in Figure 5.6, >90% of centres provided short-term follow-up at one week post-donation. This was usually conducted by telephone, although 18% of centres arrange a donor follow-up clinic appointment at this stage. In the majority of centres, no further follow-up occurred, and in only 14% of centres did the duration of follow-up extend beyond a week, with no US centres surveyed providing follow-up of RDs beyond one year post-donation.

Figure 5.6 Related donor follow-up: The duration of donor follow-up offered and the method by which follow-up is provided in US transplant centres (Anthias et al, 2015a).



#### 5.3.2.4 Comparison of care with unrelated donor care standards

I examined other aspects of care where clear policies exist for UD, but which have not been addressed in current RD recommendations. Policies regarding specific limits for donation were present in some centres but were not universal. Only 45% participants stated that their centre had a limit for the maximum number of apheresis procedures per donation, which where specified were in line with UD practice in 59% of cases. Of note, 29% of centres had used off-label plerixafor for RD mobilisation outside a clinical trial context.

BM harvest policies were more prevalent, with 68% of centres reporting a limit for aspirated BM harvest volume, most commonly 20mls/kg, and in only one case did the specified limit exceed NMDP guidelines for UD marrow harvests with a centre allowing up to 2500mls to be collected from donors weighing >50kg. Autologous blood was collected from donors and returned in 50% of centres, and collected but not returned in a further 14%. As per standard US UD practice, 64% BM harvests donors were discharged on the day of donation.

26 centres (37%) had a policy regarding subsequent donations from RDs. Interestingly, some centre's policies were more conservative than international UD recommendations

with one centre not allowing any subsequent donations.

*Table 5.5 Comparison of related donor care in US transplant centres with unrelated donor care practice*

	Number of centres	Unrelated Donor practice
<b>Existence of a policy for maximum number of apheresis procedures during initial donation</b>		
Yes, 2 procedures	20 (27%)	Maximum of 2 procedures
Yes, 3 procedures	11 (15%)	
Yes, 4 procedures	3 (4%)	
No policy	40 (55%)	
<b>Who gives the 1<sup>st</sup> GCSF dose to donors</b>		
Transplant centre	59 (81%)	Qualified nurse
Donor or their family	25 (34%)	
Another provider	15 (21%)	
<b>Medical responsibility for apheresis</b>		
Transplant physician	34 (50%)	Never a physician involved in recipient care
A Physician from another team/institution	34 (50%)	
<b>There is a written policy regarding subsequent donations</b>		
Yes	26(37%)	Registries must have a policy
No	44(63%)	
<b>Number of subsequent donations allowed</b>		
None	1	Routinely 1 further stem cell donation and 1 T cell donation with further donations potentially allowed at MD discretion (WMDA)
1	3	
2	2	
3	2	
4	1	
As per NMDP	2	
Team discussion at the time	2	
<b>BM harvests are performed by:</b>		
The transplant team caring for the recipient	35	BM harvests are never be performed by professionals involved in recipient care
Transplant physicians from a separate team	37	
Another team	4	
A policy defines the maximum volume aspirated at bone marrow harvest apheresis procedures a donor may undergo for their initial donation	44 (60%)	Maximum 20mls/kg in most registries
<b>Is plerixafor ever used in mobilisation of RDs?</b>		
Yes	20 (29%)	Plerixafor is not used
No	35 (52%)	
Only in the context of a clinical trial	13 (19%)	

*5.3.2.5 The effect of centre volume on related donor care*

I compared transplant centres performing fewer than the median 25 RD HPC transplants per year to higher volume centres (Table 5.6) and found that RD marrow harvests were more likely to be performed by the same transplant physicians caring for the recipient in lower volume centres (70% versus 38%;  $P=0.009$ ). Low volume centres were also less likely to have a policy defining the limit for BM volume aspirated at harvest, which was present in 57% lower volume versus 79% higher volume centres ( $P=0.077$ ). Transplant centre volume did not impact any other areas of related donor care.

*Table 5.6 The impact of transplant centre volume on related donor care in US transplant centres*

	Transplant centre volume		p
	<25 RD transplants per year	≥ 25 RD transplants per year	
RD health assessment pre-HLA typing	28 (75.7%)	23 (63.9%)	0.27
Willingness to donate is verified pre-HLA typing	28 (75.7%)	27 (77.1%)	0.88
Donor HLA results are disclosed first to the donor	17 (45.9%)	11 (31.4%)	0.21
Written eligibility criteria exist for acceptance of RDs	33 (89.2%)	34 (97.1%)	0.19
Is plerixafor ever used for mobilisation of RDs			
Yes	10 (29.4%)	10 (29.4%)	0.62
No	19 (55.9%)	16 (47.1%)	
Only in the context of a clinical trial	5 (14.7%)	8 (23.5%)	
There is a policy defining the limit for the number of apheresis procedures RDs may undergo for their initial donation	16 (47.1%)	17 (50%)	0.60
There is a policy regarding subsequent donations from related donors	13 (36.1%)	13 (38.2%)	0.85
Physician responsible for donor clearance has simultaneous responsibility for the recipient	2 (5.4%)	3 (8.6%)	0.38
Donor follow-up extends beyond 1 week	6 (16.2%)	8 (22.2%)	0.79
RD marrow harvests are performed by the recipient's transplant team	25 (70%)	12 (37.5%)	0.009
There is a process for credentialing physicians performing BM harvests	32 (91.4%)	29 (96.7%)	0.81
There is a policy defining the limit for the BM volume aspirated at harvest	20 (57%)	23 (76.7%)	0.077

## 5.4 CONCLUSIONS FROM THE STUDY OF US TRANSPLANT CENTRES

This study provided an opportunity to directly assess the impact of a change in regulatory standards on practice patterns in related donor care. I was able to show a significant improvement regarding the potential for conflict of interest with only 7% of centres now routinely allowing a physician to be responsible for medical clearance of an RD while having simultaneous responsibility for their recipient, compared to 32% in 2007. I also made important observations regarding aspects of RD care, which have never been previously evaluated in the US.

The centres responding to this survey perform approximately 80% adult RD transplants, and these results therefore provide an accurate overview of the care the majority of RDs currently receive. Since there was a very low response rate in the small number of centres performing <30 allografts annually, as well as centres lacking FACT accreditation or NMDP affiliation, the results cannot be generalised across these centres.

Overall, I found practice in US centres to be largely compliant with the majority of FACT requirements, including the existence of a policy for RD care, written donor eligibility criteria and a credentialing process for physicians performing BM harvests. However, this was not the case for RD follow-up, which is universally absent in US transplant centres, despite a FACT requirement and international (WBMT and WMDA) recommendations advocating 10 year follow-up for all donors.

Regarding aspects of care in which there are no regulatory requirements, but where World Marrow Donor Association Standards for UDs could be used as a comparison, practice was markedly inconsistent. Of particular concern were the observations around lack of assessment and counselling prior to HLA typing. Counselling at this

stage is essential, both to identify health issues that would preclude donation, and reluctance about donation and hence, allow early deferral of unwilling or unfit donors.

## 5.5 RESULTS OF THE STUDY IN EBMT MEMBER TRANSPLANT CENTRES

### 5.5.1 RESPONSE RATE

Excluding 2 duplicates, and four cases that prematurely terminated when respondents answered 'no' to the first question: "Does your centre perform allogeneic HPC transplants from adult (>18 years old) related donors?" responses were received from 118 of a total of 304 invited centres, a response rate of 39%. Data were not available from EBMT to identify centres that performed only paediatric transplant and would therefore have been ineligible for this study.

A significantly higher response rate was observed in JACIE-accredited compared to non-accredited centres (52% versus 33%;  $p=0.001$ ) and overall 59 (50%) responding centres had JACIE accreditation. As shown in Figure 5.7, the centres (those performing <10 allografts per year), had the lowest response rate, but no other consistent pattern in response rate by centre size was observed. The median number of first allografts per year in responding centres was 23 (range 1-172). As shown in Figure 5.8, no significant difference in response rate was observed between geographical regions ( $P=0.151$ ).

Figure 5.7 Distribution of transplant centre volumes at responding and non-responding EBMT centres (Anthias et al., 2015b)

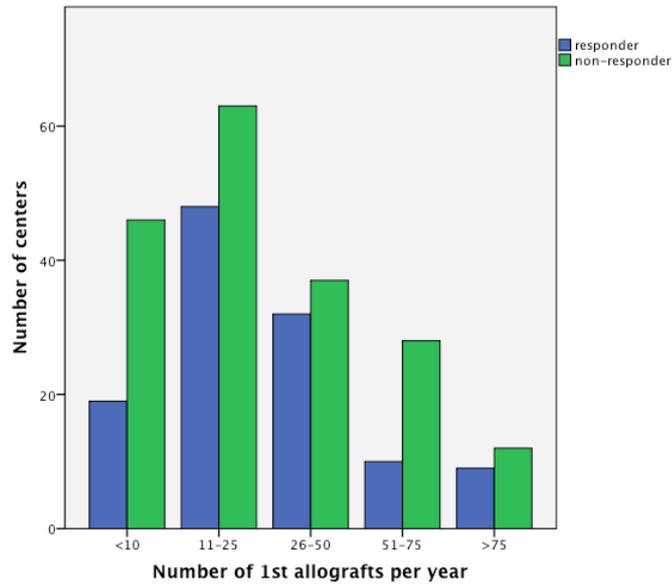
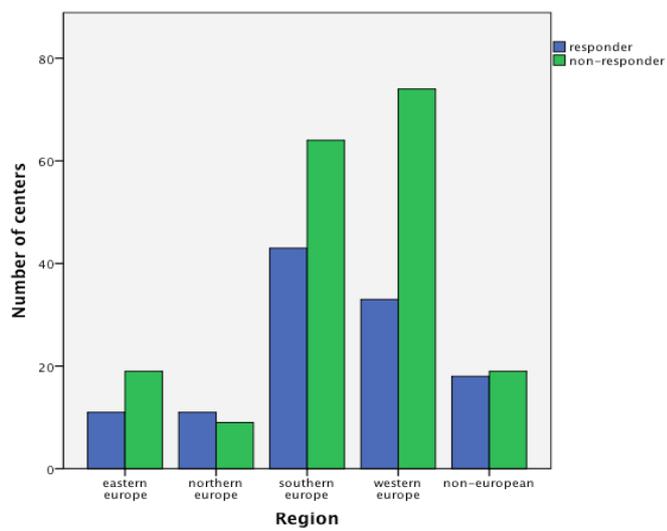


Figure 5.8 Distribution of responding and non-responding transplant centres by geographic region: Eastern Europe; Northern Europe; Southern Europe; Western Europe and Non-European Nations (Anthias et al., 2015b)



## 5.5.2 PROCEDURE FOR ASSESSMENT AND COUNSELLING DURING HLA TYPING

The first stages of RD care were delivered by the transplant team in the majority of cases with transplant physicians or specialist nurses making initial contact with donors in two thirds of centres. There was a trend towards accredited centres being more likely to provide written information to donors at this point, which was supplied by 55% of accredited and 40% of non-accredited centres. ( $p=0.073$ ). Almost all of the written information given to donors was produced locally, with only 4 centres using national sources, which in 3 cases were specified as publications produced by the national UD registry.

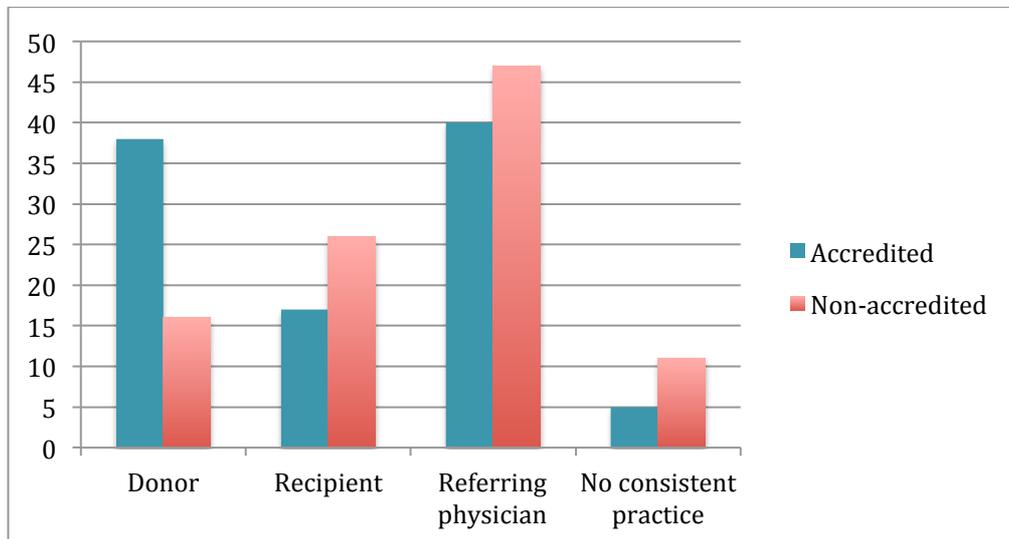
I found poor compliance, in both accredited and non-accredited centres, with recommendations on family donor care management (van Walraven *et al*, 2010) regarding assessment of donor health prior to HLA typing. No assessment of health was made in 43% of centres, and, in centres where this was undertaken it was most likely take the form of a verbal discussion with open-ended questions, with only 21% of centres using a health questionnaire.

Accredited centres were significantly less likely to first disclose the donor's HLA results to an individual other than the donor themselves (61% versus 86%;  $P=0.007$ ). In fact, non-accredited centres were more likely to disclose donor HLA results to the recipient first, than to the donor.

Table 5.7 Responses regarding the care of donors at the point of HLA typing, in accredited and non-accredited EBMT transplant centre

	<b>FACT-JACIE standard</b>	<b>JACIE accredited</b>	<b>Non- accredited</b>	<b>P</b>
<b>Healthcare provider making initial contact prior to HLA-typing</b>				
Transplant physician	No	23 (40%)	24 (41%)	0.70
Other Physician		15 (26%)	17 (29%)	
Transplant Specialist Nurse		15 (26%)	14 (24%)	
Other nurse		2 (3%)	0	
Non-clinical Admin		3 (5%)	3 (5%)	
<b>Information supplied to donors pre HLA typing</b>				
Verbal only	Requires	26 (45%)	34 (60%)	0.073
Local written information	'sufficient	31(53%)	20 (35%)	
National written information	information'	1(2%)	3 (5%)	
<b>RD health assessment pre-HLA typing</b>	Not a JACIE requirement.			
By written health questionnaire	Recommended by RD	12 (21%)	8 (14%)	0.49
Health questionnaire over phone	guidelines	3 (5%)	1 (2%)	
Verbal discussion open ended questions		18 (32%)	23 (40%)	
No assessment		24 (42%)	25 (44%)	
Willingness to donate is verified pre-HLA typing	Not a JACIE requirement. Recommended by WMDA guidelines	40 (69%)	46 (79%)	0.20
<b>Individual to whom donor HLA results are first disclosed</b>	JACIE requires donor authorisation before divulging results to the recipient			
Donor		22 (38%)	9 (16%)	0.007
Recipient		10 (17%)	15 (26%)	
Referring physician		23 (40%)	27 (47%)	
No consistent practice		3 (5%)	6 (11%)	

Figure 5.9 The individual to whom donor HLA result are first disclosed in accredited and non-accredited EBMT transplant centres (Anthias et al., 2015b)



### 5.5.3 HEALTHCARE PROVIDERS INVOLVED IN EVALUATION OF RELATED DONORS

The medical clearance of RDs was undertaken by transplant physicians in 45% of accredited and 69% of non-accredited centres ( $P=0.036$ ). Overall, in 24% of centres this physician was routinely responsible for the transplant recipient, and a further third of respondents indicated that the physician providing donor clearance would be affiliated with the transplant programme and may be involved in the recipient's care. The practice of overlapping donor and recipient care occurred more frequently in non-accredited centres (35%), than in non-accredited centres (14%) ( $P=0.008$ ).

Figure 5.10 Professional background of the provider responsible for donor clearance in EBMT transplant centres (Anthias et al., 2015b)

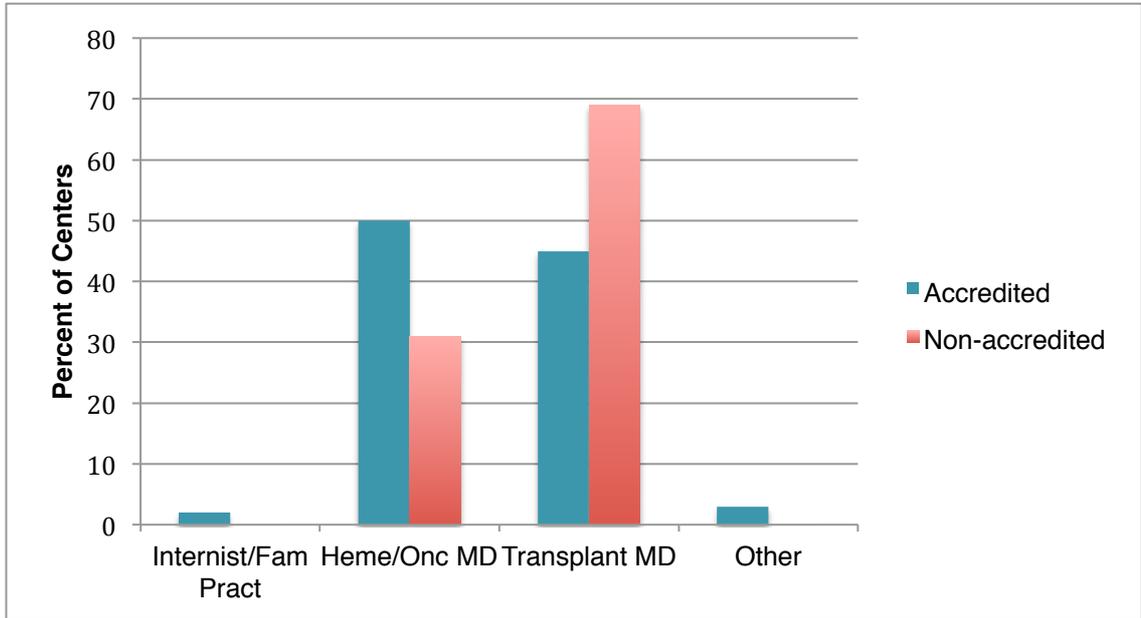
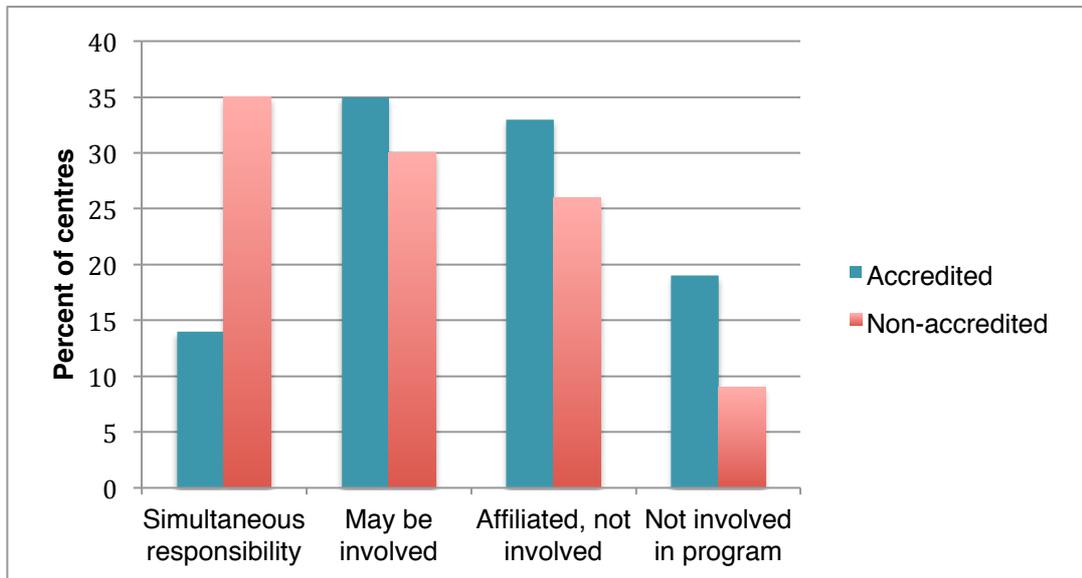


Figure 5.11 Involvement of the physician providing donor clearance in the care of the recipient in EBMT transplant centres (Anthias et al., 2015b)



The 24 respondents who stated that the physician providing donor clearance in their centre would always be simultaneously responsible for the recipient were asked

additional questions regarding the potential for conflict of interest. As shown in Figures 5.12 and 5.13, in 23 (96%) of these centres the physician(s) taking consent and providing medical management for the donor would also be routinely responsible for the recipient or might be involved in recipient care. In only a quarter of these centres would donors always have a specific donor advocate to protect their interests.

Figure 5.12 Comparison of the role of the physician consenting related donors in accredited and non accredited EBMT centres

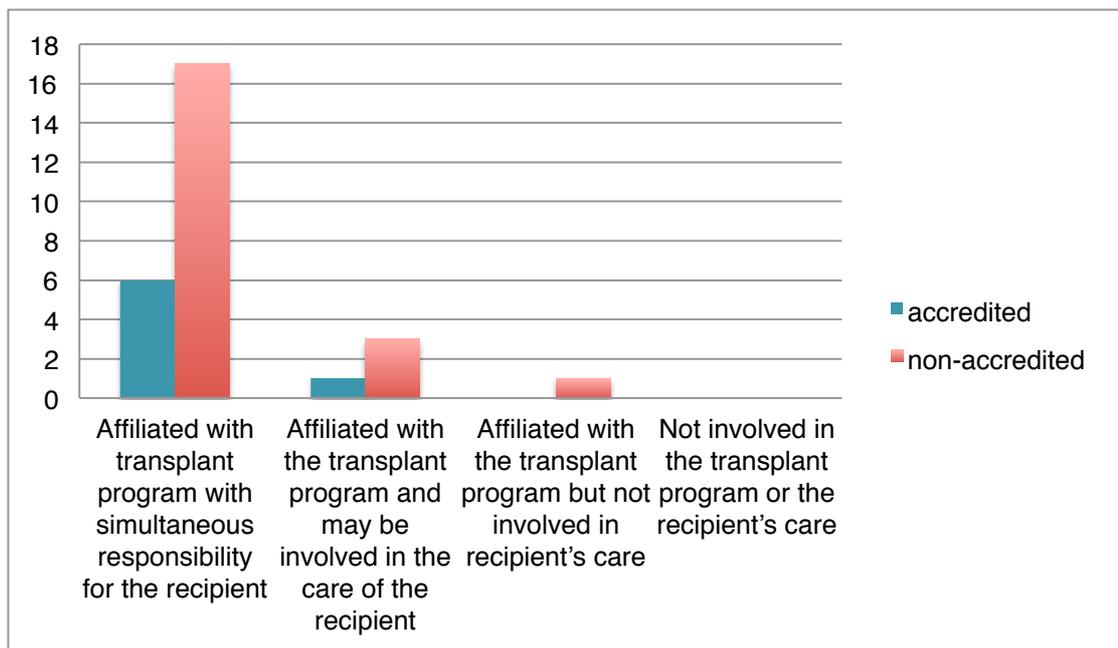
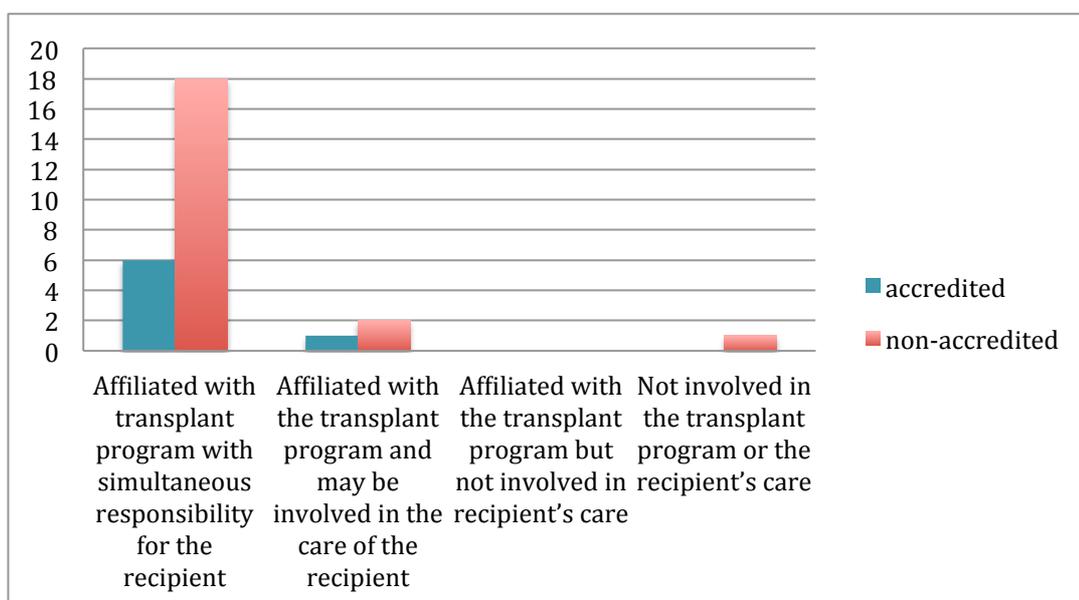


Figure 5.13 Comparison of the role of the physician medically managing related donors in accredited and non accredited EBMT centres



I explored other areas, not previously studied, where there may be a potential for conflict of interests. I found that BM harvests were performed by the same transplant physicians caring for the recipient in 82% of centres. In 80% of centres donors were asked to contact the transplant team if they developed complications during the mobilisation period, and transplant physicians were responsible for the apheresis procedure in 42% of centres. In these areas no significant difference between accredited and non-accredited centres was observed.

#### 5.5.4 DONATION POLICIES AND PROCEDURES IN RELATED DONOR CARE

As shown in Table 5.8, accredited centres were far more likely to conform to FACT-JACIE requirements regarding donor care policies. This included that accredited centres were significantly more likely to have a policy for RD care (98% versus 83%;  $P=0.004$ ), to use defined eligibility criteria to assess RDs (93% versus 78%;  $P=0.02$ ),

and to have a process for credentialing physicians performing BM harvests (86% versus 63%;  $P=0.008$ ).

A trend was also observed towards accredited centres being more likely to have a policy defining a limit to the number of apheresis procedures a donor could undergo during their initial donation (72% versus 55%;  $p=0.057$ ). However, no impact was observed on the likelihood of a policy defining BM harvest limits, which existed in 66% of centres or a policy regarding subsequent donations, which was reported by 44% of centres.

Somewhat surprisingly, a third of centres had used off-label plerixafor as a mobilising agent in related donors, with a significantly higher proportion of non-accredited centres doing so (20% accredited versus 38% non-accredited;  $P=0.032$ )

*Table 5.8 Responses regarding donor care policies in accredited and non-accredited EBMT transplant centres*

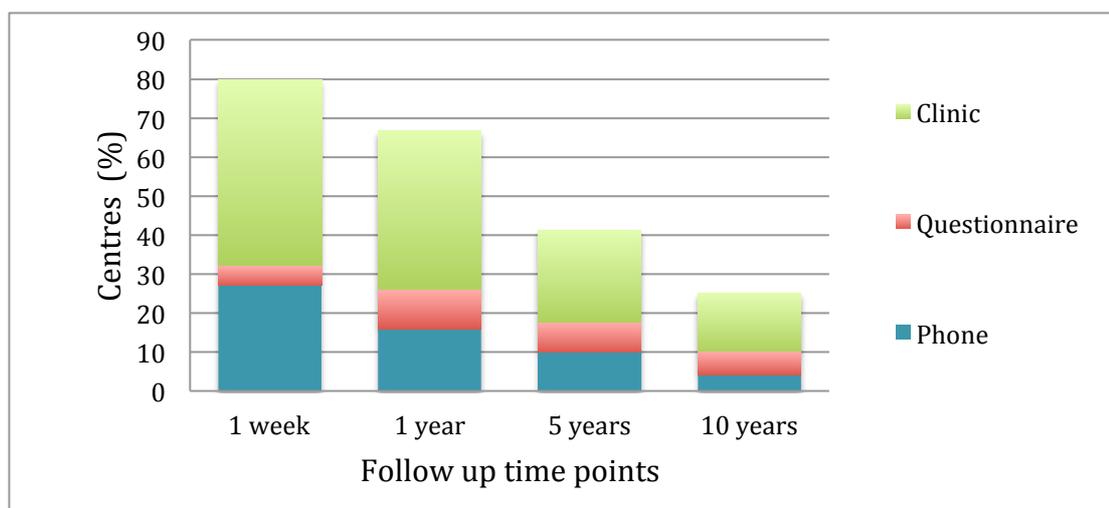
	<b>JACIE accredited</b>	<b>Non- accredited</b>	<b>P</b>
Written eligibility criteria exist for acceptance of RDs	53 (93%)	45 (78%)	0.02
<b>Source of eligibility criteria:</b>			
Locally written	30 (53%)	21 (36%)	
Based on NMDP criteria	16 (28%)	19 (33%)	
Based on WMDA criteria	27 (48%)	12 (21%)	
A health history questionnaire forms part of the assessment at donor medical	52 (91%)	41 (72%)	0.008
There is a policy defining the limit for the number of apheresis procedures RDs may undergo for their initial donation	39 (72%)	31 (55%)	0.057
<b>Plerixafor has been used for mobilisation of RDs</b>			
Yes	11 (20%)	21 (38%)	
No	38 (69%)	34 (61%)	0.032
Only in the context of a clinical trial	6 (11%)	1 (2%)	
<b>BM harvests are performed by:</b>			
Transplant physicians caring for the recipient	43 (77%)	41 (87%)	
Other transplant physicians or another team	13 (23%)	6(13%)	0.36
There is a process for credentialing physicians performing BM harvests	48 (86%)	29 (63%)	0.008
There is a policy defining the limit for the BM volume aspirated at harvest	37 (66%)	30 (65%)	0.984
Long term (10 year) follow-up is performed	20 (34%)	8 (14%)	0.05

### 5.5.5 DONOR FOLLOW-UP

As demonstrated in Figure 5.14, 89% of centres described a donor follow-up programme, which extended beyond a year post-donation in over two thirds of centres, and up to 10 years in 20% of centres. Although accreditation was not associated with the presence of donor follow-up programme, centres with FACT-JACIE accreditation more frequently adhered to WBMT and WMDA recommendations for 10-year donor

follow-up (34% versus 14%;  $p=0.05$ ). The majority of follow-up programmes included outpatient clinic appointments, with only a minority using donor questionnaires.

*Figure 5.14 Duration and methods of related donor follow-up in EBMT-member transplant centres*



### 5.5.6 THE IMPACT OF TRANSPLANT CENTRE VOLUME

Centres performing fewer than the median of 23 allogeneic HPC transplants each year were less likely to be accredited than higher volume centres. In univariate analysis the practice of a single physician having simultaneous responsibility for RD clearance and care of their recipient was significantly more likely to occur in lower volume centres, and these centres were also more likely to disclose the donor's HLA results to the recipient first. However, when these factors were included in multivariate analysis, only accreditation status remained significantly different between smaller and larger centres.

Table 5.9 The influence of transplant centre volume on related donor care

	<23 allografts per year	≥23 allografts per year	P
JACIE accreditation	37%	67%	0.002
Existence of a written SOP for RD care	90%	92%	0.63
Written eligibility criteria exist for acceptance of RDs	84%	86%	0.836
Willingness to donate is verified pre-HLA typing	77%	70%	0.376
Donor health is assessed pre-HLA typing	61%	54%	0.476
Donor's HLA results are first disclosed to the recipient	29%	12%	0.045
Recipient's physician routinely has simultaneously responsibility for their RD	32%	14%	0.030
There is a policy defining the number of RD apheresis procedures (per donation)	60%	69%	0.327
There is a policy defining the limit for the BM volume aspirated at harvest	60%	72%	0.147
There is a process for credentialing physicians performing BM harvests	75%	76%	0.824
Donor follow-up beyond one year	48/67	42/51	0.175

### 5.5.7 COMPARISON WITH THE RELATED DONOR CARE SURVEY CONDUCTED IN 2005

Although the study population and question formats differed, I was able to make comparisons between my results and those of the earlier EBMT survey (Clare *et al*, 2010) in two areas (shown in Table 5.10). I observed improvement regarding donor follow-up, with 89% of responding centres now providing a follow-up programme, compared to 60% in 2005. However, the percentage of centres ensuring that donors are first to be informed of their HLA results was lower than the earlier survey, a result which must be interpreted with the caveat that the options offered as responses differed between the two surveys. Finally, in the earlier survey, only 32% of respondents stated that RDs were consented by a professional not involved in recipient

care. Although not a direct comparison, I showed here that in 75% of centres the physician providing medical clearance of the RD was not routinely responsible for the care of the recipient.

*Table 5.10 Comparison of responses to surveys of EBMT member centres in 2005 and 2014*

	<b>2005</b>	<b>2014</b>
Donor HLA result disclosed to donor first	40%	26%
Donor follow-up programme	60%	89%

## 5.6 CONCLUSIONS FROM THE STUDY OF EBMT TRANSPLANT CENTRES

This study offers unique observations into the pathway of RD care in EBMT transplant centres. Responses were obtained from centres with diverse geographical representation and a wide range of HPC transplant volumes, which I believe gives an accurate portrayal of the current approach to RD care across Europe. Although the survey response rate was relatively low at 39%, it is likely that many of the non-responding centres were ineligible due to being purely paediatric centres, but I did not have data available to identify and exclude these centres.

I found that centres with FACT-JACIE accreditation showed better compliance with internationally recognised donor care paradigms, but also observed important deficiencies in all centres regardless of their accreditation status. Perhaps unsurprisingly, compliance with FACT-JACIE Standards was generally highest where the standards are a) very specific and b) a requirement rather than a recommendation. For example, 98% accredited centres had a written policy for donor care, 93% had

defined medical criteria for RDs, and 86% a process for training BM harvest physicians, all of which are clearly required by 5<sup>th</sup> edition standards.

However, only 38% of accredited centres ensure the donor is informed about their HLA results first, which is a JACIE requirement, but is not precisely defined in the applicable standard, which states: “The allogeneic donor shall give informed consent and authorization in advance to release the donor’s health information to the transplant physician and/or the recipient as appropriate”. But is then further explained in the accreditation manual with the statement: “The purpose of this standard is to protect donor confidentiality...the recipient does not have the right to review all the HLA typing of siblings or other potential donors who are not considered for transplant”. In a similar manner, in >10% of centres, healthcare providers of recipient and donor care routinely overlap in all aspects of donor management and consent, putting the donor in danger of real or perceived coercion, despite a FACT-JACIE recommendation against this practice.

## 5.8 CHAPTER CONCLUSIONS

The results of the two studies detailed in this chapter, in conjunction with the study of UK transplant centres described in Chapter 4, allowed me to compare care between the UK, other EBMT centres and the USA. Although the UK transplant physicians completed a longer survey with some differences between questions, I had included sufficient identical questions to allow comparison across the donor care pathway, as summarised in Table 5.11.

Good compliance across all geographical regions was seen with respect to several FACT-JACIE requirements, including the existence of a specific policy for RD care, and the use of defined eligibility criteria. The practice of a single physician being responsible for both donor and recipient care has become much less prevalent since the introduction of a specific standard in this area and is now routine practice in only a small minority of UK and US centres, but was seen in 1/3 of non-accredited EBMT centres. In a similar manner, a process for credentialing physicians performing BM

harvests (which was less consistently seen in non-accredited EBMT centres only). These findings demonstrate the impact of quality management in driving change.

One of the most striking differences between regions was the complete absence of long-term donor follow-up in the USA, compared to 41% of EBMT centres and 23% of UK centres providing follow-up to at least 5 years. This may be attributable to the development of a system for centralised reporting for related donor outcome data by the EBMT donor outcome group, in addition to national regulations mandating follow-up in some countries. The lack of US long-term follow-up may be connected to the funding streams for US RDs, where provisions are not currently made for RD follow-up by insurance companies. In addition, the FACT-JACIE standard is slightly vague in that it requires a 'policy for follow-up of donors that includes routine management and the management of donation-associated adverse events' but does not specify the duration of follow-up required.

This last point also applies to the second notable difference between regions; that while >80% UK centres ensure the donors HLA results are first disclosed to themselves, this happens in <40% of US centres and <30% EBMT centres. The FACT-JACIE standard aimed at protecting confidentiality is not particularly clear, and in both of these areas, further refinement of the relevant standard may improve compliance.

Regarding aspects of care that have not been addressed by FACT-JACIE Standards, care standards differed considerably from WMDA requirements for unrelated donors. This included that roughly 1/3 of centres in all regions do not assess donor health prior to HLA typing. In these centres a donor's medical issues will thus only be identified at the formal donor medical assessment, which usually occurs shortly before donation (often within 30 days to avoid the need for repeat virology testing). This practice may lead to donors purposefully or inadvertently failing to disclose medical issues during their medical assessment (and in doing so, putting themselves – and potentially the recipient - at risk when donating) or being cancelled at the point of donor medical clearance, which can incur a critical delay to the recipient's transplant. Secondly, over a quarter of centres in each region have used off-label plerixafor to mobilise RDs outside

the clinical trial setting. It was beyond the scope of this study to examine how plerixafor had been used. For example, administration as a one-off ‘rescue’ in a donor who has failed mobilisation, but has a contraindication to BM harvest and gives specific consent for off-label use, is a different situation to pre-emptive use to ‘boost’ stem cell yield in a donor who has not specifically consented. However, clinical trials including long-term follow-up for both patients and donors is essential before new mobilisation agents can be adopted into routine practice.

Centres in the UK were significantly more likely to supply donors with written information prior to HLA typing, possibly due to the production of specific RD information by UK donor registries and charities (Bloodwise, 2012; Anthony Nolan, 2014), which are distributed to transplant centres. UK centres were also more likely to ensure willingness to proceed before performing HLA typing. In the US and non-UK EBMT centres, autologous units are collected in >50% centres prior to RD marrow harvests. This rarely occurs in UK centres, nor is it routine practice for donor registries. Several studies have questioned the benefit of this process, since donors in whom <20mls/kg is collected should not develop significant anaemia. Definitive guidance in this area would be useful.

A limitation of these studies was that despite requesting that the survey be forwarded to the most appropriate specialist for completion, I cannot be certain that this person was familiar with all areas of donor care in their centre. However, the surveys were completed in a lot of detail, which suggests a good level of knowledge from the respondents.

Table 5.11 Comparison of responses between key areas of RD care in EBMT, US, and UK centres.

	EBMT centres	US	UK	P
<b>FACT-JACIE accreditation</b>	59 (50%)	70 (96%)	19 (86%)	<0.0001
<b>Healthcare provider making initial contact prior to HLA-typing</b>				
Transplant physician	47 (41%)	6 (8%)	0	<0.0001
Other Physician	32 (28%)	4 (5%)	2 (9%)	
Transplant Specialist Nurse	29 (25%)	45 (62%)	15 (68%)	
Other nurse	2 (2%)	8 (11%)	3 (14%)	
Non-clinical Admin	6 (5%)	10 (14%)	1 (5%)	
<b>Information supplied to donors pre HLA typing</b>				
Verbal only	52 (53%)	35 (48%)	3 (14%)	0.003
Local written information	51 (44%)	33 (45%)	16 (73%)	
National written information	4 (3%)	5 (7%)	5 (23%)	
<b>RD health assessment pre-HLA typing</b>				
By written health questionnaire	20 (17%)	5 (7%)	4 (18%)	0.27
Health questionnaire over phone	4 (3%)	7 (10%)	5 (23%)	
Verbal discussion open ended questions	42 (37%)	39 (53%)	4 (18%)	
No assessment	49 (43%)	22 (30%)	8 (36%)	
Willingness to donate is verified pre-HLA typing	86 (74%)	55 (75%)	21 (95%)	
<b>Individual to whom donor HLA results are first disclosed</b>				
Donor	31 (27%)	28 (39%)	18 (82%)	<0.0001
Recipient	25 (22%)	18 (25%)	1 (5%)	
Referring physician	40 (43%)	12 (17%)	NA	
No consistent practice	9 (8%)	14 (19%)	2 (9%)	
<b>Background of the provider with ultimate responsibility for RD clearance</b>				
Internist/GP	1 (1%)	2(3%)	NA	0.006
Non-transplant haematologist	37 (32%)	10 (14%)	9 (40%)	
Transplanter	64 (55%)	56 (77%)	11 (50%)	
Other	11 (10%)	4 (6%)	2 (9%)	
<b>Role of the physician clearing the donor in the recipient's care</b>				
Affiliated with transplant program with simultaneous responsibility for the recipient	28 (24%)	5 (7%)	1 (5%)	0.0001
Affiliated with the transplant program and may be involved in the care of the recipient	37 (32%)	22 (30%)	10 (45%)	
Affiliated with the transplant program but not involved in recipient's care	34 (29%)	43 (59%)	9 (40%)	
Not involved in the transplant program or the recipient's care	16 (14%)	2 (3%)	2 (10%)	

Existence of a written SOP for RD care	107 (91%)	73 (100%)	21 (96%)	0.24
Written eligibility criteria exist for acceptance of RDs	98 (86%)	67 (91%)	19 (86%)	0.23
<b>Source of eligibility criteria</b>				
Locally written	51 (44%)	48(66%)	3 (14%)	
Based on NMDP criteria	35 (30%)	40(55%)	1 (5%)	
Based on WMDA criteria	39 (34%)	3(4%)	0	
Based on UK UD criteria	NA	NA	10 (45%)	
A health history questionnaire forms part of the donor assessment	93 (80%)	65 (89%)	18 (82%)	0.19
There is a policy defining the limit for the number of apheresis procedures RDs may undergo for their initial donation	70 (60%)	33 (45%)	13 (60%)	0.0007
<b>Physician with responsibility for the apheresis procedure</b>				
Transplant physician	49 (42%)	34 (50%)	16 (73%)	0.083
Other physician	56 (48%)	34 (50%)	6 (27%)	
<b>Plerixafor has been used for mobilisation of RDs</b>				
Yes	32 (28%)	20 (27%)	5 (23%)	0.81
No		35 (48%)	17 (77%)	
Only in the context of a clinical trial	7 (6%)	13(18%)		
<b>BM harvests are performed by:</b>				
Transplant physicians caring for the recipient	84 (72%)	35 (48%)	16 (73%)	0.02
	25 (22%)	30 (41%)	5 (23%)	
Other transplant physicians	10 (9%)	3 (4%)	1 (5%)	
Another team				
There is a process for credentialing physicians performing BM harvests	77 (67%)	61 (84%)	18 (90%)	0.01
There is a policy defining the limit for the BM volume aspirated at harvest	67 (66%)	44 (60%)	14 (67%)	0.73
There is a policy regarding subsequent donations from related donors	45 (40%)	26 (37%)	8 (36%)	0.72
<b>Practice regarding autologous unit collection</b>				
Unit(s) collected and returned	58 (51%)	31 (43%)	1 (5%)	<0.0001
Unit(s) collected but not routinely returned	14 (12%)	8 (11%)	1 (5%)	
No autologous collection	42 (37%)	34 (47%)	20 (90%)	
<b>Donor follow-up</b>				
5y	47 (41%)	0	5 (23%)	<0.0001
10y	28 (24%)	0	3 (14%)	

## CHAPTER 6. A PROSPECTIVE STUDY EXPLORING THE FEASIBILITY OF UD REGISTRY INVOLVEMENT IN RD CARE

*A paper based on this subject was published as a Special Report in the journal Bone Marrow Transplantation in January 2015, entitled “Related hematopoietic cell donor care: is there a role for unrelated donor registries?” (see Appendix 2)*

### 6.1 INTRODUCTION

In the introduction to Chapter 4, I briefly described a session at the EBMT Annual Meeting 2013, where the question of whether UD registries should play a role in the care of RDs was debated. This session was attended by a broad range of transplant centre physicians and specialist nurses, as well as donor registry representatives. Enthusiasm was unanimously expressed regarding exploration of alternative donor care pathways and many parties felt that UD registries were well placed to provide aspects of RD care. However, a number of hurdles to UD registry input were also raised, and are broadly outlined in Table 6.1.

*Table 6.1 The perceived advantages and disadvantages of UD registry involvement in RD care, as discussed at a debate session at the EBMT Annual Meeting 2013.*

	<b>Advantages</b>	<b>Disadvantages</b>
<b>Registry functions</b>	Many existing registry procedures could be adapted	Several key registry functions e.g. donor search are not required
<b>RD health and safety</b>	RDs would be assessed by physicians with extensive experience in donor health  RD health could be assessed using standard tools.	It is not appropriate for UD suitability criteria to be used for RDs in every situation
<b>Donor consent/counselling</b>	The issue of conflict of interest would be removed since donors would not be managed by professionals involved in the care of their intended recipient.	The risk benefit ratio in RD situation is different and requires a different discussion to UDs  Registries do not currently have experience in the psychological issues of related donation
<b>BM harvests</b>	Would avoid harvests being conducted by the recipients transplant team  Harvests likely to be performed by the most experienced operators	Logistical difficulties if the harvest alone performed by registry and workup done elsewhere  Potentially more expensive?  Harvest would have to be transported to transplant centre
<b>Follow-up</b>	Allows centralised follow-up  Same process can be undertaken for UD and RD regarding collection of minimum data set	UD registries do not necessarily have appropriate team for follow-up of any psychological issues raised (however transplant centres may not have this)
<b>Financial issues</b>	The costs of donor care would become more explicit which may mean that insurance companies or governments would make specific funds available for donor care.	Likely to be more expensive for transplant centres to pay a registry for care.  Additional costs to courier cells

The study discussed in this chapter explores some of the perceived barriers to UD registry involvement in RD care. The primary objective was to establish the feasibility, both logistically and financially, of an UD registry undertaking RD care nationally, either by managing the entire donor care pathway or aspects thereof.

## 6.2 METHODS AND MATERIALS

### 6.2.1 DEVISING MODELS OF CARE

I contacted donor physicians from European registries and obtained details of successful models of RD care provided by UD registries. I assessed the pros and cons of implementing each of these in the UK, and then devised three potential models of UK RD care where the UD registry would undertake part of the care pathway. In conjunction with transplant centres and UK UD donor collection centres, I conducted an in-depth analysis of the logistics and costs of these three pathways with the intention of setting up a one-year pilot study for each of the three models.

### 6.2.2 SET-UP OF PILOT STUDIES

After defining work flows and costs for these two models of donor care, three large UK transplant centres were contacted: The Royal Marsden, King's College Hospital, and Nottingham University Hospital. These were selected for two reasons. Firstly, as large transplant centres, they use the highest number of RDs. Secondly, these centres all use the Anthony Nolan Graft Identification and Advisory service and strong links exist between Anthony Nolan and these organisations.

Following preliminary discussions with the transplant centres confirming initial interest, proposals were sent to The Royal Marsden and King's College Hospital regarding Model 1 'Provision of Related Donor care in a UD registry setting from the point of donor identification' and Model 2 'Evaluation of Related Donors within a transplant centre by an external physician' (proposals are included in Appendix 1) and a proposal

regarding Model 3 ‘Registry provision of donor follow-up’ was sent to Nottingham University Hospital (see Appendix 1).

A single pilot study of related donor follow-up by Anthony Nolan was finally undertaken from 1/10/14 for a 13-month period. The detailed material and methods is found in Chapter 2.

## 6.3 RESULTS

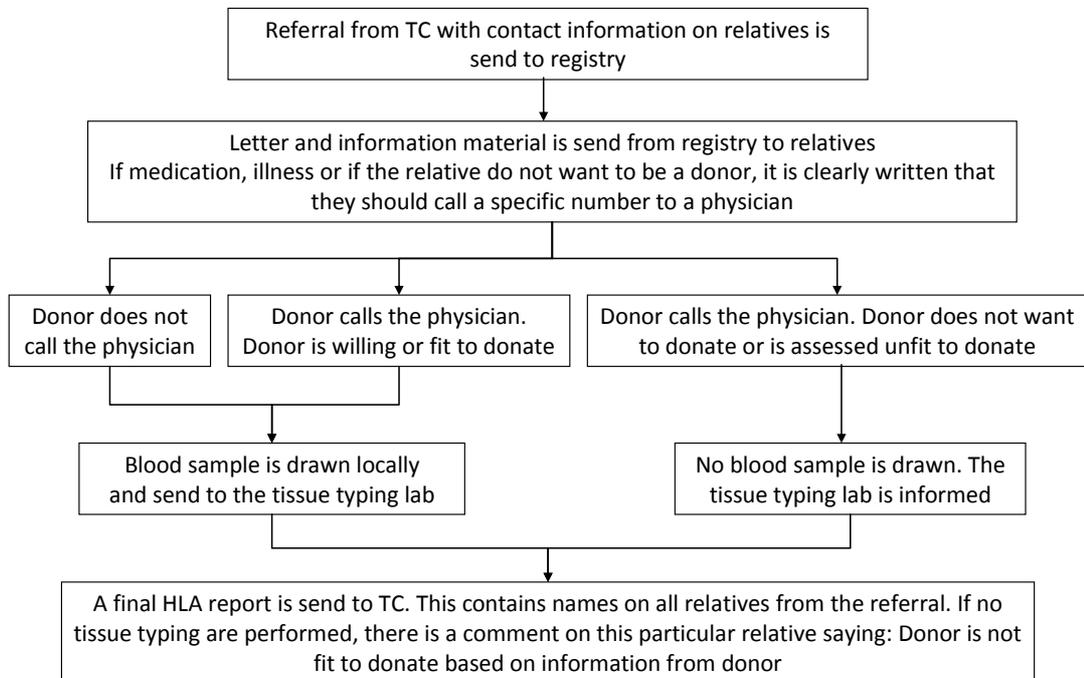
### 6.3.1 SUCCESSFUL MODELS OF RD CARE BY UD REGISTRIES

#### *6.3.1.1 Evaluation of related donors prior to HLA typing in Denmark*

As per standard practice in most countries, related donors in Denmark were historically managed by the recipient’s transplant team and initial contact to arrange HLA typing was made by transplant physicians. After incidents where RDs were deferred at a late stage when medical issues were discovered at the time of donor medical or donors were unwilling to donate, a novel procedure was developed by the UD registry.

Contact details for potential RDs are now passed directly to the UD registry, who make initial contact with RDs. Comprehensive information about donation is provided and potential RDs are instructed to contact an independent registry physician by telephone if they have any medical issues, wish to discuss donation, or do not wish to donate. If the physician decides the relative is unfit or unwilling to donate, HLA typing is not performed. A standard report is then produced stating “Donor is not fit to donate based on information from donor” for every donor who is not HLA-typed, thus preserving confidentiality.

Figure 6.1 The pathway of RD management in Denmark, with the UD registry providing care prior to HLA typing (figure supplied by Dr Betina Sorenson, Danish Bone Marrow Donor Registry)



### 6.3.1.2 Assessment of feasibility in the UK

#### Advantages

Deferral of donors who are unfit to donate at the earliest point possible is beneficial to the patient, the donor and the transplant team, and as shown in Chapter 4, assessment of RDs prior to HLA typing in the UK is varied.

Although donor confidentiality can be preserved within the transplant centre setting, a donor who is unwilling to proceed with donation may feel more comfortable discussing this with a team who are completely separate from their relative's transplant centre.

### *Disadvantages*

Unlike Denmark, the HLA typing of RDs in the UK is only performed by the registry for selected transplant centres, with many instead processing HLA typing in their local histocompatibility and immunogenetic laboratories. For this reason, it would be virtually impossible to implement this model in all UK transplant centres, without first centralising all HLA typing for patients and donors.

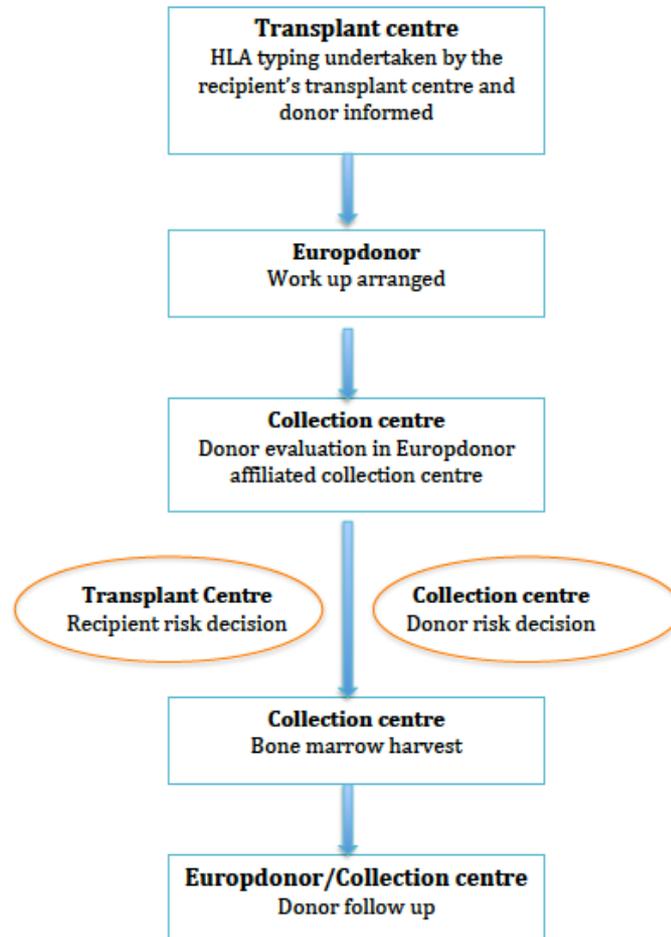
### *6.3.1.3 Bone Marrow harvesting of related donors by the Eurodonor Foundation and affiliated collection centres in the Netherlands*

As the number of HPC donors undergoing BM harvest has declined, some transplant centres in the Netherlands have become unable to comply with the minimum of one BM collection per year required by FACT-JACIE Standards. Some centres therefore requested the Eurodonor Foundation and its affiliated collection centres to undertake BM harvests on their related donors.

The logistics of the BM donation for these donors are organised by Eurodonor Foundation and an affiliated collection centre undertakes the entire donor process. Donors are evaluated using national related donor suitability guidelines, WMDA Standards and suitability criteria, and NMDP medical assessment tools are utilised. Donor clearance is undertaken by the collection centre in a similar manner to unrelated donors with decisions regarding donor safety made by the harvest centre physician, while those regarding recipient safety are referred to the recipient's transplant physician. Harvesting occurs at the collection centre.

Eurodonor Foundation and the harvesting centres are jointly responsible for RD follow-up of the donors whose harvests they have undertaken. Data collection is performed according to WBMT recommendations (Halter *et al*, 2013).

Figure 6.2 The pathways of care for RDs undergoing BM harvests in the Netherlands (Based on information supplied by Dr Anne-Marie van Walraven, Europdonor)



#### 6.3.1.4 Assessment of feasibility in the UK

##### *Advantages of implementation in the UK*

Each UK transplant centre performs relatively few bone marrow harvests on adult RDs, and there is a recognised difficulty with transplant physicians maintaining expertise in this procedure (Remberger *et al*, 2015; Anthias *et al*, 2015).

*Disadvantages of implementation in the UK*

In the current UK healthcare system, invoicing transplant centres for related donor care would be problematic because management of RDs outside the transplant setting is likely to represent a more costly option which transplant centres may not be willing or able to support. If the registry were to perform the entire RD care pathway for BM donors, decisions would need to be made jointly with transplant centres regarding the deferral criteria against which RDs would be assessed, since implementation of WMDA or national UD criteria is likely to lead to a high deferral rate for RDs.

It may be confusing for transplant centres to have two separate pathways for RDs depending on the route of donation. Furthermore, at times medical issues precluding a particular route of donation only come to light at the donor medical consult. Therefore, if a RD who intended to donate PBSC were found to only be suitable for BM donation, their care would then need to be transferred shortly before donation. Likewise, if a PBSC donor failed to mobilise, their care would then need to be urgently transferred to a separate (geographically distant) location if they were to undergo an urgent BM harvest.

*6.3.1.5 Standardized Donor follow-up of Swiss Blood Stem Cells (SBSC) for related and unrelated donors*

Prior to 2007, related donors were followed up by their recipient's transplant centre, using funding provided by the recipient's health insurance (providing the recipient remained alive).

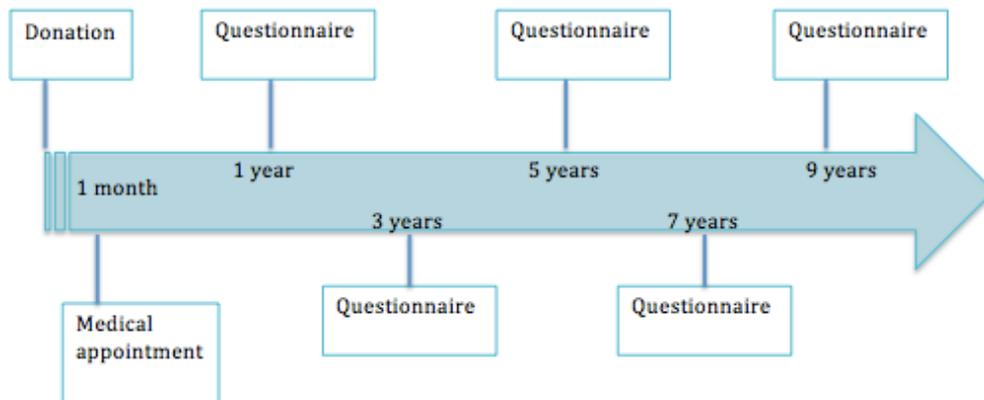
In July 2007, a change in law made donor follow-up mandatory for both unrelated and related HPC donors. The Swiss Blood Stem Cells (SBSC) and Swiss Blood Stem Cell Transplantation agreed to undertake related donor follow-up, with slight differences between related and unrelated donors.

The procedure for donor follow-up is now as follows: one month post-donation, UDs and RDs attend a medical appointment at their collection centre. At 6 months, 1 year,

and then every 2 years until 10 years post donation, UDs and RDs receive a health questionnaire from the SBSC. The data collected from these questionnaires is based on the minimum data set recommended by WBMT (Halter *et al*, 2013) and collected data is entered into the donor follow-up section of each patient’s record in the EBMT ProMISe database by SBSC. Prior to donation, donors sign informed consent for follow-up by SBSC and data transfer to EBMT.

At the time of (first) RD or UD donation, an identical lump sum for the entire follow-up process is charged to the patient’s health insurance, and then transferred to a specific donor follow-up fund at SBSC. SBSC compensates all donor follow-up activities from SBSC and involved partners out of this fund. Contracts are made with partners (collection and transplant centres) based on the transplantation law and defining all aforementioned aspects.

*Figure 6.3 Pathway of donor follow-up for related donors by Swiss Blood Stem Cells (based on information supplied by Dr Grazia Nicholoso, SBSC).*



### 6.3.1.6 Assessment of feasibility in the UK

#### *Advantages of implementation in the UK*

FACT-JACIE accreditation is mandatory in the UK, and since 2011, Standards have included a requirement for ‘a policy for follow-up of allogeneic donors that includes

routine management and the management of donation-associated adverse events' (FACT-JACIE, 2011). Management of follow-up by a registry would enable transplant centres to meet this requirement. The median total number of allogeneic HPC transplants in UK centres is 49 (BSBMT, unpublished data). For a transplant centre to set up a system for follow-up may be time consuming and is difficult to automate. In contrast, the Anthony Nolan donor registry follows up thousands of UDs, using automated systems that could be easily adapted for use in RDs. While assessment and donation of RDs is likely to be more expensive when performed outside the transplant centre, the costs of providing follow-up are minimal.

#### *Disadvantages of implementation in the UK*

Provision would need to be made for communication between the registry follow-up team and the transplant centre regarding donors who develop complications post-donation or who do not wish to be considered for further donations.

### 6.3.2 DEVELOPMENT OF POTENTIAL MODELS FOR A PILOT STUDY

Following the above analysis I worked with donor provision, donor follow-up and finance teams within Anthony Nolan, and with the largest affiliated collection centre, The London Clinic, to develop three potential models of related donor care.

#### *6.3.2.1 Model 1. Provision of Related Donor care in a UD registry setting from the point of donor identification*

##### *6.3.2.1.1 Background*

I chose to evaluate whether an UD registry could successfully provide the entire donor pathway for two reasons. Firstly, UK UD registries intermittently receive requests from transplant centres to work up related donors, in cases where there are logistical barriers to work up occurring at the transplant centre, so determining a process was felt to be an important starting point. Secondly, if the growth in haplo-identical donor

transplants continues, it may become difficult for UK transplant centres to absorb the additional work of donor care and registries may be asked to provide this service.

#### *6.3.2.1.2 Pathway logistics*

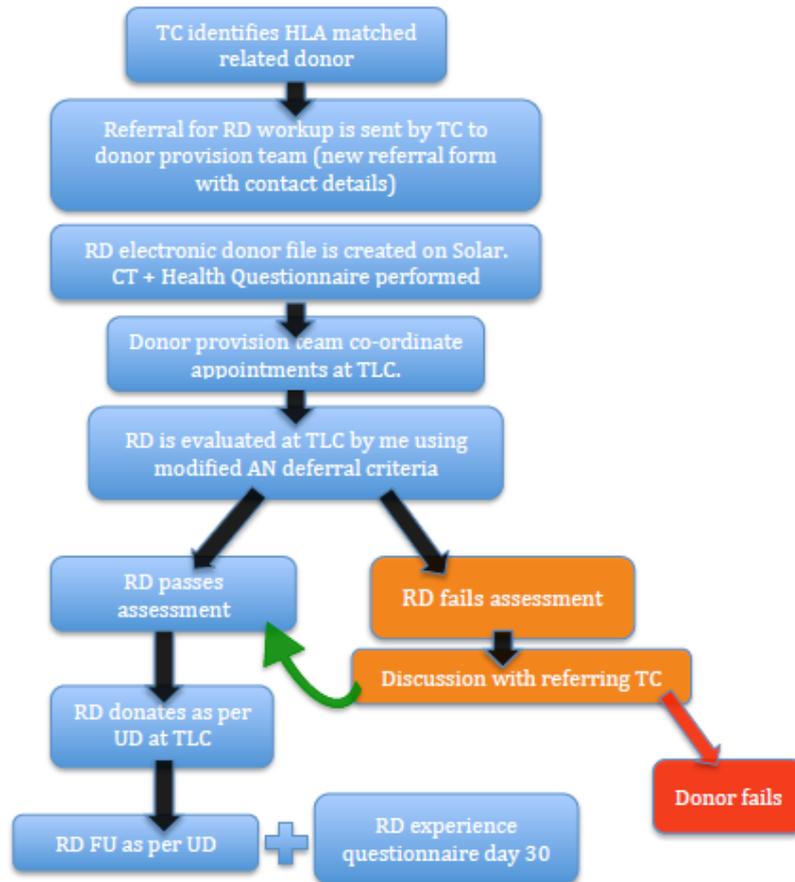
Potential matched related donors would be identified by the intended recipient's transplant centre. Related donors would be referred to the Anthony Nolan where evaluation and donation would occur at an affiliated collection centre, The London Clinic. For the purpose of the pilot study I would have an honorary appointment at The London Clinic and would perform donor evaluations. Donor assessment would be performed according to medical suitability/eligibility criteria previously agreed with transplant centres, derived from Anthony Nolan medical criteria for unrelated donors. In the event that a related donor did not meet these criteria, there would be a discussion with the transplant physicians at the referring hospital and a joint decision made about whether to accept the donor.

Following the donor medical evaluation, all investigations and the donation process would follow the same procedures used for unrelated donors.

Post donation, related donor follow-up would be performed by the Anthony Nolan, at identical time-points to unrelated donor practices, using adapted standard questionnaires. To evaluate the pathway, donors would receive an additional internet-based survey at 30 days post-donation.

Service level agreements already in existence would be adapted to include related donors.

Figure 6.4 Proposed pathway of related donor care in an UD registry setting



## 6.3.2.1.3 Cost Analysis

Table 6.2 Costs for related donor assessment at Anthony Nolan affiliated collection centre (PBSC)

Procedure	Hours per donor	Cost per hour (£)	Cost per donor (£)
Harvest coordinator	20	20	400
Medical officer	1.5	20	30
Administration for donor visit	2	15	30
Donor Follow-up			
Day 7 questionnaire	0.5	15	7.5
Day 30 questionnaire	0.5		7.5
Annual questionnaires (10 years)	0.5 per year		75
PBSC donation at collection centre	NA	1,985 1 day 3,313 2 days	2502*
GCSF cost	NA	NA	362**
GCSF Administration	NA	NA	350
Transport of cells	NA	NA	50
<b>Total</b>			<b>£3,814</b>
<b>Total excluding staff time</b>			<b>£3,264</b>

\*Calculated based on data from the study described in in Chapter 3 (61% related donors requiring one procedure, 39% required two procedures)

\*\*Based on the median dose of 789mcg/day for 4 days

*Table 6.3 Internal costs per RD donating in the transplant centre, for comparison*

	Hours per donor	Cost/hour (£)	Cost per donor (£)
<b>Nurse transplant coordinator</b>		26*	
Initial administration	1		26
Counselling and investigations	1.5		39
Coordination of apheresis/GCSF	1		26
Review on apheresis	0.25		6.5
D7 Phone call	0.25		6.5
Additional support by phone/email (1hr required for 50% donors)	0.5		13
<b>Medical transplant coordinator</b>		20	
Donor evaluation	1		20
Admin/prescribing GCSF	0.5		10
Review of results/donor clearance	1		20
Additional input required (on average)	1		20
GCSF cost	NA	NA	312
GCSF administration			0
<b>Apheresis costs</b>	NA	424 per day	572***
<b>Investigations</b>	NA	NA	
Virology			230
Other laboratory tests			50
<b>Administrative work</b>			
Donor registration/administration	1.5	15	43
Donor follow-up questionnaire (10 years)	0.5/year		
<b>Total</b>			<b>£1,394</b>

\* Based on a band 7 nurse

\*\* Based on median 789mcg/donor for 4 days

\*\*\*Calculated based on data from the study described in in Chapter 3 (61% related donors requiring one procedure, 39% required two procedures)

*Table 6.4 Summary of comparative costs per related apheresis donor (£)*

Transplant centre		Anthony Nolan & Collection centre	
Nurse coordinator	117	Donor provision	600
SPR coordinator	70	Medical officer	30
Admin staff	43	Team Support/donor advocate	120
GCSF + administration	312	GCSF + administration	362+ 350
Apheresis	572	PBSC donation	2502
Virology+bloods	280	Transport of cells	50
<b>Total</b>	<b>1394</b>	<b>Total</b>	<b>3814</b>

*6.3.2.1.4 Summary of comparison*

If all the calculated costs were passed on from the registry to the transplant centre, the transplant centre would pay approximately an additional £2,400 per related donor. If the registry were to pass on the direct costs to the transplant centre but absorb the costs of registry staff time the transplant centre would pay an additional £1,870 per related donor.

*6.3.2.1.5 Outcome*

I was able to secure funding from Anthony Nolan to offer this model as a pilot study to 10 donors from each of two transplant centres. Following discussions with both King's College Hospital and The Royal Marsden, neither finally accepted the proposal. In both cases this was due to a reluctance to undertake a new pathway for a limited number of donors without secured funding following the pilot study.

### *6.3.2.2 Model 2. Evaluation of Related Donors within a transplant centre by an external physician*

#### *6.3.2.2.1 Background*

The greatest concerns in related donor care to date have been regarding the potential conflict of interest that exists when a single physician is responsible for the care of a related donor and their intended recipient. A second issue lies in the fact that related donors are permitted to proceed with medical conditions that would confer deferral in the unrelated donor context, and there are convincing suggestions that this puts them at a greater risk of complications during donation. These two problems were addressed in my first model by providing the entire donor care pathway through a registry and their affiliated collection centre. The main issue with this approach, however, is likely to be financial constraints, with by far the biggest cost attributed to provision of the apheresis procedure by a registry-affiliated collection centre. I therefore wanted to explore a model where the donation procedure remained within the transplant centre but where evaluation and counselling are provided by an independent physician who is not part of the transplant team caring for the recipient.

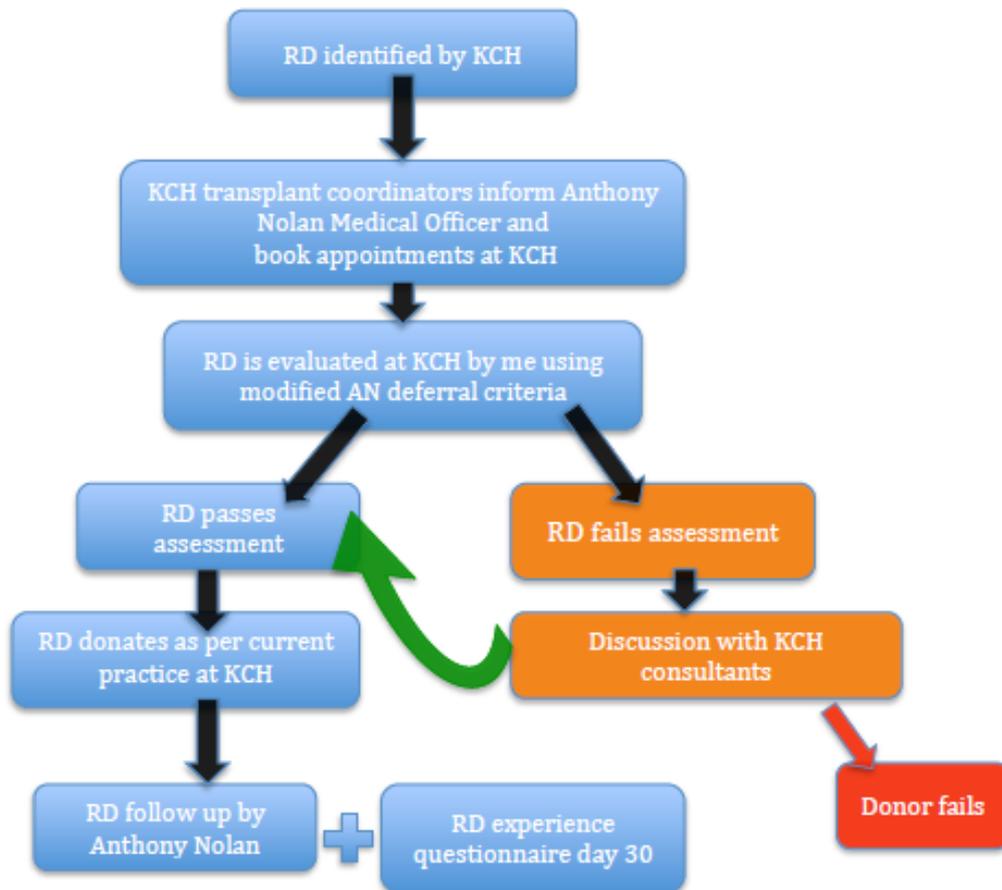
#### *6.3.2.2.2 Pathway logistics*

In this model a suitably matched related donor would be identified by the transplant centre. A donor evaluation appointment would then be booked with a physician from an external organisation with expertise in donor care. For the purposes of the pilot study I would fulfil this role, with the idea that following a successful pilot this role could be fulfilled by a physician from a separate team within the same organisation or a transplant physician from another centre. The related donor would be evaluated using identical procedures to an unrelated donor with respect to screening investigations and assessed against previously agreed medical suitability/eligibility criteria, derived from AN medical criteria for unrelated donors. In the event that a related donor did not meet these criteria, there would be a discussion with the transplant physicians and a joint decision made about whether to accept the donor. The donor would sign consent for

donation during the evaluation, and would also be asked to consent to data transfer and future follow-up by the Anthony Nolan.

The clearance paperwork would be completed by the independent physician evaluating the donor, following which donors would undergo donation according to the usual centre procedures. Donor follow-up would be performed through the Anthony Nolan with ten-year follow-up and data collection covering the minimum requirements recommended by WBMT. Donors would be asked to complete an additional survey evaluating the donor care model at 30 days post donation.

Figure 6.5 Proposed pathway of related donor care with evaluation in the transplant centre by an external physician



### 6.3.2.2.3 Cost analysis

As calculated in Model 1, the costs of providing donor follow-up by the UD registry would purely be staff time with a total cost of £122 per donor. The registry therefore agreed to absorb these costs and offer related donor follow-up as a free service for the purpose of a pilot study. For the purpose of the pilot study, no costs would be attached to the independent physician providing donor evaluation.

#### *6.3.2.2.4 Feasibility assessment*

##### *Advantages*

This model provides a lower-cost method of testing the logistics of independent evaluation of RDs and centralised donor follow-up; two areas in which care is currently lacking.

##### *Disadvantages*

Following a successful pilot, it may be difficult to set up arrangements for a physician with appropriate experience to travel to a transplant centre to perform donor evaluation. However it may be possible to create reciprocal arrangements between two transplant centres where a physician from each provides donor care in the other centre. Alternatively the independent physician could be a non-transplant haematologist or non-haematology physician within the same organisation.

#### *6.3.2.2.5 Outcome*

During the process of attempting to set up this pilot study I encountered a number of issues for which I could not find optimal solutions. These included the following:

1. If additional investigations were required following the donor medical, how would these be arranged and reviewed?
2. How would the external physician provide donor clearance from off-site?
3. How would a decision be reached if there were a difference of opinion between the external physician and the transplant consultants regarding acceptance of a donor with health risks for donation?
4. Who would make a decision regarding proceeding with donation if the donor was unwell on the day of donation?

It became clear that as an external physician I would have to work closely with an onsite coordinator (nurse or administrative) and that this person would need to send donor investigation results via secure email in some instances. This, however, was felt by the transplant coordinators to represent extra work that was not considered feasible.

This pilot study was considered, but not finally accepted, by King's College Hospital due to a recent decision to introduce a new internal system for donor care, similar to that proposed in this model, where donor assessment would be performed by a non-transplant haematologist. The Royal Marsden initially accepted the proposal for this pilot study, however the pilot study was subsequently abandoned when I accepted a post within the transplant team at that hospital and was no longer able to fulfil the role of an independent physician.

### *6.3.2.3 Model 3: follow-up of related donors by Anthony Nolan*

#### *6.3.2.3.1. Background*

The purpose of this pilot study was to explore the logistics of related donor follow-up by Anthony Nolan and to determine acceptability to transplant teams, to related donors and to the Anthony Nolan.

#### *6.3.2.3.2 Pathway logistics*

Related donors would be seen and undergo assessment and donation as per current practice at the transplant centre. Prior to the donor medical evaluation, donors would be provided with a donor information sheet outlining the pilot study and follow-up process. At the donor medical evaluation, consent would be taken for data transfer and follow-up by Anthony Nolan providing the donor was willing.

Following donation, the transplant coordinator from the transplant centre would contact the donor once at 2-3 days post-donation to ensure no immediate complications had occurred. A specific referral form for related donor follow-up would then be completed by the transplant coordinator and sent, with the consent form, to the donor follow-up team at Anthony Nolan.

From this point onwards, related donors from participating transplant centres would receive identical follow-up to Anthony Nolan unrelated donors. This would include a

health questionnaire at 7 days post-donation, a health questionnaire annually at years 1-6 and then biannually until 10 years post-donation. Follow-up questionnaires would capture the minimum information required as per WBMT guidelines and EBMT donor outcome forms. This would include a question about whether the donor would be willing to donate again if required.

Any medical issues identified during follow-up would be discussed within the medical team at Anthony Nolan. In the event of donors reporting any complications felt to be directly related to stem cell donation, the Anthony Nolan medical officers would report complications to the clinical team at the referring transplant centre with a joint discussion regarding any further action required.

Related donors would not receive any other type of communication from Anthony Nolan, such as fundraising information.

#### *6.3.2.3.3 Cost analysis*

As calculated in Model 1, the costs of providing donor follow-up by the UD registry would be purely staff time with a total cost of £122 per donor. The registry therefore agreed to absorb these costs and offer related donor follow-up as a free service for the purpose of a pilot study.

#### *Advantages*

This is by far the simplest model, and is likely to be easy to implement nationally following a successful pilot study. It allows centralised reporting of RD data, and provides assistance to transplant centres in an area of care that can be difficult to perform in a transplant centre setting (there is often no defined team responsible for this).

*Disadvantages*

This pathway does not address conflict of interest or RDs not being assessed using standardised procedures.

*6.3.2.3.4 Outcome*

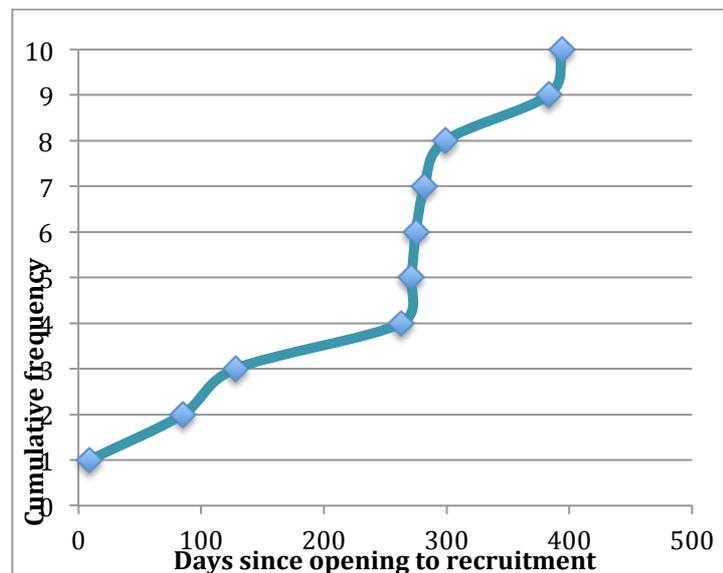
The proposal for a pilot study was accepted by Nottingham University Hospital for a 13-month period.

**6.3.3 RESULTS OF PILOT STUDY OF RELATED DONOR FOLLOW-UP BY ANTHONY NOLAN**

*6.3.3.1 Recruitment*

This study recruited from 1/09/14 to 1/10/15, during which 10 donors were enrolled. The characteristics of the participating donors are summarised in Table 6.5.

*Figure 6.6 Cumulative number of related donors recruited to donor follow-up study*



*Table 6.5 Characteristics of participating related donors*

<b>Donor characteristic</b>	<b>N</b>
Donor age: median (range)	60 (42-66)
<b>Source of HPCs donated</b>	
PBSC	10
BM	0
<b>Response to day 7 questionnaire</b>	
Yes	8
No	2
<b>Relationship to recipient</b>	
Sister	5
Brother	5

#### *6.3.3.2 Responses to day 7 donor follow-up questionnaires*

All donors were contacted via email and invited to complete a health questionnaire at 7 to 10 days post-donation administered via a secure Internet site (surveymonkey.com to January 2016, smartsurvey.com thereafter). Eight donors (80%) responded. Unfortunately, the donor follow-up team were unable to locate the data relating to one of these responses at the time of analysis, and therefore 7 responses were available for analysis.

All 7 donors (100%) reported full recovery at 7 days post donation. The median time to recovery was 5 days, and all donors reported being back to work or normal activities at 7 days post-donation. Four donors reported no symptoms at follow-up one described grade 1 stiffness and one reported grade 1 insomnia and muscle pain. No donor had started any new medications post-donation.

All donors reported feeling physically normal but responses regarding emotional state were more varied. Three donors who responded to this question (60%) reported feeling normal, one felt much better than usual and one donor described feeling much worse than usual and commented “my bit is easy, but having to wait 3 weeks until knowing whether it is a success is debilitating for me”.

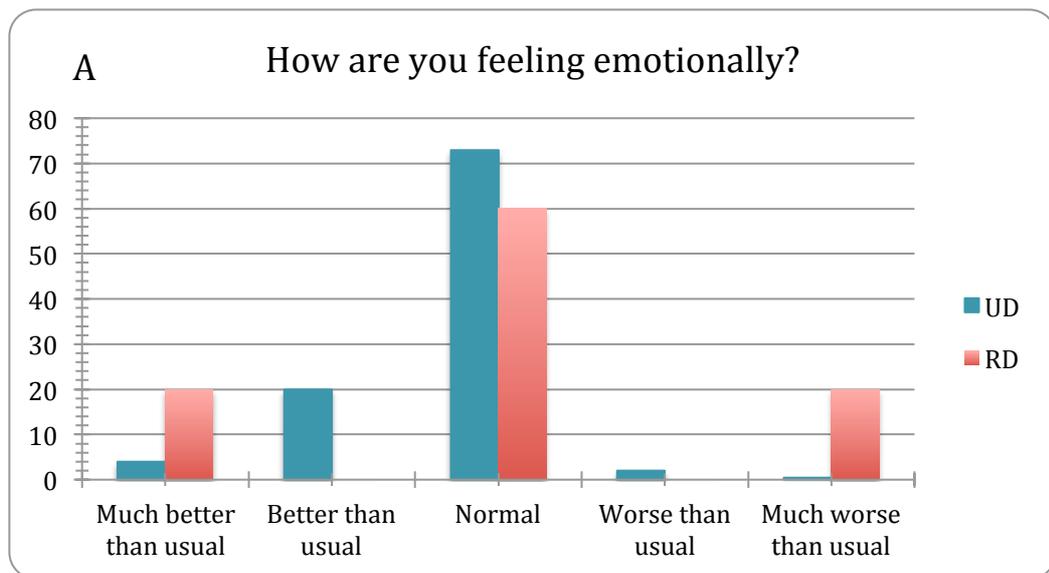
6.3.3.4 Comparison to unrelated donors responses

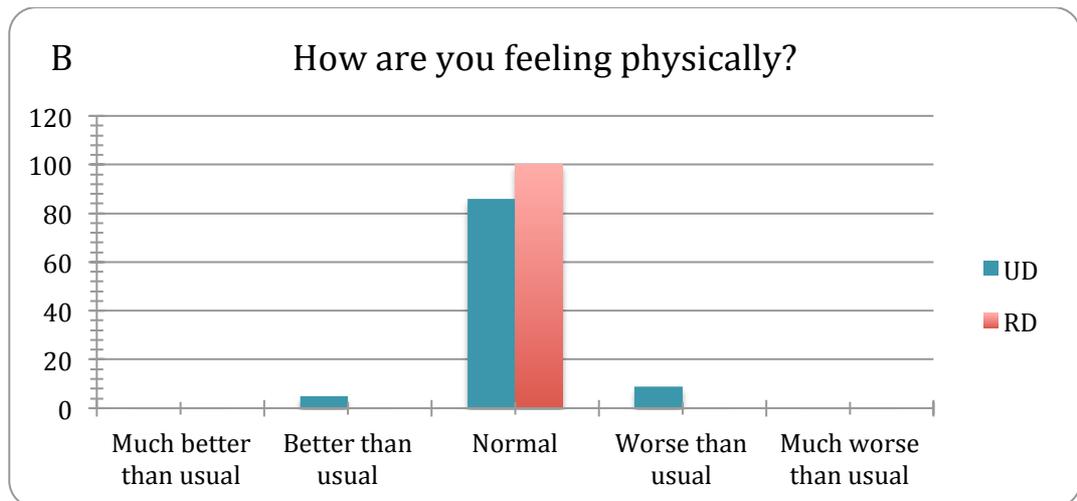
I performed an analysis of day 7 questionnaire responses on a cohort of 470 unrelated donors who donated at the Anthony Nolan between February and November 2015. As expected these donors were generally much younger than the related donors, with a median age of 29, and 90% of donors had donated PBSC. These donors took a median of 3 days to recover, and 93% reported full recovery at one week post-donation. Only 9% reported feeling worse physically at this point, and 2% felt worse than usual from an emotional point of view (shown in Figure 6.7). 1.7% donors had started a new medication post-donation.

Table 6.6 Characteristics of unrelated donors in comparison group

Unrelated donor characteristics	N
Median age (range)	29 (18-59)
Source of HPCs donated	
PBSC	423 (90%)
BM	47 (10%)
Median days to recovery (PBSC donors)	3

Figure 6.7 Responses from UD and RDs to day 7 follow-up questions regarding A) physical and B) emotional wellbeing





#### 6.3.3.5 Feedback during the pilot study

During the follow-up process, one donor, aged 49, contacted the donor follow-up team to complain that he found the approach of emailing donors impersonal and that he did not think all donors in their 50s would be able to complete electronic questionnaires. When I contacted this donor to discuss his complaint, it became apparent that he was unhappy with the donation process at the transplant centre because he did not have a good relationship with his recipient and was surprised that the staff at the transplant centre were unable to guarantee that he would be informed about his matching status before his recipient. He was also unhappy that he had been asked to administer his own GCSF injections. His concerns were fed back to the transplant centre and the donor confirmed that he was happy to continue donor follow-up by Anthony Nolan.

No concerns were voiced by the clinical contacts at the transplant centre, and the process for transfer of donor care was felt by both sides to have run smoothly. When I interviewed the donor follow-up team at Anthony Nolan following the pilot study, the sole concern was regarding how they would deal with donors who contacted them with psychological issues after donation. An agreement was reached that if expanded

nationally, it would be helpful for one of the members of the donor follow-up team to undergo formal training in counselling.

## 6.4 CONCLUSIONS

In this chapter I explored in depth three potential alternative models of related donor care, where part(s) of the care pathway would be performed by an unrelated donor registry. I was able to assess the logistic and financial feasibility of these options, with findings that can guide future efforts to improve the related donor journey in the UK.

During analysis of Model 1, I demonstrated that the costs of providing the whole donor care episode in a registry setting as opposed to a transplant centre would result in an increased cost of £2,400. Currently, this cost would need to be met by the transplant centre, which seems unlikely to be a palatable option in the current NHS climate. It is important to bear in mind that there are likely hidden costs to donor care in transplant centres above those considered in my analysis, whereas the costs of donor provision by a registry were already well defined. A second issue that arose during discussion with transplant centres was regarding the medical suitability criteria against which RDs would be assessed, with some concerns raised that deferral rates for RDs may be higher if they were assessed by medical staff who usually evaluate unrelated donors. This second issue could be solved if consensus related donor medical suitability criteria were created.

Model 2 initially presented an attractive option because it overcame the cost issues encountered in Model 1, yet still ensured independent donor evaluation by an experienced physician and standardised donor follow-up. However, as I tried to set up the pilot study, it proved increasingly complex to define a robust pathway. It became clear that in addition to an external physician, a dedicated donor coordinator onsite would be necessary. The major problem, and the ultimate reason for failure to set up a pilot study was the concerns from transplant centres regarding identification of an appropriate external physician after the closure of the pilot study. Although this role could have been fulfilled either by a registry physician or a physician from a separate

transplant centre, even large centres only facilitate approximately 30 adult RDs per year, and these donors will not be required at evenly spaced intervals throughout the year. For this reason it would be difficult to schedule a timetable for an external physician to attend on an ‘as required’ basis. In summary, although this was theoretically a desirable model of donor care, it appears to be unfeasible in the current set-up of UK transplant centre practice.

Model 3 resulted in a successful pilot study, which showed that donor follow-up by an unrelated donor registry represents a feasible way of ensuring standardised follow-up for related donors. Although only one transplant centre was enlisted in the pilot study, it would be relatively easy to offer this service to transplant centres nationally. There were no issues encountered in providing follow-up in a separate organisation and transfer of donor care between the transplant centre and the registry was very straightforward. Although the study was not powered to statistically compare recovery between related and unrelated donors, the RDs in this pilot study did not appear to require more comprehensive early follow-up. If this initiative were expanded nationally, a detailed comparison of recovery between donor cohorts would be possible. The main potential issue raised during this study was regarding management of RDs with psychological problems as a result of donation, which the registry follow-up team were not accustomed to dealing with. There is currently no provision for psychological support post-donation in transplant centres, but if this model is offered nationally some expertise in this area within the registry would be helpful.

In conclusion, I encountered a number of challenges in setting up pilot studies for the more complex models of RD care, and the first two models described in this chapter do not appear feasible at this time. Provision of donor follow-up by the registry was far more successful and the Anthony Nolan is therefore currently considering offering RD follow-up services nationally.

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## CHAPTER 7. A STUDY OF RELATED DONOR EXPERIENCE OF THE DONATION PATHWAY

### 7.1 INTRODUCTION

In Chapters 3, 4 and 5 of this thesis I demonstrated that practice patterns in related donor care have changed following the introduction of international guidelines in this area. While I was able to show improvements in specific aspects of care, I also identified some areas, such as donor follow-up, where relatively few centres comply with current recommendations. The consensus guidelines (van Walraven *et al*, 2010b; Halter *et al*, 2013) and regulatory standards (FACT-JACIE, 2012; WMDA, 2013) against which I evaluated transplant centres were formulated by experts in the field of donor health and are based on ethical principles, safety data from large donor cohorts, and in some cases, UD care paradigms. Despite some physical differences between RDs and UDs (RDs being older, and more likely to have health issues) and a remaining need for data from RD-specific safety studies, we can nevertheless be confident that adherence to such guidelines will maximally protect the physical health of RDs.

It is more difficult to be confident that adherence to current standards and recommendations will ensure that a transplant centre meets the psychological needs of RDs. There are major differences between RDs and UDs regarding the psychological investment in the transplant. Best practice in this area should be informed by the results of studies in RDs, yet there are little available data on which to base such recommendations.

The studies performed to date that have explored the psychological impact of donation for RDs have shown differing results. Although long-term psychological benefits (for example increased self-esteem), have been reported in some studies, other groups have demonstrated detrimental psychological effects post-donation, which unsurprisingly, appear to be linked to the recipient's transplant outcome (Switzer *et al*,

1998; van Walraven *et al*, 2010a; Wolcott *et al*, 1986). There are several difficulties with interpreting the results of these studies; some were conducted >30 years ago, and almost all studies were performed using very small donors cohorts (<30 donors). Furthermore, as described in Chapters 4 and 5 of this thesis, RD care is heterogeneous, and the psychological experience of donors will inevitably be partially determined by the support they receive and the information with which they are provided.

Larger studies have been performed in related renal donors, and corroborate the finding that the donor's quality of life is strongly dependent on the recipient's outcome (Giessing *et al*, 2004). However, recipients of HPC transplants have a far greater risk of mortality than recipients of renal transplants, and a much higher probability of severe long-term morbidity, so the experience for donors of these two procedures is quite different.

In order to consider future improvements in related donor care, it was first necessary to evaluate whether compliance with consensus recommendations results in an acceptable experience for the related donor, and to determine areas where donors perceive that improvements are needed.

The primary objective of this study was to determine donor experience in the setting of a transplant centre where FACT-JACIE Standards and international RD recommendations have been adopted. This included answering the following questions:

- Do donors feel fully informed?
- Do donors feel that they are presented with a choice about donating?
- Do donors experience stress about the procedure and if so why?
- Do donors feel that they are offered adequate support at the time of donation and post-donation?
- Are there any areas in which donors feel that care is lacking?

The secondary objective was to investigate whether any donor demographic factors correlate with a worse experience, or with the need for more support.

## 7. 2 METHODS AND MATERIALS

A 20-item questionnaire was developed to address the study objectives. This survey was sent by post to all adult related donors who had donated at The Royal Marsden between 1<sup>st</sup> January 2009 and 31<sup>st</sup> December 2014, with a letter explaining the study objectives (see Appendix 1). Donors were offered the option of completing the questionnaire via the internet (smartsurvey.com) or by post. Non-responders received one reminder six weeks later, using identical materials. The full materials and methods can be found in Chapter 2.

## 7.3 RESULTS

### 7.3.1 RESPONSE RATES

Responses were received from 53 of the 102 donors invited to participate, a response rate of 52%. Two factors significantly influenced the likelihood of responding: donors older than the median of 50.5 years were more likely to respond than younger donors (65% versus 39%;  $p=0.01$ ), as were donors who had previously responded to annual follow-up questionnaires (76% versus 35%;  $p<0.0001$ ). Responding donors had a median age of 55 years and had donated a median of 10 months previously. In 62% of cases the recipient remained alive.

Table 7. 1 Comparison of donor characteristics between responders and non-responders

	Responder (n=53)	Non-responder (n=49)	P
<b>Donor sex</b>			
Male	28 (53%)	31 (63%)	0.286
Female	25 (47%)	18 (37%)	
<b>Donor age at survey</b>			
< 50.5 years	20 (38%)	31 (63%)	0.01
>50.5 years	33 (62%)	18 (37%)	
<b>Donor living abroad</b>			
Yes	16 (30%)	13 (27%)	0.682
No	37 (70%)	36 (73%)	
<b>Year of donation</b>			
2009-2011	24 (45%)	29 (59%)	0.160
2012-2014	29 (55%)	20 (41%)	
<b>Recipient still alive</b>			
Yes	33 (62%)	36 (73%)	0.227
No	20 (38%)	13 (27%)	
<b>Previous response to annual follow-up</b>			
Yes	32 (60%)	10 (20%)	<0.0001
No	21 (40%)	39 (80%)	

Table 7.2 Characteristics of responding donors.

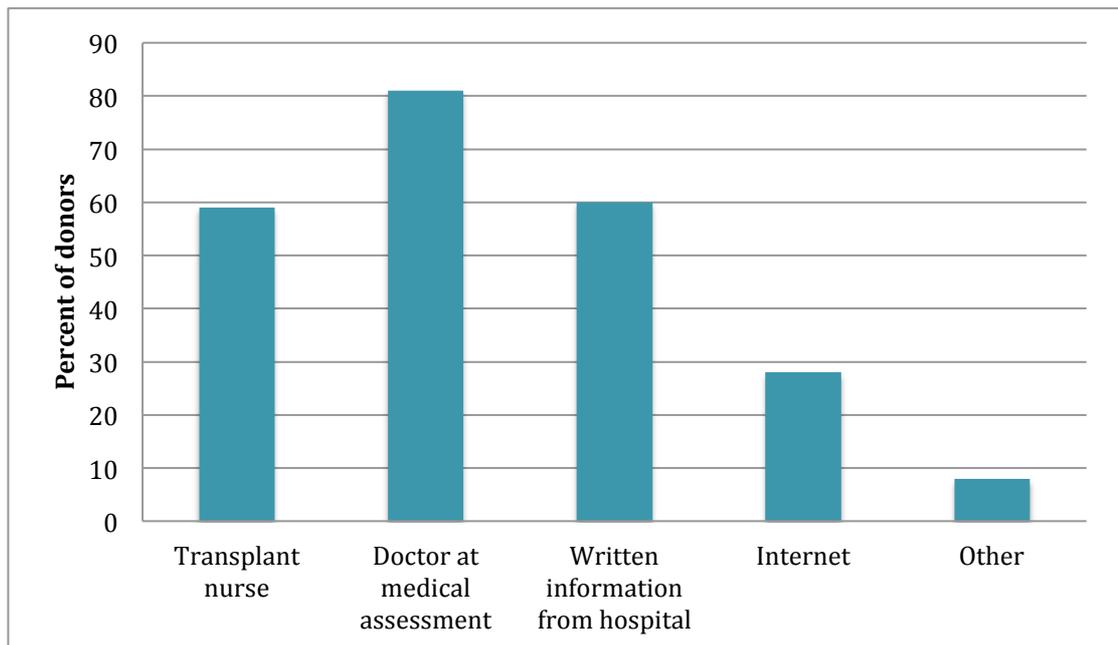
Characteristics of respondents	N=53
Median donor age at survey (range)	55 (18-78)
Donor sex male/female	28/25 (47%/53%)
Recipient sex male/female	34/19 (64%/36%)
<b>Age compared to recipient</b>	
Older	28 (53%)
Younger	25 (47%)
<b>Response method</b>	
Online	11 (21%)
Postal	42 (79%)
Months from donation median (range)	38 (8-76)
<b>Recipient status</b>	
Alive	33 (62%)
Dead	20 (38%)
Median months to death (range)	10 (2-47)

### 7.3.2 DO DONORS FEEL FULLY INFORMED ABOUT THE DONATION PROCESS?

Over 75% of donors were satisfied with the amount of information they received at each stage of the donation procedure. 87% felt that they received sufficient information to understand the donation procedure prior to HLA typing.

91% of donors stated that they had received information about the donation procedure from more than one source, and 60% recalled receiving written information from the hospital. 28% had done their own additional research about donation on the internet.

*Figure 7.1 Sources from which donors stated that they received information about the donation process*



*Table 7.3 Responses to questions examining provision of information to related donors*

<b>Questions about provision of information</b>	<b>Number of donors</b>
<b>Do you think you received enough information to understand the donation procedure <i>before your blood was tested to see if you were a match?</i></b>	
Yes	46 (87%)
No	7 (13%)
<b>From which of the following sources did you receive information about the donation procedure?</b>	
Transplant nurse	31 (59%)
Transplant doctor at medical assessment	43 (81%)
Written information from the hospital about donating	32 (60%)
Internet	15 (28%)
Other	4 (8%)
<b>Most helpful source of information</b>	
Transplant doctor	33 (63%)
Transplant nurse	23(44%)
Written information	11 (20%)
The internet	6 (11%)
<b>Were you given enough info about possible complications for your relative?</b>	
Yes	22 (42%)
No	4 (7%)
Not sure	2 (4%)
<b>Is there anything you would have liked more information about?</b>	
No	22 (42%)
Yes	6 (11%)
Side effects of donation	4 (8%)
See machine in use	1 (2%)
Post-transplant care for relative	1 (2%)

Donors were asked to identify the most helpful source of information, however the majority cited more than one source, and a quarter specifically commented that it was important to be provided with multiple sources of information with statements such as *“all [sources]; the written [information] because you can read it at leisure, then the nurse and doctor to ask questions later”*

21% of donors stated that they would have liked to be provided with more information; most commonly (13% of donors) more information about the side effects of donation,

while 4% felt they would have liked more information about the complications for their relative and 4% commented that they would have liked to see the apheresis machine in use prior to donating.

### 7.3.3 DO DONORS FEEL THAT THEY ARE PRESENTED WITH A CHOICE ABOUT DONATING?

94% of donors reported feeling no pressure to donate. In addition to selecting 'no' in response to this question, 40% reiterated this point by writing additional unsolicited comments on the questionnaire such as "*no, it was purely my choice, made by me alone*". Of the three (6%) donors who reported feeling pressurised, in two cases this pressure was from the intended recipient, while one donor reported feeling pressurised by the recipient's medical team.

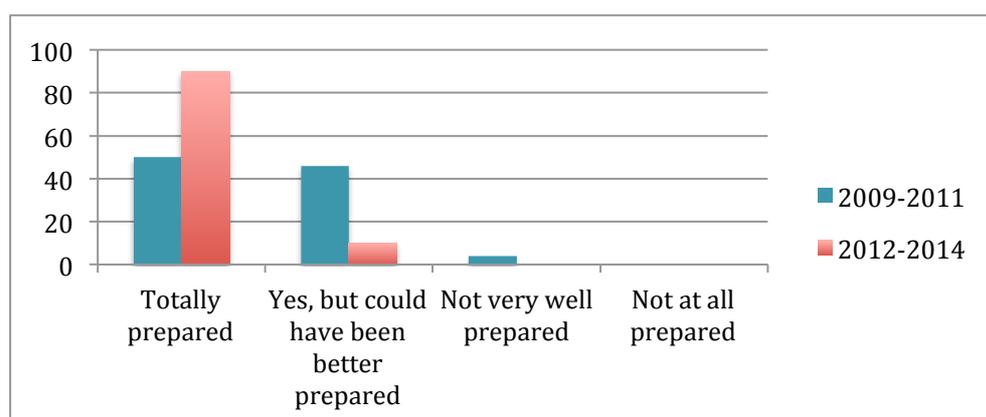
I found very low ambivalence to donation with 45 donors (85%) describing the decision to donate as requiring 'no consideration' and only one donor stated that the decision required a lot of consideration.

Regarding preparedness for donation, only one donor reported feeling 'not very well prepared' and no donors felt 'completely unprepared' for donation. Interestingly, male donors were more likely to state that the decision required some consideration, a statement made by 25% male compared to 4% female donors ( $P=0.018$ ). However, male donors were more likely to feel totally prepared for donation 93% male versus 48% female donors ( $p=0.001$ ). I also found that donors who had donated in the earlier years of the study (2009-2011) were significantly less likely to have felt totally prepared for donation, than those who donated in later years (2012-2014); 50% versus 90%;  $p=0.006$ .

Table 7.4 Responses regarding ambivalence and pressure to donate

Questions about ambivalence to donation	Number of donors
<b>Did you feel pressure to agree to donate from other people?</b>	
The relative to whom you were donating	2 (4%)
Other family	0
The medical team looking after your relative	1 (2%)
Other	0
<b>Did the decision to donate require</b>	
No consideration	45 (85%)
A little consideration	7 (13%)
A lot of consideration	1 (2%)

Figure 7.2 Responses regarding preparedness for donation from donors donating pre and post January 2012



### 7.3.4 DO DONORS EXPERIENCE STRESS ABOUT THE PROCEDURE AND IF SO WHY?

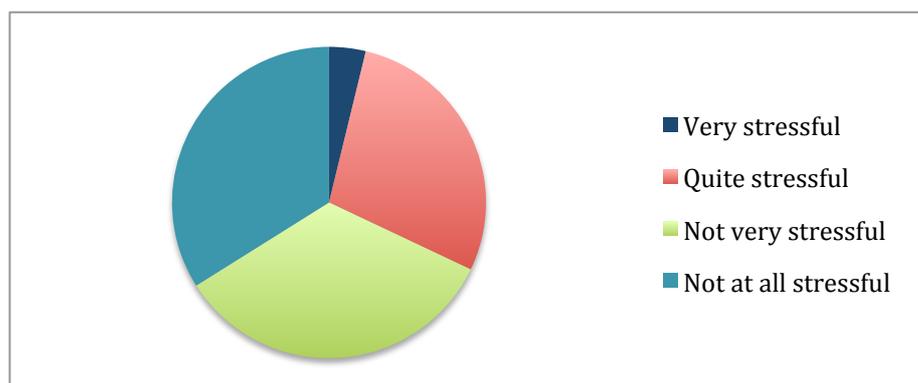
Most donors experienced some stress regarding donation, and 32% reported the process as very stressful or quite stressful. When donors were asked about sources of stress 17% stated this was due to concerns about their own health (including all donors who found the procedure ‘very stressful’), 21% reported anxiety about the donation procedure, and 16% were concerned about the logistics of donation. 13%

stated ‘other’ reasons, which in most cases was concern about the recipient’s outcome including: “concerns about the long term/short term effects on the health of the patient if I were to be sick”, “concerns about whether it would work or not” and “concerns that patient would have adverse reaction to receiving it”.

Regarding questions exploring difficulties with the logistics of donation, 48 (91%) donors described having to make significant arrangements in order to donate including education or work in 78%, and 26% suffering loss of earnings. 70% of donors had to meet costs, which included flights in 17% of cases. Two overseas donors mentioned additional difficulties in being away from their family for the donation period.

Regarding the physical experience, 21% stated that they experienced more pain or side effects than expected, of which three donors (6%) made additional comments that suggested a much worse reaction than expected. Each of these donors also commented that a more extensive discussion of the side effects would have been helpful.

*Figure 7.3 Responses regarding how stressful donors found the donation experience*



11% of donors stated that they had experienced negative emotions or psychological difficulties as a result of donation, which in all donors who elaborated, were due to the recipient’s health. Two donors described very difficult psychological experiences, with one stating, “[the transplant] not working and having a lot of guilt as a result which has

*taken a lot of counselling to clear*". The other described a difficult dynamic with his sister following donation. In both of these cases the recipients developed extensive chronic GvHD.

Figure 7.4 Sources of stress described by the related donors

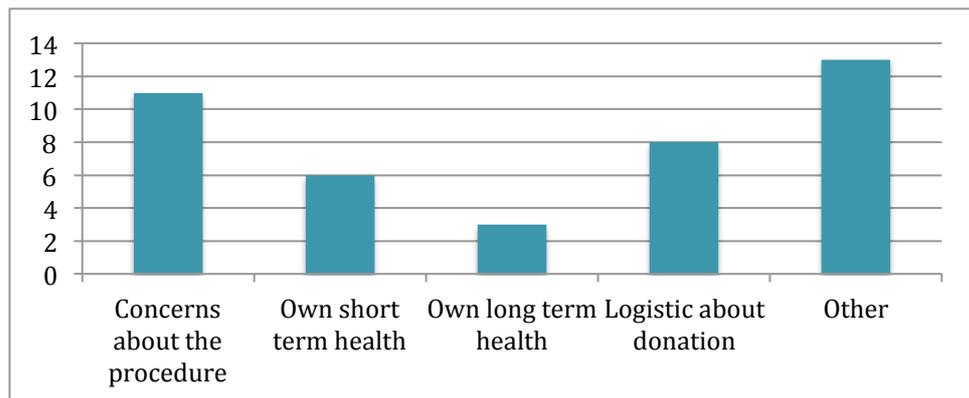
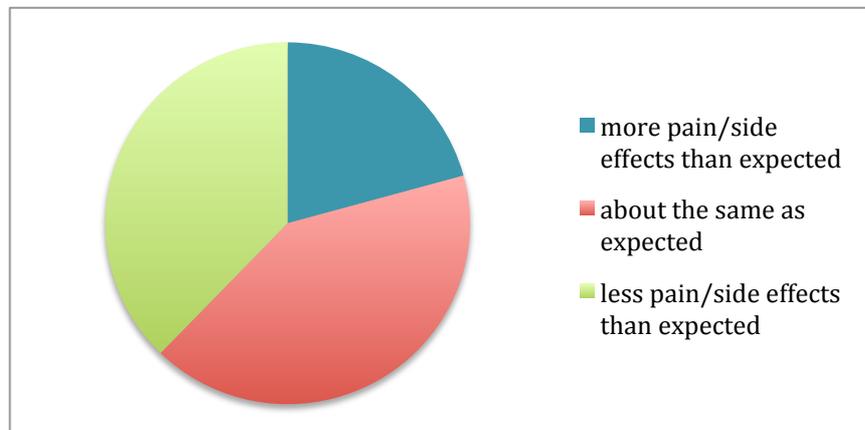
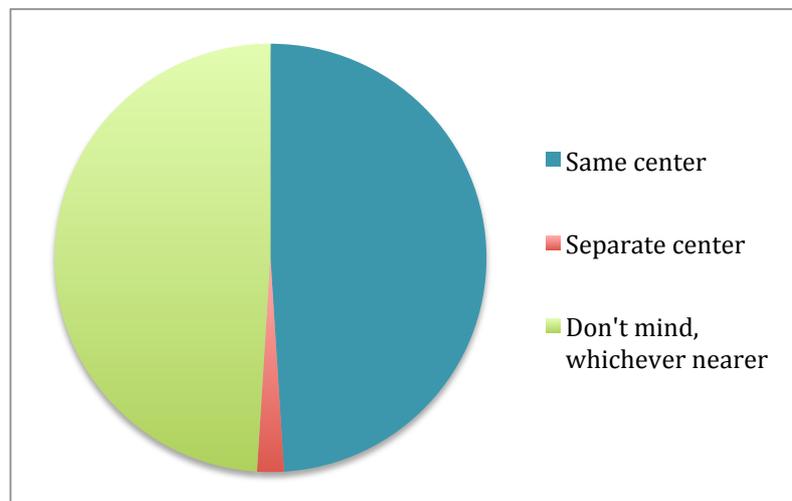


Figure 7.5 Responses regarding the physical experience of donation



Donors were asked where they would have preferred to donate; only one donor stated that they would have preferred to be treated in a separate centre to their relative. Other donors were equally split between those actively preferring to be at the same centre as their relative and those who either didn't mind or who preferred the most convenient option.

Figure 7.6 Responses regarding where donors would have preferred to donate



### 7.3.5 DO DONORS FEEL THAT THEY ARE OFFERED ADEQUATE SUPPORT?

Although 92% felt the hospital provided enough support at the time of donation, 17% felt that not enough post-donation support was available. This was reiterated when donors were asked the final open ended question, “Are there any other ways in which you feel your donation or post-donation care could have been improved?”. Although 38 (72%) donors stated that no improvements were needed, the remaining donors who suggested improvements felt that the post-donation support was inadequate, including the following statements:

- *“I feel counselling should be available, my sister cut me out of her life....she sees GVHD as a personal attack from me... I telephoned in tears and received a very negative response...Living with her death would be easier”*
- *“The hospital could have seen me after the procedure, as I had a lot of health issues but there was no support”*
- *“Yes, after care. I felt like I was on a conveyor belt and once I had donated I was forgotten”*
- *“From my experience if it doesn’t work it is awful for the donor. I don't know what anyone can do to help the donor”*

## 7.4 CONCLUSIONS

This study uniquely describes the experience of related donors who underwent a donation pathway in which care was delivered according to current regulatory standards and consensus recommendations. The response rate of 52% was very satisfactory, particularly considering that the survey was administered using postal questionnaires, and with 53 participants, this represents one of the largest studies of related donor experience to date.

I was able to demonstrate a reassuringly positive experience for the majority of donors who reported feeling well informed, non-coerced, well prepared, and experienced little or no stress, and little physical pain. However, I identified two donors (4%) who experienced very negative psychological consequences of donation, both in cases where the recipient had developed severe GvHD. Both of these donors commented on the lack of post-donation support that was available. A further three donors (6%) found the donation procedure stressful or difficult for reasons relating to their own health, and again, all felt that post-donation care was lacking.

I found very good results regarding the information donors receive about the donation procedure, particularly prior to HLA typing, which was an area highlighted as inadequate in several studies of donor care, including those I described in Chapters 4 and 5. This study reassuringly demonstrates that it is possible to provide donors with information before HLA typing, and that donors appreciate receiving information in different formats, and discussing the procedure with more than one health care professional. Nonetheless, I found that donors may benefit from further information regarding potential outcomes for their recipient. During the period studied, the written information supplied to donors did not explain the health complications of transplantation for the recipient, and while the potential for an adverse outcome was briefly touched upon in the donor consent discussions, and donors were not given specific details of the possible complications for their relative.

The findings of this study confirm previous reports (Pillay *et al*, 2012) of low ambivalence regarding the decision to donate. This was more evident here than in previous studies, with 85% of donors describing ‘no consideration’ which may reflect efforts to provide donors with adequate information prior to HLA typing. I was also able to show that males were more likely to require some consideration prior to deciding to donate. Although I did not demonstrate a difference in sources of information sought or provided to male or female donors, it may be that the additional consideration in male donors resulted in closer attention to the information provided, which may explain the increased preparedness described by male donors. Interestingly, I was also able to show an improvement over time with donors in the more recent donation era being more likely to describe themselves as totally prepared for donation. I did not find any difference in the sources of information that donors reported receiving between earlier and later time periods, however the written information booklets about donation were updated several times over the study period, which may explain this finding.

In accordance with earlier studies I found that the two donors who described severe psychological difficulties were cases where the recipient had developed severe GvHD. Both of these donors commented on the lack of post-donation support that was available. The three donors who commented on severe physical side effects also remarked that more post-donation support should be available. Current consensus guidelines recommend long-term donor follow-up, but focus on capturing specific health information to exclude an increased incidence of autoimmune or malignant disorders following donation. This information is most easily captured using a standard health questionnaire, however such follow-up will not provide the required support for the small proportion of donors who develop severe physical or emotional difficulties after donation.

Acute physical events associated with donation almost invariably occur within 30 days, and donors at the centre studied are given contact details for the transplant team in case they develop such events. In light of the findings of this study, it may be advisable to contact donors in writing at 30 days, asking them to make contact if they have any

health issues and providing written information of who to contact in the future if they develop physical or psychological health issues.

The retrospective nature of this study limited the potential to provide an in-depth analysis of the physical or psychological experience of donation, in particular to determine whether the closeness of the sibling relationships influenced the donor experience. Notwithstanding, the main objective was to assess the adequacy of a donor pathway adhering to current recommendations, and I was able to achieve this. Preventing a potential conflict of interest has been a major focus of the initiatives in donor care to date, and this study reassuringly affirmed that providing current recommendations are adhered to, donors do not feel pressurised to donate.

In summary, I have shown that providing donors with information both about the donation experience and the potential complications for the recipient is vital. While 90% of donors report a positive experience, current pathways do not provide adequate post-donation support for the minority that have a difficult experience, and efforts should next focus on addressing this issue.

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## CHAPTER 8: UK NATIONAL GUIDELINES FOR HPC RELATED DONOR CARE

### 8.1 INTRODUCTION

In Chapter 4 I demonstrated diversity between UK transplant centres at several stages of the related donor care pathway. This variation included the presence of an assessment of the health of a potential related donor before HLA typing, the duration of post-donation follow-up and the method by which this is conducted. In addition, I showed that transplant centres use differing criteria to determine the medical suitability of related donors and differing investigations during assessment. The result of these differences is that donors who would be accepted by some transplant centres would be deemed unsuitable by others.

This variation is not surprising, given that mandatory regulations in related donor care are largely focused on ensuring that donors undergo informed consent. Although the WMDA and WBMT have produced consensus statements which endeavour to fill a gap by providing recommendations for the principles of related donor care, differences in regulations and in the set-up of RD care between nations have prevented the creation of detailed and specific universal recommendations. As part of the study described in Chapter 4 I therefore sought the views of transplant physicians in the UK regarding the potential for development of national guidelines in related donor care, which >80% of transplant physicians feel would improve related donor care nationally.

This chapter describes the process of formulating UK guidelines for related donor care, endorsed by the British Committee for Standards in Haematology and the BSBMT.

The objectives of the guidelines were:

- To review the literature regarding the safety and experience of adult and paediatric HPC donors and to define evidence-based guidance for the entire donation pathway from the initial point of contact with donors through to donor follow-up

- To incorporate requirements of national competent authority, JACIE, and consider previously published expert consensus guidelines
- To use the findings of the study described in Chapter 4 to ensure that the proposed guidance is logistically possible for transplant centres to meet
- To create a set of ‘tools’ that allow efficient, standardised assessment of RDs aiming both to improve adherence to the guidelines, and to improve efficiency of the donor pathway in transplant centre
- To provide guidance for decision-making in difficult ‘grey areas’ where a potential or minor increase in risk is apparent
- To determine a process for counselling of donors who do not meet medical suitability criteria

## 8.2 METHODS AND MATERIALS

I established a working group comprising experts in the fields of adult and paediatric donor health, medical ethics, allogeneic haematopoietic cell transplantation and stem cell collection (see Table 8.1). Systematic literature searches using PUBMED for relevant publications in English were conducted up to April 2015 using the following keywords: related donor; family donor; stem cell donor; stem cell mobilisation and other search terms pertinent to subsections. After reviewing the literature the group considered a number of questions outlined below, and made recommendations based on responses to these. The draft guideline was reviewed by British Haematologists, the BSCH and the BSBMT. Where possible, these guidelines are based on published evidence, with the ‘GRADE’ system used to quote levels and grades of evidence, details of which are available at <http://bcshguidelines.com>.

*Table 8.1 Roles of experts in the guideline working group*

<b>Name</b>	<b>Job title</b>	<b>Role in guideline group</b>
<b>Dr Chloe Anthias</b>	Medical Officer Anthony Nolan	Lead author and group chair
<b>Prof Bronwen Shaw</b>	Scientific Director, CIBMTR Ex-Chief Medical Officer Anthony Nolan	Clinical expert in HPC donation and HPC transplantation
<b>Dr Rachel Pawson</b>	Consultant Haematologist Deputy Medical Director of the BBMR	Clinical expert in related and unrelated HPC donation
<b>Dr Mike Potter</b>	Transplant Director, The Royal Marsden	Clinical expert in HPC transplantation and BCSH representative for transplantation
<b>Dr Kenny Douglas</b>	Consultant Haematologist Scottish National Blood Transfusion Service	Expert in related HPC donation and apheresis
<b>Prof Bobby Farsides</b>	Professor of Clinical and Biomedical Ethics, University of Sussex	Expert in medical ethics and consent
<b>Prof Rob Wynn</b>	Director of Paediatric transplantation, Manchester University Hospitals	Clinical expert in paediatric HPC donation and transplantation
<b>Prof Nigel Russell</b>	Transplant Director, Nottingham University Hospital	Clinical expert in HPC donation and transplantation
<b>Mrs Louise Mcnamara</b>	Divisional Nurse Director, The Royal Marsden	Expert in clinical apheresis and HPC donation

## 8.3 DISCUSSIONS WITHIN THE GUIDELINE GROUP TO FORMULATE RECOMMENDATIONS

### 8.3.1 EVALUATION OF THE RISKS OF DONATION

#### *8.3.1.1 What are the risks of donation for the donor?*

The common short-term side effects of GCSF are well documented and include bone pain, flu-like symptoms, headaches, insomnia, and gastrointestinal symptoms (Miller *et al*, 2008; Hölig *et al*, 2009). The apheresis procedure is associated with symptomatic hypocalcaemia, hypovolaemia and bruising, or nerve injury related to venepuncture.

Reported serious adverse reactions include splenic rupture, cardiovascular events, cerebrovascular events, thrombotic events, anaphylaxis and complications related to central venous catheter (CVC) placement. GCSF may unmask or exacerbate pre-existing autoimmune conditions (Parkkali *et al*, 1996; Nasilowska-Adamska *et al*, 2010; Lee *et al*, 2015).

#### *8.3.1.2 What are the risks for the recipient?*

Donation of HPCs can result in the transmission of infectious, malignant or hereditary or autoimmune diseases. HPC recipients are at risk of the same infectious agents as recipients of blood products, but are also at risk of cellular pathogen transfer. Transmission of a wide variety of bacteria, viruses, fungi and parasitic infections is well documented, as detailed in Table 1.4 in the introduction to this thesis.

Transmission of malignancies can occur either due to engraftment of malignant HPCs causing haematological cancers, or through transfer of solid organ malignant cells leading to metastatic cancer in the recipient. Reported cases of malignancies transmitted by HPC transplantation have to date been limited to those of haematological origin, however transmission of solid organ cancers have been observed in recipient of organ transplants. Proven donor-derived malignancies have also been reported following solid organ transplantation. Details of these cases are provided in Table 1.5 of the introduction to this thesis.

Any hereditary diseases that originate from HPCs can potentially be transmitted, including haemoglobinopathies, Gaucher’s disease, enzyme deficiencies (Au *et al*, 2002) and cyclic neutropenia (Krance *et al*, 1982). The most commonly reported transmissions of autoimmune disease are psoriasis and autoimmune thyroid disease, but in theory any autoimmune disease could be transmitted.

#### *8.3.1.3 How can we identify donors at risk?*

Careful evaluation of HPC donors is essential to minimise the risks to both the donor and recipient. In Chapter 4, I demonstrated variation in the investigations undertaken for RDs, which in general are less extensive than those performed in healthy UD. Even if RDs are finally accepted with conditions with which a UD would be deferred, identification of such conditions is equally important and the group therefore agreed that screening procedures should as far as possible mirror those for unrelated donors. This should ideally include completion of a formal health history questionnaire, a full evaluation with a health care professional with expertise in donor health, and screening investigations similar to those used as standard in UDs.

#### *8.3.1.4 Should the suitability criteria applied to RDs differ from those used in UDs?*

Large studies in unrelated donors who are assessed against strict medical criteria have shown the incidence of SAEs to be around 1% (Pulsipher *et al*, 2009; 2014; Miller *et al*, 2008; Hölig *et al*, 2009). A study in PBSC donors in Japan (Kodera *et al*, 2013) and the study I described in Chapter 3 both suggest that acceptance of donors who do not meet UD suitability criteria is linked to a greater risk during donation. However, most experts, including the guideline group, agree that it is inappropriate to apply the same stringent UD medical criteria to RDs who have a much greater psychological investment in the transplant. The group agreed that it is wrong to expose any donor to a known substantial health risk, but there are grey areas where the risks are theoretical or inadequately defined. In the UD context, such donors would rightly be deferred but in the RD situation, the group agreed that a ‘protocol exception’ system could be used. This involves gaining specific consent from the donor regarding a potential increased risk. There was consensus agreement that any conditions posing a potential risk to

the recipient should be discussed with the recipient's transplant physician prior to acceptance of the donor.

#### *8.3.1.5 Should screening be different in older donors?*

Older donors are more likely to suffer from occult morbidities, which may increase either donor risk (e.g. cardiovascular disease) or recipient risk (e.g. malignant disease). The most important screening tool is a careful medical history and examination, aiming to exclude evidence of cardiovascular or malignant disease. The group agreed that all RDs over the age of 50 should have a chest x-ray, serum electrophoresis and prostate specific antigen (PSA) (male donors) performed. Specific additional investigations are also prudent in family donors who are donating to a recipient with a disease that may have a familial association, such as chronic lymphocytic leukaemia.

### **8.3.2 THE PROCEDURE FOR INFORMED CONSENT**

#### *8.3.2.1 How do we ensure donors are adequately counselled prior to HLA typing?*

As described in Chapter 4, 36% of UK centres do not assess the health of RDs prior to HLA typing. Ensuring that a donor is fit and willing to proceed before determining whether they are a match is advantageous to the transplant centre, the donor and the recipient by preventing transplant delays while an alternative donor is sought, saving unnecessary typing costs and preventing distress/guilt for a RD who is deferred after they are known to be a match. The group agreed that donors must be adequately informed about donation in order to make a decision to proceed with HLA typing and that written information should be provided at this point. However, there were concerns that this may not be achievable in 100% of cases, and the final recommendation was therefore that written information should be provided where possible. The group reviewed the national information for related donors currently produced by charities and agreed it to be fit for purpose (Anthony Nolan, 2014; Bloodwise, 2012).

There was unanimous agreement that donors should be informed about their HLA matching status and given time to consider before giving permission to disclose results to their potential recipient.

The guideline group agreed that an assessment of donor health should be conducted prior to HLA typing, but felt that it is difficult to achieve this universally, particularly since RDs may be identified by a referring hospital rather than a transplant centre. The decision was made to include a brief health questionnaire tool with the guidelines to promote a thorough assessment and to highlight the Anthony Nolan RD donor information that provides a checklist for RDs with health conditions that may preclude donation and encourages them to discuss any such conditions with their transplant centre contact.

*8.3.2.2 How can we prevent a potential conflict of interest in the context of current transplant centre set up where the recipient's transplant team are responsible for RDs?*

It is widely accepted that donor and recipient care should be completely separated to prevent any potential conflict of interest, which would ideally be achieved by separate teams caring for the donor and recipient. However, in Chapter 4 I showed that donor consent in the UK is provided by transplant physicians in 50% of centres, who due to the size of transplant centres, are likely to be members of the same team caring for the recipient.

FACT-JACIE Standards, to which all UK transplant centres must conform, require that the clinician evaluating the donor should not be the primary physician of the recipient. However, we felt that ideally the physician managing the donor should ensure that they do not simultaneously have direct care of the transplant recipient. Since transplant clinicians are not uniquely able to evaluate donors the group decided to describe successful alternative models of donor evaluation, for example, involving blood transfusion physicians who have similar expertise.

### 8.3.3 THE PROCEDURE FOR HPC DONATION

#### *8.3.3.1 How should RDs be mobilised for PBSC harvest?*

Granocyte® (lenograstim) and Neupogen® (filgrastim) are both licensed for stem cell mobilisation of healthy donors in the UK and have equivalent efficacy and safety profiles. There was felt to be no evidence of an improved yield using a dose above the 10mcg/kg/day used by UD registries and recommended in the summary of product characteristics. The group felt that although a small number of studies suggest equivalent efficacy for biosimilar GCSF, its use in RDs should not be recommended until further follow-up data are available (Shaw *et al*, 2011). Plerixafor is not currently licensed for use in healthy donors, and likewise, insufficient data are currently available to recommend its use routinely to mobilise RDs. However, the group agreed that in the setting of a failed mobilisation with GCSF, Plerixafor could be considered as an alternative to an emergency BM harvest following informed consent.

Since higher rates of complications are seen in donors who require central venous catheters, (Anderlini *et al*, 2001) the group agreed that their use should be limited to cases where they are absolutely necessary, which occurs in 1-2% unrelated donors (Anthony Nolan data, unpublished). In line with BCSH guidelines for central venous catheter insertion (Bishop *et al*, 2007), these should be inserted by a skilled operator under ultrasound guidance.

#### *8.3.3.2 What is the best approach to donors who fail to harvest sufficient stem cells for engraftment?*

While transplant physicians routinely request  $\geq 4 \times 10^6$  CD34+ cells/kg recipient weight, and yields of  $< 2 \times 10^6$  CD34+ cells/kg are generally considered suboptimal, engraftment is possible with lower CD34 doses, and as such, UD registries do not offer a supplementary emergency BM harvest unless the yield following two procedures is less than  $1 \times 10^6$  CD34+ cells/kg recipient weight. The group noted that fewer than 1% of healthy donors fail to reach  $1 \times 10^6$  CD34+ cells/kg following 2 apheresis procedures (Hölig *et al*, 2009; Billen *et al*, 2014), and that female donors, older donors and donors weighing less than their recipients are more likely to harvest lower doses (Teipel *et al*, 2015; Al-Ali *et al*, 2010; Billen *et al*, 2014; Richa *et al*, 2009).

As demonstrated in the study described in Chapter 4, some centres allow donors to undergo three apheresis procedures. The group did not feel there should be an absolute recommendation against this, providing that a third procedure was considered by the local apheresis expert likely to result in a total stem cell yield compatible with engraftment. The most common contraindication to a third procedure is the donor platelet count, which is  $<100 \times 10^9/l$  in almost 40% donors after two procedures (Pulsipher *et al*, 2009). The authors agreed that donor fitness to proceed with a third procedure should be assessed against local apheresis donor thrombocytopenic thresholds. In donors with a platelet count close to the donor thresholds (commonly  $80 \times 10^9/l$ ), a smaller volume ( $<2.5$  blood volumes) should be processed.

There was agreement that donors in whom a third day is deemed inappropriate, or who fail to achieve a yield considered adequate for engraftment after three procedures, could be considered for an emergency BM harvest in the absence of contraindications, and following appropriate discussion and consent.

#### *8.3.3.3 Should limits to BM harvest volume be recommended?*

Studies in UDs confirm a low incidence of adverse reactions using a maximum of 20mls/kg, following which only 5% of healthy donors have a post-procedure haemoglobin of  $<100g/l$  (Anthony Nolan data, unpublished), and allogeneic transfusion should not be necessary. Providing this limit is adhered to, evidence does not support the practice of autologous blood collection and infusion (Parkkali *et al*, 2005; Mijovic *et al*, 2006; Gouëzec *et al*, 2015). The group therefore recommended adhering to a limit of 20mls/kg and against the use of autologous unit collection beforehand. In practice, as discussed in Chapter 4, all but one UK centre that specified a limit already adhered to a maximum of 20mls/kg and only 9% of centres perform autologous collections. The group agreed that prophylactic iron supplementation should be considered peri-harvest in females of childbearing potential or those on low iron diets to speed recovery.

### 8.3.4 SPECIAL CONSIDERATIONS IN PAEDIATRIC DONORS

#### *8.3.4.1 How do we ensure ethical use of paediatric donors?*

Since there are associated risks and no direct medical benefit to the paediatric donor from donating, the accepted justification for permitting minor siblings to donate stem cells is that the donor will benefit from the greater likelihood of survival and reduced suffering of their sibling. This justification is supported by results of some studies, describing psychosocial benefits experienced by paediatric sibling donors, including increased self-esteem, pride, and worth of life and independence (Wiener *et al*, 2008; van Walraven *et al*, 2013; Packman *et al*, 2010; MacLeod *et al*, 2003). However, in some of these studies, the donation experience was linked to recipient transplant outcome with some donors of unsuccessful transplants reporting predominantly negative experiences (van Walraven *et al*, 2013).

Internationally, it is ethically considered appropriate to allow minors to donate, (American Academy of Pediatrics, 2010; Bitan *et al*, 2015), and children have served as stem cell donors for >30 years. Based on ensuring benefit and limiting harm, most experts consider donation to be justifiable only provided that there is a strong positive link (or anticipated strong positive link in very young children) and a reasonable chance of a successful transplant outcome (Pentz *et al*, 2008).

In view of the greater potential for placing undue pressure on the donor in the paediatric setting, it is crucial that the donor's care is separated from that of the recipient by ensuring that the physician responsible for the donor is not involved in the care of the recipient. For this reason HTA regulations also require that all cases of minors who are not competent to consent are reviewed by an independent assessor who interviews the donor and submits a report to the HTA (HTA, 2014).

Consent for the donation procedure in minors is provided by parents, however it is widely agreed that children should be given information in an age appropriate fashion and should participate in the decision-making process by giving their assent. Although the legal position is that parents can consent for their child, it is recognised that a

conflict of interest exists for parents of a child donating to their sibling. If the child objects, the independent assessor must explore the reasons and as far as possible explain consequences of not donating.

There was unanimous agreement that children should be permitted to serve as HPC donors but suggested definite criteria should be met, including evidence of a positive relationship with the recipient and that no medically equivalent older related donor is available.

#### *8.3.4.2 Is BM harvesting safe in paediatric donors?*

The safety profile of BM donation in children appears to be excellent, with the risk of life-threatening events of less than 0.5% (Buckner *et al*, 1984). A recent EBMT paediatric diseases working party study (Styczynski *et al*, 2012) in 313 BM donors confirmed historical reports of low incidence of adverse reactions; the main risk being that allogeneic transfusion is likely to be necessary in very young donors donating to an older sibling. However, providing that a maximum 20mls/kg donor weight is aspirated, allogeneic blood products are rarely required (Styczynski *et al*, 2012).

#### *8.3.4.3. Is PBSC donation safe in paediatric donors?*

The EBMT paediatric diseases working party study (Styczynski *et al*, 2012) included 140 PBSC donors, with the only serious adverse event recorded in a donor who developed a pneumothorax as a result of CVC insertion. The Paediatric Blood and Marrow Transplant Consortium conducted a retrospective analysis on the safety and efficacy of PBSCs donation by 201 paediatric sibling donors from 22 institutions. This study showed good yields in all age groups and few side effects (Pulsipher *et al*, 2004). Further analyses suggest that children report fewer side effects during GCSF mobilisation than adults (Karakukcu & Unal, 2015; Duong *et al*, 2014; Volker, 2013; Pulsipher *et al*, 2006).

While autologous collection of PBSCs in children is routine practice, there are several potential issues with allogeneic PBSC collection in children under 16 years, which potentially carries greater risks than BM donation. First, in donors weighing less than 20kg, priming of the apheresis circuit is almost always required, exposing the donor to

allogeneic blood products. Second, central venous access is required in smaller donors, with investigations showing that while it is possible to collect 80% of 13-16 year olds peripherally, this is only possible in a third of 7-12 year olds (Pulsipher *et al*, 2004). In children, central venous catheter insertion is likely to cause more pain and risk than the mobilisation or collection. The third issue is that in the UK, filgrastim is not licensed for stem cell mobilisation in donors under 16 years, and although lenograstim is licensed in children >2 years, including for mobilisation, the summary of product characteristics does not recommended its use, due to a lack of specific studies of mobilisation in children. Data from the severe chronic neutropenia international registry are reassuring in that no malignancies have been reported, and there are no reports of splenic rupture occurring in children.

#### *8.3.4.4 Is PBSC mobilisation effective in paediatric donors?*

A number of studies have included donors <18 years in assessments of PBSC yield following GCSF and concluded favourable efficacy in younger donors. In 2002, a Japanese group published a study examining factors associated with successful mobilisation with GCSF in PBSC donor and found a negative correlation between stem cell yield and age (Shimizu *et al*, 2002), These findings were echoed in a more recent Italian multi-centre study (Bertani *et al*, 2014) which investigated donor variables correlating with HPC mobilisation in 360 donors aged 13+ treated with GCSF and noted that younger age was associated with better mobilisation following GCSF.

A study examining the factors associated with successful mobilisation in 400 donors aged 12+ receiving lenograstim (Ings *et al*, 2006) demonstrated successful mobilisation in all younger donors, with poor mobilisation occurring exclusively in donors 54 years or older. Mobilisation has been directly compared between adults and paediatric donors, Kawano *et al* reported the CD34 yield of 25 adult and 19 paediatric donors mobilised with GCSF, finding no difference in the CD34 yield per unit of blood processed (Kawano *et al*, 1999).

A further study included 101 donors aged 16-63 years, who underwent PBSC donation and compared the efficacy of filgrastim and lenograstim as mobilising agents.

Satisfactory mobilisation occurred in both groups, and no long-term adverse events were recorded (Martino *et al*, 2005).

#### *8.3.4.5 Summary of discussions regarding the optimal donation route in paediatric donors*

The group agreed that the available evidence confirms the safety of BM donation in donors <16 years, providing that the aforementioned limit of 20ml/kg aspirated volume is adhered to. The evidence regarding PBSC donation is less clear. The group agreed that CVC insertion in paediatric donors should be avoided, and that BM should be the only donation route recommended in donors aged 12 years or younger. There was felt to be no evidence for an increased risk of PBSC donation over BM donation in donors aged 13-15 with good venous access, however the group were not certain that there are adequate data regarding the long-term safety of GCSF in this group. Following discussion with additional members of the paediatric subgroup of the BSBMT, the decision was made to recommend BM as the only donation route in donors <16 years.

#### *8.3.4.6 Can 16-17 year old donors be treated as adults?*

Since 2012, 16-year olds have been permitted to join the Anthony Nolan donor register and to donate PBSC or BM as unrelated donors. The evidence and licensing data used to make this decision were reviewed by the guideline group before formulating recommendations for RDs in this age range.

Lenograstim is used for HPC mobilisation by all UK UD registries, and is more commonly used by UK transplant centres than filgrastim, but the license in donors <18 years was unclear stating: “Granocyte is indicated in adults, adolescents and children older than 2 years for.... the mobilisation of peripheral blood progenitor cells (PBPCs), for patients as well as healthy donors”.

However, under the subsection ‘Special warnings and precautions for use’ the use of lenograstim in minors is cautioned, stating: “Based on some local regulations and lack of studies, minor donors should not be considered”.

To clarify the situation regarding minors the manufacturers, Chugai, were approached who confirmed that the term ‘minor’ in this context refers to the age of consent for medical treatment, which differs between European countries. (S Long, Medical Director, personal communication). Lenograstim and filgrastim are therefore both licensed in allogeneic donors in 16 and 17 year olds.

Chugai also provided the following summary of adverse events reported in paediatric healthy donors aged 16-18 years old treated with lenograstim, as of 30 April 2014, from their Global Argus Database detailing adverse events: “8 children aged 16-18 year olds received lenograstim. Of those 8, serious event (pneumothorax) was reported in 1 case, but causality between lenograstim and pneumothorax was ruled out both by the reporter and company. The remaining 6 cases were non-serious, whilst no adverse event was reported in the remaining 1 case.”

On review of prospective and retrospective studies that have included donors 16-17 years of age, no increased incidence of SAEs has been observed in comparison to older donors (Bertani *et al*, 2014; Kawano *et al*, 1999; Basara *et al*, 2000; Martino *et al*, 2009).

Under the provisions of the HT (Scotland) Act, children are defined as being under 16 years of age, therefore those over 16 may consent to donation in the same way as older adults. In England and Wales, children are defined as less than 18 years of age, however donation of bone marrow and PBSC by children who are Gillick competent to consent can be approved locally.

The group agreed that there is sufficient evidence for the safety and efficacy of PBSC mobilisation in donors aged 16-17. Donors in this age group can undergo the same evaluation procedure as older adults, with no need for additional investigations. In Scotland these donors may provide their own consent and in England those who are deemed Gillick competent may do so.

### 8.3.5 FOLLOW-UP OF RELATED DONORS

#### *8.3.5.1 What is the most efficient method of RD follow-up?*

The objectives of donor follow-up are twofold; firstly to capture any short-term adverse events occurring in the first 30 days after donation, and secondly, to provide long-term surveillance to exclude an increased incidence of health issues in donors compared to the normal population. Reporting of donor adverse reactions is an HTA requirement, and, although not legally required in the UK, long-term donor follow-up is a mandatory requirement of FACT-JACIE (FACT-JACIE, 2011) and is also recommended by the WBMT (Halter *et al*, 2013), and WHO guiding principles (WHO, 2010).

Greater than 50% of BM donors and 80% of PBSC donors report full recovery at one week post-donation (Pulsipher *et al*, 2013). Most transplant centres and donor registries provide follow-up within 7 days to ensure donors are recovering, often by telephone. The group agreed that provisions should be made for further follow-up of donors who have not recovered by this point to ensure that donor health events occurring within 30 days of donation are captured.

Current evidence, which has reassuringly demonstrated no increase in incidence of autoimmune disease or malignancies in donors, is based predominantly on data from large unrelated donor cohorts. RDs tend to be older and are more likely to have pre-existing health problems, but follow-up data on remain scarce, partly due to an historical lack of a centralised database to allow reporting. This has been addressed by the EBMT donor outcome committee and donor follow-up data can now be reported using specific EBMT donor outcome forms, which link this data to recipient records. In the UK, 17/22 centres surveyed provide follow-up to 30 days, allowing adverse event reporting, but currently only 23% follow donors to 5 years and 14% to 10 years. 23% of UK centres already submit donor to EBMT.

The group agreed that promotion of both short-term and long-term data collection on RDs is essential, and that ideally this data should be analysed centrally by EBMT. The authors agreed that data collection should be limited to the minimum data set recommended by WBMT, and that this could be collected by administrative rather than clinical staff (but reviewed if any concerns were raised).

*8.3.5.2. Should RDs routinely be offered psychological support post-donation?*

Several studies (including the study described in Chapter 7), have shown that poor recipient outcomes are linked to a very negative psychological experience for their related donor in a small proportion of cases (Switzer *et al*, 1998; van Walraven *et al*, 2010a; Wolcott *et al*, 1986). The emotions most commonly described are guilt and anxiety (Pillay *et al*, 2012).

It is clear that education of related donors regarding the possible outcomes for their recipient is important, but the use of additional psychological interventions has not been studied. The guideline group recognised the need for psychological evaluation as part of the donor medical procedure. Some members of the group felt that a formal separate psychological evaluation should be offered, but this was not finally formulated into a recommendation because this service is simply not available in some transplant centres. As an alternative approach it was suggested that clinicians contact the donor's GP to discuss any concerns identified.

The group agreed that there is currently inadequate psychological support for RDs post-donation, however, in the absence of interventional studies describing a benefit, it was difficult to make a specific recommendation, particularly because it was felt that these would prove impossible for transplant centres to fulfil.

*8.3.5.3 What guidance should be offered regarding subsequent donations?*

With a growing proportion of patients undergoing reduced intensity transplants, a parallel increase in donors undergoing multiple therapeutic cell donations is seen. Currently, at least 5-10% of unrelated donors provide a subsequent donation of stem

cells or lymphocytes, and probably a higher proportion of RDs, and it is conceivable that this proportion will rise further with the advent of novel cellular therapies. Providing that the initial donation is uncomplicated, there is evidence that healthy donors can safely donate HPCs on at least two occasions, with similar side effects and similarly low incidence of SARs (la Rubia *et al*, 2002; Lown *et al*, 2013). Second donations are therefore permitted by most unrelated donor stem cell registries and are in accordance with WMDA guidelines (Confer *et al*, 2011). The reported yield of subsequent donations is similar to initial donations, although some studies have demonstrated slightly lower CD34 doses in subsequent HPC donations (la Rubia *et al*, 2002; Platzbecker *et al*, 2008).

Lymphocyte collection is associated with very few short-term side effects (McLeod *et al*, 1998). Repeated collections can lead to prolonged lymphopenia in up to 50% donors, which is likely to be a greater risk in older donors (Nicolini *et al*, 2004), but there is no evidence that persistent lymphopenia in these donors is associated with significant infective risks.

The guideline group agreed that available evidence suggests that donors can safely donate HPCs on two occasions and that UDs are in some situations permitted to make a third HPC donation. In considering this issue we decided against making a definite limit for the number of subsequent donations allowed, but instead recommended that greater than two HPC donations should be considered exceptional. In the absence of lymphopenia the group agreed that donors can be permitted to donate lymphocytes on at least two occasions. All members of the group agreed that it is important that transplant centres have a policy in this regard, and that donors are re-evaluated for fitness to donate prior to any subsequent donation.

## 8.4 FINAL RECOMMENDATIONS

### 8.4.1 DONOR CARE PRIOR TO HLA TYPING

The health of related donors should be assessed before conducting HLA typing to allow early deferral of unfit donors. (1B)

Sufficient information for allogeneic donors should be provided before the potential donor undergoes HLA typing, so as to protect the potential donor from undue pressure should he/she be the only suitable donor. (1C)

It is suggested that this includes written information. (2D)

Donors should be informed of their HLA matching status and offered time to consider before giving permission to disclose results to their potential recipient. (1C)

### 8.4.2 EVALUATION OF RELATED DONORS

Donor suitability should be evaluated by a licensed health care professional who is not the primary transplant physician or health care professional overseeing care of the recipient. (1C)

Donors should be evaluated in a confidential setting. (1C)

Defined medical suitability/eligibility criteria should be used to determine acceptability of related donors. (1B)

Related donors should be carefully evaluated for the presence of any health issues that may present a risk to their health or the health of their intended recipient, including the conditions/investigations described in Tables 8.2 and 8.3. (1B)

*Table 8.2 Recommended evaluation for related HPC donors at the donor medical*

<b>Procedure</b>	<b>Information to record</b>
<b>Medical history</b>	Autoimmune symptoms/disease Inflammatory eye disease Cardiovascular symptoms/disease Neurological symptoms/disease Malignancy: to include symptoms of malignancy in donors >50 years, and adherence to national cervical/bowel/breast screening programmes Allergy history Anaesthetic history Blood transfusion history Thrombotic and bleeding history Vaccination history Back problems
<b>Life style history</b>	Travel history Pregnancies Smoking Alcohol Recreational and non-prescription drugs Sexual history Tattoos/acupuncture/piercings Exercise tolerance
<b>Examination</b>	BMI Blood pressure Oxygen saturations Venous access in PBSC donors Skin for suspicious lesions Cardiorespiratory system Lymph nodes Thyroid Abdominal system Neurological exam if indicated Iliac crests in BM donors to determine ease of access

*Table 8.3 Recommended investigations for evaluation of RDs at the donor medical*

	<b>Mandatory</b>	<b>Discretionary</b>	<b>Suggested</b>
Infectious disease markers	HIV-antibodies type 1 and 2 HBsAg, Anti-HBV core antibodies Anti-HCV antibodies HTLV-antibodies type I and II, Treponema pallidum CMV IgG antibodies, EBV IgG antibodies Toxoplasma IgG antibodies	HCV, HIV, HBV viral PCRs	Lifestyle risk factors
		Malaria antibody Trypanosoma cruzi antibody Chikungunya antibody West Nile Virus antibodies +/- PCR	Geographical exposure
<b>Haematology</b>	Full blood count Blood group and antibody screen	Coagulation screen	
		G6PD screening	Males originating from areas with prevalence
		Haemoglobinopathy testing	At risk ethnicity or suggestive haematological indices
		Blood film and peripheral blood immunophenotyping	MDS (blood film only) Sibling donors of patients with CLL
<b>Biochemistry</b>	Urea and electrolytes Liver function tests Bone profile LDH Random glucose	PSA	Males >50 years
		Serum protein electrophoresis	Donors >50 years
<b>Other Investigations</b>	ECG Urine analysis for blood and protein Pregnancy test in females of childbearing age (urine or serum)	Chest X-ray	Donor >50 years, and all donors with a respiratory history or significant smoking history

Donor evaluation should focus on identification of psychological as well as physical risks. (1C)

There should be a procedure for managing relatives who are deemed to be unsuitable as donors following evaluation. (2C)

Medical follow-up of any health issues identified during evaluation should be arranged, usually via the donor's family doctor. (2C)

### 8.4.3 TAKING INFORMED CONSENT FROM RELATED DONORS

Donor counselling should include a clear explanation of the risks of donation, including the risks for the recipient, and the possibility of a subsequent donation request. (1C)

Donors who are ineligible due to risks to the recipient, should only be permitted to proceed following discussion with the recipient's transplant physician and documented acceptance by the physician and recipient. (1C)

Acceptance of donors who do not meet standard medical suitability criteria requires additional consent and documentation for the rationale of proceeding with donation. (1C)

The donor's permission must be obtained prior to discussion of any confidential medical or lifestyle information with other health professionals or the recipient. (2C)

### 8.4.4 THE DONATION PROCEDURE

#### *8.4.4.1 PBSC*

Filgrastim or lenograstim at a dose of 10mcg/kg/day for four to five days is recommended for mobilisation of RDs (1A)

Full blood count monitoring during the mobilisation period is not required providing standard doses of GCSF are administered. (2B)

Central venous catheters should be used only when absolutely necessary and should be inserted by a skilled operator under ultrasound guidance (1B)

The use of biosimilar GCSF or alternative mobilisation agents for related donors cannot be recommended outside the context of a clinical study where follow-up is performed (2D)

It is suggested that related donors usually undergo up to two apheresis procedures as standard practice. (2C)

In donors with a platelet count close to the centre's donor thresholds (commonly  $80 \times 10^9/l$ ), a smaller volume (<2.5 blood volumes) should be processed. (2C)

PBSC donors in whom an adequate harvest for engraftment is not achieved following two apheresis procedures could undergo a third apheresis procedure or a bone marrow harvest in the absence of contraindications and following appropriate consent. (1B)

#### *8.4.4.2 Bone marrow donation*

A maximum aspiration volume of 20ml/kg donor weight is recommended at bone marrow harvest. (1B)

Health care professionals performing BM harvests should undergo specific training and continued exposure to the procedure to ensure their skill is maintained. (1B)

The collection of autologous blood prior to BM harvest is not recommended. (2B)

Iron supplementation should be considered peri-harvest in females of childbearing potential or those on low iron diets. (2C)

### **8.4.5 SUBSEQUENT DONATIONS**

It is recommended that centres define limits for the frequency and total number of donations that RDs may undergo. (1C)

The donation of HPCs on more than two occasions should be considered as exceptional. (2C)

Donors should be re-evaluated and consented before any subsequent donation. (1C)

It is suggested that all blood tests are repeated for donations occurring >3 months from the initial donation. (2C)

As with initial donations, subsequent donations are only recommended when there is a reasonable probability of a successful outcome for the recipient. (2C)

#### 8.4.6 SPECIAL CONSIDERATIONS IN PAEDIATRIC DONORS

In England and Wales, donors aged 16 or 17 may be considered for either PBSC or BM donation as per older adults, and if deemed to be Gillick competent by the assessing physician, they may consent to this procedure. (1C)

In Scotland, donors aged 16 or 17 are considered adults and standard adult consent procedures apply. (1C)

Children <16 may serve as haematopoietic progenitor cell donors providing the following criteria are fulfilled (1C):

1. There is no medically equivalent older relative who is willing and able to donate
2. There is a strong and emotionally positive relationship with the recipient
3. There is a reasonable likelihood of a successful outcome for the recipient
4. The procedure should be explained using age-appropriate materials and assent of the child should be obtained where appropriate
5. An independent donor advocate provides an assessment as per HTA requirements
6. Parental consent is obtained if the child is not Gillick competent

Medical evaluation of paediatric donors should be performed by a health care professional who is not involved in the care of the intended recipient. (1C)

BM donation is the only donation method recommended in children <16 years old. As with adults, a maximum of 20mls/kg is recommended to avoid the need for allogeneic transfusion. (1C)

Bone marrow donation is not recommended in babies of less than six months old. (1B)

#### 8.4.7 DONOR FOLLOW-UP

It is suggested that related donors are contacted within 2-7 days from donation to ensure they are recovering as expected. (2C)

It is suggested that donors who have not recovered at 7 days receive further follow-up, or are provided with contact details to report any remaining symptoms which have not subsided within the expected timeframe. (2D)

It is suggested that related donors are requested to report any morbidities occurring in the first 30 days post-donation to a designated contact in the transplant centre to allow adverse event recording. (2D)

Provision of psychological or emotional support post-donation should be considered where necessary (2C)

Long-term donor follow-up should include parameters suggested in the WBMT minimum data set and should be performed biannually to 10 years from the last donation. (1C)

It is suggested that centres report long-term RD follow-up data to EBMT to allow centralised data collection. (2D)

### 8.5 NATIONAL MEDICAL SUITABILITY AND ELIGIBILITY CRITERIA FOR RELATED DONORS

The above guidelines were designed to outline best practice in the management and assessment of RDs, but purposefully focused on educating those involved in donor care about how these procedures should ideally be conducted and the principles behind donor evaluation. The guideline group had decided not to make specific recommendations about which medical conditions should and should not be accepted in related donors, in part because it would be impossible to do so thoroughly within the scope of a guideline document. A second reason for this was that there are many areas where it is impossible to provide definitive guidance and the final decision should

be based on determination of the severity of a condition (possibly including input from other medical specialists) and frank discussion of any increased risks with the donor.

During preparation of the guidelines, it became apparent that although defining medical criteria for related donors would not be possible within the scope of the guidelines, such criteria would nevertheless be hugely valuable to the community and would complement the guidelines perfectly. The Scottish National Blood Transfusion Service (SNBTS) already produce very extensive medical criteria for related HPC donors (Douglas, 2014), originally adapted from their guidelines for acceptance of blood donors. As per all UK national blood donor guidelines, these criteria categorise the guidance as follows: obligatory deferral; protocol exception (where additional consent must be sought); discretionary acceptance; acceptance. However, these criteria are an internal SNBTS document, which is not widely used by transplant centres, and as a word document with >150 pages, it is not in a user-friendly format.

With permission from SNBTS, the group reviewed and revised this comprehensive document to create BCSH/BSBMT endorsed national medical criteria for acceptance of related HPC donors. In view of the success of the online WMDA medical suitability tool ([https://wiki.wmda.info/index.php?title=Main\\_Page](https://wiki.wmda.info/index.php?title=Main_Page)) which has been accessed >1.5 million times in the last 2 years, I decided to create a wiki-site with a similar format for our national medical RD criteria. This wiki-site is in the final stages of creation.

## 8.6 CONCLUSIONS

Although allogeneic HPC donation has an excellent safety record, with very low rates of serious adverse reactions in healthy donors it is critical that all HPC donors are thoroughly evaluated to determine any conditions or characteristics that increase their risk. Evaluation of RDs must consider the psychological risks and benefits to the donor, and in some situations the potential psychological benefit to a donor who wishes to donate must be balanced against a degree of physical risk. It may be appropriate to accept relatives as donors with medical conditions or characteristics that somewhat increase their risk, but specific informed consent regarding such risk is crucial.

These guidelines are designed to offer specific recommendations for the optimal process for donor evaluation and management at each stage of the donor care pathway. The intention was to provide clinicians with the available evidence regarding the physical and psychological risks of donation and the donor factors known to influence these, to aid decision-making in difficult areas.

It was beyond the scope of the guideline format to try to address individual medical conditions and thus I decided to create a separate paired resource for medical suitability criteria. I hope that in combination these projects will fill a much-needed gap in related donor care nationally.

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## CHAPTER 9. CONCLUSIONS

### 9.1 SUMMARY

In this thesis I have presented an in-depth investigation of the pathway of adult related donor care internationally and have been able to identify several areas where current practice is suboptimal with respect to the health or interests of related donors. After designing and undertaking three studies to determine practice patterns in related donor care (all of which resulted in publications in peer-reviewed journals) and one study evaluating the related donor care pathways from the perspective of RDs, I was able to draw my findings together to formulate national guidelines in related donor care. I also used these findings as a basis to prospectively evaluate potential novel models of related donor care, in an effort to overcome the current issues in the care pathway.

The study I conducted in Chapter 3 demonstrated the value of FACT-JACIE as a regulatory body in driving change in the field of related donor care. This study also added to current evidence regarding the increased incidence of SARs in donors not meeting UD medical suitability criteria, which led to the recommendation for a thorough evaluation of cardiovascular risk factors in older RDs in the BCSH/BSBMT guidelines.

In Chapters 4 and 5 I highlighted that despite FACT-JACIE recommendations, donor follow-up is absent in the US and is infrequently performed to the recommended duration in other regions. This finding served as a basis for the pilot study I carried out (Chapter 6) where I successfully demonstrated an alternative model of donor care where an UD registry provided RD follow-up. Other findings from the international donor care surveys served as a basis for the development of the BSCH guidelines (Chapter 8). This included the need to prevent coercion of related donors by ensuring they are fully informed prior to HLA typing, that donor permission is sought before their HLA results are disclosed to the intended recipient, and that their evaluation and consent should be by a clinician who is not involved in the care of their recipient.

In Chapter 7, I demonstrated the importance of fully informing related donors of the possible consequences of donation, both for themselves and their recipient. I identified post-donation psychological support as an area which is lacking in current donor care set-ups. Following the study in Chapter 6 the Anthony Nolan registry decided to consider providing such support, which would directly address this issue.

## 9.2 CHALLENGES

The greatest challenges I encountered during the studies described in this thesis occurred during attempts to set up pilot studies for alternative models of related donor care in UK centres. Although I confirmed initial interest from transplant centres, once I had determined all the logistics and costs for the first two models described in Chapter 6, the centres I was working with were unable to accept proposals for the pilot studies. In the case of the first model this was due to concerns with meeting the costs of such a model after the initial pilot study. In the case of the second model the concerns were logistical because the model would have required onsite support, which was unable to be guaranteed.

The other area in which I faced challenges was regarding collection of data for the international surveys of related donor care. In order to achieve a reasonable response rate I decided not to insist that transplant centres enter their own CIBMTR or EBMT centre number (which many clinicians would not know off the top of their head). However, despite specifically requesting that respondents enter their centre name in full, many centres used abbreviations (e.g. U of M) which I then had to match to the centre names held by the EBMT or CIBMTR alongside the centre numbers. This was a very time consuming process but was I think, a necessary hurdle to overcome to achieve satisfactory response rates.

## 9.3 FUTURE PROJECTS

### 9.3.1 AN INTERNATIONAL SURVEY OF PAEDIATRIC PRACTICE PATTERNS IN RD CARE

During the process of writing up publications for the two studies examining international donor care in the US and EBMT transplant centres (Chapter 5), several members of the donor health and safety working committee of the CIBMTR commented that no such studies have explored practice patterns in paediatric centres. I therefore suggested that this should be proposed as a subsequent study, and have been working with other members of the committee to formulate a study questionnaire. A proposal for this study (for which I am a primary investigator) has been accepted by the CIBMTR donor health and safety working committee.

### 9.3.2 UK RD FOLLOW-UP BY THE ANTHONY NOLAN

Following the successful pilot study of related donor follow-up I described in Chapter 6, the Anthony Nolan are planning to offer a related donor follow-up service to transplant centres. Before this point, the options for additional staff training are being reviewed to ensure that donors with psychological problems post-donation are adequately supported. This service will initially be offered without charge to transplant centres using the Anthony Nolan graft identification and advisory service, but if successful, will then be offered nationwide. This service will be audited to ensure donor and transplant centre satisfaction.

### 9.3.3 AN AUDIT OF UK CENTRE PRACTICE AGAINST THE BCSH RELATED DONOR CARE GUIDELINES

The BCSH process requires that guideline authors submit a template for proposed audit of UK centres. I plan to lead a re-audit of UK centre practice approximately 18-24 months after introduction of the guidelines.

### 9.3.4 UPDATING AND EXPANSION OF THE WIKI-PAGE FOR MEDICAL CRITERIA FOR RELATED HPC DONORS

The wiki-site for national related HPC donor medical criteria that I am creating (Chapter 8) has the provision for users to make requests or comments. As has been the case for the WMDA unrelated donor criteria, it is envisaged that users are likely to request criteria to be created for additional medical conditions. Furthermore it will be necessary to periodically update these criteria to bring them in line with new recommendations from regulatory bodies. I will lead a small group of experts in updating these criteria on an annual basis and additional recommendations will also be added on an 'as needed' basis where urgent changes to guidance are needed (for example situations such as the recent Ebola virus outbreak).

## 9.4 CONCLUSION

Although allogeneic HPC donation has an excellent safety record, this thesis has outlined several areas in which current pathways do not adequately protect the health and wellbeing of related donors. Through the studies described in this thesis I have been able both to define these areas in detail, and to determine where and how improvements are needed. These improvements I have suggested are most likely to be most realised if driven by further augmentation of FACT-JACIE Standards, and through the use of the national evidence-based guidelines and medical criteria I led on creating. This will I hope ultimately result in greater standardisation of related donor care in the UK and internationally.

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## APPENDIX 1. SUPPLEMENTARY MATERIALS

Figure S1. Survey of related donor care in UK transplant centres

Questions about the logistics of donor care at your centre

\* 1. What is the name of your centre?

2. Does your centre assess/manage adult related HPC donors?

Yes

No

---

3. How many related donors does your centre typically assess per year?

0-5

6-10

11-15

16-20

>20

4. How many transplant consultants are involved in care of adult transplant recipients at your centre?

5. Is your centre JACIE accredited?

Yes, fully accredited

Not yet accredited but has undergone first time inspection

Working towards JACIE accreditation

6. Do you have a written policy for the assessment of adult related HPC donors?

Yes

No

7. Do you have a stem cell lab on site?

- Yes
- No

8. Is apheresis done on site?

- Yes
- No

9. Is bone marrow harvesting done on site?

- Yes
- No

Questions about Initial Donor Counselling

10. What Information is shared with potential adult related donors prior to HLA typing? (please tick all that apply)

- Verbal communication
- Locally written information
- Written information from a national source (please specify)

11. Do you verify that the donor is willing to proceed before HLA testing is performed?

- Yes
- No

12. Is there an assessment of related donor health prior to HLA typing?

- Yes
- No

13. How is this health assessment completed? (please tick all that apply)

- Written health questionnaire
- Health questionnaire completed over the phone
- Verbal discussion with open-ended questions

Other (please specify)

14. Who makes the initial contact with adult related donors prior to HLA typing?

- Transplant physician
- Other physician
- Transplant specialist nurse
- Other nurse
- Other (please specify)

15. Who is told first when a matched family donor is found?

- The donor
- The recipient
- No consistent practice

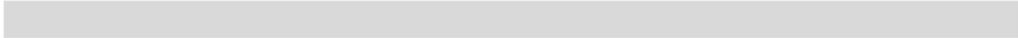
16. Who has ultimate responsibility for the medical assessment and consent of adult related donors?

- The transplant physician caring for the recipient
- A different transplant physician from the same team
- A physician from a different team within your centre
- A physician from another centre/organisation
- Other (please specify)

Questions about the donor medical evaluation

17. Does your unit have medical suitability criteria for adult related donors?

- Yes  
 No

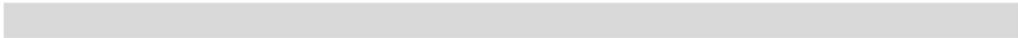


18. Where are these criteria derived from?

Locally created

Based on national unrelated donor criteria (please specify)

Based on international unrelated donor criteria (please specify)



19. Do adult related donors complete a health history questionnaire as part of their assessment?

- Yes  
 No

20. Please tick the most appropriate statements regarding the following donor factors

	Our centre has criteria	I think there should be defined criteria
Age	<input type="checkbox"/>	<input type="checkbox"/>
BP	<input type="checkbox"/>	<input type="checkbox"/>
Maximum BMI	<input type="checkbox"/>	<input type="checkbox"/>
Minimum weight	<input type="checkbox"/>	<input type="checkbox"/>
Length of deferral following tattoos/piercings	<input type="checkbox"/>	<input type="checkbox"/>
Length of deferral following allogeneic blood transfusion	<input type="checkbox"/>	<input type="checkbox"/>



21. Do you accept donors with the following medical conditions?

	Yes	No
Diabetes mellitus on oral hypoglycaemics	<input type="radio"/>	<input type="radio"/>
Diabetes mellitus on insulin	<input type="radio"/>	<input type="radio"/>
Asthma on tablet medication (montelukast, theophylline or oral corticosteroids)	<input type="radio"/>	<input type="radio"/>
Previous ischaemic heart disease	<input type="radio"/>	<input type="radio"/>
Systemic auto-immune diseases	<input type="radio"/>	<input type="radio"/>

22. What is your practice regarding the following investigations?

	Performed on all donors	Performed if clinically indicated	Never performed
CXR	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
ECG	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
US Abdomen	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Haemoglobinopathy testing	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Urinalysis	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
ECHO	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Bone marrow aspiration	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>

23. Which of the following blood tests are performed routinely on ALL related donors at your centre?

- Full blood count
- Coagulation
- Renal function and electrolytes
- Bone profile
- Thyroid function
- Liver function tests
- LDH
- ESR
- C3/4
- Serum protein electrophoresis
- Pregnancy test (women with childbearing potential)

### Questions about PBSC donation

24. Who administers the GCSF? (tick all that apply)

	First GCSF dose	Subsequent doses
Your centre	<input type="checkbox"/>	<input type="checkbox"/>
GP/district nurses	<input type="checkbox"/>	<input type="checkbox"/>
The donor themselves/their family	<input type="checkbox"/>	<input type="checkbox"/>

25. Which GSCF is used for stem cell mobilisation in your related donors

- Lenograstim  
 Filgrastim  
 Biosimilar

26. Regarding plerexifor use in related donors:

	Yes	No	Only in the context of a clinical trial
Do you ever use it?	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Would you ever use it?	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>

27. Who has the medical responsibility for the apheresis procedure itself?

- A transplant physician  
 A physician from another team/organisation

28. Do you have a limit for the number of apheresis procedures a related donor will undergo (during their initial donation)?

- No  
 Yes (please specify)

29. Who are donors asked to contact if they develop complications during the mobilisation period?

- Their GP/A+E
- The transplant team at your centre
- Another team at your centre (please specify)

Questions about related bone marrow donation

30. Do you have a process for credentialing doctors who undertake bone marrow harvests?

- Yes
- No

31. Who performs bone marrow harvests at your centre?

- Transplant team responsible for care of recipient
- Other transplant physicians
- Another team

32. Do you have a defined limit for the amount of bone marrow to harvest?

- No, it is decided on a case by case basis
- Yes (please specify the limit)

33. During their in-patient stay where do related bone marrow donors stay?

- The same ward as their recipient
- A different ward
- We do not routinely keep bone marrow donors in overnight

34. Do related adult bone marrow donors routinely receive the following?

	Yes	No
Collection and return of autologous unit(s)	<input type="radio"/>	<input type="radio"/>
Collection of an autologous unit which is not routinely returned	<input type="radio"/>	<input type="radio"/>
A course of oral iron	<input type="radio"/>	<input type="radio"/>

#### Questions about the follow-up of related donors

35. At which of the following time point post-donations are your donors followed up?

- <1 week
- 30 days
- 1 year
- 2 years
- 3 years
- 4 years
- 5 years
- 6 years
- 7 years
- 8 years
- 9 years
- 10 years
- >10years
- Any other time points (please specify)

36. How is donor follow up performed at your centre? (tick all that apply)

- By telephone
- By written questionnaire
- Routine outpatient appointment
- GPs are asked to follow up donors
- We do not follow up our related donors

37. Do you use EBMT donor outcome forms/promise reporting?

- Yes
- No, but I am familiar with these
- No and I am not familiar with these

38. Who are donors asked to contact if they develop medical issues following their donation which may be potentially donation related?

- The transplant team
- Another team at your centre
- Their GP

39. Do you have a written policy regarding subsequent donations from related donors?

- Yes
- No

40. Is there a limit to the number of subsequent donations at your centre?

- No
- Yes (please specify the limit)

Questions about potential models of related donor care

41. Do you feel current care of related donors in the UK is

- Extremely satisfactory
- Satisfactory
- Neither satisfactory nor unsatisfactory
- Unsatisfactory
- Extremely unsatisfactory

42. If unsatisfactory please specify which in which areas care is lacking?

- Potential conflicts of interest
- Lack of standardised medical eligibility criteria
- Follow-up is inadequate
- Workload is onerous for transplant centres
- Other (please specify)

43. Do you think related donor safety would be improved if national medical suitability criteria were created?

- Yes
- No

44. Do you think management of related donors would be improved if national guidelines for whole donation process were created?

- Yes
- No

**45. Which of the following models do you think would enhance related donor care in the UK?**

- Separate teams within a centre would be responsible for medical assessment of RDs, care during the donation period and would arrange donor follow-up
- Consent and donor follow-up by an external organisation, with donation process performed by the transplant centre
- Donors would visit a geographical 'related donor hub' which would be responsible for the whole process of assessment/donation/followup
- Donor registries would be responsible for the whole process of related donor assessment/donation/followup
- None- there is no need for change
- Another model (please specify)

**46. Which of these models do you think would be logistically possible at your centre**

- Separate teams within a centre would be responsible for medical assessment of RDs, care during the donation period and would arrange donor follow-up
- Consent and donor follow-up by an external organisation, with donation process performed by the transplant centre
- Donors would visit a geographical 'related donor hub' which would be responsible for the whole process of assessment/donation/followup
- Donor registries would be responsible for the whole process of related donor assessment/donation/followup
- None- there is no need for change

**47. Thank you very much for your participation. Would you like to make any other comments about the care of family donors?**

Figure S2. Survey of related donor care in US and EBMT transplant centres

**\*1. What is your CIBMTR or EBMT center number?**

**2. Does your center perform allogeneic HPC transplants from adult (>18 years old) related donors**

Yes

No

**Questions about the logistics of donor care at your centre**

**3. How many related donors does your center typically assess per year?**

0-10

11-40

41-70

71 or more

**4. What percentage of adult related donors at your center donate bone marrow rather than PBSC?**

<5

6-10

11-20

21-30

31-40

41-50

>50

**5. How many transplant physicians are involved in the care of adult transplant recipients at your center?**

**6. Is your center FACT/JACIE accredited?**

Yes, fully accredited

Not yet accredited but has undergone first time inspection

Working towards accreditation

**7. Do you have a written policy/SOP for the assessment and care of related donors?**

Yes

No

**Questions about Initial Donor Counselling****8. Who makes initial contact with a related donor prior to HLA typing?**

- Transplant physician
- Other physician
- Transplant specialist nurse/Advanced Practice Provider
- Other nurse
- Non-clinical administrator

**9. What information is shared with potential related donors prior to tissue typing?  
(check all that apply)**

- Verbal communication
- Locally written information
- Written information from a national source (please specify)

**10. Is there an assessment of donor health prior to tissue typing?**

- Yes
- No

**11. How is this health assessment made? (check all that apply)**

- Written health questionnaire
- Health questionnaire completed over the phone
- Verbal discussion with open ended questions

Other (please specify)

**12. Do you always verify that a related donor is willing to donate prior to HLA typing?**

- Yes
- No

**13. Who is told first when a matched family donor is found?**

- The donor
- The recipient
- The referring physician
- No consistent practice

**14. What is the primary professional background of the provider with ultimate responsibility for medical clearance of adult related donors?**

- Internist/Family Practitioner
- Pediatrician
- Hematology/Oncology Physician (not transplant physician)
- Transplant Physician
- Mid-level provider (physician assistant or nurse practitioner)
- Other (please specify)

**15. Which of the following best describes this provider's potential role in the care of the recipient? (Note: clinical care is defined as any direct involvement with a recipient or donor by a provider, including consultation.)**

- Affiliated with the same transplant program, with simultaneous responsibility for the recipient's care
- Affiliated with the same transplant program, and may be involved in recipient care before the related donor's collection/harvest is complete
- Affiliated with the same transplant program, but not involved with the recipient's care before the related donor's collection/harvest is complete
- Not involved with the transplant program or the recipient's care

**16. Do related donors at your center have a donor advocate (an individual distinct from the transplant recipient's primary treating physician who works to fully inform the donor of the collection procedure and promotes the interests, well being, and safety of the donor)?**

- Always
- Often
- Sometimes
- Never

**17. What is the primary professional background of the provider who is ultimately responsible for obtaining informed consent for the donation process**

- Internist/Family Practitioner
- Pediatrician
- Hematology/Oncology Physician (not transplant physician)
- Transplant Physician
- Mid-level provider (physician assistant or nurse practitioner)
- Other (please specify)

**18. Which of the following best describes this provider's potential role in the care of the recipient?**

- Affiliated with the same transplant program, with simultaneous responsibility for the recipient's care
- Affiliated with the same transplant program, and may be involved in recipient care before the related donor's collection/harvest is complete
- Affiliated with the same transplant program, but not involved with the recipient's care before the related donor's collection/harvest is complete
- Not involved with the transplant program or the recipient's care

**19. What is the primary professional background of the provider who is ultimately responsible for the donor's medical management?**

- Internist/Family Practitioner
- Pediatrician
- Hematology/Oncology Physician (not transplant physician)
- Transplant Physician
- Mid-level provider (physician assistant or nurse practitioner)
- Other (please specify)

**20. Which of the following best describes this provider's potential role in the care of the recipient?**

- Affiliated with the same transplant program, with simultaneous responsibility for the recipient's care
- Affiliated with the same transplant program, and may be involved in recipient care before the related donor's collection/harvest is complete
- Affiliated with the same transplant program, but not involved with the recipient's care before the related donor's collection/harvest is complete
- Not involved with the transplant program or the recipient's care

**Questions about the donor medical evaluation**

**21. Does your unit have written/defined eligibility criteria for adult related donors?**

- Yes
- No

**22. Where are these criteria derived from?**

- Locally created
- Based on NMDP criteria
- Based on WMDA criteria

**23. Do you use a health history written questionnaire as part of your adult related donor assessment?**

Yes

No

**24. Is this completed by**

transplant programme personnel

blood bank personnel

**Questions about PBSC donation**

**25. Does your center perform PBSC harvests on related donors?**

Yes

No

**26. Who administers the GCSF? (tick all that may apply)**

	First GCSF dose	Subsequent doses
Your center	<input type="checkbox"/>	<input type="checkbox"/>
Another healthcare provider	<input type="checkbox"/>	<input type="checkbox"/>
The donor themselves/their family	<input type="checkbox"/>	<input type="checkbox"/>

**27. Regarding plerexifor use in related donors:**

	Yes	No	Only in the context of a clinical trial
Do you ever use it?	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Would you ever use it?	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>

**28. Who has the medical responsibility for the apheresis procedure itself?**

A transplant physician

A physician from another team/institution

**29. Do you have a limit for the number of apheresis procedures a related donor will undergo for their initial donation?**

No

Yes (please specify)

\_\_\_\_\_

**30. Who are donors asked to contact if they develop complications during the mobilization period?**

- The transplant team at your center
- Another team at your center
- Another healthcare provider (please specify)

**Questions about related bone marrow donation****31. Does your center perform bone marrow harvests on related donors?**

- Yes
- No

**32. Who performs bone marrow harvests at your center?**

- The transplant team responsible for care of recipient
- Other transplant physicians
- Another team

**33. Do you have a process for credentialing bone marrow harvest physicians?**

- Yes
- No

**34. Do you have a defined limit for the amount of bone marrow to harvest?**

- No, it is decided on a case by case basis
- Yes (please specify the limit)

**35. If you admit bone marrow donors following harvest, where do they stay?**

- The same ward as their recipient
- A different ward
- We do not routinely keep bone marrow donors in overnight

**36. Do related adult bone marrow donors routinely receive the following?**

	Yes	No
Collection and return of (an) autologous unit(s)	<input type="radio"/>	<input type="radio"/>
Collection of autologous unit(s) which is/are not routinely returned	<input type="radio"/>	<input type="radio"/>
A course of oral iron	<input type="radio"/>	<input type="radio"/>

**Questions about the follow-up of related donors**

**37. At which of the following time point(s) and through which of the following means, are your related donors followed up post-donation?**

	By telephone	Written questionnaire	Clinic review
Within 1 week	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
1 year	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
2 years	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
3 years	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
4 years	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
5 years	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
6 years	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
7 years	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
8 years	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
9 years	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
10 years	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
>10years	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

Any other time points (please specify)

**38. Who are donors asked to contact if they develop medical issues following their donation which may be potentially donation related?**

- The transplant team
- Another team at your center

Another healthcare provider (please specify)

**39. Do you have a written policy regarding subsequent donations from related donors?**

- Yes
- No

**40. Is there a limit to the number of subsequent donations a related donor may undergo at your center?**

- No
- Yes (please specify the limit)

**41. Thank you for your participation. Would you like to make any other comments about the care of family donors?**

*Figure S3. Proposal for pilot study of related donor management by Anthony Nolan and The London Clinic*

## **Proposal for pilot of related donor management by Anthony Nolan**

### **Background**

International standards ensure uniformity in assessment and care of volunteer unrelated donors (UDs) and guarantee the quality of stem cells for UD transplant recipients. In contrast, the care of related donors is more varied and less well regulated. Several parties (Clare<sup>1</sup>, O'Donnell<sup>2</sup>, van Walraven<sup>3</sup>) have highlighted the discrepancies between unrelated and related donor care, particularly with respect to the heterogeneity of medical eligibility criteria used, potential conflicts of interest when the same team is involved in the care of the donor and recipient, and the lack of related donor follow up. As a result, JACIE standards<sup>4</sup> now stipulate that "allogeneic donor suitability should be evaluated by a physician who is not the physician of the recipient" and, regulations are likely to become more specific in the future with respect to the independent evaluation of donors.

Recent studies have shown an increased incidence of adverse reactions in both a) related donors compared to unrelated donors<sup>5</sup>, and b) related donors who do not meet UD eligibility criteria compared to those who do<sup>6,7</sup>. Consequently, it has been suggested that practice of caring for related donors should be in line with that of unrelated donors, and that ideally suitability criteria and evaluation of family donors should be standardised. At present, data regarding the risks of donation in older donors (>65 years) are lacking, and it is unclear whether older donor who pass a thorough medical assessment are more likely to experience adverse events related to donation compared to younger donors.

There are logistical obstacles to implementing independent and standardised evaluation of related donor in the setting of transplant centres, where related donors have traditionally been assessed and managed by the same team of transplant physicians involved in the care of the HSCT recipient. This has raised the question of whether there is a role for HPC donor registries in assuming responsibility for part, or all, of the RD care pathway. When this issue was discussed at a joint WMDA-EBMT debate in April 2013, there was unanimous enthusiasm from the transplant community to explore alternative models of related donor care.

A further consideration, is the potential for a large increase in the number of related donors undergoing donation. Patient outcomes following haplo-identical transplants have vastly improved in recent years, and some countries are seeing a significant increase in the number of these transplants being performed. Assessment of stem cell donors is a very time consuming process for transplant centres, and an increased proportion of related donors may prove challenging in terms of donor capacity for many centres.

### **Pilot study proposal**

To begin to develop an alternative pathway of related donor care, we hope to pilot a process where the assessment and donation and follow-up of RDs is provided by a separate organization.

Given extensive joint experience The London Clinic/AN in facilitating HPC donations and strong existing links between AN and transplant centres, we propose to test the logistics of an alternative model of related donor care, where related donors are seen by an

independent physician and receive care equivalent to that of an unrelated donor, at The London Clinic.

### **Aims**

1. To explore whether an alternative model of donor care where donors are evaluated and donate is acceptable to:
  - a) Transplant physicians
  - b) Related stem cell donors
  
2. To prospectively investigate the proportion of family donors who would fail donor medical if the suitability criteria for UDs were used, and determine where these criteria could be relaxed (eg for upper age limit) providing a thorough medical assessment is performed.

### **Logistics**

HPC transplant directors at the largest London-based centres would be contacted and asked to participate by referring their related donors for assessment and donation at TLC. We would hope to facilitate a total of 20 related donations over a 1 year period. Related donors would be seen and assessed at The London Clinic in the same manner as unrelated volunteer stem cell donors.

Following the donor medical assessment, all investigations, the donation process, and post-donation follow up would be performed according to the same procedures used for unrelated donors. One month after donation, a short evaluation form about the donor experience would be sent.

Service level agreements already exist between AN and participating transplant centres, and between AN and The London Clinic, which would be adapted to include related donors.

### **Costs**

The London Clinic would offer equivalent fees for donor investigations and the donation process to those currently offered to AN for unrelated donors. AN is providing funding for this project for the duration of the pilot study.

### **Expected outcomes of pilot study**

1. The data collected in this pilot study would form the basis for a publication discussing alternative pathways of related donor care.
2. Following a successful pilot study we hope to be able to offer this pathway of related donor care to transplant centres nationwide.

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Figure S4. Proposal for assessment of related donors at King's College Hospital

## **Proposal for assessment of related donors at King's College Hospital**

### **Background**

As part of my MD in the assessment and care of related HPC donors at Anthony Nolan, I am in the process of setting up pilot studies to trial alternative pathways of related donor care.

The background to this project is that several studies have drawn attention to discrepancies between the aspects of related and unrelated donor care, particularly with respect to potential conflicts of interest when the same team is involved in the care of the donor and recipient, and the lack of related donor follow up. Although the most recent JACIE standards have addressed these issues, in many transplant centres independent donor assessment and donor follow-up are logistically difficult to achieve. We are therefore looking at alternative pathways that could both enhance related donor care, and enable transplant centres to comply with JACIE standards.

### **Potential pilot study at King's**

The proposal for a pilot study at King's would be for an independent physician (me) to perform the medical assessment of related donors onsite at King's. All other aspects of donor care would be performed at King's as per current practice, but follow-up post-donation would be provided by Anthony Nolan.

### **Aims**

The aims of this pilot study are to explore an alternative model of donor care and determine acceptability of this model to

- a) transplant teams
- b) related donors

### **Logistics (these are flexible and subject to discussion with King's team)**

We would plan to conduct this pilot study over a 6-9 month period. When matched related donors were identified, the King's transplant coordinators would contact me and (where feasible with respect to timing) I would perform the donor medical assessment at King's. All other aspects of donor work-up would be arranged as per current practice at Kings. Following donor medical I would arrange donor clearance either electronically or, if necessary, by returning in person. We propose that I would use current Anthony Nolan suitability criteria for unrelated donors with exception to certain agreed deviations eg age. If related donors do not meet these criteria, I would discuss individual cases with the transplant team at Kings to reach a decision regarding acceptance of the donor.

GCSF prescription and administration and the donation procedure would be performed as per current practice at Kings, and the King's team would be responsible for donor care over this period.

**Donor Follow up**

Following donation, we propose donors would be followed up by Anthony Nolan, receiving identical follow up to unrelated donors. This would include a phone call at 2-3 days post-donation, a survey monkey health questionnaire at 7 days post donation, and then a health questionnaire annually for the next five years, one at year six and eight and finally at year ten.

At the time of donor medical, donors would be given a one-page information sheet/consent form outlining the follow up process. By signing this consent they would agree to data transfer and follow up by Anthony Nolan.

Related donors would not receive any other type of communication from Anthony Nolan such as fundraising information.

Any medical issues identified during follow up would be discussed within the medical team at Anthony Nolan. In the event of donors reporting any complications felt to be directly related to stem cell donation, the Anthony Nolan medical officers would liaise with the clinical team at King's to discuss whether any further action is required.

Medical issues identified during follow up would be discussed within the medical team at Anthony Nolan. In the event of donors reporting any complications felt to be directly related to stem cell donation, the Anthony Nolan medical officers would liaise with the clinical team at King's to discuss whether any further action is required.

*Figure S5. Proposal for follow-up of Nottingham University Hospital related HPC donors by Anthony Nolan*

## **PROPOSAL FOR FOLLOW UP OF NUH RELATED DONORS BY ANTHONY NOLAN**

### **Introduction/Background**

In order to identify health issues related to donation procedures or stem cell mobilization, it is vital to monitor the health of stem cell donors post-donation. Donor follow up has now become a JACIE requirement, but it can be logistically difficult for transplant centres to achieve follow up measures. Furthermore, centralised recording of this follow up data for both related and unrelated donors is necessary if we are to improve our understanding of donation risks.

Anthony Nolan has an established process of donor follow up for unrelated donors, and we propose to undertake a pilot study extending this process to related donors.

### **Aims of pilot study**

To explore the logistics of related donor follow up by Anthony Nolan and ensure acceptability to transplant teams and related donors.

### **Logistics**

Related donors would be seen and undergo assessment and donation as per current practice at Nottingham University Hospitals NHS Trust. At the time of donor medical, donors would be given an information sheet/consent form outlining this pilot study and the follow up process. By signing this consent they would agree to data transfer and follow up by Anthony Nolan.

Following donation, the transplant coordinator from the NUH would contact the donor once at 2-3 days post-donation to ensure no immediate complications have occurred. The 'referral for family donor follow up' form would then be completed and sent with the consent to follow up to Anthony Nolan Team Support on the day of, or after donation.

After this point, related donors would receive identical follow up to Anthony Nolan unrelated donors, with a survey monkey health questionnaire at 7 days post donation, a further questionnaire at 1 month, and then a health questionnaire annually for the next five years, one at year six and eight and finally at year ten. The follow up questionnaires would include asking whether the donor would be willing to undergo a further donation to their relative if requested.

Related donors would not receive any other type of communication from Anthony Nolan such as fundraising information.

Any medical issues identified during follow up would be discussed within the medical team at Anthony Nolan. In the event of donors reporting any complications felt to be directly related to stem cell donation, the Anthony Nolan medical officers would report complications to the clinical team at NUH with a joint discussion regarding any further action required.

### **Study period**

We propose to undertake recruitment to this pilot study over a one-year period to begin at a mutually agreed time-point. All related donors donating at NUH within this period would be invited to participate and each of these donors would receive follow up by Anthony Nolan for the full ten-year follow up period.

If successful, this follow up pathway could in the future be offered to transplant centres nationally.

**Costs**

Since the costs of donor follow up will be relatively modest, we are able to offer donor follow up without charge for the period of this pilot study.

Figure S6. Request for family donor follow up at Anthony Nolan



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**REQUEST FOR FAMILY DONOR FOLLOW UP**

Donor Name	
DOB	
Address	
Email	
<b>DONATION DETAILS</b>	
Date of Donation	
Route of donation	PBSC <input type="checkbox"/> BM <input type="checkbox"/>
Date of post donation phone call	
Any immediate complications?	

Please send this form, together with donor consent to follow up by email:  
 Email: [familydonorfollowup@anthonynolan.org](mailto:familydonorfollowup@anthonynolan.org)

@anthonynolan anthonynolan

Anthony Nolan is a registered charity no 803716/SC038827 and registered as a limited company no 2379280 in England and Wales. Registered address: Royal Free Hospital, Pond Street, London NW3 2QG



Figure S7. Donor information and consent for related donor follow-up pilot study



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0303 303 0303

## CONSENT TO PARTICIPATE IN PILOT STUDY OF FAMILY DONOR FOLLOW UP

### Introduction

We invite you to participate in a pilot study we are running, where follow up after your donation would be provided by the Anthony Nolan.

### Who are Anthony Nolan?

We are the largest UK stem cell donor registry, our work includes finding matched donors for patients needing a transplant who don't have a suitable matched family donor. Since the launch of our register in 1974, we have facilitated over 10,000 stem cell transplants, and we are responsible for the care of these donors at all stages of their donation process. We also monitor the health of these donors after their stem cell donation.

We are an independent charity, and also do pioneering research into the treatment of blood cancers and disorders and improving the effectiveness of stem cell transplants.

See more at: <http://www.anthonynolan.org/about-us/frequently-asked-questions-who-we-are-what-we-do>

### What is our role in donor follow up?

We perform donor follow-up for unrelated volunteer donors in the UK. Follow up for family donors is currently provided by the individual transplant centres where they have donated. Although it is exceedingly rare for donors to develop health problems related to donation, it is nevertheless important for all donors, including family donors, to be followed up. This is so that we can continue to be certain that donors are not experiencing later health problems as a result of their donation. It makes sense for one organisation to perform all this follow-up so that we have large enough donor numbers to identify any rare health issues occurring in donors. Since Anthony Nolan already has an established process for donor follow up, we have suggested extending this to include family donors.

### Purpose of this pilot study

This pilot study is to test the logistics of a new system of donor follow up where the health of family donors is monitored by the Anthony Nolan. This process will not require you to undergo any extra investigations or procedures, and follow up will be performed according to standard procedures and regulations.

### What will happen?

Your transplant team at NUH will contact you within a few days of the donation to check that you are recovering as we would expect. The Anthony Nolan will then contact you with a very short health survey a week after your donation, again just to ensure you are recovering. We then send you a health questionnaire annually for the next five years, then one at year six and eight and finally at year ten, to find out whether you have developed any new health issues.

 @anthonynolan  anthonynolan

Anthony Nolan is a registered charity no 803716/SC038827 and registered as a limited company no 2379280 in England and Wales. Registered address: Royal Free Hospital, Pond Street, London NW3 2QG





Figure S8. Standard operating procedure for family donor follow-up at Anthony Nolan

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## STANDARD OPERATING PROCEDURE

TITLE:	Follow-up procedures for family donors	
VERSION No:	001	
DATE OF ORIGINAL ISSUE:		
REVIEW INTERVAL:	12 months	
ORIGINAL PREPARED BY:	Chloe Anthias	
QM REVIEWED BY:	Salmah Mahmood	
AUTHORISED BY:	Catherine Burlton	
COPY and LOCATION (circle appropriate copy)	Master Copy – Q pulse 1. Quality Team Cabinet	
<b>Document review history</b>		
Review date	Reviewed by	Comment

<Insert Q pulse doc number>

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**Contents:**

1. Introduction
2. Procedure for following up family donors who have donated in their recipient's Transplant Centre

**1. Introduction**

This SOP describes the procedure to be followed for family donors who have donated at their recipient's transplant centre but for whom AN has agreed to provide follow-up.

**2. Procedure for following up family donor who have donated at their recipient's transplant centre.**

- i) At the time of donor consent at the transplant centre, the donor will receive information sheet and will sign consent DOC3012 for data transfer and follow-up by Anthony Nolan.
- ii) The 'request for follow up' form DOC3013 and the donor consent will be emailed to 'familydonorfollowup@anthonymolan.org' and the donor will be added to the family donor follow up spreadsheet located G:Operations/Medical Officer/Family donor follow up
- iii) The transplant centre will perform follow up until day 7 at which point the donor will be sent the Family donor 7 medical questionnaire using the email template (DOC 2952), as per DOC 2386.
- iv) On receipt the questionnaire is reviewed by the Donor Relationship Advisor or Medical Officers and if no medical issues remain the donor is signed off. Anthony Nolan Medical or Quality team shall advise the Collection Centre of any SAE and/or SAR which occur post-donation.
- v) Follow up will be continued for 10 years with an annual questionnaire (DOC 2951) using email template (DOC 2953) sent at 1,2,3,4,5,6,8,10 years.

<Insert Q pulse doc number>

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- vi) Any donor medical issues identified during the follow up process will be discussed with the medical officers and a decision made regarding whether the issue requires discussion with the referring transplant centre.
- vii) If family donors indicate during the follow up process that they are not willing to donate further products to their recipient in the future, the transplant centre should be informed.
- viii) Donors will receive medical follow up only, with no marketing, fundraising or event information.
- ix) It is intended that these family donors will undergo standard follow up as per Anthony Nolan policy for unrelated donors. If standard follow up for unrelated donors is changed, the follow up procedure for family donors will be adjusted accordingly

Figure S9. Day 7 follow-up questionnaire for pilot study of related donors followed up by Anthony Nolan

**1. What is your date of birth?**

DD MM YYYY  
Enter date  /  /

**2. What is your name?**

**3. How have you donated?**

PBSC (peripheral blood stem cells)  
 BM (bone marrow under general anesthesia)

**4. Have you fully recovered from your donation?**

Yes  
 No

Please specify

**5. How long did it take you to recover following donation?**

**6. Are you back at work and participating in normal activities?**

Yes

No

Please specify

**7. How do you feel physically?**

Much better than usual

Better than usual

Normal

Worse than usual

Much worse than usual

Please specify

<b>8. Are you experiencing any of the following symptoms at the moment?</b>	
Present	If present, please list grading (explanation in table below)
Allergy	<input type="text"/>
Anorexia (Loss of appetite)	<input type="text"/>
Back pain	<input type="text"/>
Bleeding	<input type="text"/>
Bruising	<input type="text"/>
Dizziness	<input type="text"/>
Donation site pain	<input type="text"/>
Fatigue	<input type="text"/>
Fever	<input type="text"/>
Headache	<input type="text"/>
Infection	<input type="text"/>
Injection site reaction	<input type="text"/>
Insomnia (difficulty sleeping)	<input type="text"/>
Muscle ache	<input type="text"/>
Nausea (feeling sick)	<input type="text"/>
Any other pain	<input type="text"/>
Rash	<input type="text"/>
Throat pain	<input type="text"/>
Vomiting	<input type="text"/>

Please supply additional information or any other symptoms you are experiencing.

Toxicity Score	1	2	3	4
Allergy	Mild reaction not requiring treatment	Rash or other reaction which requires treatment Symptoms last less than 24 hours	More severe or prolonged reaction	Life-threatening
Anorexia/Loss of appetite	without alteration in eating habits	Food intake altered without significant weight loss	Significant weight loss	Life-threatening
Back Pain	Mild	Moderate	Severe	Disabling
Bleeding	Mild without need for transfusion		Requiring transfusion	Life-threatening
Bruising	Localised	Generalised		
Dizziness	Mild unsteadiness	Moderate unsteadiness; limiting activities other than self-care	Severe unsteadiness; limiting self-care activities	
Donation site pain	Mild	Moderate	Severe	Disabling
Fatigue	Fatigue, relieved by rest	Fatigue not relieved by rest; limiting activities other than self-care	Fatigue not relieved by rest, limiting self-care activities	
Fever	38-38.9°C	39-39.9°C	40+°C for <= 24hrs	>40°C for >24hrs
Headache	Mild	Moderate	Severe	
Infection	Mild	Moderate infection, requiring tablet antibiotics; limiting activities other than self care	More severe infection, requiring Treatment hospital admission; limiting self-care activities	Life-threatening
Injection site reaction	Tenderness with or without other symptoms (e.g. warmth, itching)	Pain, swelling, or distortion of the skin	Skin breakdown - requiring surgery.	Life-threatening
Insomnia (difficulty sleeping)	Mild	Moderate	Severe	
Myalgia/Muscle ache	Mild	Moderate	Severe	
Nausea	Loss of appetite without alteration in eating habit	Food intake altered without significant weight loss	Significant weight loss	
Pain	Mild	Moderate	Severe	
Rash	Rash covering <10%	Rash covering 10-30 %	Rash covering >30% of body	Life-threatening
Throat Pain	Mild	Moderate	Severe	Disabling
Venous Access Complication	Primary suture repair, but not requiring transfusion	Primary suture repair for injury, requiring transfusion	Vascular occlusion requiring surgery or bypass for injury	
Vomiting	1-2 episodes in 24 hours	3-5 episodes in 24 hours	6 or more episodes in 24 hours	Life-threatening

**9. How do you feel emotionally?**

- Much better than usual
- Better than usual
- Normal
- Worse than usual
- Much worse than usual

Please specify

**10. Have you started any new medications in the last week?**

- Yes (please specify below)
- No

Please specify

Figure S10. Annual follow-up questionnaire for pilot study of related donors followed up by Anthony Nolan



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 Registered charity number  
 803716/SC038827  
 4190P

## ANNUAL CONFIDENTIAL DONOR FOLLOW-UP QUESTIONNAIRE

Year of follow-up 1 2 3 4 5 6 8 10

### DONOR DETAILS

1. Initials	<input type="text"/>	2. Donor ID	<input type="text"/>
3. Date of birth	<input type="text"/>	4. Date of collection	<input type="text"/>
5. Route of donation	<input type="checkbox"/> PBSC	<input type="checkbox"/> BM	

### A. YOUR HEALTH

6. Do you feel you have made a full recovery from your donation?  Yes  No
7. How do you feel physically?  much better than usual  better than usual  normal  worse than usual  much worse than usual
8. How do you feel emotionally?  much better than usual  better than usual  normal  worse than usual  much worse than usual
9. Have you been diagnosed with cancer since your donation? If yes, please give further details below.  Yes  No
10. Have you been diagnosed an autoimmune condition since your donation?\* If yes please give further detail below.  Yes  No
11. Have you been diagnosed with any other medical condition since your donation? If yes, please give further details below.  Yes  No

\*Examples include ulcerative colitis, rheumatoid arthritis and lupus

Details



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### B. CONSENT TO DONATE AGAIN

12. If applicable, do you wish to remain available to donate to your recipient again in the future if required?

Please tick all that apply  PBSC  Bone marrow  Lymphocytes

### C. YOUR CONTACT DETAILS

Has your home address changed?  Yes  No  
If yes, please give your new address below:

Title \_\_\_\_\_ First name \_\_\_\_\_

Surname \_\_\_\_\_

Address \_\_\_\_\_

\_\_\_\_\_

Telephone (home) \_\_\_\_\_ Telephone (mobile) \_\_\_\_\_

Telephone (work) \_\_\_\_\_

E-mail \_\_\_\_\_

### D. FURTHER COMMENTS

Please use this space for any further information you wish to share with us. You may continue overleaf if required.



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Please use this space for any further information you wish to share with Anthony Nolan

**FOR MEDICAL OFFICER USE ONLY**

Haematologic malignancy?	<input type="checkbox"/> Yes	<input type="checkbox"/> No	<input type="checkbox"/> Unknown
If yes, ICD-10 Code	___/___/		
Diagnosis confirmed by medical data?	<input type="checkbox"/> Yes	<input type="checkbox"/> Unconfirmed	
Non-haematologic malignancy?	<input type="checkbox"/> Yes	<input type="checkbox"/> No	<input type="checkbox"/> Unknown
If yes, ICD-10 Code	___/___/		
Diagnosis confirmed by medical data?	<input type="checkbox"/> Yes	<input type="checkbox"/> Unconfirmed	
Autoimmune disease?	<input type="checkbox"/> Yes	<input type="checkbox"/> No	<input type="checkbox"/> Unknown
If yes, ICD-10 Code	___/___/		
Diagnosis confirmed by medical data?	<input type="checkbox"/> Yes	<input type="checkbox"/> No	

MO name and signature

Date

Figure S11. Survey questionnaire sent to related donors to evaluate experience of the donation pathway at The Royal Marsden

## Survey of Related Donor Care at The Royal Marsden

1. Please enter your unique identifier (supplied with the link to this page)

### Questions about the care you received before your donation

2. Do you think you received enough information to understand the donation procedure *before* your blood was tested to see if you were a match?

- Yes  
 No

3. Did you feel pressure to agree to donate from other people? (Please tick all that apply)

- The relative to whom you were donating  
 Other family  
 The medical team looking after your relative  
 Other (please specify):

4. Did the decision to donate require:

- No consideration  
 A little consideration  
 A lot of consideration

5. From which of the following sources did you receive information about the donation procedure? (Please tick all that apply)

- Transplant Nurse  
 Transplant doctor at the time of medical assessment  
 Written information from the hospital about donating  
 The Internet  
 Other (please specify):

6. What was the most helpful source of information?

**7. Did you feel well prepared for the donation experience? (Please tick one answer)**

- Yes, totally
- Yes but could have been better prepared
- Not very well prepared
- Not at all prepared

**Questions about the donation procedure**

**8. In terms of the physical experience was it.. (Please tick one answer)**

- More painful/more side effects than expected
- About what you expected
- Less pain/side effects than you expected

**9. Did you find the donation procedure... (Please tick one answer)**

- Very stressful
- Quite stressful
- Not very stressful
- Not at all stressful

**10. If you found it stressful was this due to....(Please tick all that apply)**

- Concerns about the procedure itself
- Concerns about the short term impact on your health
- Concerns about long term effects on your health
- Concerns about the logistics of donation
- Other concerns (please specify):

**11. Did you feel you had enough emotional support at the time of donation?**

- Yes
- No

**12. Do you think you received enough support from The Royal Marsden at the time of donation?**

- Yes
- No (please explain if you are able to)

**13. Which of the following arrangements did you have to make/change in order to donate? (Please tick all that apply)**

- Education
- Work
- Childcare
- Care for other dependent
- Other significant arrangements (please specify)

**14. Which of the following costs did you have to meet in order to donate? (Please tick all that apply)**

- Flights
- Train
- Accommodation
- Care for a dependent
- Other (please specify)

**15. Did you suffer loss of earnings in order to donate?**

- Yes
- No

**16. If you could choose, where would you have preferred to donate?**

- At the transplant centre where your relative was cared for
- At a separate centre to where your relative was cared for
- Wouldn't mind/whichever was more convenient

**Questions about your care after the donation**

**17. Do you feel you received enough information about possible outcomes/complications for your relative before you agreed to donate?**

- Yes
- No
- Not sure

**18. Are there any aspects of donation that you would have liked more information about?**

**19. Do you think you have experienced any negative emotions or psychological difficulties as a result of donation?**

- No
- Yes (please specify if you are able to)

**20. Do you think you were offered enough support from the hospital after donation?**

- Yes
- No (please specify what could have been improved):

**21. Are there any other ways in which you feel your donation or post donation care could have been improved?**

Thank you very much for completing this survey!

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## APPENDIX 2. PUBLISHED MANUSCRIPTS