The impact of donor health and psychosocial factors on the donation experience and recovery

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Author's Declaration

I, Annelies Billen, 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.

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Date

Abstract

Donation of haematopoietic stem cells (HSCs), either through bone marrow (BM) or peripheral blood stem cell (PBSC) collection, is a generally safe procedure for healthy donors, although adverse reactions (ARs) are a known and definable risk. The physical reactions to donation have been established for some time, but less is known about factors predicting poorer experiences.

In my thesis, I explore the donation experience in a prospective study involving 275 PBSC and 37 BM donors and focus attention on health-related quality of life (HRQOL) factors associated with recovery. Detailed interviews of 14 PBSC donors explore these findings using qualitative methodology. In addition, I characterise donors at risk of not meeting the HSC dose requested by transplant centres and therefore at risk of additional procedures and associated ARs.

My key finding was that pre-donation HRQOL markers were the strongest predictors of time to recovery; poorer pre-donation physical health was associated with longer recovery ($p = 0.017$) and certain side-effects in PBSC donors, and poorer mental health was associated with longer recovery in BM donors ($p = 0.03$) and pain following PBSC donation ($p = 0.003$). Physical HRQOL scores declined significantly from pre-donation to 4 weeks post-donation, but returned to pre-donation values at 3 months. This decline was greater for BM donors. Mental HRQOL scores remained high throughout for PBSC donors, this may be explained by the strong, intrinsic motivation as well as remarkable determination donors described in the qualitative analysis.

Understanding that toxicity profiles vary with certain donor characteristics is crucial as this knowledge could influence future practice in numerous ways including modification of joining policies and provision of tailored donor information, pre-emptive analgesia and donor follow-up. Based on my study findings, I initiated a pilot study that offers a different approach to donors at higher risk of a delayed recovery.

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Peer-reviewed presentations

Oral sessions

- WMDA IDRC Conference London April 2014 (presented by Rachel Pawson):

  Annelies Billen, Ying Li, David Winstone, Catherine Chapman, Rachel Pawson. Stem cell donation by donors with a high BMI: Is it safe?
- WMDA IDRC Conference Minneapolis November 2014:

  Chloe Anthias, Rebecca Arkwright, **Annelies Billen**, J. Alejandro Madrigal and Bronwen E. Shaw. Longer Procedure Duration and Large Volume Harvests Reduce the Likelihood of Achieving the Requested Cell Dose from Unrelated Bone Marrow Donors

Poster sessions

- American Society of Haematology (ASH) Conference New Orleans December 2013:

  Billen A., Madrigal JA., Shaw BE. Male and possibly younger donors provide the best chance of meeting requested cell dose for PBSC transplantation.
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  Billen A., Madrigal JA., Shaw BE. Male and possibly younger donors provide the best chance of meeting requested cell dose for PBSC transplantation.
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- WMDA IDRC Conference Minneapolis November 2014:

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- BMT Tandem San Diego February 2015:

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- BMT Tandem San Diego February 2015:

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  A change in donor medical suitability criteria resulted in decreased rates of donor attrition in a registry study

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Glossary

	Definition
Allogeneic haematopoietic stem cell transplant (allo-HSCT)	In humans, allo-HSCT refers to the use of donated HSC from another individual for transplantation. Examples of HSC sources for allo-HSCT include: syngeneic (twin) donor, HLA-identical sibling donor, haploidentical related donor, unrelated adult donor, cord blood unit.
Anthony Nolan (AN)	AN is a UK charity that works in the area of HSCT. It manages and recruits donors to the AN Register, which is the largest UK registry. It is aligned with the Welsh Bone Marrow Donor Registry and the National Blood Service ran British Bone Marrow Registry (BBMR). It also carries out research to help make bone marrow transplants more effective.
Apheresis	Apheresis is a technique in which the blood of a donor or patient is passed through a machine that separates out one particular constituent (haematopoietic stem cells in the case of PBSC donation) and returns the remainder to the circulation.
BM	See 'Bone Marrow'
BMDW	Bone Marrow Donors Worldwide. A global collaborative collation system designed to provide a searchable interface for unrelated donors listed by participating registries.
Bone Marrow	The soft blood-forming tissue that fills the cavities of bones and contains fat and immature and mature blood cells, including white blood cells, red blood cells, and platelets.
BSBMT	The British Society of Blood and Marrow Transplantation
CD 34	CD34 molecule is a cluster of differentiation molecule present on certain cells within the human body and has been a focus of interest

	ever since it was found expressed on a small fraction of human bone marrow cells. The CD34+-enriched cell population from marrow or mobilised peripheral blood appears responsible for most of the haematopoietic activity and CD34 has therefore been considered to be the most critical marker for HSCs.
CIBMTR	The Center for International Blood & Marrow Transplant Research, or CIBMTR, collaborates with the global scientific community to advance haematopoietic cell transplantation and cellular therapy research worldwide. A combined research program of the National Marrow Donor Program and the Medical College of Wisconsin, CIBMTR facilitates critical research that has led to increased survival and an enriched quality of life for thousands of patients.
Collection centre	A medical centre equipped to carry out collection of haematopoietic stem cells, either by peripheral blood stem cell apheresis or bone marrow harvest. Many will also undertake medical assessment of donors to establish fitness to donate.
Conditioning	A chemotherapy regimen with or without radiotherapy or immunotherapy designed to prepare the recipient bone marrow or immune system for receipt of donor HSC. Regimens may be myeloablative (full-intensity) or non-myeloablative (reduced-intensity).
Confirmatory typing (CT)	Blood sample confirmation for possible donor/recipient HLA match
Cord blood unit (CBU)	A donation of blood, rich in HSC, derived from the umbilical cord and placenta of a new born infant. Cord blood units are generally cryopreserved and may be used for allo-HSCT if found to be appropriately matched to a patient.
DLI	See 'Donor Lymphocyte Infusion'
Donor	Any individual, living or dead, providing solid organs, tissues or cells for the purposes of transplantation or transfusion. For the purposes

	of this thesis, a donor is an individual providing haematopoietic stem cells or lymphocytes for the allogeneic transplantation.
Donor lymphocyte infusion	The process of giving lymphocytes from a donor to a recipient following allo-HSCT, usually for treating disease relapse or mixed donor/recipient chimerism. The lymphocytes may be stored from the original donation, or the donor may need to undergo further apheresis to provide the cells.
EBMT	The European Group for Blood and Marrow Transplantation
FDA	The Food and Drug Administration or FDA is a Consumer Protection Agency of the U.S. Government responsible for protecting the public health by assuring the safety, efficacy, and security of human and veterinary drugs, biological products, medical devices, the nation's food supply, cosmetics, and products that emit radiation. The FDA also provides accurate, science-based health information to the public.
G-CSF	G-CSF or granulocyte colony stimulating factor is a haematopoietic cytokine glycoprotein produced by monocytes, fibroblasts, and endothelial cells whose principal role in normal haematopoiesis is to regulate production, differentiation, and functional activation of neutrophils. Recombinant G-CSF given at pharmacological doses stimulates the development of primitive HSCs and the release of CD34+ progenitors from the marrow into the circulation.
Graft-vs-host disease (GvHD)	Immune cells (white blood cells) in the graft recognise the recipient (the host) as "foreign". The transplanted immune cells then attack the host's body cells. It can affect several organs including the skin, gastrointestinal tract and liver.
Graft-vs-leukemia effect (GVL)	A desired effect of allo-HSCT, describing the immunological activity of the engrafted donor immune system against malignant recipient cells.

Haematopoietic stem cell (HSC)	A multipotent immature cell capable of self-replication and differentiation into cells of myeloid, erythroid or lymphoid lineage. CD34 has been considered to be the most critical marker for HSCs.
HSCT	Haematopoietic stem cell transplantation, which may be autologous (self-transplant), or allogeneic (donor, allo-HSCT)
HTA	See 'Human Tissue Authority'
Human leukocyte antigen (HLA)	The human leukocyte antigen (HLA) system is the locus of genes that encode for proteins on the surface of cells that are responsible for regulation of the immune system in humans. Any cell displaying some other HLA type is "non-self" and is seen as an invader by the body's immune system, resulting in the rejection of the tissue bearing those cells. This is particularly important in the case of transplanted tissue, because it could lead to transplant rejection.
Human Tissue Authority (HTA)	The UK legislative authority responsible for regulation pertaining to the handling of human cells, tissues and organs.
JACIE	Joint Accreditation Committee ISCT-EBMT. A Collaborative global organisation providing standards, inspection and accreditation of organisations involved in the collection, processing and transplantation of haematopoietic stem cells and related products.
Mobilisation	Mobilisation is a process in which certain drugs (for example G-CSF) are used to cause the movement of HSCs from the bone marrow into the blood.
NHS Blood and Transplant (NHSBT)	The National Health Service department responsible for collection and provision of blood-products, tissues, organs and cells for the purpose of transfusion or transplantation.
NMDP	The National Marrow Donor Program. It is the largest HSC registry in the United States.
PBSC	See 'Peripheral blood stem cells'

Peripheral blood stem cells	Peripheral blood stem cells (PBSC) are HSCs that circulate in the blood. Most of the HSCs in the body can actually be found in the bone marrow. However, a small proportion of HSCs - PBSC - circulate in blood. This proportion can be increased by a process called mobilisation, when HSCs from the BM move into the blood.
RD	See 'related donor'
Related donor	A related donor can be a syngeneic (twin) donor, HLA-identical sibling donor or a haploidentical related donor (half-matched related donor)
SAR	See 'Serious adverse reaction'
Serious adverse reaction	Any life-threatening adverse event or adverse event leading to death, hospitalization (initial or prolonged), disability or permanent damage.
SF-36	The SF-36 or short-form 36 is a widely used questionnaire for measuring self-reported physical and mental health status. It contains 36 questions. The original SF-36 came out from the Medical Outcome Study.
TC	See 'Transplant centre'
Transplant centre	A unit (usually within a hospital) capable of carrying out haematopoietic stem cell transplantation. For the purposes of this thesis, these centres carry out allogeneic HSCT.
Unrelated donor	When the donor has no family connection to the recipient it is called unrelated donor. These donors are found through an unrelated donor registry and are volunteers.
URD	See 'unrelated donor'
WMDA	The World Marrow Donor Association. The WMDA was founded in order to provide a global forum for all matters relating to donors of haematopoietic stem cells.
Work-up	The pre-donation work-up involves the clinical evaluation of the potential donor. The potential donor's state of health must be evaluated, as must the presence of criteria for exclusion from donation and risk factors related to the type of donation. It involves a

	detailed history, clinical examination, blood tests and often a chest X-ray and ECG.

Thesis overview

The primary aim of my thesis is to provide an in depth analysis of the short and long-term physical and psychological donation experience as well as an analysis of factors influencing donor recovery and the identification of donors who are at risk of poorer donation experiences. The results will help towards more targeted strategies concerning donor recruitment, selection, work-up and donor follow-up and I believe such strategies will improve the donation experience.

I started my research with a review of the literature, which is outlined in chapter 1. This chapter explores the donation experience, both from a physical and psychological perspective. It gives in insight into factors that are associated with a poorer donation experience, and details methods that are currently in place to optimise donor safety.

I subsequently designed the prospective study described in chapters 4 and 5. This study is the core of my thesis and assesses the physical and psychological donation experience and defines groups at increased risk of a poorer donation experience. I evaluate both the impact of demographic factors (chapter 4) and baseline health related quality of life scores (chapter 5). This study was designed by myself in close collaboration with my supervisors. As part of the preparation of my prospective study and in order to ensure the adequate capture of my outcome data (adverse reactions at certain time points and time to complete recovery), I audited the collection of donor

follow-up data for our register. The first part of chapter 3 describes this audit as well as the subsequent changes I implemented based on this.

Following the analysis of my prospective study, I designed a study that further explores the main findings of the study in a qualitative matter (chapter 7). This study involves 14 in depth donor interviews and assesses the influence of pre-donation physical health on the donation experience. Additionally, the study evaluates the role of donor preparedness and donor ambivalence in our donor population, factors that have previously shown to influence the donation experience, but that were not investigated in the prospective study.

Chapters 3 and 6 investigate the PBSC (chapter 3) and BM (chapter 6) donor and collection characteristics that are more likely to be associated with reaching the stem cell dose requested by the transplant centre. The reason I decided to investigate these areas are twofold. Firstly, additional procedures may be needed if the requested dose is not reached after 1 day; these procedures may be associated with increased adverse reactions and hence the importance of characterising donors who are at risk of not reaching the requested dose. Secondly, if we aim to change policies (e.g. recruitment) for donors at high risk of adverse reactions, it is important to realise how this change in practice will affect the yields. Similar factors that are analysed concerning donor safety in chapter 5 (e.g. BMI, weight and age) are therefore investigated with regards to their influence on yields.

The methodology of all the studies is described in chapter 2. Chapter 8 summarises the thesis, discusses some of the challenges I faced, and presents future directions this work may take

Chapter 1 - background

*A review article based on the text of this introduction was published in the journal of Bone Marrow Transplantation in January 2014, entitled "*A review of the haematopoietic stem cell donation experience: is there room for improvement?"

(See Appendix 3)

1.1 Introduction

1.1.1 General principles of haematopoietic stem cell transplantation

Haematopoietic stem cell transplantation (HSCT) is the treatment of choice for several malignant and non-malignant haematological diseases. It involves eliminating a patient's haematopoietic system by chemotherapy and/or radiotherapy in a procedure called conditioning and replacing it with healthy haematopoietic stem cells (HSCs). This conditioning is designed to eradicate the patient's haematopoietic system and, if present, malignancy. In addition, it helps to suppress the host immune system and thereby prevents rejection of "foreign" stem cells. In allogeneic SCT, these stem cells are from another individual.

HSCT is mainly used in haematological malignancies, for example acute and chronic leukemia, but it also has a role in the treatment of non-malignant haematological diseases. The exact role of HSCT in each of these diseases is complex and depends on several factors including disease severity, remission status, age of the patient and availability of a donor. Although allogeneic HSCT can be curative, it has a significant

morbidity and mortality associated with it. One of the major reasons for this is any immunological incompatibility between donor and patient, therefore matching for the human leukocyte antigens (HLA) is critical and determines whether or not a transplant can go ahead. Despite HLA matching complications may still occur and may be due to numerous different factors beyond the scope of this thesis. The complications may manifest as immunodeficiency, graft-versus-host disease (GvHD) or graft failure. GvHD is a condition caused by donor-derived immune cells reacting against recipient tissues. It can affect several organs including the skin, gastrointestinal tract or liver. Paradoxically, there is also a graft-versus-leukemia (GVL) effect which underlies much of the success of the procedure. Another major cause of transplant-related complications is the risk of bacterial, fungal and viral infections due to an impaired immune system. Disease relapse may also occur.

A major evolution in allogeneic HSCT is the shift that has occurred from myelo-ablative conditioning regimens to non-myeloablative conditioning. Myeloablative regimens completely eradicate the patient's bone marrow, whereas non-myelo-ablative regimens cause enough immunosuppression to allow engraftment but without completely eradicating the patient's own bone marrow. These "mini-transplants" have reduced the morbidity and mortality of allogeneic HSCT and have extended the age range for transplantation (Mielcarek et al., 2002). They rely heavily on the ability of GVL effect to cure the underlying malignant disease. The relapse rates in "mini-transplants" are higher (McSweeney et al., 2001) and in this context, they are associated with a higher use of donor lymphocyte infusions (DLI). The principle of DLI is that peripheral blood mononuclear cells are collected from the original allograft donor and directly infused into the patient at the time of disease relapse or to prevent relapse by strengthening the graft. DLI infusions encourage complete engraftment and can induce GVL effects.

Ideally patients receive stem cells from a matched related (sibling) donor. But as there is only a 25% chance for a sibling to be HLA matched, only about 30% of patients have a sibling matched donor and this number is expected to continue to drop as the average family size keeps going down in the Caucasian population. An alternative donor source is an unrelated HLA matched donor that can be identified through volunteer unrelated donor registries. Strong evidence for significantly improved transplant outcome in unrelated donor HSCT by matching for HLA using high resolution typing between patient and donor has been published over recent years (Petersdorf, 2004, Petersdorf et al., 2007, Petersdorf, 2008, Flomenberg et al., 2004). Surveys from Europe and the United States show that there are now more unrelated than related haematopoietic stem cell donations in these areas (Pasquini and Wang, 2012). This increase can be explained by the improved outcome of unrelated donor transplantation owing to more precise HLA typing and advances in patient care during the last decade. Even though the unrelated donor pool steadily expands, approximately 90% of Caucasians but as low as 40% of non-Northern Europeans are able to find a match (NHSBT, 2010, Lown and Shaw, 2013). Non-HLA factors that also need to be taken into account for donor selection include CMV status, ABO blood group and donor age. An alternative approach for patients without HLA-matched donors is the use of a haploidentical donor or umbilical cord blood. Haploidentical donors have one haplotype in common with the recipient, so they match in at least half of their HLA loci. These are most commonly relatives, such as parents, children or siblings.

1.1.2 Collection of HSCs

Stem cells can be collected from the bone marrow (BM), the peripheral blood (peripheral blood stem cells or PBSC) or from umbilical cord blood.

BM donation involves the repeated insertion of large bore needles into the donor's posterior iliac crests to remove up to 2 litres of marrow under general or spinal anaesthesia. The amount of extracted BM depends on the donor weight, but should not exceed 20 mls/kg (based on international recommendations). The average hospital stay is 8-72 hours and many collection centres routinely admit their donors following donation (Favre et al., 2003, Gandini et al., 2001, Nishimori et al., 2002).

PBSC are collected using a cell-separator machine connected to the donor via a peripheral cannula or a central venous catheter if donors have inadequate veins. Blood is taken from the donor and circulated in the machine where mononuclear cells are collected by centrifugation before the red cells are returned to the donor, a process called leukapheresis. This process may take several hours and PBSC donors are generally not admitted to hospital. A second day leukapheresis may be needed if insufficient HSCs were harvested on day 1. Peripheral blood contains too few HSCs for successful transplantation, hence growth factors (granulocyte colony stimulating factor or G-CSF) are injected daily the 4 or 5 days preceding the leukapheresis. G-CSF is a haematopoietic cytokine glycoprotein produced by monocytes, fibroblasts, and endothelial cells whose principal role in normal haematopoiesis is to regulate production, differentiation, and functional activation of neutrophils. Recombinant G-CSF given at pharmacological doses stimulates the development of primitive HSCs and the release of CD34+ progenitors from the marrow into the circulation (Pamphilon et al., 2008). CD34 has been considered to be the most critical marker for HSCs.

In the last decade, PBSC have replaced BM as the main source of HSCs. The cell composition of unmanipulated PBSC and BM allografts differs significantly. The total numbers of T cells, monocytes, and natural killer cells contained in a PBSC allograft are more than 10 times higher than those in a BM allograft (Ottinger et al., 1996).

Also, Russell et al demonstrated that G-CSF causes the mobilisation of large numbers of type 2 dendritic cells and the presence of large numbers of CD4 cells expressing the T-helper 2 phenotype (Klangsinsirikul and Russell, 2002), which contrasts with the predominantly type 1 dendritic cell and T-helper 1 phenotype in BM harvests . As a consequence, there is a major difference in the proportion of Th1 and Th2 cells infused in BM and PBSC recipients. This difference in graft composition may explain the increased risk of acute and chronic GvHD reported in several large randomised controlled trials (Schmitz et al., 1995, Bensinger et al., 1995, Blaise et al., 2000, Powles et al., 2000, Bensinger et al., 2001, Morton et al., 2001, Couban et al., 2002, Schmitz et al., 2002) when using a PBSC source.

PBSC also have a much higher content of blood progenitor cells compared to bone marrow. This is associated with faster haematological recovery in recipients (Tanaka et al., 1994, Bensinger et al., 1995, Anasetti et al., 2012). The recipient might also profit by an enhanced GVL reaction exerted by the high number of natural killer cells contained in such grafts and several authors have reported a decreased relapse rate, especially among patients with high-risk blood cancers (Powles et al., 2000, Nagler et al., 2012). However, most studies found no significant differences in long-term survival rates between PBSC and BM; this may be explained by the finding that PBSC reduces the risk of graft failure whereas bone marrow reduces the risk of chronic GvHD (Powles et al., 2000, Friedrichs et al., 2010, Anasetti et al., 2012). Another consideration when deciding on the HSC source should be the donation perspective. Several authors have reported a delayed recovery and an increased risk of serious adverse reactions in BM donors, whereas G-CSF has been a topic of debate concerning its long-term safety.

1.1.3 The donation experience

Although the donation process is generally considered safe, adverse reactions (ARs) are a well-established risk. Optimizing the donation experience is essential for several reasons. Most importantly, the act of donating BM or PBSC for HSCT is a humanitarian gesture rewarded only by the potential sense of satisfaction derived from an altruistic act (Boo et al., 2011). Hence, care must be taken to minimize the potential of harm and donor safety should be a first priority for everyone involved. In addition, stem cell donation requires that we balance the conflict between ensuring there are a sufficient number of willing donors while protecting their safety.

The overall experience of the donor includes both physical and psychological aspects, from the time of their first contact with the registry until full recovery. Common physical adverse reactions of BM and PBSC donation are well known (de la Rubia et al., 2008, Holig et al., 2009, Miller et al., 2008, Pulsipher et al., 2009b, Pulsipher et al., 2013, Siddiq et al., 2009), although studies examining the psychological aspects of donation and examining which groups of donors are at increased risk have been limited (Pulsipher et al., 2009b, Pulsipher et al., 2013, Murata et al., 1999, Chen et al., 2011, Miller et al., 2008, Gandini et al., 2001, Billen et al., 2014, Switzer et al., 1996, Stroncek et al., 1996, Yuan et al., 2010). The latter are important as it could help to identify strategies to improve donor safety and result in a more personalized approach to higher risk groups. In this chapter, I will review the most common physical and psychological reactions to the donation process and concentrate on groups of donors that are at increased risk of adverse reactions. I will also discuss procedures that are already in place to ensure donor safety and outline the aims of my thesis.

1.2 Physical adverse reactions

Almost all BM donors will experience some mild to moderate common side effects such as pain, nausea, vomiting, throat pain and headache (table 1.1) (Karlsson et al., 2004, Pulsipher et al., 2013, Favre et al., 2003, Miller et al., 2008, Gandini et al., 2001, Nishimori et al., 2002, Stroncek et al., 1993). Although rare, BM donation can also be associated with several potentially more serious risks. Bone and soft tissue trauma at the harvest site may cause pain, bleeding or nerve damage. Damage to a nerve root or penetration into the pelvic cavity may cause severe morbidity. Anaesthesia carries an unavoidable risk of life-threatening cardiac or respiratory events, as well as the possibility of reactions to anaesthetic agents. Removal of large volumes of blood may cause symptoms of hypovolemia or anaemia. In many centres, autologous red cell units are collected prior to the harvest and re-infused after the harvest, in order to prevent post-operative anaemia and associated tiredness. Others see no need to collect autologous units arguing that red cell donation renders donors anaemic on the day of surgery, making transfusion – autologous or even allogeneic – more likely. Transfusion is associated with limited, but potentially fatal risks including immune-related transfusion reactions. These reactions most often occur because of errors made in matching the recipient's blood to the blood transfused. In addition, red cell donations often expire due to postponement of the donation.

Almost all PBSC donors will experience mild to moderate short-term side effects of G-CSF. They include bone pain, headache, nausea, vomiting and fatigue (table 1.1) (Karlsson et al., 2004, de la Rubia et al., 2008, Pulsipher et al., 2013, Pulsipher et al., 2009b, Murata et al., 1999, Chen et al., 2011, Miller et al., 2008, Holig et al., 2009, Fortanier et al., 2002, Martino et al., 2009). Haematological effects include an 8-fold increase in the absolute number of neutrophils (D'Souza et al., 2008). Other complications of PBSC donation can be related to the insertion of a catheter and the

process of apheresis. As a consequence of venepuncture, bruising, bleeding or nerve injury may occur. Apheresis might cause symptomatic hypovolemia and hypocalcaemia is common as a result of the use of citrate anticoagulation in the circuit. A reduction in platelet count is an inevitable consequence of PBSC donation. This is due to platelet depletion by the leukapheresis procedure itself (Majolino et al., 1997, Rhodes and Anderlini, 2008), as well as a temporary suppression of megakaryopoiesis by G-CSF and a significant increase in spleen size (Stroncek et al., 2003). The platelet count rarely drops to a level where the bleeding risk is significantly increased (Stroncek et al., 1999, Murata et al., 1999). Murata et al reported a decrease in platelet count of approximately 33% after one apheresis. Rarer side effects of PBSC donation may be associated with the G-CSF-induced rapid expansion of the myeloid pool and PBSC donation has been associated with the exacerbation of gouty arthritis and with an increase in spleen size. This effect is transient, but at least 3 separate case reports of spontaneous splenic rupture after G-CSF administration in healthy donors have been reported (D'Souza et al., 2008). Other rare events related to G-CSF include flare-ups of autoimmune activity and cardiovascular complications secondary to a transient prothrombotic state.

Table 1. 1 Common side effects of BM and PBSC donation

(Karlsson et al., 2004, de la Rubia et al., 2008, Pulsipher et al., 2013, Pulsipher et al., 2009b, Murata et al., 1999, Chen et al., 2011, Miller et al., 2008, Holig et al., 2009, Fortanier et al., 2002, Martino et al., 2009, Gandini et al., 2001, Nishimori et al., 2002, Favre et al., 2003, Stroncek et al., 1993)

Adverse Reaction	BM donation	PBSC donation
Bone pain	23%-87%	61%-97%
Fatigue	38%-88%	33%-77%
Headache	15%-18%	27%-74%

Joint pain	Rare	40%
Insomnia	10%-15%	1%-48%
Myalgia	22%-25%	29%-90%
Anorexia	8%-10%	11%-22%
Nausea	6%-26%	11%-26%
Throat pain	30%-33%	Not applicable
Harvest site reactions	11%-15%	Not applicable

Several prospective studies describing common toxicities in BM and PBSC unrelated donors (URDs) have been published recently (Pulsipher et al., 2013, Pulsipher et al., 2009b, Miller et al., 2008, Gandini et al., 2001, Holig et al., 2009, Kennedy et al., 2003, Nishimori et al., 2002), some comparing BM and PBSC donation (Pulsipher et al., 2013, Miller et al., 2008, Kennedy et al., 2003). The earlier studies only reported descriptions of general toxicity, and serious adverse reactions were ill defined. A uniform grading system for common toxicities was not used, making it difficult to compare toxicity outcomes with other studies. The NMDP was the first register to add Common Toxicity Criteria Adverse Event (CTCAE) toxicity grading to donor reporting requirements in 2004. These recent studies show that the discomfort following PBSC donation usually starts within 24-48 hours of administration of G-CSF but resolves fairly quickly after collection, with just over 10% of donors reporting discomfort at 1 week post collection (Pulsipher et al., 2013). For BM donors, pain had resolved for 80% at 1 month after donation (Miller et al., 2008) and complete recovery was reported in 67% of donors at 1 month (Pulsipher et al., 2013). Most BM donors experience substantial pain and physical limitations, but general health scores remain high (Nishimori et al., 2002). Although the peak symptom burden of PBSC donors does not differ from those reported by BM donors, the temporal patterns are different with some studies showing that discomfort peaks on day +5 of G-CSF for PBSC donors compared to 48 hours after collection for BM donors (Pulsipher et al., 2013,

Rowley et al., 2001). The latter tend to experience a delayed recovery compared to PBSC donors (Pulsipher et al., 2013, Favre et al., 2003, Heldal et al., 2002, Bredeson et al., 2004, Siddiq et al., 2009).

1.2.1 Serious adverse reactions (SARs)

Prospective studies have reported an incidence of serious adverse reactions (SARs) ranging from 0.6-1.1% in PBSC and from 1.34% to 2.38% in BM donors (Pulsipher et al., 2014, de la Rubia et al., 2008, Pulsipher et al., 2009b, Miller et al., 2008, Holig et al., 2009). The definition of SARs has not been well defined in all studies, which makes the incidence challenging to compare. Most SARs have been reported as case reports or by retrospective studies, hence causality can usually not be determined (Halter et al., 2013). Some of these SARs, such as thrombotic and cardiovascular events or splenic rupture may be explained by the biological effects of G-CSF (Halter et al., 2013, Halter et al., 2009, Anderlini and Champlin, 2008, D'Souza et al., 2008, Pamphilon et al., 2008, McCullough et al., 2008) or are associated with the collection procedure used (harvest site pain with subsequent disability, anaesthesia or central venous catheter related) (Halter et al., 2013, Favre et al., 2003, Halter et al., 2009, Kennedy et al., 2003, Pulsipher, 2012, Pulsipher et al., 2014). Two cases of heparin-induced thrombocytopenia associated thrombo-embolic disease (Halter et al., 2009) due to the systemic use of heparin as an anti-coagulant have been described. This practice is now not longer recommended. Fat embolism syndrome following bone marrow harvesting has also been reported (Baselga et al., 1991). A large study from the European Group for Blood and Marrow Transplantation (EBMT), reported 7.25 serious adverse reactions (SARs) per 10 000 and significantly less in BM than PBSC donors (Halter et al., 2009). This is however a questionnaire based retrospective study and has very low overall rates of serious adverse reactions so might represent

underreporting. The same author reported that the incidence of donor fatalities was 0.98 per 10 000 donors, all in related donors, four after PBSC and one after BM donation (Halter et al., 2009). The cases reported included cardiac arrest and pulmonary embolus. In most of these donors, pre-existing medical conditions were identified post-mortem, highlighting the need for strict medical eligibility criteria and assessment of donors. Death in unrelated donors (URDs) is exceedingly rare with only one death reported to the WMDA between 2003 and 2012 (Shaw et al., 2013). This was caused by an extensive haemothorax secondary to traumatic jugular vein catheter insertion. Second donations of stem cells are not associated with an increased risk of donor adverse reactions, however the need for informed consent is clear (Confer et al., 2011). Table 1.2 provides an overview of studies that have evaluated short term physical outcomes in URDs and related donors (RDs).

Table 1. 2 Overview of studies assessing adverse reactions (ARs) and serious adverse reactions (SARs) in BM and PBSC donors

Study	Method (n)	URD/RD	ARs	SARs
Chang (Chang et al., 1998)	BM (77)	URD vs RD	More acute physical pain in related donors	Not specified
Murata (Murata et al., 1999)	PBSC (94)	URD	67% reported bone pain, 31% reported fatigue	1 donor reported grade 3 bone pain with need for opioids
Anderlini (Anderlini et al., 2001)	PBSC (1488)	RD	No end point	15 events (1.1%), one third was catheter related
Gandini (Gandini et al., 2001)	BM (103)	URD	77% reported pain, 40% reported fatigue	No acute life threatening events

Rowley (Rowley et al., 2001)	PBSC (31) vs BM (38)	RD	Similar symptom burden in PBSC and BM donors, but PBSC donors recover faster than BM donors	BM: 2 (DVT, autologous transfusion), PBSC: 1 (haematoma)
Fortanier (Fortanier et al., 2002)	PBSC (33) vs BM (31)	RD	61% suffered with bone pain or headache during G-CSF administration Highest pain scores similar for PBSC and BM, timing of highest pain is different	Not specified
Heldal (Heldal et al., 2002)	PBSC (30) vs BM (31)	RD	AR in 60% PBSC, 93% of BM donors Symptom burden in PBSC donors lower than in BM donors	Not specified
Nishimori (Nishimori et al., 2002)	BM (565)	URD	112/565 donors reported donation site pain all of the time Donors experience considerable pain and physical limitations 1 week following donation Quality of life is back to baseline at 3 months	Not specified
Favre (Favre et al., 2003)	PBSC (163) versus BM (166)	RD	AR in 65% PBSC, 57% of BM donors PBSC less of a burden than BM donation in terms of duration of hospitalization and recovery time	PBSC: 7%, BM: 1%
Kennedy (Kennedy	BM (30) vs PBSC (29)	RD	20/25 bone marrow donors experienced harvest site pain	No SAR reported

et al., 2003)	(both G-CSF stimulated)		Similar AR in both groups apart from more back pain in BM group, similar recovery times	
Bredeson (Bredeson et al., 2004)	PBSC (91) vs BM (93)	RD	BM donors experienced worse fatigue and lack of energy 1 week after donation compared to PBSC donors	Not specified
Karlsson (Karlsson et al., 2004)	PBSC (116) vs BM (55)	RD	Moderate or severe pain in 68% of PBSC, 85% in BM donors Duration of pain longer in BM donors, more significant fatigue in BM donors	BM: 2, PBSC: 3
De la Rubia (de la Rubia et al., 2008)	PBSC (1278)	RD	AR in 68% Clinical side effects of PBSC donation are generally mild	<1 %
Miller (Miller et al., 2008)	BM (2505) vs PBSC (4476)	URD	89% of PBSC donors reported pain (bone pain at various sites) and 82% of BM donors reported pain (back or hip) 59% of BM donors reported fatigue versus 70% of PBSC donors PBSC donors reported faster recovery from their donation than BM donors	SAR occurred more frequently in BM donors (1.34% versus 0.6% for PBSC) and a few led to long-term complications not reported by PSBC
Halter (Halter et al., 2009)	BM (24 099) vs PBSC (15 111)	URD/RD	No end point	Death: 0.98 per 10 000 transplants, all in related donors (5 cases: medical error, pulmonary

				embolus, subarachnoid haemorrhage, cardiac arrest) SAR: 7.25 per 10 000, significantly fewer in BM than PBSC
Holig (Holig et al., 2009)	PBSC (3928)	URD	AR (bone pain) in 93.5%	Less or equal than 1.1% of donor population during follow-up period of 5 years
Leitner (Leitner et al., 2009)	PBSC (171)	RD	70/95 donors experienced G-CSF related side effects	Not specified
Martino (Martino et al., 2009)	PBSC (184)	RD	71% reported bone pain	No SAR reported
Pulsipher (Pulsipher et al., 2009a)	PBSC (2408)	URD	80% experienced bone pain, other common AR were myalgia and headache	6% experienced grade III-IV CALGB toxicities and 0.6% experienced toxicities that were considered serious and unexpected
Siddiq (Siddiq et al., 2009) (Cochrane review)	BM (264) vs PBSC (254)	RD	PBSC donors experienced more pain prior to donation (G-CSF related) BM donors experienced more overall adverse events and more days of restricted activity	More SARS in BM donors compared to PBSC donors (Haemorrhage, anaemia, hypotension)
Yuan (Yuan et al., 2010)	PBSC (15763)	URD	No end point	0.37% 19 pre-syncope/syncope (PS), 4 citrate reaction

				(CR), 17 PS + CR, 12 vascular injuries
Chen (Chen et al., 2011)	PBSC (516)	URD	Most common AR was bone pain in 64.9%	2 donors discontinued GCSF (severe hypertension, anaphylaxis)
Kodera (Kodera et al., 2013)	PBSC (3264)	RD	Not defined	1.44%, some SARs were potentially life-threatening (subarachnoid haematoma, interstitial pneumonitis)
Pulsipher (Pulsipher et al., 2013)	BM (2726) vs PBSC (6768)	URD	60-70% of AR in BM and PBSC donors, peak of AR on D2 (BM) versus D5 GCSF (PBSC) Similar AR for BM and PBSC donors in peri-collection period. At later evaluations, BM donors more likely to report persistent pain and have delayed recovery	3% of female PBSC donors needed hospitalisation and 1% of male PBSC donors No full recovery in 3% of BM donors at 6 months compared to 0% in PBSC donors
Wiersum-Osselton (Wiersum-Osselton et al., 2013)	PBSC (268)	RD	Few short-term problems in both eligible and deferrable (donors who would be deferred for unrelated donation) related donors	2%
Pulsipher (Pulsipher et al., 2014)	PBSC (6768) and BM (2726)	URD	No end point	2.38% in BM vs. 0.56% in PBSC donors ($p < 0.001$)

1.2.2 Long term safety debate regarding G-CSF

A dilemma facing the medical community is whether the use of G-CSF is related to an increased risk of developing malignancies, especially haematological diseases (Hasenclever and Sextro, 1996, Confer and Miller, 2007, Kaplinsky et al., 2007, Anderlini and Champlin, 2008, Avalos et al., 2011). An early study by Nagler and colleagues suggested that epigenetic changes characteristic of malignancy were present in the lymphocytes of related donors previously administered G-CSF (Nagler et al., 2004). However, Hirsch and colleagues could not find evidence of G-CSF induced chromosomal instability (Hirsch et al., 2011) and this is supported by a recent UK study (Nacheva E. personal communication). No epidemiological studies in related or unrelated donors to date suggest an increased risk of haematological malignancy following PBSC donation (Holig et al., 2009, Makita et al., 2004, de la Rubia et al., 2008, Confer and Miller, 2007, Cavallaro et al., 2000), but vigilance in monitoring post donation should remain the rule.

1.2.3 Related donors

Literature on the topic of related (RD) donor safety has been scarce (Karlsson et al., 2004, Rowley et al., 2001, Heldal et al., 2002, Favre et al., 2003, Leitner et al., 2009, de la Rubia et al., 2008, Wiersum-Osselton et al., 2013, Bredeson et al., 2004, Fortanier et al., 2002, Kennedy et al., 2003, Martino et al., 2009, Anderlini et al., 2001, Kodera et al., 2013) and adverse reactions are not as well categorised in terms of frequency and severity compared to URDs. Current research suggests that the risks associated with donation seem to be higher for RDs compared to URDs with the caveat of the lack of an adequate amount of prospective follow-up data in the related donor setting (Halter et al., 2009). This increased risk has several explanations. Transplant centres may use less stringent criteria to determine donor eligibility in RDs

(Wiersum-Osselton et al., 2013). The percentage of RDs who have a contagious disease, who are pregnant or who have other medical conditions that would be considered contraindications in URDs is unknown. Moreover, the same transplant centre and occasionally the same physician caring for the recipient may evaluate the RD (O'Donnell et al., 2010). This could represent potential conflict of interest in favour of the recipient. To the benefit of the donor, an independent physician for donor clearance and counselling ought to be provided (O'Donnell et al., 2010, Shaw, 2010, van Walraven et al., 2010). Special attention to the clinical, psychological and social needs should be paid to children who are being evaluated as potential donors. Often parents are expected to consent for their children, which may create additional conflict of interest circumstances (Horowitz and Confer, 2005, O'Donnell et al., 2010). In Europe, any potential donation of bone marrow or PBSC from adults or children who lack competence to consent, must be assessed by an Accredited Assessor (Human Tissue Authority, 2007). As opposed to URDs, RDs are not self-nominated, have personal motivations and are likely to be willing to take more risks and underreport conditions that could impact adverse reactions. Additionally, as data show better survival after transplantation when a younger donor is used, this has led to clinicians choosing the youngest available URD. This differs with RDs who often match the age of their recipients. These donor groups have specific problems (increased end organ dysfunction and cancer in older donors and size issues in paediatric donors). Studies comparing RD and URD outcomes are limited (Chang et al., 1998). This study reported that related marrow donors experience more acute physical pain, possibly resulting from higher stress levels being manifested by an increased vulnerability to pain. The NMDP is currently running a study comparing RD and URD outcomes (Pulsipher et al., 2010).

1.3 Donors at increased risk of adverse reactions

There are a limited number of studies examining which donors are at increased risk of experiencing adverse reactions. The findings of these studies are important as they could lead to a more personalised approach to higher risk groups. Table 1.3 lists donor and treatment related characteristics that have been found to influence the donation experience.

Apart from headache and moderate to severe pain (Pulsipher et al., 2013, Murata et al., 1999), younger donors do not appear to be at increased risk of experiencing complications during PBSC donation (Pulsipher et al., 2013, Chen et al., 2011, Yuan et al., 2010, Stroncek et al., 1996). Moreover, they have not been found to experience more pre-syncopal and syncopal events as demonstrated in whole blood donors (Yuan et al., 2010, Eder et al., 2008, Wiltbank et al., 2008). On the other hand, older PBSC donors were more likely to experience citrate toxicity and persistent toxicities at 1 week (Yuan et al., 2010, Pulsipher et al., 2013), reflecting a slower recovery period compared to younger donors. The latter has also been described in older BM donors (Pulsipher et al., 2013). However, the day of donation is generally tolerated better in older donors (Pulsipher et al., 2013, Switzer et al., 1996). This may be a result of older donors being more experienced with medical procedures in general (Switzer et al., 1996).

Multiple studies have shown that female gender is associated with a higher risk of apheresis related adverse reactions compared to men, ((Martino et al., 2009), Pulsipher et al., 2013, Pulsipher et al., 2009b, Murata et al., 1999, Chen et al., 2011, Stroncek et al., 1996). Women experience more fatigue, pain, nausea, vomiting and side effects of hypocalcaemia. Female gender is also associated with more pain,

fatigue and toxicities following BM donation (Gandini et al., 2001, Switzer et al., 1996, Yuan et al., 2010, (Horowitz and Confer, 2005). Women are also more likely to experience SARs (Miller et al., 2008, Yuan et al., 2010) and are twice as likely to require extended hospitalization (Pulsipher et al., 2013, Pulsipher et al., 2009b).

There is some evidence that donors who are overweight or obese tend to experience more pain during PBSC donation (Pulsipher et al., 2009b, Pulsipher et al., 2013, Chen et al., 2011). This could partially be explained by the relatively higher doses of G-CSF received in this group. Several studies have illustrated that many G-CSF side effects are dose dependent and more common at higher doses (Kroger et al., 2002, Murata et al., 1999, Chen et al., 2011, Engelhardt et al., 1999). Likewise, the life-threatening side effect of splenic rupture has mostly been reported when doses higher than 10 mcg/kg/day were given (Nuamah et al., 2006, Balaguer et al., 2004). There have been no studies examining the influence of weight on adverse reactions in BM donors and most collection centres already have strict body mass index (BMI) restrictions for BM donors due to procedural difficulties in donors with higher BMIs.

There are limited studies that compare general versus regional anaesthesia for BM harvesting (Miller et al., 2008, Machaczka et al., 2010, Lavi et al., 1993, Knudsen et al., 1995, Burmeister et al., 1998). Most studies found no difference in the numbers of adverse events. This strongly implies that the choice of anaesthesia should depend on the anaesthetist's or donor's preference (Machaczka et al., 2010). Blood donors had more physical difficulty with BM donation, and their previous experience with blood donation may have led them to underestimate the physical impact of bone marrow donation (Switzer et al., 1996). Being a blood donor is also correlated with higher number of days off work, this may be secondary to lower baseline haemoglobin

levels in those donors (Gandini et al., 2001). Jobs involving mild to moderate daily work activities have been associated with fewer days off work following BM donation compared to jobs involving more heavy duties (Gandini et al., 2001). An increased length of the BM harvest procedure has also been consistently associated with increased post-donation physical limitations and adverse reactions (Miller et al., 2008, Nishimori et al., 2002).

Table 1. 3 Factors influencing donor adverse reactions (in PBSC donation, BM donation or both)

Factor	Outcome	PBSC or BM donation
Age	• Older donors at less risk of pain in the peri-collection period, but more likely to experience persistent pain, fatigue and other toxicities at 1 week following donation (Pulsipher et al., 2013)	• PBSC and BM
	• Older donors at risk of more serious complications (Miller et al., 2008)	• PBSC and BM
	• Higher incidence of headache in donors aged under 35 (Murata et al., 1999)	• PBSC
	• Older donors more likely to experience citrate related toxicity (Yuan et al., 2010)	• PBSC
	• No influence on ARs (Chen et al., 2011, Stroncek et al., 1996)	• PBSC
	• Older donors reported somewhat less difficulty with donation (Switzer et al., 1996)	• BM
Female gender	• More likely to require extended hospitalization following donation (Pulsipher et al., 2013)	• PBSC and BM

	• Greater physical difficulty with donation (Pulsipher et al., 2013, Switzer et al., 1996, Nishimori et al., 2002, Horowitz and Confer, 2005)	• PBSC and BM
	• Associated with more serious complications (Yuan et al., 2010, Miller et al., 2008)	• PBSC and BM
	• Higher incidence of most apheresis related adverse reactions (Pulsipher et al., 2009b, Pulsipher et al., 2013, Chen et al., 2011, Stroncek et al., 1996) (Murata et al., 1999, Martino et al., 2009, Stroncek et al., 1996)	• PBSC
	• More likely to require a line (Pulsipher et al., 2009b)	• PBSC
	• More fatigue following donation (likely due to higher relative blood volume depletion) (Gandini et al., 2001)	• BM
	• Longer period of convalescence (Gandini et al., 2001)	• BM
	• Less likely to experience complete recovery (Pulsipher et al., 2013)	• BM
Weight	• Higher BMI (>25) associated with more G-CSF side effects (fatigue, myalgia, sweats) (Chen et al., 2011)	• PBSC
	• Obese donors experienced more pain and toxicity (Pulsipher et al., 2013, Pulsipher et al., 2009b)	• PBSC
Donors with smaller total blood volumes	• Higher incidence of adverse reactions (Yuan et al., 2010)	• PBSC

Lower net fluid balance	• Associated with pre-syncopal complications (Yuan et al., 2010)	• PBSC
Higher G-CSF doses	• Doses of 16 mcg/kg associated with higher toxicity compared to 10 mcg/kg (Kroger et al., 2002) • Associated with more toxicity (Chen et al., 2011, Engelhardt et al., 1999) • Doses > 9 mcg/kg associated with higher incidence of headache and fatigue (Murata et al., 1999, Martino et al., 2009)	• PBSC
Regional vs general anaesthesia	• No difference found (Machaczka et al., 2010, Lavi et al., 1993, Knudsen et al., 1995, Burmeister et al., 1998) • Regional anaesthesia associated with serious complications (Miller et al., 2008)	• BM
Longer duration of harvest	• Associated with physical limitations (Nishimori et al., 2002) • Associated with serious complications (Miller et al., 2008)	• BM • BM
Average blood volume depletion	• Associated with higher number of days off work in female donors (Gandini et al., 2001)	• BM
Blood donors	• More physical difficulty with donating (Switzer et al., 1996) • Correlated with higher number of days off work in male donors (Gandini et al., 2001)	• BM • BM
Active vs sitting job	• Active job associated with more number of days off work (Gandini et al., 2001)	• BM

Peripheral blood White Blood Cell Count (WBC)	• Higher WBC count post the 3rd dose of G-CSF associated with fatigue (Chen et al., 2011) • High WBC (> 50 x 10^9/l) following 5 doses of G-CSF not associated with more side effects during mobilization than those with WBC < 50 x 10^9/l (Chen et al., 2011) • Baseline mononuclear cell count > 2.7 x 10^9/l associated with increased fatigue and pain peri-collection (Pulsipher et al., 2013)	• PBSC
Related vs unrelated	• More moderate to severe pain in related donors (Chang et al., 1998)	• BM

1.4 Psychological aspects of donation

Most studies have concentrated on the physical outcomes following donation and only few have evaluated the psychological impact (Simmons et al., 1993, Butterworth et al., 1993, Munzenberger et al., 1999, Christopher, 2000, Switzer et al., 2001, Fortanier et al., 2002, Williams et al., 2003, Bredeson et al., 2004, Pillay et al., 2012). The psychological reactions following donation are generally positive (Butterworth et al., 1993, Switzer et al., 2001) and most subjects feel deep personal satisfaction and gratitude for an opportunity to donate (Christopher, 2000). Common experiences include feeling like a better person as a result of donation (Butterworth et al., 1993). A large NMDP study found that donors believed to be distinct from others in the centrality of the traits of helpfulness and generosity. This belief often stemmed from a strong emphasis on helping in their families (Simmons et al., 1993). The psychological outcomes appear to be associated with physical adverse reactions experienced during the donation process, the outcome in the recipient and the psychological state of ambivalence (table 1.4). The term ambivalence involves doubts

and worries, feeling unsure about donation and wishing someone else would donate in one's place (Switzer et al., 2013).

Butterworth and colleagues assessed the psychosocial effects of BM donation in 493 URDs (Butterworth et al., 1993). The authors found that donors with longer collection times or lower back pain were more likely to have less positive psychosocial outcomes. A large Canadian randomized trial assessed mood states and health-related quality of life (HRQOL) prior to donation and 1 week and 4 weeks following donation in BM and PBSC donors (Bredeson et al., 2004). Both the mood and HRQOL scores were worse after BM donation, compared to PBSC donation. The authors commented that physical morbidity can affect mood and this is in keeping with a generally reported delayed physical recovery in BM versus PBSC donors.

One study looking into reactions of unrelated bone marrow donors when the recipient dies, found that death of the recipient produced feelings of grief and was often surprisingly intense, given the fact that the recipient was a stranger (Butterworth et al., 1992). Studies in related donors are complicated by the direct affiliation of donors with the patient. Poor outcomes can have devastating effects and "survivor's guilt" is well documented in the literature. A study in BM donors found that donors whose sibling died had significantly higher scores on the Beck Depression Inventory (BDI) compared to those whose siblings remained alive (Chang et al., 2003). The BDI is a 21-question multiple-choice self-reported inventory, one of the most widely used instruments for measuring the severity of depression

The psychological state of the donor should be assessed prior to donation, in particular the donor's motivations for considering donation. Switzer reported that a

psychological state of ambivalence was a better predictor of a negative donation experience than actual physical difficulty with donation (Switzer et al., 1996). Ambivalence was assessed using a 7-item ambivalence scale. Items asked about doubts and worries about donating (e.g. “I sometimes feel unsure about donating”) and commitment to donating (e.g. “I would really want to donate myself even if someone else could do it”). All items were dichotomised (0 [item not endorsed], 1 [item endorsed]) and an index of ambivalence was performed by summing the number of items endorsed by the respondent (0 [no items endorsed, not at all ambivalent]), to 7 [all items endorsed, extremely ambivalent) (Switzer et al., 1996). People who were less happy in general, less optimistic about the patient’s chances to survival, more educated and less likely to have been blood donors were more likely to experience pre-donation ambivalence (Switzer et al., 1996, Switzer et al., 2003, Switzer et al., 1997, Switzer et al., 2005). Donors who were driven by an intrinsic commitment to donate, rather than extrinsic pressure, were less ambivalent about donating (Switzer et al., 2003). The same author reported ethnic variation in the donation experience and found that Asian Americans were more ambivalent and more anxious than other US ethnic groups (Switzer et al., 2005).

Related donors may have different motivations from unrelated donors and may be subject to increased emotional and physical stress associated with donation (Christopher, 2000). A more positive experience has been reported if there is a better emotional support from family, friends and hospital staff (Pillay et al., 2012). Routine provision of psychosocial support to donors as well as recipients is therefore important.

Table 1. 4 Factors influencing psychological outcomes

Factor	Outcome
More physical difficulty with donation	• Associated with feeling less positive psychologically about the donation (Switzer et al., 1996) • BM donation was associated with more physical morbidity and negative effects on QOL up to 1 month after donation than was PBSC donation (BM vs PBSC) (Bredeson et al., 2004) • BM donors mood scores were worse 1 week after compared to before donation, whereas PBSC scores did not change (BM vs PBSC) (Bredeson et al., 2004) • More likely to experience donation as stressful (Butterworth et al., 1993, Christopher, 2000)
Longer collection times/large volumes collected	• Less positive psychological outcomes (Butterworth et al., 1993) • Less willing to donate again in future (Butterworth et al., 1993)
Death of the recipient/ worse outcome in recipient	Unrelated donors: • Grief was often surprisingly intense, given the fact that the recipient was a stranger, feelings of guilt were rare (Butterworth et al., 1992) • Donors demonstrated a range of feelings such as sadness, disappointment, grief, and helplessness. These feelings were often unexpectedly intense given the fact that the recipient was a stranger (Wanner et al., 2009) Related donors: • Associated with a more stressful experience (Christopher, 2000) • Recipient deterioration may significantly adversely impact donor psychosocial status (Wolcott et al., 1986)

	• Significantly higher Beck depression scores 6 months following donation (Chang et al., 2003) • Donors felt less as if their donation had really helped their sibling as time passed. However, bereaved donors experienced global psychological gains including enhanced self-esteem, happiness and life-satisfaction compared to donors whose siblings were still living (Switzer et al., 1998)
Ambivalence	• Greater ambivalence associated with more physical and psychological difficulties with donation (Switzer et al., 1996) • Factors associated with higher ambivalence: higher education, donors who were discouraged by others (Switzer et al., 1996), exchange motives (weighing costs and benefits), idealized helping motives (Switzer et al., 1997), extrinsic pressure (Switzer et al., 2003), some ethnicities (Asian Americans) (Switzer et al., 2005) • Factors associated with lower ambivalence: more frequent blood donors, happier individuals, those who believed the patient's chances of survival were better (Switzer et al., 1996), empathy motives (Switzer et al., 1997), intrinsic commitment (Switzer et al., 2003)
Related vs unrelated	• Depression scores significantly higher in related donors, pre and post donation (Chang et al., 1998)
Family dynamics and emotional support	• More positive experience if better emotional support from family, friends and hospital staff (Pillay et al., 2012, Christopher, 2000) • Married donors had fewer negative psychological reactions shortly following donation (Switzer et al., 1996)
Preparation for donation	• Adequacy of preparation for donation influences experience (Pillay et al., 2012)

1.5 Procedures to ensure donor safety

Unrelated donor safety is guided through published World Marrow Donor Association (WMDA) standards covering donor recruitment, consent, medical assessment, donor follow-up and a global combined effort in adverse event reporting (Petersdorf, 2010, Shaw et al., 2010). No equivalent standards currently exist for related donor care. Although less prescriptive than the WMDA standards, guidelines developed by accreditation systems - the Foundation for Accreditation of Cell Therapy (FACT) in the USA and the Joint Accreditation Committee of ISCT (Europe) and the EBMT (JACIE), termed the FACT-JACIE Standards (FACT-JACIE, 2008) - also contain some requirements for the selection, evaluation and management of donors and the reporting of adverse events. Other legally-binding requirements are those of the National Competent Authorities in Europe who are required to implement the EU Directive on Tissues and Cells via specific regulations (Human Tissue Authority, 2007) and those of the US Food and Drug Administration (FDA) (US Food and Drug FDA, 2013, US Food and Drug FDA, 2010).

Several procedures aimed at optimising donor safety are summarised in table 1.5.

There are three stages in the typical pathway of an unrelated HSC donor from joining a registry to donation, namely: recruitment, confirmatory typing (CT) stage and work-up stage. The intensity of the assessment differs at each stage in the process, and there may be conditions that necessitate deferral at certain stages in the process but not in others (Lown et al., 2014). There are two main reasons for thorough medical assessments, namely recipient safety and donor safety. Donation of HSC is an act of altruism and donors must be protected from harm as much as possible. Medical criteria for conditions that may increase donor risk are necessarily stringent, and more so than would be the case if the individual were undergoing a procedure for

therapeutic benefit. Assessing the risk for both donors and recipients requires a targeted screening history, a search for physical signs of disease and laboratory testing for specific pathogens or traits.

There are numerous infectious agents that, if present in the donor, pose a definite or theoretical risk to the transplant recipient. HSCT can transmit the same infectious agents transmissible by blood transfusion (including hepatitis B and C virus and human immunodeficiency virus). Additionally, some congenital or acquired conditions, such as genetic defects, immune deficiencies or cancers, are potentially transmissible to the recipient.

Screening questionnaires at recruitment and CT stage typically pick up permanent conditions that warrant deferral for donor reasons (for example insulin dependent diabetes mellitus or cardiac disease). The medical consultation during donor work-up is more detailed and focuses on all matters relevant for the anticipated donation, including psychological issues. For all donors, this includes a review of known health problems, allergies, and family history. Marrow donors should be questioned about prior anaesthesia and have a careful review of systems directed toward neurological, respiratory, cardiovascular and musculoskeletal problems. Peripheral blood donors should be questioned about prior whole blood or apheresis donations as well as specific questions about a history of venous access problems, autoimmune diseases, splenic disorders and haemoglobinopathies. The donor's physical examination should focus upon the neurological, respiratory and cardiovascular systems (Horowitz and Confer, 2005). In general, donors with moderate or severe organ impairment are deferred and this usually includes those with coronary artery disease, renal, pulmonary or hepatic impairment (Lown and Shaw, 2012). Many other medical

conditions may prevent donation for the sake of donor safety. For example, donors with pre-existing back pain tend to be excluded from BM donation as there is a potential causal link between bone marrow harvest and back injury.

Table 1. 5 Current procedures to optimise donor safety

Time point	Procedure in place
Recruitment and Confirmatory Typing (unrelated donors)	Medical screening and exclusion of donors who have medical conditions that would increase their risk ➢ Questionnaire based
Medical consultation	Formal medical assessment and exclusion of donors who have medical conditions that would increase their risk ➢ History: addresses risks both to the donor and the recipient, including psychological issues ➢ Clinical examination ➢ ECG ➢ Often urine dip, chest X-ray Informed consent
Donation	Up-to-date harvest centre facilities Experienced harvest physicians
Post-donation	Reporting of serious adverse events through the WMDA (only for unrelated donors) Donor follow-up

Potential donors must receive a full description of the procedure and its risks at the time of their medical assessment. Donors should be educated about common as well as rare, but potentially life-threatening complications (for example splenic rupture in PBSC donors). Emergency contact details ought to be provided. It is recommended

that donors are counselled about the possibility of subsequent donations of stem cells or lymphocytes before their first donation (Confer et al., 2011).

The Worldwide Network for Blood and Marrow Transplantation (WBMT) and WMDA recommend that unrelated donor registries should follow-up donors in the short term and for at least 10 years after donation (Halter et al., 2013). The reporting of serious events and adverse reactions (SEARs) is mandatory for all WMDA-accredited registries, representing the vast majority of unrelated adult donations worldwide. Anonymised summary reports of SEARs are published and distributed on an annual basis.

1.6 Stem cell yields

Several days of apheresis are frequently required for PBSC donors to ensure a sufficient collection of CD34+ cells and around 20% of donors need a second day of apheresis (Holig et al., 2009). A further reduction in platelet counts and increased psychological stress are potential risks associated with additional days of apheresis (Stroncek et al., 1999). In order to reduce the discomfort and possible additional risks to the donor, the WMDA recommends that registries have policies in place concerning the total number of days of apheresis allowed (WMDA, 2010) and a recent survey showed that most registries allow a total of 2 days of apheresis (WMDA, 2009). If insufficient HSCs are harvested during the days of apheresis, a group defined as “poor mobilisers”, bone marrow harvesting is performed as a salvage procedure. There are well described additional risks associated with this procedure.

It is therefore of clinical importance to characterize donors who are at risk of not meeting the HSC dose requested by the transplant centres, as this group may benefit from an alternative mobilisation regimen in order to avoid additional days of apheresis or bone marrow harvesting. In addition, this knowledge may allow registries to focus on the recruitment of donors who are more likely to mobilise sufficient CD34+ cells. The advantages of such a strategy are clear both for the donors and the recipients. Because patients have already received therapy by the time donor cells are collected in most centres, the lack of availability of adequate stem cells is a significant and potentially life threatening problem.

Previous studies have reported that several donor characteristics influence PBSC mobilisation. Table 1.6 lists all the factors that have been previously found to affect the PBSC yield in allogeneic donors. Table 1.7 lists all the factors that have shown to affect the BM yield.

Table 1. 6 Factors influencing CD34+ yield in PBSC donors

Factor	Associations	References
Female gender	Lower CD34+ yield	(Ings et al., 2006, Miflin et al., 1996, Martino et al., 2006, Wang et al., 2008, Platzbecker et al., 2005, Engelhardt et al., 1999, Fischer et al., 2005)
	No influence on CD34+ yield	(Suzuya et al., 2005, Sohn et al., 2003, Anderlini et al., 1997, Lysak et al., 2005)
	Lower pre-apheresis CD34+ count peripheral blood	(Vasu et al., 2008)

BMI	Higher BMI associated with higher CD34+ yield	(Favre et al., 2003, Wang et al., 2008, Chen et al., 2014)
	No influence on CD34+ yield	(Platzbecker et al., 2005)
Weight	Higher weight associated with higher CD34+ yield	(Ings et al., 2006, Favre et al., 2003)
	No influence on CD34+ yield	(Sohn et al., 2003, Shimizu et al., 2002)
	Higher weight associated with higher pre-apheresis CD34+ count peripheral blood	(Vasu et al., 2008)
Age	Higher age associated with lower CD 34+ yield	(Anderlini et al., 1997, Shimizu et al., 2002, Martino et al., 2006, Wang et al., 2008, de la Rubia et al., 2008, Lysak et al., 2005, Diaz et al., 2003, Suzuya et al., 2005, de la Rubia et al., 2002, de La Rubia et al., 2001, Engelhardt et al., 1999, Anderlini et al., 1999)
	No influence on CD34+ yield	(Miflin et al., 1996, Arbona et al., 1998, Sohn et al., 2003, Platzbecker et al., 2005)
	Higher age associated with lower pre-apheresis CD34+ count peripheral blood	(Suzuya et al., 2005, Ings et al., 2006, Vasu et al., 2008)
Ethnicity	Pre-harvest CD34+ count peripheral blood count highest in Asian/Pacific donors, followed by blacks, Hispanics and then whites	(Vasu et al., 2008)

Once vs twice daily filgrastim	Twice daily dosing associated with higher CD34+ yield	(de la Rubia et al., 2002, Kroger et al., 2000, Arbona et al., 1998)
	No influence on CD34+ yield	(Anderlini et al., 2000)
Type of G-CSF	Higher CD34+ yield with lenograstim compared to filgrastim, but only in males	(Fischer et al., 2005)
	No influence on CD34+ yield	(Suzuya et al., 2005, Ings et al., 2006, Martino et al., 2006)
Total amount of G-CSF given	Higher total amount associated with higher CD34+ yield	(Anderlini et al., 1997, Engelhardt et al., 1999, Martinez et al., 1999)
	Higher total amount associated with higher pre-harvest CD34+ counts peripheral blood	(Tanaka et al., 1996, Grigg et al., 1995, Vasu et al., 2008)
CD34+ count in preapheresis blood	Higher count associated with higher CD34+ yield	(Suzuya et al., 2005, Okano et al., 2008, Sohn et al., 2003, Platzbecker et al., 2005, Moncada et al., 2003, Arbona et al., 1998)
CD34+ yield mid-point harvest	Higher mid-point yield associated with higher final CD34+ yield	(Ings et al., 2006)
Serum level of G-CSF	No influence	(Suzuya et al., 2005)
Preapheresis platelet count	Higher platelet count associated with higher CD34+ yield	(Suzuya et al., 2005, Lysak et al., 2005)
Baseline platelet count	Higher platelet count associated with higher pre-	(Vasu et al., 2008)

	apheresis CD34+ count peripheral blood and CD34+ yield	
Preapheresis WBC count	Higher WBC count associated with higher CD34+ yield	(Sohn et al., 2003, Wang et al., 2008, Martino et al., 2006)
	No influence on CD34+ yield	(Anderlini et al., 1997, Shimizu et al., 2002)
Baseline WBC count	No influence on CD34+ yield	(Anderlini et al., 1997)
Preapheresis MNC count	Higher MNC count associated with higher CD34+ yield	(Moncada et al., 2003)
	No influence on CD34+ yield	(Anderlini et al., 1997)
Baseline MNC count	Higher MNC count associated with higher CD34+ yield	(Lysak et al., 2005)
	No influence on CD34+ yield	(Anderlini et al., 1997)
	Higher MNC count associated with higher pre-apheresis CD34+ count peripheral blood	(Vasu et al., 2008)
Pre-apheresis circulating immature cell count	Higher count associated with higher CD34+ yield	(Wang et al., 2008, Kozuka et al., 2004, Yang et al., 2010)
Type of cell separator	No influence on CD34+ yield	(Suzuya et al., 2005)
Type of access	Arterial access (as opposed to venous access) associated with higher CD34+ yield	(Wang et al., 2008)
	No influence on CD34+ yield	(Suzuya et al., 2005, Holig et al., 2012)

Large volume leukapheresis	Associated with higher CD34+ yield	(Diaz et al., 2003)

Table 1. 7 Factors influencing harvest yields in BM donors

Factor	Associations	References
BMI	Higher BMI associated with higher CD34+ yield	(Favre et al., 2003)
Weight	Higher weight associated with higher CD34+ yield	(Favre et al., 2003)
	Higher weight associated with higher TNC/ml	(Kao et al., 2009, Wang et al., 2011)
Gender	No influence on CD34+ yield	(Favre et al., 2003)
	No influence on TNC/kg	(Gandini et al., 2001)
Age	No influence on CD34+ yield	(Favre et al., 2003)
Baseline WBC count	Higher WBC count associated with higher TNC/ml	(Kao et al., 2009, Wang et al., 2011)
Volume harvested	Negatively associated with TNC/ml	(Kao et al., 2009, Wang et al., 2011)
Collection procedure	Small volume aspirations and multiple puncture sites associated with higher TNC/kg and minimal contamination by peripheral blood	(Spitzer et al., 1994, Bacigalupo et al., 1992, Batinic et al., 1990)
Aspiration needle with multiple holes	No influence on CD34+ yield, but 50% reduction in operating time	(Lannert et al., 2008)
	Associated with higher TNC/ml	(Wang et al., 2011)
Checking midway TNC count	Associated with higher TNC/ml	(Wang et al., 2011)

Raising room temperature during procedure	No influence on cell yield, but associated with reduction in BM harvest time	(Zeller et al., 1995)
G-CSF stimulated	Associated with increased TNC/kg donor weight	(Ji et al., 2002)
	Not associated with increased TNC or CD34+ count, but associated with more rapid engraftment	(Isola et al., 1997)

1.7 Conclusion and aims of this thesis

Voluntary donation of BM or PBSC for haematopoietic cell transplantation is a well-established altruistic act, performed by thousands of healthy related or unrelated donors throughout the world. Although allogeneic stem cell donation is a safe procedure with very low rates of serious adverse reactions, there are some potential risks and every effort should be made to minimalize this. This introduction provides an overview of adverse and serious adverse reactions following PBSC and BM donation. In addition to the known procedural risks and associated symptoms, other important issues that have not received as much attention are the factors that may be implicated in delayed donor recovery and the psychosocial and longer-term post-donation physical and psychological effects of donation. Several mechanisms to ensure donor safety are already in place, but no customised donor care currently exists. Data on donors that are at increased risk of adverse reactions may allow registries to tailor donor care; this may include the alteration of joining and recruitment policies, management of expectations and the improvement of supportive measures and donor follow-up procedures.

While stem cell registers are the most valuable source of unrelated donor outcome data, only a fraction of these data are currently published. Most registers collect some level of donor outcome data but a small number have large scale follow-up programs. Further effort should be directed to standardise operational definitions on post donation physical and psychological outcomes and adverse reactions and to develop a prospective global data collection (Pamphilon et al., 2009). Recently, the EBMT developed a reporting system for both related and unrelated donor outcomes, but this is not a mandatory requirement yet and only covers EBMT centres (EBMT, 2013). Additionally, a sustained effort to develop clinical trials is required.

The primary aim of my thesis is to provide an in depth analysis of the short and long-term physical and psychological donation experience as well as an analysis of factors influencing donor recovery. In Chapter 3, I will describe an audit of the unrelated donor outcome data collection for our register and the changes which I implemented based on this to investigate novel methods of donor follow-up. In chapters 4 and 5, I will prospectively assess the physical and psychological donation experience in our donors and define groups at increased risk of a poorer donation experience. I will evaluate both the impact of demographic factors (chapter 4) and baseline health related quality of life scores (chapter 5). Chapter 7 will describe a qualitative study that further explores the influence of general health on side effects and recovery in PBSC donors. It will also assess how well informed and prepared donors felt prior to donation as well as the role of ambivalence in our donor population. Chapter 6 will investigate which donors are more likely to reach the stem cell doses requested by the transplant centres.

Overall, the main aim of this thesis is to illuminate the donor and collection characteristics associated with poorer donation experiences. The results will help towards more targeted strategies concerning donor recruitment, selection, work-up and donor follow-up and we believe such strategies will improve the donation experience.

Chapter 2 - Materials and methods

2.1 Introduction

This chapter details the methodology used in the four studies detailed later in this thesis, namely the audit examining the donor follow-up system at Anthony Nolan (AN), a retrospective study of factors influencing donor yields in PBSC donors, the prospective study assessing the predictors of the haematopoietic stem cell donation experience and assessing the factors influencing yields in BM and PBSC donors and the qualitative study described in chapter 7.

2.2 An audit examining the donor follow-up system at AN

Thirty donor files were reviewed in alphabetical order for the year 2011, these included 15 PBSC and 15 BM donor files. The presence of pre-defined donor follow-up forms (table 3.1) in the donor files was evaluated, as well as the completeness of the forms and the amount of medical information derived from the forms. The donor follow-up forms are outlined in our internal AN standard operating procedures and based on WMDA recommendations (WMDA, 2014). Medical information was defined as any documentation of donor physical or psychological symptoms, serious adverse reactions or details on donor recovery. Medical information was defined “adequate” if enough information was provided in order to comply with WMDA standards (WMDA, 2014).The haematopoietic stem cell (HSC) collection procedures are outlined in section 2.4.1.2.

In accordance with The Anthony Nolan policy, the G-CSF injections for PBSC donors were given by a fully qualified nurse from our home care provider, an independent company that provides healthcare services to individuals within their own homes or work place in the UK. Under normal circumstances, the nurse remains with the donor for 1 hour after each injection to ensure that no adverse events have occurred. This is done for a total of 3 days. The fourth injection is given at the blood stem cell collection centre. The home care provider nurse is fully trained to manage adverse reactions, should they occur, and carries the appropriate emergency kit to deal with any allergic response to the drug.

2.3 A retrospective study of factors influencing donor yields in PBSC donors

2.3.1 Donor characteristics

All sequential PBSC collections facilitated by Anthony Nolan (n = 323) from January through December 2011 were analysed retrospectively. Donors for paediatric recipients were excluded (n = 15) with 308 donors remaining for analysis. All subjects were healthy unrelated donors at least 18 years of age with a BMI < 35. All donors passed a rigorous medical history, clinical examination, blood tests including haematology, biochemistry and virology (Lown, 2013), ECG and chest X-ray and gave written, informed consent.

2.3.2 Mobilisation and apheresis

All donors were mobilised with lenograstim (glycosylated G-CSF; Chugai Pharma, London UK). Lenograstim was given at a dose of 10 μg/kg/day subcutaneously ± 10%

for 4 consecutive days and apheresis was commenced on day 5. If the CD34+ target yield was not achieved, a further dose of G-CSF was given. A maximum of two aphereses were performed. Donors remained outpatients during the days of collection, even if a second day collection was required. Apheresis was carried out in 1 of 4 collection centres using the Spectra COBE v. 4.0 MNC Manual technique, 6.1 auto PBSC or Spectra Optia v 5.0 or 7.0 separator (Terumo BCT, USA). The end point for the procedure on the COBE separators was 2-2.5 times the total blood volume (n = 147). The end point on the Spectra Optia separators was 240 minutes (n = 161). Acid citrate dextrose solution was used as the anticoagulant. Requests of up to 4 x 10^6 CD34+ per kg were considered routine. Requests exceeding 5 x 10^6 CD34+ per kg required detailed information and were reviewed by our medical director prior to acceptance

The CD34+ cell concentration in the leukapheresis product was measured according to international standards (Barnett et al., 1999). Harvest CD34+ cells were determined by flow cytometry using phycoerythrin (PE)-conjugated CD34 monoclonal antibody staining (Beckton Dickinson, San Jose, CA, USA). In order to exclude incomplete red cell lysis, a CD45 fluorescein isothiocyanate (FITC) antibody (Beckton Dickenson) was added. 7-amino actinomycin D (7-AAD) (Beckton Dickenson) was added to determine cell viability. This was followed by red cell lysis (Coulter Q-prep) and flow cytometry (Coulter FC-500, Beckman Coulter, High Wycombe, Beds, UK). The CD34+ cell profile was taken from the total leukocyte population determined by forward/side scatter, followed by CD45 discrimination to exclude platelet aggregation and incomplete red cell lysis. The viability of total cells and CD34- cells were determined from the 7-AAD region.

2.3.3 Statistical analysis

The primary outcome of the study was whether the target yield was reached, this was analysed both as a binary (yes/no) and a continuous outcome (the difference between the obtained yield and the requested yield). For the binary outcome, we allowed the obtained CD34+ dose to be up to 10% less than the requested dose. This is our cut-off used in deciding the need for a second day collection. Our secondary outcome was poor mobilisation. This was defined as a mobilisation of less than 2 x 10^6 CD34 cells per recipient weight after 1 day of apheresis. Associations between continuous donor variables and the continuous outcome were determined using linear regression analysis. Differences in characteristics between 2 groups were determined using the t-test or Mann-Whitney-U test as appropriate. Chi square tests were used to determine differences between categorical variables. All the variables that were significant in univariate analyses were included in a multivariate stepwise logistic regression analysis. Statistical analysis was performed using SPSS software. A two-tailed p value < 0.05 was considered significant.

2.4 A prospective study in unrelated haematopoietic stem cell donors assessing the predictors of the haematopoietic stem cell donation experience

2.4.1 Patients and methods

2.4.1.1 Study population

The study population comprised of unrelated donors from the UK whose bone marrow or G-CSF mobilised PBSC donation was facilitated by Anthony Nolan between February and November 2013. All donors passed a rigorous physical eligibility screening according to World Marrow Donor Association (WMDA) recommendations (Lown, 2013) and were at least 16 years of age with a BMI of < 35 for BM donors and

< 40 for PBSC donors. Donors gave informed written consent for the donation process as per normal practice, as well as additional verbal informed consent for the health related quality of life (HRQOL) assessment questionnaires. Written study information was provided (Figure S1 appendix 1). Ethical approval was obtained from the registry's ethics review board.

2.4.1.2 Stem cell collection methods

All PBSC donors were mobilised as described in section 2.3.2. Apheresis was carried out in 1 of 4 collection centres using the Spectra Optia v 5.0 or 7.0 separator (Terumo BCT, USA). The end point on the Spectra Optia separators was 2-2.5 times the total blood volume or 240 minutes. CD34+ enumeration is described in section 2.3.2.

Donors who donated BM underwent harvest from both iliac crests under general anesthesia. In line with WMDA guidelines no more than 20 mls per kg donor weight was extracted. BM donation took place in 1 of 4 collection centres. The number of puncture holes was not recorded. Our policy is to admit BM donors the evening before the harvest and to discharge them the day after the procedure. Acid citrate dextrose solution was used as the anticoagulant. The total volume of the harvested BM was obtained by subtracting the volume of anticoagulant from the volume of the mix. The total nucleated cell (TNC) counts of the harvested BM were determined using an automatic haematology analyzer. The TNC density or the quality of the harvested BM was determined by dividing the number of TNCs by the volume of the harvested BM.

2.4.2 Data collection

2.4.2.1 Demographic and donor follow-up data

Donors were recruited at the time of the donor's medical evaluation, which took place on average 17 days (range 8-30) prior to donation. Data collection continued on day -4, day -3 and day -2 prior to donation for PBSC donors (figure S2 appendix 1) and on the day of collection for both types of participants (day 0) (figures S4, S5 appendix 1). Our donor provision team subsequently contacted BM and PBSC donors via telephone 2 or 3 days after donation (figure S6 appendix 1). Donors were contacted again using an online questionnaire 1 week following donation and weekly thereafter up until complete recovery (http://www.surveymonkey.com/s/PCT3GWY, last accessed March 2015). The forms that were used are fully described in chapter 3.

Complete recovery was determined on the day 2-3 or weekly questionnaire and defined as the absence of ongoing symptoms as well as return to pre-donation health. The assessment at each time point involved a self-reported checklist of specific adverse reactions, including allergy, anorexia, back pain, bleeding, bruising, dizziness, fatigue, fever, headache, infection, injection site reaction, insomnia, myalgia, nausea, any other pain and vomiting. Each adverse reaction was scored using the CTCAE (Common Terminology Criteria for Adverse Events) toxicity index. Demographic factors analysed as potential influencing factors of time to recovery or adverse reactions were gender, age, BMI (body mass index), support network (number of dependents, marital status) and being a blood donor.

2.4.2.2 Health related quality of life (HRQOL)

HRQOL was measured using the SF-36v2 questionnaire (Figure S7 appendix 1), given to donors (either by post or email) before donation, 4 weeks and 3 months following donation. The SF-36 is a generic indicator of HRQOL derived from the 245-item Medical Outcomes questionnaire. The SF-36 questionnaire is the most widely

used health status assessment tool in clinical trials, with more than 1300 published articles documenting randomised controlled trials utilising the SF-36 score (Ware, 2008). It has been validated both in patients with acute and chronic diseases as well as in healthy volunteers (Ware, 2008). Several studies examining the HSC donation experience (Bredeson et al., 2004, Nishimori et al., 2002) have also used the SF-36 questionnaire. A recent study by Switzer et al used the SF-8 questionnaire (Switzer et al., 2014). The SF-8 was developed to replicate the SF-36 with one question for each health domain. The SF-8 could potentially increase return rates, as it is quicker to complete compared to the SF-36. However, it covers a narrower range of health than the SF-36 with a potential of loss of information. Other HRQOL questionnaires (e.g. QLQ-C30, QWB and CDC HRQOL-14) were reviewed, but they were deemed to be less suited given their rather limited assessment of mental health status.

The SF-36 includes multi-item scales to measure the following 8 dimensions: physical functioning (PF), role limitations due to physical health problems (RP), bodily pain (BP), general health perception (GH), vitality (VT), social functioning (SF), role limitations due to emotional problems (RE) and general mental health (MH). The Physical Component Summary (PCS) and Mental Component Summary (MCS) scores provide a broad physical and mental health perspective (Ware, 2008). Norm based scoring was used to interpret the different dimensions' and summary scores (Ware, 2008). This scoring is created by computing the 0-100 score for a scale and then adjusting this score by the general population's average and standard deviation on that scale. As a consequence, the population mean and standard deviation of all scores are 50 and 10 respectively with higher scores reflecting more positive health states.

2.4.3 Statistical analysis

2.4.3.1 Factors influencing time to recovery and individual adverse reactions

The primary endpoints were time to recovery and individual adverse reactions at different time points as defined earlier. Characteristics analysed as potential influencing factors were the previously defined demographic factors and the PCS and MCS measures.

The probabilities of complete recovery were calculated using the Kaplan-Meier estimator and groups were compared using the log rank test. PCS and MCS measures were split into 4 groups, based on the 25^{th}, 50^{th} and 75^{th} percentiles. Factors significant in univariate analysis at the ≤ .0.05 level were entered into a stepwise proportional hazards regression analysis.

The influence of the previously defined demographic and HRQOL factors on individual adverse reactions was examined using either a chi square for categorical variables (for example gender, number of dependents) or t-test or mann-Whitney-U test as appropriate for continuous variables (for example age, weight). Binary summary scores were established for pain (headache, myalgia, back pain and any other pain) and any adverse reaction for each time point. In addition, summary scores for each adverse reaction involving all the time points from D0 onwards were established. Factors with a p-value ≤ .0.20 in the univariate analysis were included in a stepwise logistic regression analysis.

Comparison between BM and PBSC donors was performed using the chi square test for categorical variables and the t-test or Mann-Whitney-U test for continuous variables.

2.4.3.2 Changes in SF-36 scores over time

Our secondary end points included the assessment of changes in SF-36 scores before, 4 weeks after and 3 months after donation. Paired sample t-tests were used to compare the SF-36 scores before and after donation. Stepwise linear regression analysis was performed to identify significant variables that could be used to predict HRQOL (using PCS and MCS scores) at 4 weeks following donation.

2.4.3.3 Factors influencing PBSC and BM yields

Another secondary outcome of the study was whether the target yield was reached, this was analysed as per section 2.2.3. Linear regression analysis was used to evaluate the relationship between continuous variables and the quality of the BM harvest (TNC/ml). One-way ANOVA or Kruskall-Wallis ANOVA were used to determine differences of BM harvest quality and volumes collected between the different collection centres.

All statistical analysis was performed using SPSS software. A two-tailed p value < 0.05 was considered significant.

2.5 A qualitative analysis of the donation experience

2.5.1 Participants

Fourteen PBSC donors who had previously participated in the prospective study (described in 2.3 and chapters 4 and 5) were selected. The donors were purposively selected based on their pre-donation SF-36 Physical Component Summary (PCS) scores; seven out of 53 donors with scores in the lowest quartile (≤ 56) as well as seven out of 53 donors with scores in the highest quartile (> 60) were selected and approached. There was no purposive sampling with regards to age or gender.

Recruitment was completed when saturation on key themes was reached. Saturation was defined as the point in data collection when new data produced little or no change to the thematic framework process and analysis (Bryman, 2001). All 14 individuals approached gave verbal informed consent for the telephone interview and ethical approval was obtained from the registry's ethics review board.

2.5.2 Methods

All participants were interviewed over the telephone by myself and audiotaped for between 25 and 70 minutes. Interviews took place between 1 and 1.5 years following donation. The interview schedule is described in document S3. The interview schedule consisted of three question areas designed to engage the participants and allow a variety of viewpoints to be expressed. The question areas were health-related quality of life during the donation process, donor preparedness and ambivalence. Open semi-structured format questions were used flexibly, being omitted, adapted or elaborated according to the demands of individual interviews. Whilst trying to avoid directive or closed questions or interpretations, an approach of responding to the participants' answers was adopted. In this way, questions were used to promote a two-way dialogue.

All audiotaped interviews were fully transcribed and analysed. The thematic analysis for the second part of the qualitative study was performed in line with Braun and Clarke's outline of the process involving 6 phases (familiarisation with data, generating of initial codes, searching for themes, reviewing themes, defining and naming themes and production of a report) (Braun and Clarke, 2006). Detailed reading and re-reading of transcripts led to the generation of initial codes. Codes were generated in a systematic fashion across the entire data set. Subsequently, codes were combined under overarching themes (tables S5 and S6 appendix 1). Themes

were chosen so that they were internally coherent and consistent and without overlapping too much. Both supervisors (Andre Strydom and Katrina Scior) read 3 transcripts prior to discussing and agreeing the resulting themes to ensure themes captured the full range of data.

Chapter 3 – A review of the donor follow-up system and a retrospective and prospective analysis of factors influencing PBSC yields

3.1 Introduction

This chapter details three studies, namely an audit reviewing our registry's (Anthony Nolan) donor follow-up system and a retrospective and prospective analysis examining the factors that influence donor yields in PBSC donors.

3.2 An audit examining the donor follow-up system at Anthony Nolan (AN)

3.2.1 Introduction

In chapter 1, I reviewed the donor's experience, both physically and psychologically and the factors that are believed to influence this. As part of the preparation of my prospective study (chapter 4 and 5); a study that aims to further describe and predict the donation experience, I evaluated our registry's existing donor follow-up program.

3.2.2 Methods

The methods of this study are outlined in section 2.2.

3.2.3 Results

Table 3.1 outlines the follow-up forms that were used in our registry at the time of the audit, their presence in the donor file and the degree of medical information derived from the form.

Table 3. 1 Donor follow-up contacts at different time points

Time point	Form	Presence	Content
Days -4 until day -2 prior to donation	Home care provider form on days of G-CSF administration (PBSC only)	53%	Limited medical information
Day 0 (day of donation)	Visit form filled out by volunteer or Anthony Nolan visitor	100%	No medical information
Day 2-3 post donation	Telephone call (PBSC only)	87%	Limited medical information
Day 8 post donation	telephone call (BM only)	87%	Limited medical information
Day 28 post donation	Day 28 questionnaire	60%	No medical information
Day 28 post donation	Full blood count and GP surgery nurse review (BM only)	93%	Adequate medical information
Annually post donation (every year until year 6, then at year 8 and year 10)	Annual follow-up form	33%	Adequate medical information

3.2.3.1 Home care provider form

Results

This form is filled out by nurses who administer the G-CSF injections. We collect this form on the days that the injection is given via our home care provider (from day -4 until day -2). Only 53% (24/45) of these forms were present in the donor file. It was not possible to determine whether the responsibility of this poor result lay with the home care provider not sending the form, the postal services or with Anthony Nolan. The donor and drug details (dose, route, batch number) were documented correctly in 100% of returned forms. A pregnancy test was performed in 100% (1/1) of female donors on the first day of injection. The duration of the visit was documented in 100% of cases, however 3/24 (13%) of visits were less than an hour and 2 of these 3 (75%) were first time visits. This incorporates a potentially high risk as there is a risk of anaphylaxis, especially on the first day of G-CSF. Adverse reactions were only documented in a limited number of cases (14/24) (the form did not require this information). Only 3/14 adverse reactions had a grading documented. This grading was using subjective terms such as “mild” or “moderate”, rather than following the international CTCAE grading (NIH, 2010) The documentation of observations (pulse, temperature, blood pressure and respiratory rate) was also suboptimal, with 4/24 (17%) lacking any documentation of observations. An additional 4/24 forms had missing post-GCSF observations on the first day, when the risk of anaphylaxis is the highest.

Recommendations

I presented the results of this audit internally at our Medical Affairs meeting. Following this meeting, I drafted a letter to our home care provider outlining the results. This was followed by several meetings with myself, representatives of the Quality and

donor provision department and our home care providers. Rather than using hand filled forms that require posting, we suggested the introduction of electronic forms. This electronic system was effectively introduced in May 2013. Nurses now use a laptop to fill out the form and this is transferred directly via a portal which can be accessed by the Anthony Nolan medical team in real time. The content of the new form was specified based on the findings of this audit (figure S2 appendix 1). It now includes a checklist of common adverse reactions (allergy, anorexia, dizziness, fatigue, fever, headache, infection, injection site reaction, insomnia, myalgia, nausea, other pain, rash, vomiting and any other adverse reactions). Nurses are required to go through each adverse reaction and add a CTCAE grading if the adverse reaction is present. Forms with CTCAE grading scales are provided to assist nurses with this task (figure S3 appendix 1). The added advantage of an electronic form is the ability to make certain fields mandatory. This introduction of mandatory fields was implemented in July 2014 and this led to a further improvement of the quality of the forms. Our Service-Level Agreement (SLA) was changed in May 2013 and now specifies that every first visit should last an hour and that pre and post G-CSF observations should be taken during this visit. Subsequent visits should last at least half an hour. The SLA also states that unexplained events or severe predicted adverse events aught be reported to the Medical Officer and the Quality team. We now organise teaching sessions for the nurses twice a year.

3.2.3.2 Visit form

Whilst donors are at the Collection Centre, a volunteer visitor or member from the donor follow-up team visits the donor.

Recommendations

Given that, in general, 100% of the donor visits take place I realized it was a wasted opportunity not to collect any formal medical information from this visit, especially since the peak of adverse reactions for PBSC donors is around the day of donation (Pulsipher et al., 2009b). Following the presentation of this audit, it was agreed to introduce a medical questionnaire for PBSC (figure S4 appendix 1) and BM donors (figure S5 appendix 1). This questionnaire contains a checklist of adverse reactions and a CTCAE grading, which is identical to the Home care provider form. Several teaching sessions for our donor follow-up team and our donor visitors have taken place, in order to educate them in how to fill out this form.

3.2.3.3 Telephone call day 2-3 and day 8 following donation

Results

An Anthony Nolan donor coordinator is responsible for a telephone call on day 2 or 3 (PBSC donors) or day 8 (BM donors) following donation. This telephone call is intended to pick up any adverse reactions and encourages the donor to address any concerns or questions present at that stage. This form was present in the majority of donor files. However, the format was more a follow-up “chat” rather than a formal checklist of medical symptoms.

Recommendations

Similar to the previous time point, it seemed a wasted opportunity not to collect any medical information from this phone call. I introduced a standardised form (figure S6 appendix 1 for PBSC donors), containing the same checklist with adverse reactions

as specified previously. In order to create consistency, it was decided that the telephone call would take place on day 2 or 3 both for PBSC and BM donors.

3.2.3.4 Weekly follow-up

Recommendations

The major limitation of the follow-up system was felt to be the "gap" in the collection of medical information between the day 2-3 phone call and the annual follow-up form, which makes it impossible to define the time to complete recovery for the majority of donors. The lack of any documentation of psychological wellbeing was another limitation. This led to the introduction of the day 7 electronic medical questionnaire (http://www.surveymonkey.com/s/PCT3GWY, last accessed March 2015), using Surveymonkey. If a donor has no access to the internet, this is replaced by a telephone call. This questionnaire is sent out weekly until the donor has fully recovered. All the forms from donors that have not fully recovered are reviewed by a Medical Officer and donors are contacted as required. As with previous forms it contains a checklist with adverse reactions and a grading.

3.2.3.5 Day 28 post donation

Results

Four weeks following donation, a donor feedback form is sent to the donor. This document contains questions regarding donor experience, wish to stay on the register and helping Anthony Nolan further in other ways. It does not contain any medical information. The return of this form was only 60%.

In addition, bone marrow donors attend a check-up and have a full blood count one month after donation. This check-up is usually carried out by the donor's GP and the results of this appointment are returned by the GP surgery. My audit found a good return rate.

Recommendations

It was not deemed necessary to change the content of this part of the follow-up system. The day 28 feed-back questionnaire was changed to an electronic form and is now sent out automatically. This has increased the return rate considerably.

3.2.3.6 Annual follow-up

Results

The aim of the annual follow-up form is two-fold. Firstly, to ensure donor safety and to allow the reporting of SARs to the WMDA (including the development of auto-immune conditions and malignancies following donation). Secondly, to pick up donors who have developed a medical condition that would make them not eligible to remain on the register. The return of this form was only 30%. The degree of medical information on the form was felt to be adequate, as it served the goals mentioned above.

Recommendations

It was not deemed necessary to change the content of this part of the follow-up system. The form was changed to an electronic form in order to increase the returns.

3.2.4 Conclusion

This small audit showed that the donor follow-up system within our register was generally not compliant with WMDA standards. The main concern was the lack of standardised medical questions and the possibility of missing serious adverse reactions. The other major limitation was the "gap" of any medical information derived between the day 2-3 phone call and the annual follow-up form, making it impossible to determine the time to recovery for a significant number of donors. Time to recovery is a strong and necessary end point for research purposes, for example when examining the impact of certain donor characteristics on the donation experience. With donor eligibility criteria constantly changing – for example the allowance of BMIs up to 40 for PBSC donors or the allowance of 16 and 17-year olds- it would seem incorrect not to record this information, as it will not be possible to establish whether these new groups are at increased risk of a delayed recovery or adverse reactions. Another limitation is the lack of any psychological donor follow-up. The new system now involves standardised medical questions on the days of G-CSF administration, the day of donation, 2-3 days following donation and weekly until complete recovery. It also assesses the donor's psychological state following donation. Our current donor follow-up system is based on NMDP practice, the first donor register to introduce a comprehensive follow-up (CIBMTR, 2014) (http://www.cibmtr.org/DataManagement/TrainingReference/eLearning/Documents/777_sample.pdf). There has not been a formal follow-up audit yet after the instigation of these changes. As part of a global data collection effort, we are currently examining the possibility of linking our donor follow-up system with the EBMT database Promise (EBMT, 2013) (http://www.ebmt.org/Contents/DataManagement/Registrystructure/MED-ABdatacollectionforms/Documents/Donor%20Outcome%20Manual.pdf). This database has been recently set up to store and analyse short and long term donor

follow-up reports from related and unrelated donors and is available for EBMT registered centres.

3.3 A retrospective and prospective study of factors influencing donor yields in PBSC donors

A paper based on the findings of this study was published in the journal Transfusion in May 2014, entitled: Female donors and donors who are lighter than their recipient are less likely to meet the CD34+ cell dose requested for peripheral blood stem cell transplantation. (See appendix 3)

3.3.1 Introduction

Registry staff involved in the medical assessment and consent of donors are obliged to ensure that the risk to the donor (and recipient) is minimized by allowing only the fittest to donate. In addition, registries have a duty to make sure that the cells collected meet the transplant centre's requested dose and other requirements. This is not necessarily a conflict of interest; by establishing which donors are more likely to meet the requested dose, additional apheresis procedures or even an emergency bone marrow harvest could potentially be avoided.

During the last decade, peripheral blood stem cells (PBSC) have superseded bone marrow (BM) as the main source of haematopoietic stem cells (HSCs). Commonly requested CD 34+ doses vary between 3 and 5 x 10^6 per kg of recipient weight, although the minimum dose to ensure engraftment for allogeneic transplantation remains controversial (Mavroudis et al., 1996, Shpall et al., 1998, Mehta et al., 2009,

Pulsipher et al., 2009a, Heimfeld, 2003). Advantages of higher doses are the reduced risk of graft rejection and the increased graft-versus-tumour effect (Nakamura et al., 2008). A dose-response relationship between the number of cells infused and the rate of haematopoietic recovery has also been described (Mehta et al., 2009, Shpall et al., 1998, Pulsipher et al., 2009a). Some authors have reported an association between lower cell doses and higher transplant related mortality (Pulsipher et al., 2009a, Heimfeld, 2003). On the other hand, higher cell doses have been found to increase the risk of acute (Przepiorka et al., 1999) and chronic (Przepiorka et al., 2001, Zaucha et al., 2001, Heimfeld, 2003) graft versus host disease.

Several days of apheresis are frequently required for PBSC donors to ensure a sufficient collection of CD34+ cells and around 20% of donors need a second day of apheresis (Holig et al., 2009). Our registry allows a maximum of 2 days of apheresis. The physical side effects of PBSC donation have been well described and common side effects include fatigue, bone pain and bruising (Pulsipher et al., 2013, Pulsipher, 2012). A further reduction in platelet counts and increased psychological stress are potential risks associated with additional days of apheresis (Stroncek et al., 1999). If insufficient HSCs are harvested during the days of apheresis, bone marrow harvesting is performed as a salvage procedure. There are well described additional risks associated with this procedure, such as the risk of general anaesthesia, blood loss and mechanical injury.

It is therefore of clinical importance to characterize donors who are at risk of not meeting the HSC dose requested by the transplant centres, as this group may benefit from an alternative mobilisation regimen in order to avoid additional days of apheresis or bone marrow harvesting. In addition, this knowledge may allow registries to focus

on the recruitment of donors who are more likely to mobilise sufficient CD34+ cells. The advantages of such a strategy are clear both for the donors and the recipients. Because patients have already received therapy by the time donor cells are collected in most centres, the lack of availability of adequate stem cells is a significant and potentially life threatening problem.

These studies were performed to evaluate the frequency of PBSC collections that meet the transplant centre's requested dose, therefore taking the transplant centres' requirements into account. The role of potential donor factors including age, gender, weight and difference between donor and recipient weight was examined.

3.3.2 Retrospective analysis

3.3.2.1 Methods

The methods of this study are outlined in section 2.3.

3.3.2.2 Results

3.3.2.2.1 Donor and collection characteristics

Donor and collection characteristics are listed in table 3.2. Of the 295 donors with recorded ethnicities, 96% (n = 284) were white, the remaining donors were of African, African-Caribbean, Asian, Mediterranean, Middle Eastern or of a mixed origin.

Table 3. 2 Donor and collection characteristics

Characteristic	
Age (Years)	
Median (range)	32 (18-58)
Gender (Male/Female)	247/61
Weight (kg)	
All - Median (range)	81 (52-125)
Female – Median (range)	66.5 (52-111)
Male - Median (range)	83 (55-125)
Central lines (percentage)	3/324 (< 1%)
Blood volume processed day 1 (l)	
Median (range)	12.2 (3-22)
Blood volume processed day 2 (l)	
Median (range)	10.8 (4-17)
CD34+ cells (x $10^{6)}$/kg recipient weight day 1	
Median (range)	2.75 (0.44-14.0)
CD34+ cells (x $10^{6)}$/kg recipient weight day 2	
Median (range)	2.3 (0.55-7.6)

3.3.2.2.2 Association between demographic data and reaching the target yield

The median cell dose requested was 4 x 10^6 CD34+cells/kg recipient weight (range 2-10). There were 16 requests exceeding 5 x 10^6 CD34+ per kg (table 3.3). The median CD34 dose collected was 6.3 x 10^6/kg (median 145% of requested dose, range 20-495% of requested dose). 75% of requests were met after 1 day of apheresis and 94% of requests were met after 2 days of collection.

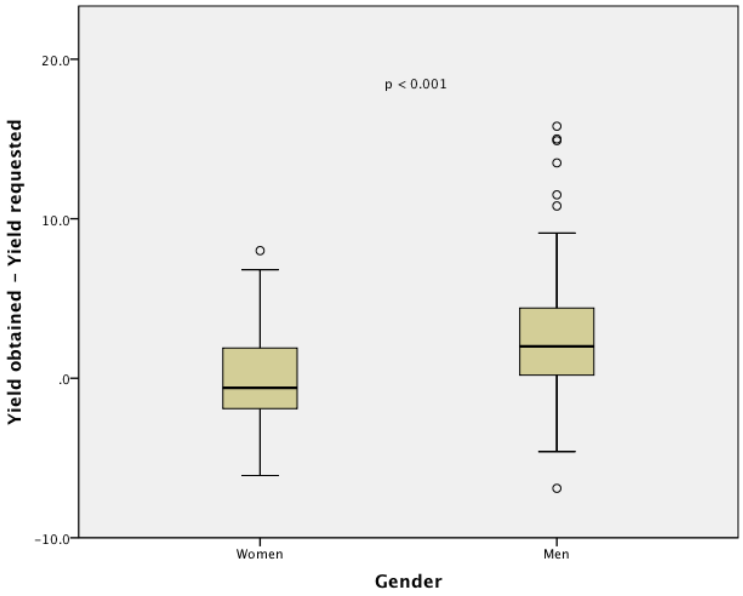
Table 3. 3 Indications for higher requested stem cell doses (CD 34 > 5 x 10^6/kg) (n=16)

Disease (n)	Reason given (n)
AML(5)	High risk disease (3)
	Previous allograft – graft failure (1)
	Unknown (1)
MDS (3)	High risk disease (3)
CML (1)	Unknown
Myelofibrosis (2)	Risk of poor engraftment (1)
	Previous allograft – graft failure (1)
CLL (1)	High risk disease
Hodgkin Disease (1)	High risk disease
Philadelphia positive ALL (1)	Previous allograft – graft failure
Unknown (2)	Unknown (2)

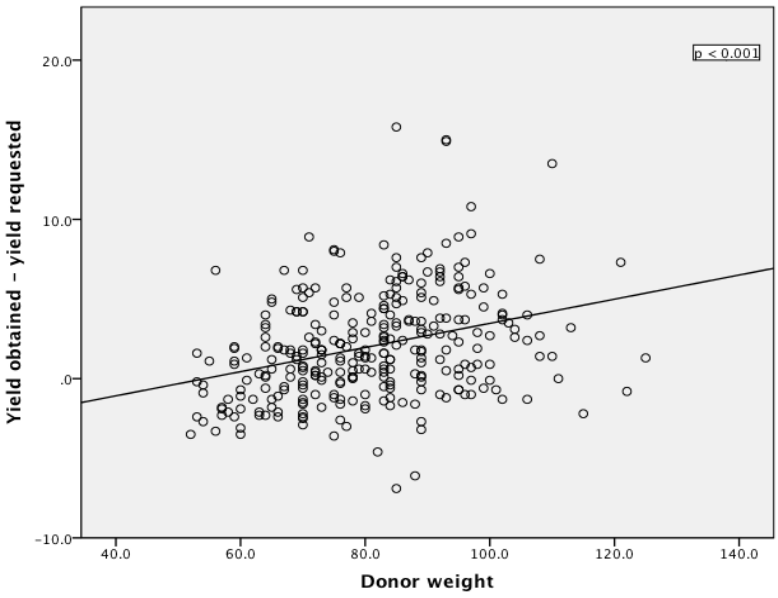
In univariate analyses (figure 3.1, tables 3.4 and 3.5), we found that reaching the target yield was significantly associated with: a higher donor weight (85.6 kg vs 75.3 kg, $p < 0.001$), male donor gender (82% vs 44%, $p < 0.001$), a positive difference in weight between donor and recipient (4.3 kg vs -8 kg, $p < 0.001$) and a higher volume of blood processed (13.8 l vs 11.9 l, $p < 0.001$). If I categorise the difference in weight between donor and recipient as being either negative or positive, the odds ratio of reaching the target for a positive difference was 2.6 (95% CI 1.5, 4.4) after 1 day of collection and 4.0 (95% CI 1.2, 12.8) after 2 days of collection. Donor age was not significantly associated with reaching the requested cell dose. All the above findings were valid both after 1 day and 2 days of collection

Figure 3. 1 Associations of obtaining the requested yield according to gender, weight, difference between donor and recipient weight and volume of blood processed. A: Box plot with the horizontal line representing the median, the box the 25th percentile and the whiskers the 75th percentile. Female donors were significantly less likely to meet the requested cell dose. A lower weight (B) and a negative difference between donor and recipient weight (C) were associated with not meeting the requested dose. Lower volumes of blood processed (D) were associated with not reaching the requested dose.

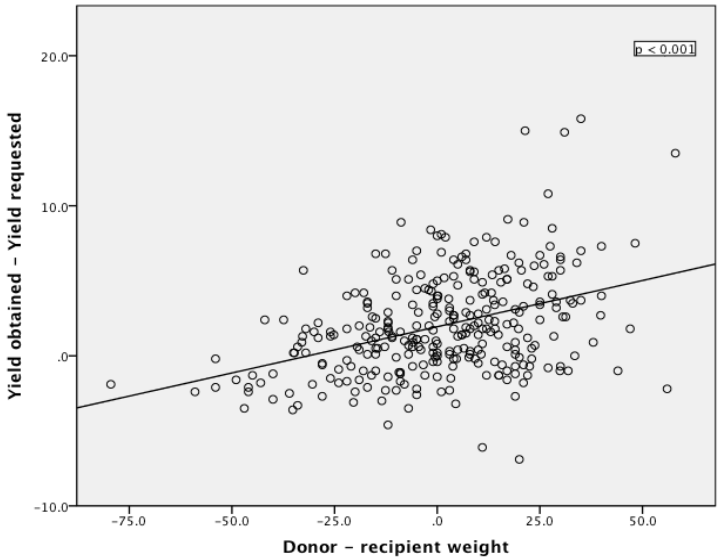
A.



B.



C.


p < 0.001
Yield obtained – Yield requested
20.0
10.0
.0
-10.0
-75.0
-50.0
-25.0
.0
25.0
50.0
Donor – recipient weight

D.

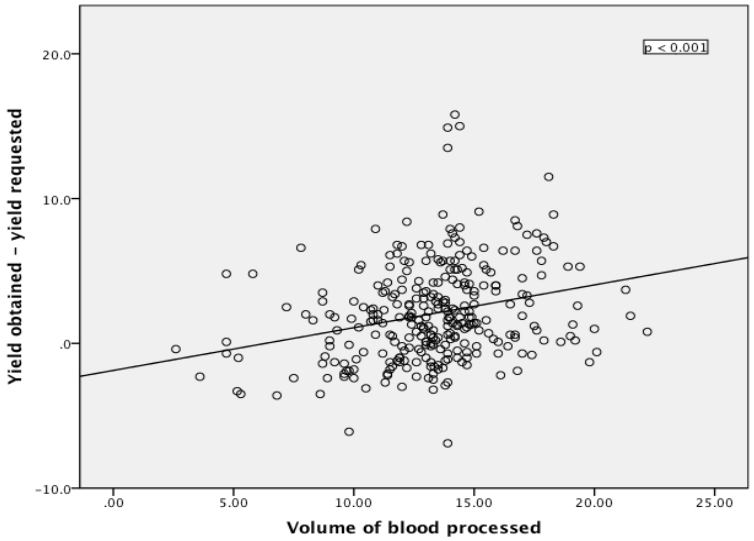

p < 0.001
Yield obtained – yield requested
20.0
10.0
.0
-10.0
.00
5.00
10.00
15.00
20.00
25.00
Volume of blood processed

Table 3. 4 Univariate analysis of factors associated with reaching the requested yield on day 1 and day 1+2 of collection (yield obtained as a binary outcome). Values are expressed using mean (range) for continuous variables.

Variable	**Yield obtained day 1**			**Yield obtained day 1+2**		
	Value not reached (n = 78)	Value reached (n = 230)	p-value	Value not reached (n = 16)	Value reached (n = 287)	p-value
Age	34.5 (19, 54)	32.8 (18, 58)	0.17	35.4 (19, 54)	33.2 (18, 58)	0.35
Donor weight (kg)	75.3 (52, 122)	82.6, (53, 125)	< 0.001	69.3 (56, 89)	81.5 (52, 125)	< 0.001
	-8 (-79.5, 56)	4.3 (-54, 58)	< 0.001	- 12.8 (-46, 21)	1.8 (-79.5, 58)	< 0.01
Blood volume processed (l)	11.9 (2.6, 20.1)	13.8 (4.7, 22.2)	< 0.001	20.2 (9.8, 28.2)	22.8 (6.9, 35.1)	< 0.001
Gender (M/F)	44/34	203/27	< 0.001	6/10	239/48	< 0.001

Table 3. 5 Univariate analysis of factors associated with reaching the requested yield on day 1 and day 1+2 of collection (yield obtained as a continuous variable)

	Variable	Yield obtained minus yield requested day 1 (continuous)	Yield obtained minus yield requested day 1+2 (continuous)
Continuous	Age	p = 0.94	p = 0.66
	Donor weight	p < 0.001	p < 0.001
	Donor minus recipient weight	p < 0.001	p < 0.001
	Blood volume processed	p < 0.001	p = 0.10
Categorical	Gender	p < 0.001	p < 0.001

Only gender (p < 0.001) and a positive difference between donor and recipient weight (p = 0.005) remained significantly associated with the target yield being met after 1 day of collection after stepwise binary logistic regression analysis (table 3.6).

Table 3. 6 Multivariate logistic regression of factors influencing the likelihood of reaching the target yield on day 1[a] and day 1+2[b] of collection

Variable	OR	95% CI	p-value
Donor minus recipient weight (kg)	1.02[a]	1.01 - 1.03[a]	= 0.005[a]
	1.03[b]	1.003-1.052[b]	= 0.025[b]
Gender			
Female	1.00		
Male	4.76[a]	2.5 - 9.6[a]	<0.001[a]
	5.3[b]	1.8-15.1[b]	= 0.002[b]

Interestingly, donor weight lost significance after adjusting for gender (p = 0.94). When excluding the donors with cell dose requests exceeding 5 x 10^6 CD34+ per kg, the analysis produced very similar results (table 3.7).

Table 3. 7 Multivariate logistic regression of factors influencing the likelihood of reaching the target yield on day 1 of collection (analysis excluding requests exceeding 5 x 10^6 CD34+ per kg)

Variable	OR	95% CI	p-value
Donor minus recipient weight (kg)	1.03	1.01 - 1.04	= 0.001
Gender			
Female	1.00		
Male	3.69	1.8 – 7.6	<0.001

3.3.2.2.3 Poor mobilisers

Poor mobilisers were defined as a mobilisation of less than 2 x 10^6 CD34 cells per recipient weight after 1 day of apheresis. In univariate analyses, I found that poor mobilisation was significantly associated with: a lower donor weight (65.8 kg vs 81.7 kg, p < 0.001), female donor gender (63% vs 17%, p < 0.001), a negative difference in weight between donor and recipient (-23.0 kg vs 2.7 kg, p < 0.001) and a lower volume of blood processed (9.6 l vs 13.5 l, p < 0.001). Only the difference between donor and recipient weight (p < 0.001) and the volume of blood processed remained significant after multivariate analysis (p < 0.001) (table 3.8).

Table 3. 8 Multivariate logistic regression of factors influencing poor mobilisation

Variable	OR	95% CI	p-value
Donor minus recipient weight (kg)	1.05	1.02 - 1.08	< 0.001
Blood volume processed (l)	1.4	1.2-1.7	< 0.001

3.3.3 Prospective analysis

Our prospective study described in chapters 4 and 5 assesses the influence of pre-donation characteristics on the donation experience. A secondary end point of this study was to evaluate the frequency of PBSC collections meeting the transplant centre's requested dose, but now in a prospective manner. I examined the role of potential donor and collection characteristics in accordance with our retrospective study and I also examined the role of BMI and baseline haematology results, such as baseline platelet and white cell count.

3.3.3.1 Methods

The full material and method can be found in chapter 2 (section 2.4.3.3).

3.3.3.2 Results

3.3.3.2.1 Donor and collection characteristics

Participants were donors who were recruited in our prospective study described in chapters 4 and 5 and they all donated in 2013. Donors for paediatric recipients were

excluded from this analysis (n = 15) as well as donors with incomplete documentation of yields data (n = 7), with 253 donors remaining for analysis. Characteristics are shown in table 3.9. 248 donors were of Northern European origin, the remaining were of other white background (n = 3), mixed ethnicity (n = 2), Asian (n = 2), African and Caribbean (n = 1) or unknown ethnicity (n = 4).

Table 3. 9 Donor and collection characteristics

Characteristic	
Age (Years)	
Median (range)	30.8 (17-63)
Gender (Male/Female)	195/58
Weight (kg)	
Median (range)	81 (51.9-125)
BMI	
Median (range)	25.9 (17-41.6)
Central lines (percentage)	260/274 (5%)
2 day collections (percentage)	74/274 (27%)
Blood volume processed day 1 (l)	
Median (range)	10.5 (3-17.6)
Blood volume processed day 2 (l)	
Median (range)	10.5 (4.6-15.3)
CD34+ cells (x 10^6)/kg recipient weight day 1	
Median (range)	2.9 (0.6-3.9)
CD34+ cells (x $10^{6)}$/kg recipient weight day 2	
Median (range)	2.5 (0.6-6.7)

3.3.3.2.2 Association between demographic data and reaching the target yield

The median cell dose requested was 4 x 10^6 CD34+cells/kg recipient weight (range 3-6). Only 4 requests exceeded 5 x 10^6 CD34+ per kg (table 3.10). The median CD34

dose collected was 6.0 x 10^6/kg. 67.7% of requests were met after 1 day of apheresis and 87% of requests were met after 2 days of collection.

Table 3. 10 Indications for higher requested stem cell doses (CD 34 > 5 x 10^6/kg) (n=4)

Disease (n)	Reason given (n)	Dose requested
AML(2)	High risk disease (2)	6 x 10^6/kg
MDS (1)	High risk disease (1)	6 x 10^6/kg
Hodgkin Disease (1)	Relapse (1)	6 x 10^6/kg

I found that a higher donor weight (85.9 vs 75.3 kg, $p < 0.001$), a higher donor BMI (27.3 vs 24.6, $p < 0.001$), male gender (83% vs 64%, $p = 0.001$) and a positive difference in weight between donor and recipient (8.5 kg vs -9.2 kg) were significantly associated with reaching the target yield in univariate analysis (table 3.11). All these findings were valid both after 1 day and 2 days of collection. A younger age (32.2 vs 35, $p = 0.024$) and a higher blood volume processed (12.3 l vs 11l, $p < 0.001$) were also associated with reaching the target yield, but only on day 1 of collection. When I categorised the difference in weight between donor and recipient as being either negative or positive, the odds ratio of reaching the target for a positive difference was 3.2 (95% CI 1.8, 5.6) after 1 day of collection and 3.0 (95% CI 1.3, 7.2) after 2 days of collection. The baseline white cell count and the pre-harvest white cell count were not significantly associated with reaching the requested dose after 1 or 2 days of collection. A higher baseline platelet count was significantly associated with reaching the target after 2 days of collection (248 vs 215 x 10^9/l; $p = 0.002$), but not after one day.

Table 3. 11 Univariate analysis of factors associated with reaching the requested yield on day 1 and day 1+2 of collection (yield obtained as a binary outcome). Values are expressed using mean (range) for continuous variables.

Variable	Yield obtained day 1			Yield obtained day 1+2		
	Value not reached (n = 77)	Value reached (n = 176)	p-value	Value not reached (n = 27)	Value reached (n =226)	p-value
Age	35 (17-62)	32.2 (21-60)	0.024	34.6 (2-58)	32.9 (17-62)	0.35
Donor weight (kg)	75.3 (51.9-119.2)	85.9 (53-125)	< 0.001	72.9 (51.9-99)	83.9 (53-125)	< 0.001
Donor minus recipient weight (kg)	-9.2 (-65.3-39.2)	8.5 (-49.2-61.5)	< 0.001	-14.5 (-65.3-34)	5.2 (-60.5-61.5)	< 0.001
BMI	24.6 (17-36.8)	27.3 (17.9-41.6)	< 0.001	24.4 (19.5-36.8)	26.7 (17-41.6)	0.005
Blood volume processed (l)	11.0 (3-17.6)	12.3 (5.6-21.5)	< 0.001	21.5 (17.8-28.7)	21.1 (13.2-32)	0.79
Baseline platelet count (x 10^9/l)	237 (140-438)	248 (146-407)	0.13	215 (140-438)	248 (146-407)	0.002
Baseline white cell count (x 10^9/l)	6.6 (4-11.3)	6.6 (3.2-12.9)	0.87	6.5 (4-8.9)	6.6 (3.2-12.9)	0.66

Pre-harvest white cell count (x 10^9/l)	40.9 (22.5-73.7)	42.6 (19.7-76.0)	0.37	38.2 (22.5-53.2)	42.4 (19.7-76.0)	0.24
Gender (M/F)	49/28	146/30	0.001	15/12	180/46	0.013
Central line (N/Y)	73/4	166/9	0.99	25/2	214/11	0.63

After stepwise binary logistic regression analysis (table 3.12), male gender, a positive difference between donor and recipient weight, higher BMI, lower age and a higher baseline platelet count were significantly associated with the target yield being met after 1 day of collection.

Table 3. 12 Multivariable logistic regression of factors influencing the likelihood of reaching the target yield on day 1[a] and day 1+2[b] of collection

Variable	OR	95% CI	p-value
Age	0.95[a]	0.92-0.99[a]	0.005[a]
BMI	1.12[a]	1.01-1.24[a]	0.027[a]
	1.06[b]	0.91-1.24[b]	0.45[b]
Donor minus recipient weight	1.04[a]	1.02 - 1.06[a]	<0.001[a]
	1.04[b]	1.02-1.07[b]	0.002[b]
Baseline platelet count	1.008[a]	1.002-1.02[a]	0.014[a]
	1.03[b]	1.02-1.04[b]	< 0.001[b]
Gender			
Female	1.00		
Male	2.2[a]	1.03 – 4.8[a]	0.041[a]
	5.22[b]	1.8-15.5[b]	0.003[b]

3.3.3.2.3 Poor mobilisers

Poor mobilisers were defined as a mobilisation of less than 2 x 10^6 CD34 cells per recipient weight after 1 day of apheresis. We found that a lower donor weight (66.1 vs 83.8 kg, $p < 0.001$), a negative difference in weight between donor and recipient (-28.1 vs 5.1 kg, $p < 0.001$), lower BMI (23.2 vs 26.7, $p = 0.002$) and female gender (68.8% vs 19.7%,$p < 0.001$) were associated with poor mobilisation in univariate analysis (table 3.13).

Table 3. 13 Univariate analysis of factors associated with poor mobilisation. Values are expressed using mean (range) for continuous variables.

Variable		Poor mobilisation		
		Yes (16)	No (244)	p-value
Continuous	Age	32.7 (21-50)	33.1 (17-62)	0.90
	Donor weight (kg)	66.1 (51.9-74.7)	83.8 (53-125)	< 0.001
	Donor minus recipient weight (kg)	-28.1 (-65.3-2.6)	5.1 (-60.5-61.5)	< 0.001
	BMI	23.2 (19.5-36.8)	26.7 (17-41.6)	0.002
	Blood volume processed (l)	10.7 (9-13.4)	12.1 (3-21.5)	0.088
	Baseline platelet count	232 (173-333)	244 (128-438)	0.35
	Baseline white cell count	6.1 (4.1-7.8)	6.7 (3.2-12.9)	0.18
	Pre-harvest white cell count	33.9 (22.5-42.4)	42.4 (19.7-76.0)	0.059
Categorical	Gender (M/F)	5/11	196/48	< 0.001

Only the difference between donor and recipient weight remained significant after stepwise binary logistic regression analysis (table 3.14).

Table 3. 14 Multivariable logistic regression of factors influencing poor mobilisation

Variable	OR	95% CI	p-value
Donor minus recipient weight (kg)	1.15	1.03 - 1.29	0.014

3.3.4 Discussion

Previous studies have reported that several donor characteristics influence PBSC mobilisation. Table 1.6 lists all the factors that have been previously found to affect the PBSC yield in allogeneic donors. Most of these studies have used the stem cell yield, either per donor or recipient weight, as a primary outcome. This study was performed to evaluate the frequency of PBSC collections that meet the transplant centre's requested yield (allowing for yields within 10% of the requested yield), therefore taking the transplant centres' requirements into account.

My retrospective study found that a lower donor weight, a negative difference between donor and recipient weight, female gender and lower volumes of blood processed were associated with not reaching the target yield in univariate analysis. Only 3 donors needed insertion of a central line so the effect of this could not be examined statistically. In contrast to several other studies, age was not significantly associated with reaching the requested cell yield. The difference between donor and

recipient weight and gender remained statistically significant in the multivariate analysis.

Donor weight was found to be positively associated with yields in previous studies. To our knowledge, the influence of the difference between donor and recipient weight has not been studied previously. Our study showed that any negative difference between donor and recipient was significantly associated with not reaching the requested cell dose. Based on these results, transplant centres and registries could consider selecting donors who are heavier than their recipient, if more than one fully HLA-matched donor is available. For example, at CT stage, a warning could be sent to the transpant centre when a donor is selected who is lighter than the recipient. This practice may however compromise donor safety as several studies have shown that heavier donors experience more bone pain (Pulsipher et al., 2013, Pulsipher et al., 2009b, Chen et al., 2011). In addition, vascular access may be more problematic in heavier donors.

Gender was considered to have an effect in many previous studies (table 3.9) (Fischer et al., 2005, Martino et al., 2006, Vasu et al., 2008, Miflin et al., 1996), although no correlation was found by others (Anderlini et al., 1997, Lysak et al., 2005, Sohn et al., 2003). Vasu et al reported that gender lost significance after adjusting for weight and the total amount of G-CSF administered (Vasu et al., 2008). We found that gender retained significance after adjusting for weight and total volume of blood processed. The finding that gender remained significant after taking donor weight into account may be explained by the possible influence of sex steroids on haematopoiesis (Lopez-Holgado et al., 2005). This has only been reported in 2 other studies to date (Martino et al., 2006, Miflin et al., 1996). Lopez-Holgado et al reported

a higher production of all types of progenitors in males compared to females and, moreover, a better stromal confluence and hence a better microenvironment. Other possible influencing factors may be the difference in fat distribution and body constitution and subsequent different pharmacological profiles of G-CSF.

Similarly to the retrospective study, the prospective analysis found that male gender and a positive difference between donor and recipient weight were significantly associated with the target yield being met in multivariate analysis. In addition, the prospective analysis showed that a lower donor age, a higher BMI and a higher baseline platelet count were significantly associated with the target yield being met.

Lower donor age was associated with reaching the target on day 1 of collection. Lower age has been found to be associated with higher CD34+ yields in several other studies (table 3.9) (Anderlini et al., 1997, Shimizu et al., 2002, Suzuya et al., 2005, Martino et al., 2006, Wang et al., 2008, Anderlini et al., 1999). Previous authors have identified 38 years (de la Rubia et al., 2002) and 55 years (Anderlini et al., 1999, Ings et al., 2006) as ages above which progenitor yields are, on average, reduced. In our data set, donors aged 55 years or more were significantly less likely to reach the target yield on day 1 of collection (70% target reached if < 55 years vs 25% target reached if ≥ 55;$p = 0.032$). The reason we did not find this effect in our retrospective study may be related to the smaller age range of donors in that study (18-58 versus 17-63).

BMI was considered to have an effect on cell yield in several previous studies (table 3.9) (Favre et al., 2003, Wang et al., 2008, Chen et al., 2014). In my data set, donors with a BMI of 30 or more were significantly more likely to reach the target yield on day

1 of collection (90% target reached if BMI ≥ 30 vs 65% target reached if BMI < 30; p < 0.001).The finding that overweight or obese adult donors who are otherwise healthy had better responses to G-CSF is interesting. Firstly, recent animal studies have demonstrated that adipose tissue contains significant numbers of HSCs (Han et al., 2010, Cousin et al., 2003, Minana et al., 2008). However, it is yet to be confirmed whether these HSCs are also present in human adipose tissues. Additionally, the exact mechanisms determining the number of HSCs in fat tissue are currently unknown. Secondly, we based the G-CSF dose on donor weight. Donors with higher BMI's may have received relatively higher doses of G-CSF than if ideal body weight was used for determination of G-CSF dose. The efficacy of the G-CSF dose as determined by ideal body weight remains to be investigated. Thirdly, improved responses to G-CSF mobilisation in donors with higher BMI's may be accounted for by other intrinsic biomedical factors that are associated with obesity.

A higher baseline platelet count was also associated with reaching the target yield. This has been described in one previous study (Vasu et al., 2008). An explanation of this finding may be due to common pathways of thrombopoiesis and progenitor cell mobility. Increased plasma levels of SDF-1 have been shown to enhance human thrombopoiesis and mobilise human colony forming cells in mice (Perez et al., 2004).

When using poor mobilisation (defined as a mobilisation of less than 2 x 10^6 CD34 cells/kg) as an outcome, both the retrospective and prospective analysis found that a negative difference between donor and recipient weight remained significantly associated with poor mobilisation in the multivariate analysis. My retrospective data showed that a lower volume of blood processed was significantly associated with poor mobilisation, this was not confirmed in the prospective analysis. The optimal volume of blood to be processed during apheresis remains an area of debate. Some authors

have suggested that apheresis of large volumes may be more efficient than standard volume leukapheresis (Passos-Coelho et al., 1997, Diaz et al., 2003, Bojanic et al., 2011), however several comparative studies have not been able to confirm this (Demirer et al., 2002, Schwarer et al., 2000, Anderlini et al., 2000).

The subject of improving CD34+ yields has been picked up recently by several registries and some have already started to alter their recruitment strategies. The preferential recruitment of male donors has been adopted by several. Increasing the minimum weight allowance at recruitment can also be considered. However, donor weight may have changed over time between joining and donation, given that some donors remain on the register for decades prior to being selected. One could also consider the preferential recruitment of younger donors. This has already been adopted by several registries, but mainly due to a different reason; several studies have shown that a lower donor age is associated with improved overall survival in the recipient (Kroger et al., 2013, Lanino et al., 2008). This finding has also led to transplant centres choosing the youngest donor at CT stage, if there is a choice of more than one fully HLA-matched potential donor.

Alternatively, groups at risk of poor mobilisation may benefit from a different mobilisation regimen in order to avoid additional procedures. Some studies have shown that G-CSF administered every 12h at doses of 5 or 6 µg/kg is associated with better yields compared to a dose of 10 µg/kg once daily, without an increase in morbidity (Kroger et al., 1999, Arbona et al., 1998, Kroger et al., 2000). The justification for a twice-daily schedule is based on the fact that the elimination half-life of G-CSF after subcutaneous injection is only 3 to 4 hours (de la Rubia et al., 2002). This twice-daily regimen is however associated with logistical difficulties and

increased costs as it involves twice daily nurse visits. It may also result in more donors having to take time off work during the injections. Most registries including our registry don't allow the self-administration of G-CSF given the low, but potentially life-threatening risk of anaphylaxis (Tulpule et al., 2009).

Plerixafor, a CXCR4 antagonist, could be of benefit in groups at risk of poor mobilisation. Plerixafor reversibly inhibits chemokine (CXC motif) receptor 4 (CXCR4) binding to stromal cell derived factor -1a (SDF -1a). Stem cells express CXCR4 and are known to migrate to the bone marrow through a chemo-attractant effect of SDF-1a that is produced locally by bone marrow stromal cells. Once in the marrow, it is also believed that stem cell CXCR4 can act to anchor these cells to stromal cell surface SDF-1a. Plerixafor induced leucocytosis and elevations in haematopoietic progenitor cell levels are thought to result from a disruption of these chemo-attractant and cell adhesion effects, resulting in the appearance of both mature and pluripotent stem cells in the systemic circulation (Broxmeyer et al., 2005). The pharmacokinetic behaviour of plerixafor is characterised by peak plasma levels occurring 0.5 – 1 hour after administration (Stewart et al., 2009, Cashen et al., 2008) and an elimination half-life of approximately 3 hours. The peripheral blood CD34+ count increases rapidly, with peaks seen 9-14 hours after administration. Plerixafor is currently only licensed for autologous donations. It was licensed for this indication following 2 large randomised clinical trials indicating safety and efficacy (table 3.15).

Table 3. 15 Core evidence for the use of plerixafor + G-CSF in autologous transplantation

Trial	Regimen	Outcome
Multiple myeloma randomised clinical trial (n = 302) (DiPersio et al., 2009b)	Salvage use following G-CSF monotherapy Failure to collect at least 0.8×10^6 CD34+ cells/kg after two apheresis days or 2×10^6 CD34+ cells/kg in four apheresis days	Safe and efficient HPC mobilisation for autologous BMT
Non Hodgkin lymphoma randomised clinical trial (n = 298) (DiPersio et al., 2009a)	Salvage use following G-CSF monotherapy Failure to collect at least 0.8×10^6 CD34+ cells/kg after two apheresis days or 2×10^6 CD34+ cells/kg in four apheresis days	Safe and efficient HPC mobilisation for autologous BMT

Studies using plerixafor in unrelated donors are limited, some have used plerixafor in monotherapy (table 3.16), others in combination with G-CSF (table 3.17).

Table 3. 16 Studies of PBSC mobilisation with plerixafor only

Study	Number of donors (n)	Plerixafor dose	Number of doses	Yield > 2 x 10^6 per kg of recipient weight n (%)
(Devine et al., 2008)	25	240 µg/kg	Up to 2	16/24 (67%) after 1 dose 22/24 (92%) after 2 doses
(Leotta et al., 2011)	1	240 µg/kg (in addition to 1 dose of G-CSF)	1	1 (100%)
(Lemery et al., 2011)	21	Variable doses up to 480 µg/kg	2	Not reported

Plerixafor appeared to be at least as safe as G-CSF in the short term, as no healthy unrelated donor experienced more than grade 1 toxicity (Devine et al., 2008, Hauge et al., 2013). The most frequently adverse reactions reported are injection site reactions, diarrhoea, nausea, paraesthesias and headache (Liles et al., 2003, Hubel et al., 2004, Devine et al., 2008). Devine et al reported no long-term consequences, with at least a median follow-up of 9 months after donation (Devine et al., 2008). Longer follow-up and greater numbers of donors will be needed to ascertain the overall safety of plerixafor in healthy volunteer donors.

Table 3. 17 Studies or case reports of PBSC mobilisation with G-CSF and plerixafor

Study	Number of donors (n)	Timing of plerixafor	Plerixafor dose	Yield > 2 x 10^6 per kg of recipient weight n (%)
(Hauge et al., 2013)	6	After 2 days of collection (n = 2) After 1 day of collection (n = 2) Based on peripheral blood CD34+ counts, before apheresis (n = 2)	240 µg/kg	6 (100%)
(Neumann et al., 2011)	1	After 1 day of collection	240 µg/kg	1 (100%)
(Schriber et al., 2011)	1	After 2 days of collection	240 µg/kg	1 (100%)

Combinations of G-CSF and plerixafor, using plerixafor as a salvage treatment, are promising and additive effects on the number of circulating progenitor cells when administered with G-CSF have been described (Liles et al., 2005). This off label use of plerixafor may be considered as an alternative to an emergency bone marrow harvest after failed mobilisation with G-CSF. Plerixafor incorporation in first-line mobilisation protocols in donors who are predicted to be poor mobilisers should be clarified in the future. Plerixafor has also been used as an “emergency” PBSC mobiliser in a normal donor for whom a routine bone marrow harvest attempt failed unexpectedly and the recipient had already undergone conditioning (Leotta et al., 2011). In this situation, the short time required for PBSC mobilisation with plerixafor may be a clear advantage. Studies in animal models have shown that delaying the

infusion of haematopoietic stem cells after conditioning with total body irradiation for longer than 4 days can lead to a significant risk of non-engraftment or graft failure (Ding et al., 2009). Mobilising with G-CSF alone would delay haematopoietic stem cell infusion by 5 to 6 days, which would increase the risk of rejection. However, the use of this agent in healthy donors is clearly limited by the fact that it is still unlicensed for this indication. I would recommend that registries set up or participate in clinical trials using plerixafor in this setting (http://clinicaltrials.gov/show/NCT01954914).

In conclusion, these studies show that female gender, a negative difference between donor and recipient weight, lower BMI and lower donor age are associated with a decreased likelihood of meeting the transplant physician's requested dose. This is clinically significant if there is a choice of more than one fully HLA-matched potential donor, in that a male or heavier or younger donor would be preferable. These findings may also influence future recruitment and mobilisation strategies.

Chapter 4. A prospective study to investigate the predictors of the donation experience in unrelated haematopoietic stem cell donors: Part I

A paper based on the findings of the study was published in the journal of Biology of Blood and Marrow Transplantation in February 2015 entitled "Pre-donation health related quality of life scores predict time to recovery in haematopoietic stem cell donors" (See Appendix 3)

4.1 Introduction

In the first chapter, I reviewed the most common physical and psychological reactions to the donation process and concentrated on groups of donors that are at increased risk of adverse reactions (table 1.4). The primary aim of this prospective study is to better understand the factors that influence donor recovery and that are most commonly associated with certain adverse reactions. Factors assessed include both demographic factors such as gender, age, ethnicity, weight, BMI, number of dependants, being a blood donor and marital status (outlined in this chapter) and baseline health related quality of life (HRQOL) scores using the Short-Form 36 Health Survey (SF-36) questionnaire, which will be described in the next chapter. The secondary aims of this study involve a description of the physical and psychological donation experience by comparing pre- and post-donation HRQOL markers (chapter 5). Other secondary aims also include an analysis of demographic and collection characteristics influencing PBSC (chapter 3) and BM yields (chapter 6).

An analysis of donor characteristics associated with poorer donation experiences is important, as donor stratification based on the anticipated donation risk may lead to changes in donor selection criteria, tailored donor counselling approaches or tailored supportive measures or follow-up procedures. As a preparation of this study, our regular donor follow-up system was altered in order allow for the collection of standardised donor follow-up data (section 3.2).

4.2 Materials and Methods

The full material and method can be found in chapter 2 (section 2.4).

4.3 Results

4.3.1 Characteristics, adverse reactions and recovery of BM and PBSC donors

Tables 4.1 and 4.2 show clinical and collection characteristics of BM and PBSC donors enrolled in the study. A central line was inserted in 5% of PBSC donors. 2% of male donors compared to 15% of female donors ($p < 0.001$) needed insertion of a central line. There was no difference in BMI between donors needing and not needing a central line ($p = 0.14$). 27% of PBSC donors (74/275) required a two day collection.

Table 4. 1 Donor characteristics at time of donation

Characteristic	PBSC (n)	%	BM (n)	%
Number of donors	275	88	37	12
Number of apheresis/ harvest centres	4		4	
Gender				
Male	210	76	33	89
Female	65	24	4	11
Ethnicity				
United Kingdom and Ireland	99	36	11	29
Europe (White)	161	58	22	61
Other (White)	4	2	1	2
Asian	3	1	0	0
African and Caribbean	2	0.5	1	2
Mixed ethnicity	2	0.5	0	0
Decline/unknown	4	2	2	6
Donor age at donation				
16-30	122	44.5	21	55
31-40	93	33.5	6	18
41-63	60	22	10	27
Median (range)	30.9 (17, 63)		27.9 (19, 55)	
Donor BMI				
Underweight (< 18.5)	3	1	0	0
Normal (18.5, 24.9)	100	36	14	37
Overweight (25, 29.9)	108	40	13	37
Obese (> 30)	53	19	10	26
Unknown	11	4	0	0
Median (range)	25.9 (17, 41.6)		26.7 (19.7, 33.9)	

Table 4. 2 Collection characteristics for PBSC and BM donors

Characteristic	
PBSC collection (n = 275)	
2 day collection	
n (%)	74 (27%)
Volume of blood processed on day 1 (litres)	
Median (range)	10.5 (3-17.6)
Volume of blood processed on day 2 (litres)	
Median (range)	10.5 (4.6-15.3)
Presence of a central line	
n (%)	14 (5%)
BM collection (n = 37)	
Volume of bone marrow collected (ml)	
Median (range)	1350 (290-1740)
Volume of bone marrow collected (ml)/kg donor weight	
Median (range)	15.0 (3.9-23.0)
Duration of procedure (mins)	
Median (range)	40 (20-120)
Difference (g/dl) between haemoglobin prior to donation and haemoglobin post donation	
Median (range)	2.6 (1.1-5.9)

Figures 4.1 and 4.2 show common adverse reactions experienced in PBSC donors and BM donors. Short term adverse reactions for both types of donation were very similar, but the temporal pattern differed. Pain in PBSC donors consisted mainly of bone pain or headache. Pain peaked during administration of G-CSF with 85% of donors experiencing pain of any type on the third day of G-CSF administration. The pain was graded as CTCAE 1 in 80% of cases, only 1 donor experienced grade 3 pain. Pain in BM donors was generally localised to the site of donation or the throat

(following incubation). The peak of pain for BM donors was reported on day 2-3 following donation for back pain (76.5 %) and on the day of donation for throat pain (48.6%). For BM donors, most side-effects were classified as CTCAE grade 1, no donors experienced grade 3 or 4 side-effects in this small cohort. All apart from 1 donor were discharged from hospital the day following BM harvest. Fatigue and bruising were the most common other adverse reactions of both BM and PBSC donors.

Figure 4. 1 Frequency of common side-effects following PBSC donation

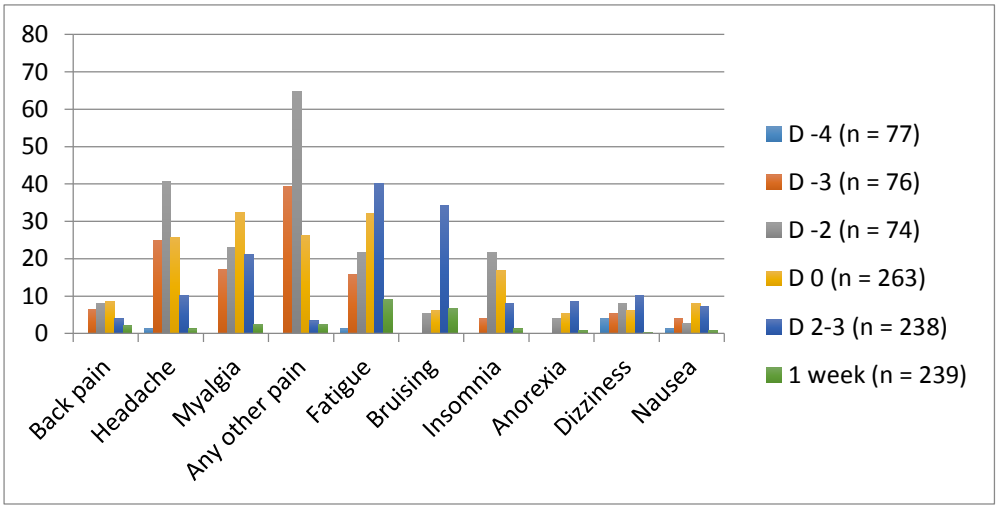
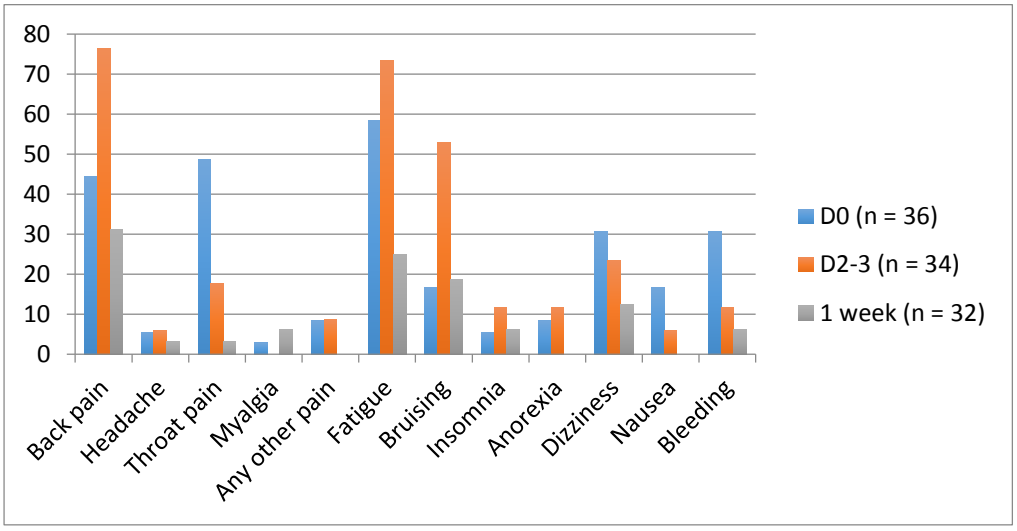


Figure 4. 2 Frequency of common side-effects following BM donation



The peak of these symptoms was day 2-3 following donation for both types of donation. Fatigue was experienced in 40.0% of PBSC donors; bruising in 34.2 %. For BM donors, fatigue was experienced in 73.5% and bruising in 53.4% of donors. Only one BM donor was started on iron replacement following donation, his haemoglobin had fully recovered at 4 weeks post donation. 2/26 donors that were not started on iron replacement had not recovered their haemoglobin at 4 weeks (defined as haemoglobin < 13 g/dl in men and < 11.5 g/dl in women). Both donors were started on iron replacement at 4 weeks following donation.

The mean time to recovery for BM donors was 14.3 days as opposed to 5.2 days for PBSC donors ($p < 0.001$) (figure 4.3). Only 50% of BM donors felt they had recovered after 1 week and 68.8% had returned to work, compared to 90.3% and 98.3% of PBSC donors respectively ($p < 0.001$). Pain was experienced significantly more in BM donors compared to PBSC donors 1 week following donation ($p < 0.001$). 75% (207/278) of PBSC donors required analgesia during G-CSF administration and 2.5% of donors still required analgesia 7 days following donation, as opposed to 10% of BM donors still needing analgesia at 7 days (3/29). BM donors also reported more adverse reactions in general compared to PBSC donors 1 week following donation ($p < 0.001$). When asked the questions about how donors felt physically or emotionally 1 week after donation, BM donors felt physically worse compared to PBSC donors ($p = 0.001$), but felt similar emotionally (figure 4.4).

Three donors experienced a serious adverse reaction (0.9%); all were PBSC donors. One young, male donor developed grade 3 back pain after administration of the 2nd dose of G-CSF. He required intravenous morphine, but was able to continue G-CSF injections at the same dose whilst receiving codeine and paracetamol at home. A

second donor developed gout 1 day after PBSC donation. He had never experienced gout before and it was felt that this was likely associated with G-CSF administration. A third donor developed palpitations following PBSC donation. This was further investigated and she was diagnosed as having a sinus tachycardia most likely to be related to psychological stress. Her symptoms, however, only resolved after several weeks.

Figure 4. 3 Probability of self-reported complete recovery after PBSC vs. BM donation

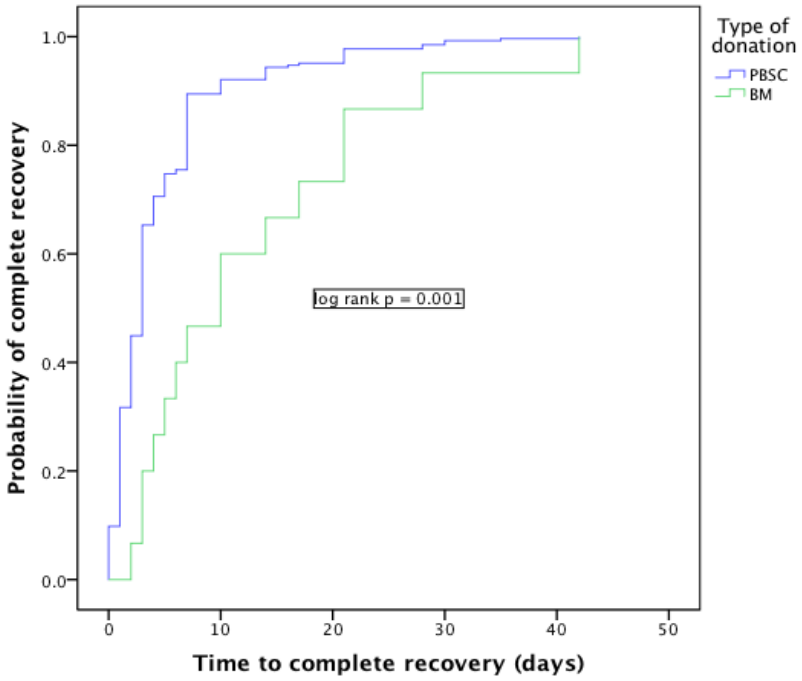
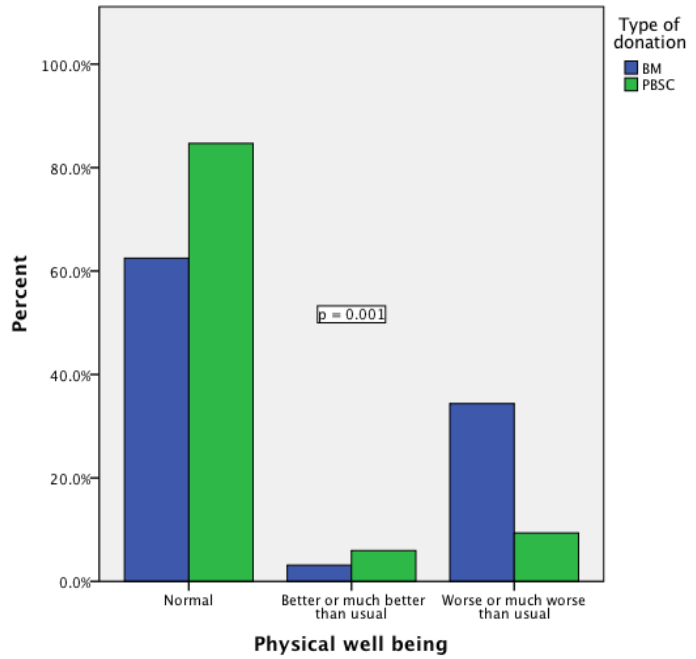
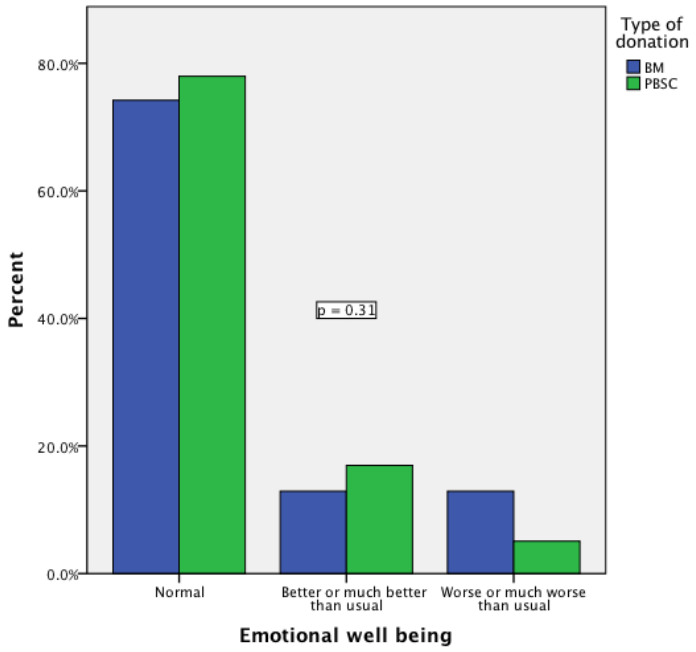


Figure 4. 4 Physical and emotional well-being 1 week following donation in BM and PBSC donors





4.3.2 Demographic and collection characteristics predicting time to complete recovery

4.3.2.1 PBSC donors

The factors influencing time to recovery in univariate analysis were gender and age (figure 4.5 a, b and table 4.3); donors of younger age or male gender were more likely

to recover more rapidly. There was no significant association between BMI (p = 0.23), marital status (p = 0.23), being a blood donor (p = 0.37), number of days of collection (p = 0.1), volume of blood processed on day 1 (p = 0.51) or day 2 (p = 0.77) or pre-harvest white blood cell count (p = 0.85) and time to recovery. There was a trend towards statistical significance for the number of dependants (p = 0.057) (figure 4.5 c and table 4.3); donors with fewer dependants were more likely to recovery faster compared to donors with more dependants. The absence of a central line also has a borderline association with a faster recovery (p = 0.067) (figure 4.5 d and table 4.3).

Figure 4. 5 Factors predicting probability of self-reported recovery after PBSC donation

Figure 4. 5a. Gender predicts probability of self-reported complete recovery after PBSC donation

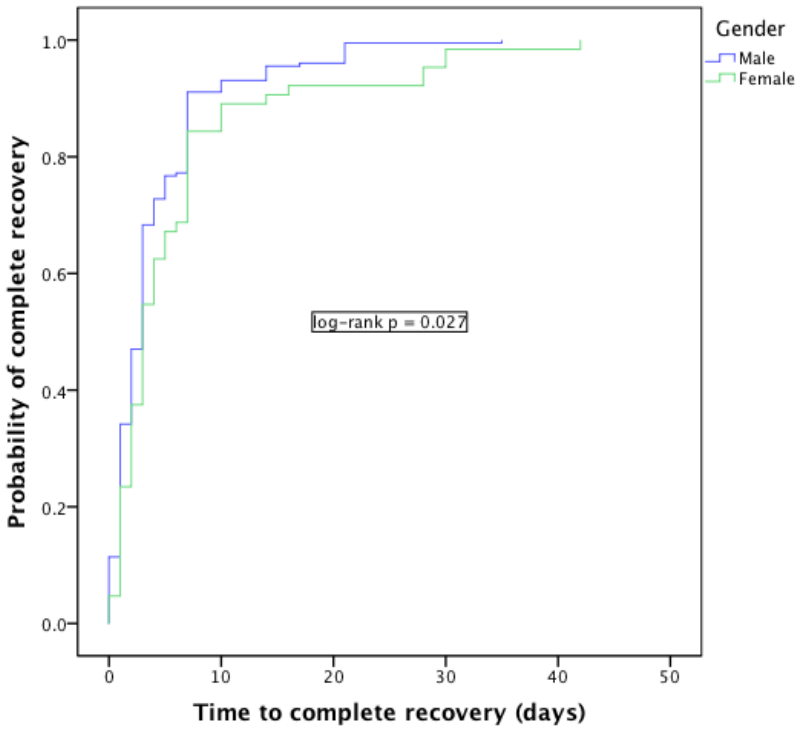


Figure 4. 5 b Age predicts probability of self-reported complete recovery after PBSC donation

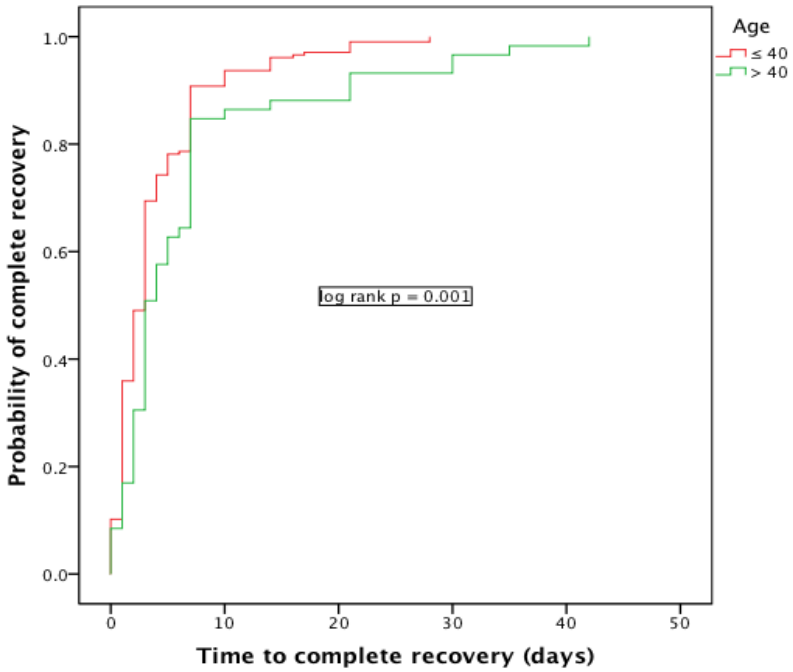


Figure 4. 5c. Number of dependants and probability of self-reported complete recovery after PBSC donation

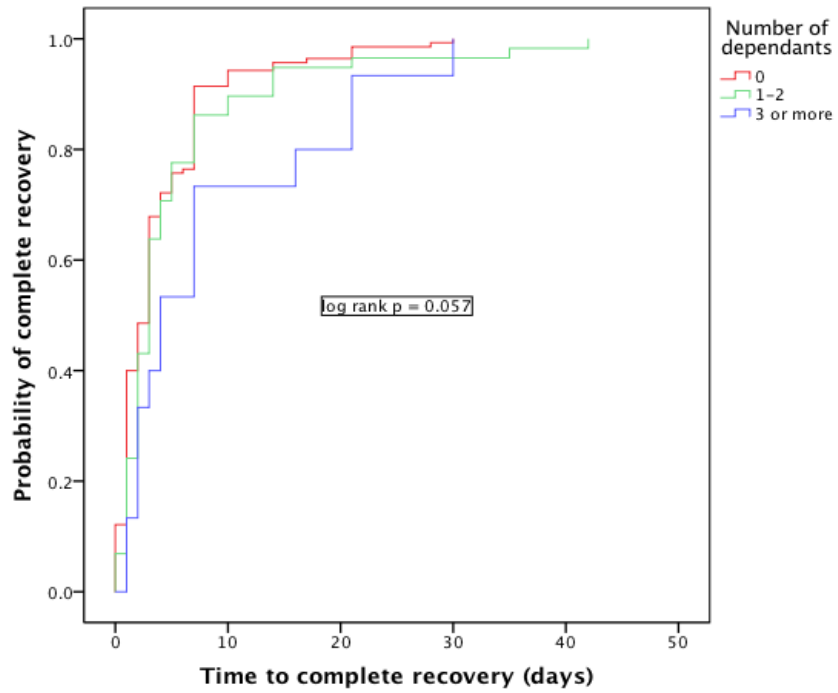


Figure 4. 5d Presence of a central line and probability of self-reported complete recovery after PBSC donation

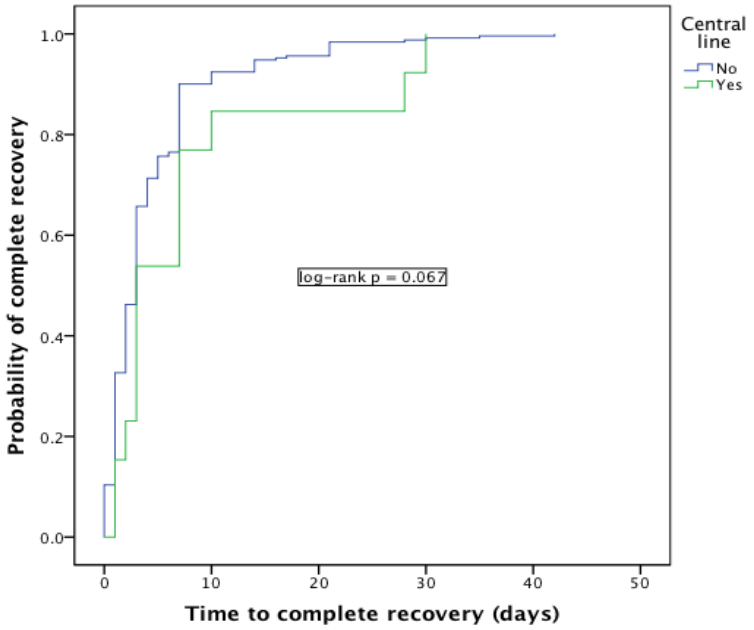


Table 4. 3 Univariate analysis of factors influencing time to recovery following PBSC donation. Time to complete recovery documented for 266 donors (missing data n = 9).

Factors (n)	Time to complete recovery (days) Mean (range)	p-value
Gender		= 0.027
Male (202/266)	4 (0-35)	
Female (64/266)	6 (0-42)	
Age		= 0.003
≤ 30 (116/266)	3.5 (0-28)	
30-40 (91/266)	4.3 (0-28)	
> 40 (59/266)	6.8 (0-42)	
Number of dependants		= 0.057
0 (140/266)	3.94 (0-30)	
1-2 (58/266)	5.16 (0-42)	
3 or more (15/266)	8.64 (1-30)	

Missing data (53/266)		
Central line		= 0.067
Yes (13/266)	8.08 (1-30)	
No (252/266)	4.35 (0-42)	
Missing data (1/266)		

Younger age remained significantly associated with a faster time to complete recovery in multivariate analysis (table 4.4); the probability of a faster recovery was 50% higher in donors aged ≤ 40 compared to donors aged > 40 (HR 1.5; 95% CI 1.1-2.0; p = 0.009).

Table 4. 4 Multivariate analysis of factors influencing time to recovery following PBSC donation (using age as categorical variable)

Factor	p-value	HR (95% CI)
Age (Categorical)	= 0.009	
≤ 40		1.5 (1.1-2.0)
> 40		1
Gender	= 0.087	
Male		1.3 (0.96-1.7)
Female		1

4.3.2.2 BM donors

There was no statistically significant association between gender (p = 0.18), age (p = 0.42), BMI (p = 0.88), marital status (p = 0.62), number of dependants (p = 0.21) and time to recovery. Although not statistically significant, male gender and a lower number of dependants appeared to be associated with faster recovery (figure 4.6 a, b and table 4.5). There was no significant association between duration of the procedure (p = 0.98), volume of BM harvested per kg donor weight (p = 0.95),

haemoglobin following donation (p = 0.57), the difference between pre and post haemoglobin (p = 0.80) and time to recovery

Figure 4. 6 Factors associated with self-reported recovery after BM donation

Figure 4. 6a. Gender and probability of self-reported complete recovery after BM donation

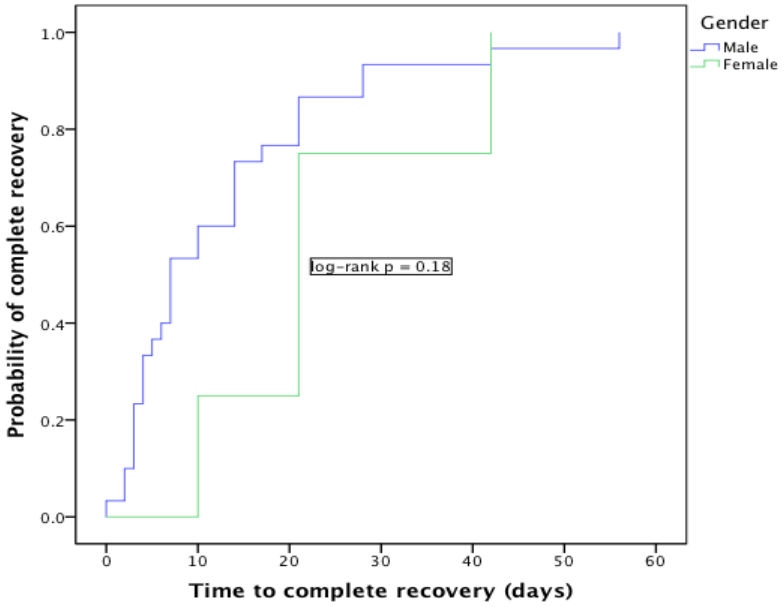


Figure 4. 6b. Number of dependants and probability of self-reported complete recovery after BM donation

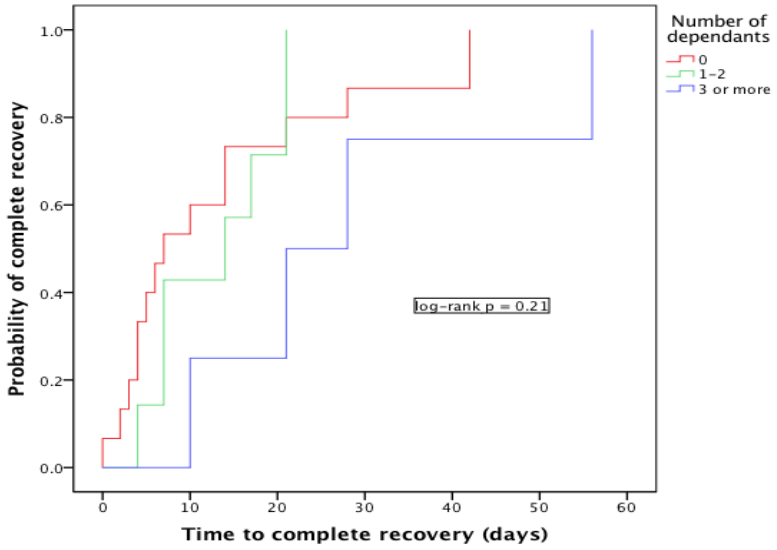


Table 4. 5 Univariate analysis of factors influencing time to recovery following BM donation

Factors (n)	Time to complete recovery (days) Mean (range)	p-value
Gender		= 0.18
Male (30)	12.6 (0-56)	
Female (4)	23.5 (10-42)	
Number of dependants		= 0.21
0 (15)	13 (0-42)	
1-2 (7)	13 (4-21)	
3 or more (4)	28.75 (10-56)	

4.3.3 Demographic and collection characteristics predicting adverse reactions

4.3.3.1 PBSC donors

Table S1 appendix 1 shows the univariate analysis of demographic and collection characteristics influencing adverse reactions at different time points following PBSC donation. Only factors that remained significant (or borderline significant) in the multivariate analysis are shown in table 4.6. Table 4.7 displays the multivariate analysis of factors influencing the occurrence of any adverse reaction at different time points. Factors taken into account include age, gender, BMI, being a blood donor, number of dependants, presence of a central line, one versus two day collection and pre-harvest white blood cell count.

Table 4. 6 Multivariate analysis of factors influencing adverse reactions at different time points following PBSC donation. All time points are defined as the day of donation (D 0), 2-3 days after donation (D2-3) and weekly after donation up until full recovery. Factors taken into account include age, gender, BMI, being a blood donor, number of dependants, presence of a central line, number of days of collection and pre-harvest white cell count.

Outcome: Symptom and time point	**Factor**	**p-value**	**OR (95% CI)**
Bruising D0	Central line	= 0.016	
	Yes		6.9 (1.4-33.2)
	No		1
Fatigue D 0	Gender	= 0.014	
	Male		1
	Female		2.2 (1.2-4.0)
Headache D 0	Gender	= 0.005	
	Male		1
	Female		2.8 (1.4-6.9)
	Number of dependants	=0.039	
	0		1
	1-2		1
	3 or more		4.0 (1.1-14.5)
Nausea D 0	Age (continuous)	= 0.011	0.91 (0.85-0.98)
Summary Pain D 0	Gender	= 0.018	
	Male		1
	Female		2.5 (1.2-5.5)
Bruising D 2-3	BMI (continuous)	0.006	1.1 (1.03-1.2)
	Central line	= 0.007	
	Yes		7.0 (1.7-29.2)
	No		1

	Second day collection	< 0.002	
	Yes		4.1 (2.0-8.3)
	No		1
Headache D 2-3	BMI (continuous)	= 0.026	1.1 (1.02-1.3)
Bruising 1 week	Central line	= 0.027	
	Yes		9.2 (1.3-65.3)
	No		1
All time points	Gender (F/M)	= 0.028	
fatigue	Male		1
	Female		1.9 (1.07-3.5)
	Age (continuous)	= 0.018	1.04 (1.01-1.07)
All time points	Central line	= 0.002	
bruising	Yes		26.7 (3.4-208.2)
	No		1
	Second day collection	= 0.005	
	Yes		2.3 (1.3-4.1)
	No		1
All time points	Central line	= 0.004	
bleeding	Yes		43.6 (3.3-572.6)
	No		1
All time points	Number of dependants	= 0.052	
headache	0		1
	1-2		1
	3 or more		3.1 (0.99-9.5)

Table 4. 7 Multivariate analysis of factors influencing the occurrence of any adverse reaction at D0 or D2-3 following donation. Factors taken into account include age, gender, BMI, being a blood donor, number of dependants, presence of a central line, number of days of collection and pre-harvest white cell count.

Outcome: Symptom and time point	Factor	p-value	OR (95% CI)
Summary all adverse reactions D 0	Gender	= 0.018	
	Male		1
	Female		2.8 (1.1-7.3)
Summary all adverse reactions D 2-3	Gender	= 0.041	
	Male		1
	Female		2.2 (1.03-4.5)
	BMI (continuous)	= 0.067	1.06 (0.97-1.1)

4.3.3.1.1 Gender

Women had an odds ratio of experiencing fatigue of 1.9 (95% CI 1.07-3.5; p = 0.028) at all time points compared to men. Experiencing any type of pain (including back pain, headache, myalgia or other pain) on the day of donation was also associated with female gender with an odds ratio of 2.5 (95% CI 1.2, 5.5; p = 0.018). Women were even more likely to experience any adverse reaction on the day of donation compared to men (OR 2.8, 95% CI 1.1, 7.3; p = 0.018) and on day 2-3 following donation (OR 2.2, 95% CI 1.03, 4.5; p = 0.041). They were also more likely to experience bleeding symptoms at all time points (p = 0.047) in univariate analysis, but this lost significance in multivariate analysis, when taking the presence of a central line into account.

4.3.3.1.2 Age

Younger age was the only factor significantly associated with nausea on day 0 (p = 0.011) with younger donors being more likely to experience nausea. Fatigue at any time point was also associated with age (p = 0.018); donors aged > 40 had on odds ratio of experiencing fatigue of 1.9 (95% CI 1.02-3.5) compared to donors aged ≤ 40.

4.3.3.1.3 BMI

Donors with a higher BMI were more likely to experience headache following donation (p = 0.026)**.**

4.3.3.1.4 Number of dependants

Headache on the day of donation or at any time point was associated with the number of dependants. Donors who had 3 or more dependants had an odds ratio of 4 of experiencing headache (95% CI 1.1-14.5; p-value 0.039) on the day of donation compared to donors with less than 3 dependants.

4.3.3.1.5 Presence of central line

A central line was inserted in 5% of PBSC donors. The insertion of a central line was associated with bruising (OR 26.7, 95% CI 3.4-208.2; p = 0.002) and bleeding symptoms (OR 43.6, 95% CI 3.3-572.6; p = 0.004) at any time point.

4.3.3.2 BM donors

Table S3 appendix 1 displays the univariate analysis of demographic and collection characteristics associated with individual adverse reactions. Factors taken into account for the multivariate analysis include age, gender, BMI, being a blood donor,

number of dependants, duration of the procedure and volume of BM harvested per kg donor weight.

4.3.3.2.1 Age

Younger age was the only factor associated with symptoms of vomiting at any time point ($p < 0.001$). Younger age was also associated with increased symptoms of anorexia following donation ($p < 0.001$), but this lost significance in multivariate analysis ($p = 0.31$).

4.3.3.2.2 Number of dependants

A higher number of dependants was associated with myalgia ($p = 0.002$) at any time point following donation in univariate analysis, but this lost significance in multivariate analysis ($p = 0.99$).

4.3.3.2.3 Volume BM harvested per kg donor weight

A larger volume harvested per kg donor weight was associated with anorexia at any time point ($p = 0.003$) and this remained borderline significant in multivariate analysis ($p = 0.069$).

A larger volume harvested per kg donor weight was associated ($p = 0.03$) with symptoms of bruising at any time point in univariate analysis, but this lost significance in mulitivariate analysis ($p = 0.19$).

4.3.3.2.4 Duration of procedure

A longer duration of the procedure was the only factor associated with fatigue following donation in univariate analysis ($p = 0.013$).

4.4 Discussion

This chapter prospectively assesses the donation experience in AN donors and defines groups at increased risk of poorer donation experiences, based on donor demographic factors and collection characteristics. To allow for a more detailed understanding of the donation experience, I introduced comprehensive data tools into our register. These tools include assessments modelled on key toxicities donors regularly experience and their CTCAE grading. Assessments took place on the first 3 days of G-CSF administration, the day of donation, 2-3 days following donation and weekly until complete recovery. Nearly 100% of the day of donation assessments were obtained, as well as > 85% of assessments of day 2-3 and weekly assessments. Complete recovery was determined on the day 2-3 or weekly questionnaire and defined as the absence of ongoing symptoms as well as return to pre-donation health (self-reported).

This study found that the majority of both PBSC and BM donors reported ARs, however ARs were mainly classified as mild and the incidence was consistent with those previously described by other centres (Karlsson et al., 2004, de la Rubia et al., 2008, Pulsipher et al., 2013, Pulsipher et al., 2009b, Murata et al., 1999, Chen et al., 2011, Miller et al., 2008, Holig et al., 2009, Fortanier et al., 2002, Martino et al., 2009, Gandini et al., 2001, Nishimori et al., 2002, Favre et al., 2003, Stroncek et al., 1993). I found that 5% of donors required the insertion of a central line, this is in accordance with the experiences from most other centres (Pulsipher et al., 2013, Anderlini et al., 1999), although some centres have reported lower (Leitner et al., 2009, Holig et al., 2009) or higher (Miller et al., 2008) rates. Our policy allows for central venous lines to be placed in the donor if blood flow from the standard peripheral venous line is not adequate. The placements of central lines are one of the leading causes of SARs and

should generally be discouraged. One study reported that 5 of the 39 SARs were complications from central line placements (Miller et al., 2008). In addition, one unrelated donor death reported to the WMDA was caused by a traumatic jugular vein catheter insertion (Shaw et al., 2013). No SARs were related to the insertion of central lines in this cohort. We did not consistently document data on the position of central lines. Women were much more likely to require a central line, this was also observed in a previous study (Pulsipher et al., 2013) and may be explained by their smaller body sizes and smaller veins compared to men.

The peak of discomfort was on the third day of G-CSF for PBSC donors and on day 2-3 following collection for BM donors, these results are similar to data from a large prospective NMDP trial (Pulsipher et al., 2013). The majority of ARs were CTCAE grade 1, this is also consistent with previous reports (Pulsipher et al., 2013). Our register did not document adverse reactions on the 4th day of G-CSF and the incidence of ARs may have been even higher on this day. BM and PBSC donors experienced approximately the same levels of pain on their peak day of discomfort. However, a significant number of BM donors still experienced pain 1 week following donation and BM donors recovered significantly slower compared to PBSC donors (14.3 versus 5.2 days). This is in keeping with previous reports (Pulsipher et al., 2013, Favre et al., 2003, Heldal et al., 2002, Bredeson et al., 2004, Siddiq et al., 2009). All donors recovered fully after some period of time and the longest time to self-reported recovery was 56 days for a BM donor.

0.9% of PBSC donors experienced a SAR, this again is similar to published reports (Pulsipher et al., 2014, de la Rubia et al., 2008, Pulsipher et al., 2009b, Miller et al., 2008, Holig et al., 2009). No BM donor experienced a SAR.

There were no PBSC collection characteristics that influenced the time to complete recovery. The only donor factor that influenced recovery time in multivariate analysis for PBSC donors was donor age, with donors > 40 recovering significantly slower. Older age was also associated with increased symptoms of fatigue following donation. This has been previously reported (Yuan et al., 2010, Pulsipher et al., 2013). Our BM cohort was too small to obtain any statistically significant results when examining the relationship between the different characteristics and recovery, but female gender and having a higher number of dependants appeared to be associated with a slower recovery. Our BM cohort was also too small to assess the influence of the different characteristics on individual adverse reactions in multivariate analysis.

Female PBSC donors were more likely to experience any adverse reaction, in particular pain and fatigue. This has also been previously reported (Martino et al., 2009), Pulsipher et al., 2013, Pulsipher et al., 2009b, Murata et al., 1999, Chen et al., 2011, Stroncek et al., 1996). The explanation for these findings is likely multifactorial. Higher pain scores in a number of conditions in women have been described in research in other medical specialties (Ruau et al., 2012). This may signify a gender difference in pain experience (Ruau et al., 2012) and physical performance (Taenzer et al., 2000). In addition, women have been found to experience more drug side effects, this may be explained by hormonal, immunological and pharmacokinetic differences (Rademaker, 2001). Yuan et al stated that a smaller total blood volume in women may partially explain the increased incidence of citrate toxicity (Yuan et al., 2010). Despite the increased risk of adverse reactions, gender was not significantly associated with recovery in PBSC donors in the multivariate analysis.

Donors with a higher BMI were more likely to experience headache following PBSC donation. This may be a result of relatively higher doses of G-CSF received in this group (Chen et al., 2011) since extracellular fluid and haematopoietic mass do not increase in direct proportion to BMI. The headache was mainly classified as grade I. I did not find an increase in other adverse reactions, as opposed to some other studies (Pulsipher et al., 2009b, Pulsipher et al., 2013). This finding is reassuring, given that more and more registries allow heavier donors to donate, including our register and donors with BMIs up to 40 were included in this cohort.

My data did not show a negative relationship between pre-harvest white blood cell count and recovery or adverse reactions. This is in keeping with current advice stating that there is no indication for monitoring white cell counts during administration of G-CSF, as no conclusive evidence of a link between baseline haematology results and ARs exists (Chen et al., 2011, Pulsipher et al., 2013). Donors who are found to be at unacceptably high risk of adverse reactions are generally excluded from donation. For example the knowledge that G-CSF can cause exacerbations of auto-immune disease (Pamphilon et al., 2008) has led to stricter eligibility criteria concerning auto-immune diseases within many stem cell registries. Selection criteria could be altered in the future based on the awareness that certain donors are at increased risk of adverse reactions. Some registers have already started to concentrate on the recruitment of male donors. Although this is often driven by increased availability and stem cell yields amongst males and a decreased incidence of graft-versus-host disease (Spierings et al., 2013) in the recipient, it may also result in fewer ARs (Ings et al., 2006, Vasu et al., 2008, Platzbecker et al., 2005, Miflin et al., 1996) in the donor. On the other hand, restricting the recruitment to male donors may influence the numbers of donors on the register and consequently availability of HSCs and the overall HLA repertoire. Similarly, the finding that older donors (40 years was the cut-

point found in my study) are at a higher risk of a delayed recovery and experiencing SARs, could further enhance the trend towards recruiting younger donors. Additionally, younger donors are less likely to have dependants, and this was found to be a risk factor for headache following donation. The practice of registries recruiting younger donors is currently mainly driven by the finding that transplant outcomes are improved when using these donors (Kroger et al., 2013, Ayuk et al., 2013, Kollman et al., 2001), but has clear additional advantages. Some studies have shown that donors who are overweight (BMI > 25) or obese (BMI > 30) experience more bone pain (Pulsipher et al., 2013, Chen et al., 2014). Given that several studies have reported a positive correlation between donor weight and stem cell yields (Anderlini et al., 1997, Martino et al., 2006), restricting recruitment to "lighter" donors would carry an inherent conflict. However, both my data and the studies mentioned above show that these adverse reactions are mainly graded I, meaning they are mild. Based on this, accepting donors with higher BMIs may be acceptable practice as long as these donors are well informed. Giving a lower dose of G-CSF to overweight donors or calculating the dose based on ideal body weight, could also be considered. Further research will have to establish whether this practice provides sufficient HSCs.

The management of donors' expectations is important, especially in donors at increased risk of adverse reactions. PBSC donors at higher risk such as overweight, female or older donors must be made aware of this at the time of their medical assessment and pre-operative patient education has demonstrated improved recovery times in surgery (Ibrahim et al., 2013, GTA, 2005). It may be that improved pre-donation education regarding symptom anticipation and management would reduce anxiety and improve the overall donation experience. Other possible interventions for high risk donors may include the use of pre-emptive analgesia, an approach that has proven to be effective in BM donors (Chern et al., 1999) and

general surgery patients (Mardani-Kivi et al., 2013, Duellman et al., 2009). This is a strategy overweight PBSC donors may benefit from. In addition, a more stringent short-term follow-up could be considered in donors who are at increased risk to allow early intervention. This may for example involve regular phone calls following donation.

Chapter 5. A prospective study to investigate the predictors of the donation experience in unrelated haematopoietic stem cell donors: Part II

A paper based on the findings of the study was published in the journal of Biology of Blood and Marrow Transplantation in February 2015 entitled "Pre-donation health related quality of life scores predict time to recovery in haematopoietic stem cell donors" (See Appendix 3)

5.1 Introduction

The previous chapter identified several donor characteristics such as gender and age that can influence donor recovery and adverse reactions. Part II of my prospective study will focus on the influence of baseline health related quality of life (HRQOL), including physical and mental health on the donation experience. Research in orthopedic surgery has shown a significant relationship between pre-operative HRQOL and recovery (Browne et al., 2014, Gong and Dong, 2014). Specifically, negative mood was shown to exacerbate pain. Given that pain is the most common side-effect in the peri-donation period, investigation into the relationship between pre-donation HRQOL and recovery may also be relevant in the haematopoietic stem cell donation setting.

I describe the role of pre-donation HRQOL scores, using the SF-36 form, and determine whether HRQOL scores could be used in addition to, or even replace, donor or collection characteristics in determining the donation risk. I will also explore the option of risk-stratifying donors and will prepare a proposal for a tailored approach for donors in different risk groups.

In addition, I will describe the changes in HRQOL, using the SF-36 form, following donation by examining the evolution of HRQOL scores at baseline, 4 weeks and 3 months following donation and compare the scores between PBSC and BM donors. This chapter will also aim to identify factors that may influence long-term physical or emotional health following donation.

5.2 Materials and methods

The full material and method can be found in chapter 2 (section 2.4). In brief, the SF-36 questionnaire measures the following 8 dimensions: physical functioning (PF), role limitations due to physical health problems (RP), bodily pain (BP), general health perception (GH), vitality (VT), social functioning (SF), role limitations due to emotional problems (RE) and general mental health (MH). The Physical Component Summary (PCS) and Mental Component Summary (MCS) scores provide a broad physical and mental health perspective (Ware, 2008). Norm based scoring was used to interpret the different dimensions' and summary scores (Ware, 2008). This scoring is created by computing the 0-100 score for a scale and then adjusting this score by the general population's average and standard deviation on that scale. As a consequence, the population mean and standard deviation of all scores are 50 and 10 respectively with higher scores reflecting more positive health states.

5.3 Results

5.3.1 HRQOL forms

The response rates for the SF-36 questionnaires for PBSC donors were 72% (198/275) before donation, 72% (199/275) 4 weeks after and 72% (198/275) 3 months

after donation. Fifty-eight percent of PBSC donors returned all three questionnaires. 16/275 donors were not provided with SF-36 forms as they had not provided verbal consent. 14/16 were not contactable; they did not respond to at least three telephone calls or at least one e-mail. The remaining two donors did not provide verbal consent, as they stated they were not interested in the study. The remaining non returned forms were from donors who had consented to participate in the study but who didn't return the questionnaire, despite reminders. Donors not returning the forms were more likely to be younger ($p < 0.001$) and male ($p < 0.05$) (table 5.1). There was no statistical difference between collection characteristics in those returning compared to not returning forms (table 5.1).

Table 5. 1 Demographic and collection characteristics in respondents and non-respondents (PBSC)

Measurement	Age (years) Mean (range)	Gender (% male)	Total volume of blood processed (range)	Donors with a 2 day collection (% of total)	Presence of a central line (%)
Baseline					
Respondents (n = 198)	34.1 (17-60)	73%	14.2 (1.5-32)	27%	5.5%
Non respondents (n = 77)	30.6 (20-63)	86%	14.8 (1.3-30.6)	27%	4%
p-value	**< 0.005**	**< 0.05**	0.39	0.99	0.77
4 weeks following donation					

Respondents (n = 198)	34.6 (17-63)	72%	14.1 (1.5-32)	28%	5%
Non respondents (n = 77)	29.4 (20-50)	88%	15.0 (1.3-30.6)	25%	5%
p-value	**< 0.001**	**< 0.005**	0.24	0.65	0.99
3 months following donation					
Respondents (n = 197)	34.6 (17-63)	72%	14.5 (1.3-32)	30%	5.5%
Non respondents (n = 78)	30.1 (20-50)	85%	14.3 (8.7-27.2)	21%	4%
p-value	**< 0.001**	**< 0.05**	0.77	0.11	0.78
All 3 questionnaires					
Respondents (n = 157)	34.7 (17-60)	71%	14.3 (1.5-32)	29%	5%
Non respondents (n = 118)	31.0 (20-63)	83%	14.5 (1.3-30.6)	25%	5%
p-value	**< 0.001**	**< 0.05**	0.72	0.49	0.99

The response rates for the questionnaires for BM donors were 75% (28/37) before donation, 59.5% (22/37) 4 weeks after donation and 67.6% (25/37) 3 months after donation. Forty-nine percent (18/37) of BM donors returned all three questionnaires. Only 1 out of 37 donors did not provide verbal consent, as he stated that he was too busy to participate in the study. There were no statistical differences in demographic and collection characteristics in those returning vs. not returning forms (table 5.2).

Table 5. 2 Demographic and collection characteristics in respondents and non-respondents (BM)

Measurement	Age (years) Mean (range)	Gender (% male)	Duration of BM harvest (min) Mean (range)	Marrow harvested per unit of donor's weight (ml/kg) Mean (range)
Baseline				
Respondents (n = 28)	32.1 (19-55)	89.7%	42.5 (20-120)	14.6 (3.9-23.0)
Non respondents (n = 9)	31.1 (22-46)	88.9%	35 (30-45)	14.7 (7.7-22.1)
p-value	0.79	0.95	0.46	0.93
4 weeks following donation				
Respondents (n = 22)	31.3 (19-55)	86.4%	39.5 (20-100)	15.3 (4.2-23.0)
Non respondents (n = 15)	32.6 (22-47)	93.8%	31.8 (25-120)	13.6 (3.9-20.3)
p-value	0.71	0.62	0.80	0.24
3 months following donation				
Respondents (n = 25)	32.0 (19-55)	92%	44.2 (20-120)	14.1 (4.2-22.0)
Non respondents (n = 12)	31.6 (22-46)	84.6%	33.3 (25-40)	13.8 (3.9-22.1)
p-value	0.90	0.60	0.25	0.38

All 3 questionnaires				
Respondents (n = 18)	32.9 (19-55)	90%	39.8 (20-100)	14.9 (4.2-22.0)
Non respondents (n = 19)	30.9 (22-47)	88.9%	31.2 (25-120)	14.3 (3.9-22.1)
p-value	0.56	0.99	0.88	0.65

5.3.2 Baseline HRQOL scores predicting time to complete recovery

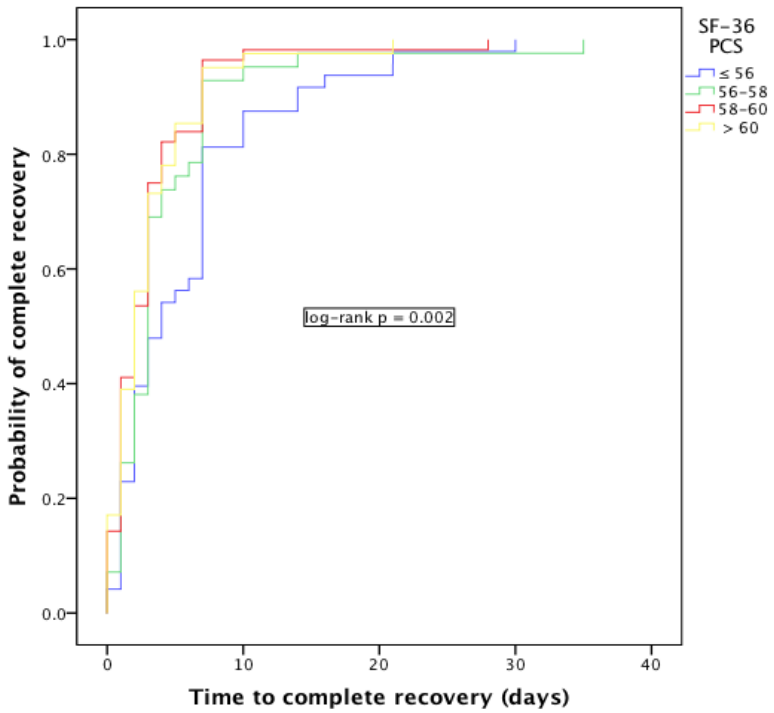
5.3.2.1 PBSC donors

Donors with a higher baseline physical component summary (PCS) score were more likely to recover more rapidly ($p = 0.002$) (table 5.3, figure 5.1). When assessing the individual components of the physical component summary, higher physical functioning (PF) ($p < 0.01$), less role limitations due to physical health problems (RP) ($p < 0.05$) and lower bodily pain (BP) ($p = 0.005$) were associated with a more rapid recovery. Baseline mental component summary score ($p = 0.29$) was not significantly associated with time to recovery.

Table 5. 3 Univariate analysis of factors influencing time to recovery following PBSC donation. Time to complete recovery documented for 266 donors (missing data n = 9).

Factors (n)	Time to complete recovery (days) Mean (range)	p-value
PCS		= 0.002
≤ 56 (49/266)	5.8 (0-30)	
56-58 (43/266)	4.3 (0-35)	
58-60 (57/266)	3 (0-28)	
> 60 (43/266)	3 (0-21)	
Missing PCS data (74/266)		

Figure 5. 1 Physical component summary score predicts probability of self-reported complete recovery after PBSC donation



When I repeated the multivariate analysis considering the PCS and donor demographic factors (described in chapter 4), baseline PCS score and age remained significant (table 5.4), while gender lost its significance.

Table 5. 4 Multivariate analysis of factors influencing time to recovery following PBSC donation (age and PCS as continuous variables)

Factor	p-value	HR (95% CI)
PCS (continuous)	= 0.013	1.057 (1.01-1.1)
Age (continuous)	= 0.026	0.98 (0.97-0.99)
Gender	= 0.26	
Male		1.2 (0.87-1.7)
Female		1

Donors with a baseline PCS higher than 56 had a 50% higher probability of faster recovery compared to donors with scores lower or equal to 56 (lowest quartile) (HR 1.5; 95% CI 1.06-2.06; p = 0.023). Donors aged less or equal to 40 had a 50% higher probability of faster recovery compared to donors over 40 (HR 1.5; 95% CI 1.06-2.06; p = 0.023).

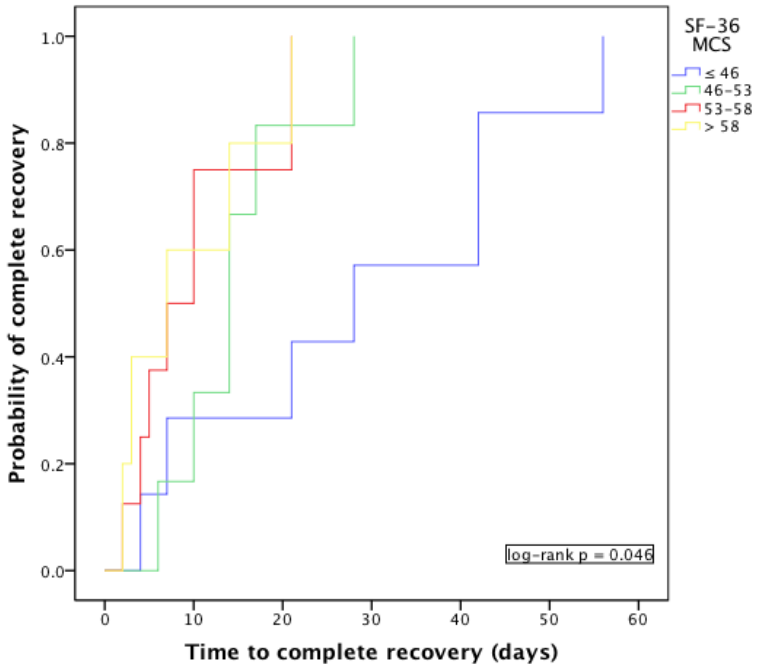
5.3.2.2 BM donors

The only factor influencing time to recovery was the baseline mental component summary (MCS) score (p = 0.046); donors with higher scores were more likely to recover more rapidly (table 5.5, figure 5.2). There was a borderline significant association between physical component summary score (p = 0.077) and time to recovery.

Table 5. 5 Univariate analysis of factors influencing time to recovery following BM donation

Factors (n)	**Time to complete recovery (days) Mean (range)**	**p - value**
MCS		p = 0.046
≤ 46 (7/28)	28 (4-56)	
46 – 53 (7/28)	13.7 (6-28)	
53 – 58 (9/28)	10 (2-21)	
> 58 (5/28)	9.4 (2-21)	
Missing MCS data (n = 9)		

Figure 5. 2 Mental component summary score predicts probability of self-reported complete recovery after BM donation



As mentioned in 4.3.2.2, no demographic or collection characteristics were significantly associated with recovery. In multivariate analysis, donors with baseline MCS scores higher than 46 had a 3.8 times higher probability of faster recovery

compared to donors with scores lower or equal to 46 (lowest quartile) (HR 3.7; 95% CI 1.2-11.7; p = 0.011) (table 5.6).

Table 5. 6 Multivariate analysis of factors influencing time to recovery following BM donation using MCS as a continuous or categorical variable

Factor	p-value	HR (95% CI)
MCS (continuous)	p = 0.035	1.07 (1.005-1.15)
MCS (categorical)	p = 0.011	
≤ 46		1
>46		3.8 (1.2-11.7)

5.3.3 Baseline HRQOL scores predicting adverse reactions

5.3.3.1 PBSC donors

Tables S1 and S2 appendix 1 show the univariate analysis of factors influencing adverse reactions at different time points following PBSC donation. All time points are defined as the day of donation (D 0), 2-3 days after donation (D2-3) and weekly after donation up until full recovery. Table 5.7 displays the multivariate analysis. All factors with a p-value ≤ .0.20 in the univariate analysis were included in the multivariate stepwise logistic regression analysis. Only factors that remained significant (or borderline significant) in the multivariate analysis are shown.

5.3.3.1.1 PCS score

Donors with pre-donation SF-36 PCS scores in the lowest quartile were more likely to experience fatigue (OR 4.7, 95% CI 1.8-12.7; p = 0.002) on day 2-3 following donation or at any time point following donation (OR 2.9, 95% CI 1.2-7.1; p = 0.016) compared to donors with PCS scores in the highest quartile.

The baseline PCS score was also associated with dizziness at any time point following donation. Donors with a baseline PCS score below or equal to the median had an odds ratio of 2.9 (95% CI 1.2, 7.2; p = 0.016) compared to donors with a score above the median.

Lower baseline PCS scores was associated with experiencing any type of pain at any time. Donors with baseline PCS scores in the lowest quartile had an odds ratio of 5.6 (95% CI 1.8, 17.6; p = 0.011) of experiencing pain compared to donors with baseline PCS scores in the highest quartile.

Donors with pre-donation SF-36 PCS scores in the lowest quartile were more likely to experience any adverse reaction (OR 3.0, 95% CI 1.1-8.5; p = 0.008) on day 2-3 following donation compared to donors with PCS scores in the highest quartile.

5.3.3.1. 2 MCS score

Donors with a pre-donation MCS score in the lowest quartile were more likely to experience pain at any time point compared to donors with scores in the highest quartile (OR 2.8, 95% CI 1.1-7.1; p = 0.027).

5.3.3.1.3 Gender

Experiencing any type of pain (including back pain, headache, myalgia or other pain) on the day of donation was associated with female gender with an odds ratio of 2.5 (95% CI 1.2-5.2; p = 0.012)

5.3.3.1.4 Age

Fatigue at any time point was associated with higher age (p = 0.034).

Table 5. 7 Multivariate analysis of factors influencing adverse reactions at different time points following PBSC donation. All time points are defined as the day of donation (D 0), 2-3 days after donation (D2-3) and weekly after donation up until full recovery. Factors taken into account include PCS, MCS, age, gender, BMI, being a blood donor, number of dependants and marital status.

Outcome: Symptom and time point	**Factor**	**p-value**	**OR (95% CI)**
Back pain D0	MCS (continuous)	= 0.037	0.89 (0.81-0.99)
Dizziness D0	PCS (continuous)	= 0.005	0.79 (0.67-0.93)
Headache D0	MCS (continuous)	= 0.06	0.93 (0.86-1.003)
	Gender	= 0.024	
	Male		1
	Female		2.8 (1.1-6.7)
	Number of dependants	= 0.04	
	0		1
	1-2		1
	3 or more		5.0 (1.1-22.9)
Myalgia D0	PCS (continuous)	= 0.05	0.91 (0.83-1.0)
Summary pain D0	MCS (continuous)	= 0.03	0.93 (0.87-0.99)
	Gender	= 0.012	
	Male		1
	Female		2.5 (1.2-5.2)
Dizziness D2-3	PCS (continuous)	= 0.059	0.88 (0.76-1.005)
Fatigue D2-3	PCS (continuous)	= 0.002	0.85 (0.76-0.94)
			1.06 (1.02-1.1)

	Age (continuous)	= 0.001	
Myalgia D 2-3	PCS (continuous)	= 0.029	0.89 (0.81-0.98)
Summary pain D 2-3	PCS (continuous)	= 0.008	0.88 (0.79-0.97)
Summary all adverse reactions D 2-3	PCS (continuous)	= 0.008	0.83 (0.72-0.95)
Back pain 1 week	PCS (continuous)	= 0.039	0.8 (0.64-0.99)
Fatigue 1 week	PCS (continuous)	= 0.041	0.87 (0.76-0.99)
Summary all adverse reactions 1 week	PCS (continuous)	= 0.033	0.88 (0.78-0.99)
All time points fatigue	PCS (continuous)	= 0.016	0.89 (0.81-0.98)
	Age (continuous)	= 0.034	1.04 (1.003, 1.07)
All time points	PCS (continuous)	= 0.016	0.84 (0.73-0.96)
dizziness	MCS (continuous)	= 0.059	0.91 (0.84-1.003)
All time points myalgia	PCS (continuous)	= 0.009	0.87 (0.78-0.96)
All time points	PCS (continuous)	= 0.011	0.88 (0.79-0.97)
pain	MCS (continuous)	= 0.027	0.92 (0.86-0.99)

5.3.3.2 BM donors

Tables S3 and S4 appendix 1 display the univariate analysis of demographic and collection characteristics associated with individual adverse reactions. Factors taken into account for the multivariate analysis include age, gender, BMI, being a blood donor, number of dependants, duration of the procedure, volume of BM harvested per kg donor weight, PCS and MCS score.

5.3.3.2.1 PCS score

A lower PCS score was associated with increased symptoms of anorexia following donation ($p = 0.028$), but this lost significance in multivariate analysis ($p = 0.12$).

5.3.4 Changes in SF-36 score from pre-donation, through 4 weeks and 3 months post-donation

As shown in Table 5.8, PCS scores declined significantly from pre-donation to 4 weeks post-donation ($p < 0.001$), with a return to pre-donation values at 3 months. This was shown both for PBSC and BM donors, but the decline in PCS scores was much greater for BM donors (table 5.9). At 4 weeks following donation, the PF ($p = 0.001$), RP ($p < 0.001$) and BP ($p = 0.002$) subscores were worse for BM donors compared to PBSC donors. Mental summary score did not change throughout donation for PBSC donors, but was significantly lower at 4 weeks for BM donors ($p < 0.01$); this returned to normal levels at 3 months.

The most significant subscore change in PBSC donors was for RP score with a mean difference between 4 week score and pre-donation of – 1.6 ($p < 0.001$). When

assessing the individual subscore changes in BM donors, the most significant decrease between pre-donation and 4 weeks within the physical scores, was for RP (mean -7.8; p = 0.004), followed by BP (mean – 5.8; p = 0.021) and PF (mean -1.5; p = 0.049). The most significant decrease between pre-donation and 4 weeks within the mental scoring (BM donors), was for VT (vitality) scores with a mean decrease of 8.1 on the norm based vitality score (p < 0.001), followed by SF (social functioning) component (mean – 6.0; p = 0.001). There were no changes in general health perception (GH) (p = 0.27), role limitations due to emotional problems (RE) (p =0.074) or mental health (MH) score (p = 0.42).

Table 5. 8 Changes in pre-donation and post-donation scores

Type of donation	Scoring type	Mean of difference between score at 4 weeks and baseline (range)	p-value	Mean of difference between score at 3 months and baseline (range)	p-value
PBSC	PCS	- 0.92 (-14.9, 13.2)	**< 0.001**[1]	0.009 (-12.5, 16.0)	0.98[2]
	MCS	- 0.2 (- 26.3, 29.5)	0.64[1]	-0.1 (-19.5, 21.2)	0.79[2]
BM	PCS	-5.02 (-18.4, 8.6)	**= 0.009**[3]	- 0.3 (-12.2, 9.6)	0.71[4]
	MCS	-3.9 (-28.5, 9.5)	**= 0.017**[3]	-1.2 (-21.0, 7.4)	0.37[4]

[1]calculated comparing pairs with pre and 4 week scores (n = 169)

[2]calculated comparing pairs with pre and 3 month scores (n = 151)

[3]calculated comparing pairs with pre and 4 week scores (n = 18)

[4]calculated comparing pairs with pre and 3 month scores (n = 23)

Table 5. 9 Differences in HRQOL scores between BM and PBSC donors

Time point	Dimension	BM Mean	PBSC Mean	p-value
Pre donation	Physical functioning	56.0	56.8	0.13
	Role limitation due to physical health problems	56.7	56.5	0.61
	Bodily pain	58.4	57.0	0.28
	General health perception	56.7	57.8	0.42
	Vitality	54.2	55.5	0.42
	Social functioning	54.6	55.9	0.11
	Role limitations due to emotional problems	52.8	54.8	0.07
	General mental health	52.6	54.6	0.08
	PCS	58.3	57.5	0.29
	MCS	52.0	54.1	0.24
4 weeks after donation	Physical functioning	47.0	52.9	**0.001**
	Role limitation due to physical health problems	41.9	50.9	**< 0.001**
	Bodily pain	44.1	53.1	**< 0.005**
	General health perception	48.5	53.6	0.14
	Vitality	42.4	51.2	**< 0.05**
	Social functioning	42.5	51.8	**0.001**
	Role limitations due to emotional problems	43.1	51.4	**< 0.01**
	General mental health	45.0	51.2	0.32
	PCS	45.1	51.8	**< 0.005**
	MCS	42.4	49.1	0.34
3 months after donation	Physical functioning	56.1	56.2	0.90
	Role limitation due to physical health problems	56.7	56.0	0.27

	Bodily pain	58.2	58.3	0.93
	General health perception	58.2	57.2	0.57
	Vitality	55.9	54.8	0.55
	Social functioning	54.1	54.7	0.74
	Role limitations due to emotional problems	53.0	54.8	0.12
	General mental health	54.1	54.1	0.98
	PCS	58.2	57.8	0.64
	MCS	52.6	53.6	0.47

5.3.5 Factors predicting physical and emotional health 4 weeks following PBSC donation

Based on the finding that HRQOL is significantly affected 4 weeks following donation, I aimed to clarify whether I could establish predictive factors for PCS and MCS scores 4 weeks following donation using multivariate linear regression analysis. I found that there were no demographic factors predictive of HRQOL following donation. Only a lower pre-donation PCS and experiencing any kind of pain 2-3 days following donation were associated with lower PCS outcomes at 4 weeks in PBSC donors (Table 5.10).

Table 5. 10 Associations between pre-donation demographics and donation related problems on day 2-3 following PBSC donation and PCS scores at 4 weeks

Explanatory variable[a]	Coefficient (beta)	p-value	95% CI
Pre-donation PCS score	0.64	**< 0.001**	0.44, 0.84
Any pain on day 2-3	-1.721	**= 0.03**	-3.2, -0.2

a: Explanatory variables included gender, age, BMI, number of dependents, marital status, being a blood donor, pre-donation PCS score, any side-effect on day 2-3 summary score and any pain on day 2-3.

Similarly, a lower pre-donation MCS score and experiencing any kind of pain 2-3 days following donation were associated with lower MCS outcomes at 4 weeks (Table 5.11).

Table 5. 11 Associations between pre-donation demographics and donation related problems on day 2-3 following PBSC donation and MCS scores at 4 weeks

Explanatory variable[b]	Coefficient (beta)	p-value	95% CI
Pre-donation MCS score	0.71	**< 0.001**	0.53, 0.87
Any pain on day 2-3	-2.2	**= 0.01**	- 4.3, - 0.18

b: Explanatory variables included gender, age, BMI, number of dependents, marital status, being a blood donor, pre-donation MCS score, any side-effect on D2-3 summary score and any pain on D2-3.

5.4 Discussion

In this prospective study, I found that pre-donation HRQOL markers were important factors associated with recovery and the development of adverse reactions in unrelated donors. Certain demographic factors such as age and gender also remained significantly associated with recovery and/or adverse reactions when taking HRQOL into account. To my knowledge, there have been no studies addressing the influence of pre-donation HRQOL on recovery and adverse reactions in HSC donors. The importance of both pre-donation general physical well-being (measured with the PCS subscore) and mental wellbeing (MCS) in determining recovery and adverse events was demonstrated with quartiles providing cut-points as splitting into quartiles allows for an simpler interpretation of odds or hazard ratios. If treated as continuous variables, significant results were also obtained. A lower pre-donation PCS score and higher donor age were the main factors associated with delayed recovery for PBSC donors in multivariate analysis. Three scales (physical functioning, role limitations due to physical health problems and bodily pain) correlate most strongly with the physical component and contribute most to scoring of the PCS measure. Lower PCS scores indicate more limitations in physical functioning, role participation due to physical problems, a higher degree of bodily pain and a poorer self-reported general health. Interestingly, mean pre-donation PCS scores were well above the mean of the general population (+ 0.76 SD; $p < 0.001$), reflecting the strict medical assessment of donors. Examples of reasons for lower pre-donation PCS scores in this cohort included mild limitations to perform work or vigorous activities or having a history of mild or moderate bodily pains. Despite these mild limitations, lower pre-donation PCS scores were associated with a slower recovery. Experiencing very common adverse reactions, such as pain, fatigue and dizziness were also associated with a lower pre-donation PCS score.

Lower pre-donation MCS scores were associated with an increased likelihood of experiencing pain in PBSC donors. Similar to the PCS scores, mean pre-donation MCS scores were above the mean of the general population (+ 0.41 SD; $p < 0.001$). For the MCS measure, a lower score is indicative of more frequent psychological distress, social and role disability due to emotional problems and a poorer general health. Examples of reasons for lower pre-donation MCS scores in this cohort included feeling nervous, downhearted or worn out a lot of the time. A negative association between mental or emotional health and an altered pain experience has been described previously (Gong and Dong, 2014, Browne et al., 2014, Segal et al., 2014, Lautenbacher and Krieg, 1994, Syrjala et al., 2014, Sullivan et al., 2001, Banks SR, 1996, Sheinfeld Gorin et al., 2012). Moreover, psychosocial interventions are often part of a multimodal approach of the management of pain (Sheinfeld Gorin et al., 2012) and negative mood has emerged as a strong and reliable predictor of postoperative outcomes (Sullivan et al., 2001). I found similar results in the BM cohort; a lower pre-donation MCS score was the only and most important factor associated with delayed recovery. A possible explanation of the finding that MCS scores predicted recovery in BM donors but not in PBSC donors, may be related to the very distinct nature of the two procedures. As BM donation was associated with pain symptoms at later time points, I would speculate that pre-existing symptoms of anxiety or low mood would have a significant impact on this outcome.

When examining the evolution of HRQOL during the donation process, I found a decrease in general health for BM and PBSC donors at 4 weeks with a return to normal levels 3 months following donation. The 3 month values were well above the mean of the general population (+ 0.79 SD for PCS, + 0.34 SD for MCS; $p < 0.001$). Most scores at 4 weeks were significantly lower for BM donors compared to PBSC donors, reflecting the delayed recovery and the increased symptoms of pain at later time intervals for BM donors described in chapter 4. At 4 weeks following donation,

BM donors had scores for PCS and MCS that were comparable to scores of patients with chronic medical conditions (Cheng et al., 2003). Based on the above findings, the potential donor experience should be taken into account when deciding on the stem cell source, especially if there is no specific patient indication for a BM source. I did not find improved mental scores following donation, as described in a recent study (Switzer et al., 2014). To the best of my knowledge this is the first study to show that, even in PBSC donors, physical health is significantly (although minimally) reduced 4 weeks following donation compared to pre-donation. The largest decrease was within the RP subscore. The RP scale covers an array of physical health-related role limitations, including limitations and reductions in the amount of time spent at work or other activities (such as sports). Despite the significant decrease in physical state compared to baseline, PCS scores at 4 weeks were still comparable with scores of the general population (+ 0.18 SD; $p = 0.11$). There were no significant changes in MCS scores during the donation process for PBSC donors, as opposed to BM donors. The main MCS subscore affected in BM donors was the vitality score. These findings may reflect an association between physical morbidity and vitality and are in keeping with a delayed physical recovery in BM versus PBSC donors. Despite considerable pain in BM donors, mental health scores remained high, indicating that donors did not feel distressed by pain. This had also been previously reported (Nishimori et al., 2002). Moreover, several studies found that the vast majority of BM and PBSC donors indicated they would be willing to donate again in the future (Switzer et al., 2001, Heldal et al., 2002). Only one donor (PBSC) in this cohort asked us to be removed from the register following donation.

Taking into account the finding that HRQOL were significantly decreased at 4 weeks, I aimed to predict which adverse reactions were associated with poorer outcomes when accounting for pre-donation HRQOL. I found that experiencing pain on day 2-3

was a significant predictor of general physical and mental health at 4 weeks following donation in PBSC donors, regardless of pre-donation physical and mental health. This information could be very valuable in order to monitor this high risk group more closely.

There are certain limitations in my study that must be acknowledged: The SF-36 only captures part of overall HRQOL and a more comprehensive psychological assessment tool or formal qualitative interview process may need to be the focus of future studies. Additionally, pre-donation ambivalence has been found to be one of the major determinants in the donation experience. Donation ambivalence involves doubts and worries about donation and this is not covered by the SF-36 score. Furthermore, the influence of socio-economic status (SES) in relation to the donation experience and the SF-36 score would have been a useful variable to study. Unfortunately, I only documented the profession of donors, not their household income, which did not allow me to record the SES reliably. A recent CIBMTR study reported a minimal influence of SES on the donation experience (verbal communication from Prof. B. Shaw, article in press). Also, I included a limited number of BM donors, which limited the analysis in this group. For example, the number of BM donor participants was too small in order to obtain significant results in multivariate analysis when assessing the factors affecting individual adverse reactions at different time points. The numbers were also too small to assess the factors predicting physical and emotional health 4 weeks following donation.

In conclusion, I found that pre-donation quality of life markers contribute significantly to recovery and toxicity profile following BM or PBSC donation. I believe they should be used alongside demographic markers in order to risk stratify the donor population and to help identify donors at risk for poorer outcomes. HRQOL questionnaires such as the SF-36 are highly standardised and their introduction at the time of donor

medical screening should be considered in order to establish which donors are potentially at risk of delayed recovery

Chapter 6 – Factors influencing yields in BM donors

6.1 Introduction

A secondary end point of the prospective study described in the previous chapters was to evaluate the frequency of PBSC (chapter 3) and BM collections meeting the transplant centre's requested dose. I examined the role of potential donor and collection characteristics including age, gender, BMI, weight, difference between donor and recipient weight, volume of harvest and duration of harvest procedure.

Commonly accepted doses for BM harvests vary between 3-5 x 10^8 total nucleated cells (TNC) per kg recipient weight. Higher TNC doses have been associated with improved graft function and patient survival (Sierra et al., 1997, Rocha et al., 2002, Dominietto et al., 2002, Barrett et al., 2000). Cell doses of < 2 x 10^8 have previously been described as unacceptably low (Wang et al., 2011). Because patients have already received therapy by the time donor cells are collected, the lack of availability of adequate stem cells is a significant problem. It is therefore of great clinical importance to establish the donor and collection characteristics associated with not meeting the requested HSC dose. Table 1.7 lists all the factors that have been previously found to affect the BM yield (using either CD34+ or TNC count) or quality of the harvest in allogeneic donors.

6.2. Methods

The full material and method can be found in chapter 2 (section 2.4.3.3).

6.3 Results

6.3.1 The frequency BM collections that meet the transplant centre's requested dose and predictors

6.3.1.1 Donor and collection characteristics

Donor and collection characteristics are outlined in table 6.1 (n = 110).

Table 6. 1 Donor and collection characteristics

Characteristic	
Age (Years)	
Median (range)	28 (18-56)
Gender (Male/Female)	80/30
Weight (kg)	
Median (range)	82 (53-119)
BMI	
Median (range)	25.8 (18.1-36.1)
Volume collected (mls)	
Median (range)	1200 (450-1900)
Duration of procedure (mins)	
Median (range)	30 (7-120)
Pre-donation haemoglobin (g/dl)	
Median (range)	15.0 (10.2-16.8)
Post-donation haemoglobin (g/dl)	
Median (range)	12 (7.9-14.8)
Pre-donation minus post-donation haemoglobin (g/dl)	
Median (range)	2.8 (0.7-5.9)

In view of the small number of BM donors included in my prospective study (n = 37), I added all donors who donated BM in 2013 but were not included in the study (n = 35) as well as all donors who donated BM in 2012 (n = 38).

The distribution of BM procedures between the 4 collection centres was 66% (n = 73), 20% (n = 22), 10% (n = 11) and 4% (n = 4). When comparing donor and collection characteristics between donations in 2012 and 2013, I found that the volume of BM collected per kg donor weight was higher in the 2013 donors (table 6.2).

There was no difference in the TNC yield/kg recipient weight or actually meeting the requested yield when comparing 2012 vs 2013 donors (53% vs 48%; p = 0.7). When comparing study participants versus non-study participants, I found that there were significantly more male donors in the study participant group (table 6.2). Donors for paediatric recipients were included in the analysis. This was decided partially due to the high number of these donors in this cohort (n = 46). Also, an important end point of this analysis (TNC count per ml) eliminates the confounding factor of recipient weight.

Table 6. 2 Comparison of donor and collection characteristics of donors who donated in 2012 versus 2013 and of prospective study participants versus non-participants

Measure-ment	Age (years) Mean (range)	Gender (% male)	Donor minus recipient weight Mean (range)	Volume harvested/ kg donor weight Mean (range)	Duration of procedure Mean (range)	TNC dose requested (x 10^8 TNC cells/kg recipient weight) Mean (range)	TNC dose collected (x 10^8 TNC cells/kg recipient weight) Mean (range)
Comparison of donors who donated in 2012 and 2013							
Donations in 2012 (n = 45)	32 (20, 53)	66%	35.9 (-28, 96)	12.9 (4.76, 19.7)	33.4 (7, 120)	4.6 (3, 10)	9.7 (1.4, 84.4)
Donations in 2013 (n = 65)	30.4 (18, 56)	77%	26.7 (-33, 94)	15.5 (4.4, 23)	34.2 (18, 90)	4.8 (2, 12)	8.6 (1.4, 100.1)
p-value	0.39	0.28	0.13	**0.002**	0.79	0.66	0.74
Comparison of donors who participated in prospective study and non-study participants							
Non-study participants (n = 73)	31.2 (18, 56)	64%	34.5 (-28, 96)	13.9 (4.8, 23)	33.0 (7, 120)	4.7 (2, 12)	9.9 (1.4, 100.1)
Study participants (n = 37)	30.7(18, 53)	89%	22.5 (-33, 94)	15.5 (4.4, 23)	35.5 (18, 90)	4.9 (3, 10)	7.5 (1.4, 69.7)
p-value	0.78	**0.006**	0.06	0.069	0.43	0.63	0.48

6.3.1.2 Association between demographic data and reaching the target TNC count

The median cell dose requested was 4 x 10^8 TNC cells/kg recipient weight (range 2-12). The median TNC dose collected was 4.2 x 10^8/kg (range 1.4-100.1) and

requested TNC dose was achieved in 49% of harvests (54/110). The collected CD34+ dose (x 10^6)/kg recipient weight was only reported in limited cases (n = 34). The median CD34+ dose collected was 3.33 x 10^6/kg (range 1-28).

The only donor characteristic that was significantly associated with reaching the TNC dose in univariate analysis was a larger difference in weight between donor and recipient (19.2 kg vs 42.1 kg; p < 0.001) (table 6.3).

Table 6. 3 Univariate analysis of factors associated with reaching the requested TNC dose. Values are expressed using mean (range) for continuous variables.

Variable		**Requested TNC dose achieved**		
		Not achieved (n = 56)	Achieved (n = 54)	p-value
Continuous	Age	30.8 (18-53)	31.3 (18-56)	=0.78
	Donor weight (kg)	82.9 (53-119)	81.5 (55-108)	=0.59
	Donor minus recipient weight (kg)	19.2 (-31-86)	42.1 (-32.9-95.7)	< 0.001
	BMI	26.3 (18.3-34.9)	26.3 (18.1-36.1)	0.99
	Volume collected (mls)	1252 (450-1710)	1044 (450-1900)	< 0.001
	Procedure duration (minutes)	36.4 (15-120)	31.2 (7-90)	=0.075
Categorical	Gender (M/F)	41/15	39/15	0.99
	Collection centre (1/2/3/4)	1/37/6/12	3/36/5/20	0.74

The odds ratio for reaching the target for donors > 20 kg heavier than their recipient was 3.5, compared to donors ≤ 20 kg heavier than their recipient (OR 3.5, 95% CI 1.6-7.9; 0 = 0.002). Higher volume harvests were significantly less likely to achieve the requested TNC dose (1252mls vs 1044 mls; p < 0.001) in univariate analysis. The odds ratio for reaching the target for a collected volume of ≤ 1200 mls was 3.7 (95% CI 1.7-8.1; p = 0.001) compared to a collected volume of > 1200 mls. There was a trend towards statistical significance for shorter duration of the procedure and reaching the requested TNC dose (36.4 mins vs 31.2 mins; p = 0.075).

After stepwise binary logistic regression analysis (table 6.4), a larger difference in weight between donor and recipient and a lower volume of blood collected remained significantly associated with requested TNC dose being met.

Table 6. 4 Multivariable logistic regression of factors influencing the likelihood of reaching the requested TNC dose with variables expressed as a continuous or categorical variable.

Variable		OR	95% CI	p-value
Continuous	Donor minus recipient weight (kg)	1.02	1.00-1.033	=0.05
	Volume collected (mls)	0.99	0.99-1.00	=0.033
Categorical	Donor minus recipient weight (kg)			
	Donor minus recipient weight ≤ 20	1		
	Donor minus recipient weight > 20	2.8	(1.2-6.5)	=0.019
	Volume collected (mls)			
	Volume collected ≤ 1200	2.9	(1.3-6.7)	= 0.011
	Volume collected > 1200	1		

6.3.2 Factors affecting the quality of the BM harvest

The TNC count/ml collected marrow was used as a marker of quality of the harvest. The median TNC/ml collected was 18.2 x 10^6/ml (range 9-182 x 10^6/ml). I found that a greater positive difference between donor and recipient weight (p = 0.004; figure 6.1), a higher BMI (p = 0.038; figure 6.2) and a lower volume of BM collected (p < 0.001; figure 6.3) were significantly associated with a better harvest quality in univariate analysis. Donor weight (p = 0.37), donor age (p = 0.48), duration of the procedure (p = 0.93) and gender (p = 0.19) were not significantly associated with quality of the harvest.

Figure 6. 1 Association between difference in weight between donor and recipient and TNC/ml

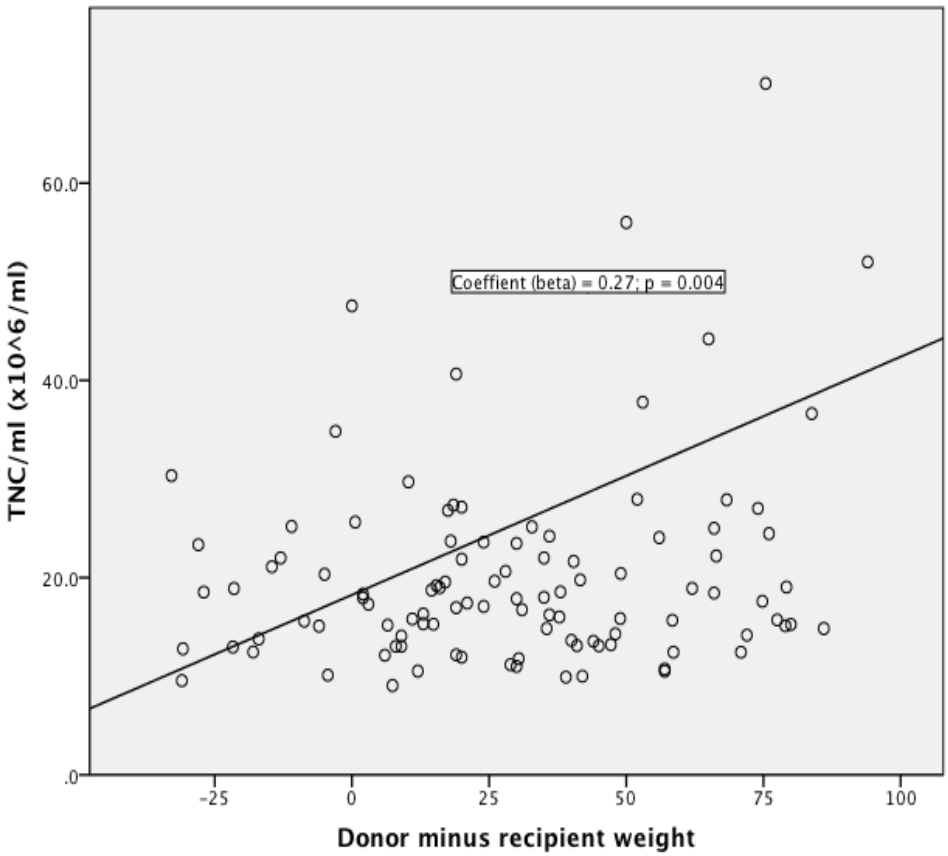


Figure 6. 2 Association between donor BMI and TNC/ml

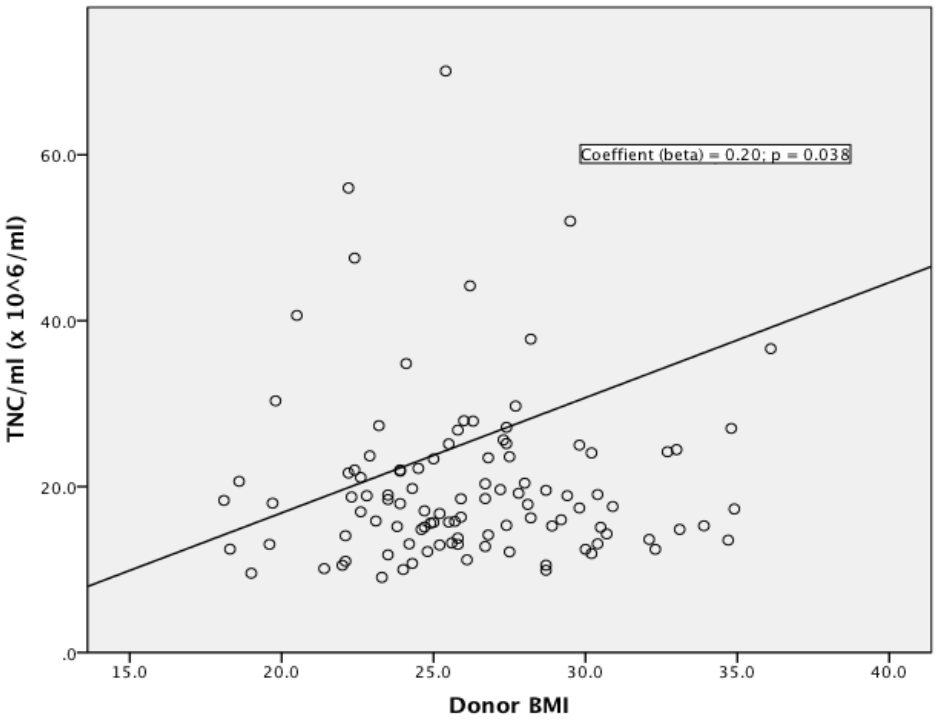
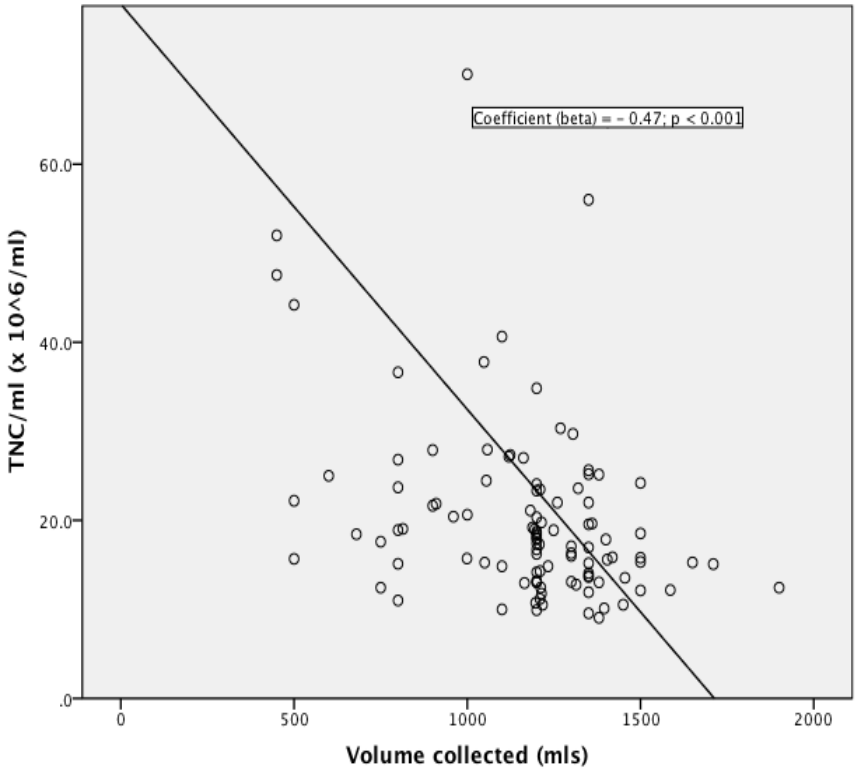


Figure 6. 3 Association between the collected BM harvest volume and TNC/ml



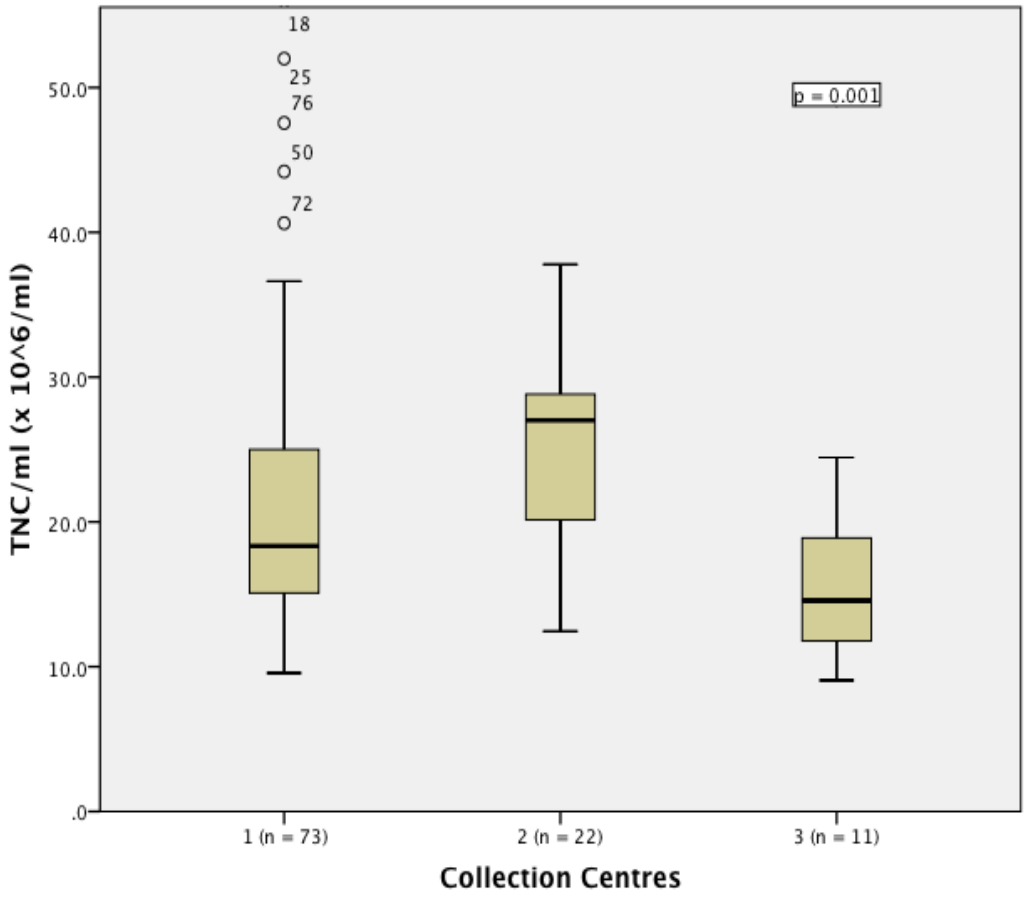
A lower volume of BM collected and a higher BMI remained significantly associated with better harvest quality in multivariate linear regression analysis (table 6.5).

Table 6. 5 Multivariate linear regression analysis. Explanatory variables included all factors significant (p < 0.05) in univariate analysis.

Explanatory variable	Coefficient (beta)	p-value
Volume collected	-0.51	< 0.001
Donor BMI	0.21	= 0.018

A significant variation in harvest quality was observed when comparing the different collection centres (p = 0.001; figure 6.4). The collection centre with the smallest number of BM harvests (n = 4) was excluded from this analysis. Centre 3 provided the worst quality harvest; the difference was highest between centre 1 and 3 (0.28 vs 0.15 x 10^6/ml; p = 0.001) and centre 2 and 3 (0.25 vs 0.15 x 10^6/ml; p = 0.001). There was no significant difference between the different collection centres in donor BMI (p = 0.68) and donor minus recipient weight (p = 0.93); the donor characteristics that were implicated in a better harvest quality. I found a borderline significant difference in the volume collected per kg donor weight between centre 1 and 3 (13.9 vs 15.8 mls/kg; p = 0.054), but not between centre 2 and 3 (14.5 vs 15.8 mls/kg; p = 0.40). The duration of the procedure was significantly longer in centres 1 (32 vs 28 mins; p = 0.007) and 2 (41 vs 28 mins; p = 0.01) compared to centre 3.

Figure 6. 4 TNC/ml displayed per collection centre. Box plot with the horizontal line representing the median, the box the 25th percentile and the whiskers the 75th percentile.



6.4 Discussion

This study investigated the donor and collection factors that are implicated in reaching the requested TNC dose for BM donors. I also investigated the factors implicated in the quality of the harvest (TNC/ml). The latter has been used as a marker of quality of the harvest.

My study found that a larger difference between donor and recipient weight and a lower volume of marrow collected were associated with reaching the requested TNC dose in multivariate analysis. Similar to previous studies, age and gender were not found to be associated with reaching the requested dose (Favre et al., 2003, Gandini et al., 2001). I did not find an association between BMI and reaching the requested

dose in multivariate analysis. One study had previously reported a positive relationship between BMI and CD34+ yield (Favre et al., 2003).

Similar to the PBSC donors, my study showed that a larger positive difference between donor and recipient weight was significantly associated with reaching the requested cell dose. This finding was most significant for donors who were more than 20 kg heavier than their recipient. This result can help guide physicians in selecting an optimal donor to provide a sufficient BM cell dose. This practice will become increasingly relevant with the number of volunteer HSC donors increasing worldwide. A recent NMDP report noted that 56% of patients have ≥10 suitable HLA matched donors in the current NMDP files (Confer, 2007). Once the donor is chosen, the yield of the collected BM depends on the harvest procedure.

The only harvest procedure characteristic significantly associated with reaching the requested dose was a lower volume of BM collected. Additionally, when using the quality of the harvest as an outcome, lower volume harvests were strongly associated with higher TNC counts per ml in multivariate analysis. TNC count per ml is a better indicator for the analysis of donor and collection characteristics in BM donors because of eliminating the confounding factors of collected marrow volume and recipient weight (especially since donors for paediatric recipients were included in this analysis). A negative correlation between the TNC/ml and the total volume harvested has been previously reported (Kao et al., 2009, Wang et al., 2011) and can be explained by a decreased contamination with peripheral blood in smaller samples. Peripheral blood contamination and high volume aspirates should be avoided, given the risk of immune mediated transfusion reactions in the recipient if there is a major ABO mismatch between the donor and the recipient. Also, peripheral blood cell

contamination leads to anaemia (Nishimori et al., 2002) and increased symptoms of fatigue in the donor. Peripheral blood contamination is often caused by aspirating too much BM from one puncture hole. Several authors have reported that small volume aspirations and multiple puncture sites are associated with minimal contamination by peripheral blood and higher TNC counts (Spitzer et al., 1994, Bacigalupo et al., 1992, Batinic et al., 1990). This practice may however be associated with an increased risk of back pain following donation. In addition, increasing the number of puncture holes may lead to longer harvest procedures, which are associated with increased side effects and complications of anaesthesia (Lannert et al., 2008).

One way to improve the quality of the harvest, without increasing the length of the procedure, may be by using a multi-hole aspiration needle. This practice is associated with fewer puncture holes and could potentially be less traumatic for the donor. Wang et al reported an improved TNC per ml using this device (Wang et al., 2011). They restricted the volume per aspiration to 30 mls per aspiration (approximately 5 mls/needle hole). Another study reported a 50% reduction in operating times using this device (Lannert et al., 2008). They did not find an improvement in TNC yields, but this could result from the effect of haemodilution by a large amount of aspiration per puncture site used in the study (200 mls per aspiration). Moreover, the small number of cases in this study may have caused the study to have insufficient power.

Another strategy that could potentially improve the quality of the harvest is by performing midway TNC counts, as reported by Wang et al (Wang et al., 2011). The influence of the midway TNC count may result from the fact that staff were aware of the unsatisfactory TNC counts and attempted to improve the harvest by further decreasing the volume of aspiration to reduce haemodilution, using new puncture locations. Conversely, satisfactory midway TNC counts may result in reduced

unnecessary puncture holes and volume aspirated. A requirement for midway TNC counts is a timely laboratory turnaround time, which may have practical implications for collection centres. Several studies found increased yields and improved engraftment with G-CSF stimulated BM. However, this method will significantly increase the cost of BM harvesting and also raises concerns with regards to donor ARs.

The only donor factor that was significantly associated with TNC count per ml was donor BMI. The mechanism behind this phenomenon is not clear and this has also not been previously reported. It is possible that this donor feature reflects a robust haematopoiesis inside the bone marrow so that higher concentrations of nucleated cells can be collected.

Finally, I found a significant variation of BM harvest quality between centres. This has also been reported in another study (Spitzer et al., 1994). Interestingly, the centre performing the worst was found to have the highest volumes aspirated per kg donor weight and the shortest procedure time. These findings strongly suggest that high volumes were aspirated per puncture hole. Fewer puncture holes mean a shorter procedure time in order to achieve the required volume. High volume aspirations are associated with dilution with peripheral blood and a reduced quality of the harvest. Unfortunately, our centres did not document the number of puncture holes, so I am not able to confirm this. However, this information reiterates the importance of the procedure technique and the need for exploring devices such as the multi-hole aspiration needle. Given the declining number of requests for BM harvests, it is crucial these are performed by the most experienced centres and that systems exist to ensure operators retain their expertise.

Chapter 7: A qualitative analysis of the donation experience

7.1 Part I: Exploration of health related quality of life (HRQOL) during the donation process and donor preparedness

7.1.1 Introduction

Chapters 4 and 5 described the influence of pre-donation HRQOL and demographic factors on recovery and adverse reactions (ARs). One of the most important conclusions was the finding that baseline HRQOL scores, measured using the SF-36 questionnaire, can significantly predict recovery following donation. The baseline Physical Component Summary (PCS) was found to be an especially important factor in determining recovery and ARs in peripheral blood stem cell (PBSC) donors. The first part of this qualitative study was developed in order to further explore the influence of pre-donation physical health on the donation process in PBSC donors, the largest group of participants in the prospective study. This qualitative analysis involved in-depth telephone interviews with 14 PBSC donors (who participated in the original study), seven with low pre-donation PCS scores and seven with high PCS scores. The SF-36 is a self-reported general health measure and some of the questions are formulated in a way that may be subjective, for example “Have you accomplished less than you would like in the last 4 weeks as a result of your physical (or mental) health” or “Have you had difficulty performing work or other activities”. These questions may be answered differently by two people who have similar mental and physical health, depending on what they see as normal for them. Qualitative exploration may allow a more complete picture of participants’ general health and the factors associated with recovery. I also aimed to explore the physical and

psychological reactions to the donation process and assess how well donors coped with ARs following donation, and identify if donors felt inadequately informed about the donation process.

7.1.2 Methods

The full material and method can be found in chapter 2 (section 2.5).

7.1.3 Results

The characteristics of the participants (n = 14) are shown in table 7.1. Participants 1 to 7 were selected based on pre-donation PCS scores in the lowest quartile (≤56), participants 8 to 14, based on pre-donation PCS scores in the highest quartile (> 60). Pre-donation MCS scores were not taken into account when selecting donors.

Table 7. 1 Donor and HRQOL characteristics of qualitative study participants, Marital status includes M(arried), S(ingle) or having a P(artner)

ID	Age	Gender	Ethnicity	Marital status	Depen-dants (n)	Blood donor	Pre-donation PCS score	Pre-donation MCS score
p1	40s	M	White Northern European	Missing data	0	N	45.33	56.8
p2	30s	F	White Northern European	M	≥ 3	Y	51.5	55.97
p3	40s	M	Jewish	M	≥ 3	N	47.45	50.64

p4	40s	M	White Northern European	M	Missing data	N	50.1	58.05
p5	60s	F	White Northern European	M	0	Y	48.92	61.13
p6	40s	M	White Northern European	P	≥ 3	N	49.3	56.97
p7	30s	M	White Northern European	S	0	Y	44.84	55
p8	40s	F	White Northern European	M	1-2	N	60.45	58.45
p9	40s	M	White Northern European	Missing data	≥ 3	N	60.62	58.97
p10	30s	M	White Northern European	M	1-2	Y	63.04	49.89
p11	20s	M	White Northern European	S	0	Y	61.88	54.31
p12	30s	M	White Northern European	Missing data	Missing data	Y	61.79	53.61
p13	20s	M	Other (White)	P	0	N	61.52	54.33
p14	20s	M	White Northern European	Missing data	1-2	Y	63.71	48.38

7.1.3.1 HRQOL during the donation process

Table 7.2 displays the donors' responses when asking about their pre-donation physical health. Donors with lower scores (p 1-7) were very healthy in general, but often had mild limitations explaining their lower PCS scores. The main reason for

scoring slightly lower than the other donors was often due to pain symptoms, usually back pain, limiting daily life activities to a minor degree. Only one donor (p4) reported considerable limitations in daily life due to back pain. There was a close agreement between the information that was derived from the interview and the answers on the pre-donation SF-36 form, filled out 1-1.5 years earlier (table 7.2 italic). Donor (p7) was an exception, but he later remembered having finished a 30-mile walk two days prior to filling out his SF-36 form. Donors with high scores (p 8-14) were in extremely good shape and were often marathon runners or engaged in physical exercise on a daily basis.

Donors were asked about their worst symptoms, physical or psychological, during the donation process. Donors with lower scores experienced more severe symptoms in general, reflecting the main findings of my prospective study. These symptoms often significantly influenced daily work and social life. Two donors mentioned low mood as their most serious side effect following donation (p 3 and p7); both had lower pre-donation PCS scores. Donors with high scores had a generally excellent donation experience with limited impact on their daily life.

Table 7. 2 Pre-donation physical health, data derived from the interview (retrospective) and the SF-36 form completed at the time of the prospective study (italic) and physical and psychological reactions to the donation process

Participant ID	Pre-donation physical health	Reaction to donating
p1	Knees little bit stiff when standing up for long periods of time (required for his job) *SF-36: Mild pain symptoms, interfering with work some of the time*	"I got an awful lot of pain, it felt like a pressure in my tummy like maybe there was something going to burst" He took time off work (he was advised not to work because of symptoms)
p2	Mild symptoms back and joints interfering with some activities like bending *SF-36: Mild pain symptoms, limited work a little of the time*	"I had quite a lot of headaches, they lasted for a couple of weeks" She had to cut down on social activities
p3	Back pain, interfering with high impact sports (running and squash) *SF-36: Mild pain, interfering with work little of the time. Limited a lot in vigorous activities*	Quite a lot of bone pains during injections and feeling low He worked from home around the time of injections and the day after donation
p4	Back pain, on tramadol and codeine pre-donation, interfering with daily activities *SF-36: Moderate bodily pains, limiting work some of the time*	"I developed bad hip pain and needed a shot of morphine" He took the week off (this was decided beforehand)
p5	Chronic back pain, on morphine patches, but very active lifestyle (Swimming and gym 3 times a week)	"I developed quite a lot of pain in my bones"

	SF-36: Moderate pain interfering a bit with normal activities	She had to take more rest and take everything slower as it was very painful
p6	In very good health, very active *SF-36: Mild pain, limited a little in work*	Low in mood and quiet following donation for some time He took it easier around the time
p7	Very active, cycles to work every day *SF-36: Severe bodily pains, interfering with work*	"I developed severe back pain and was advised to go to A&E for pain control" He was signed off from work during the donation process and took it easy
p8	Skiing, surfing and daily cycling *SF-36: No restrictions*	"The headaches were horrendous. I was cranky and less patient and I shouted more easily" Significantly impacting work and social life
p9	Mountain bikes a lot *SF-36: No restrictions*	Fatigue following donation He went mountain biking after work the day after donation
p10	Very fit, recently ran a marathon *SF-36: No restrictions*	No symptoms at all, he continued to play cricket all day during the injections "It was like a day out in London really"
p11	Very healthy and active with no limitations	Limited back pain, it didn't restrict normal activities at all

	SF-36: No restrictions	
p12	Fitter than most other people	Bit of sore back not impacting work or social life
	SF-36: No restrictions	
p13	Healthy and fit	Bit of stiffness for 2 hours with no impact on work or life whatsoever
	SF-36: No restrictions	
p14	Plays rugby 3 times a week	Bit of a cold, but not sure it was donation related
	SF-36: No restrictions	"It was almost identical to platelet donation, instead of one needle, there are two"

7.1.3.2 Donor preparedness

When asked how well informed they felt about the donation, all donors felt that they had received the right amount and type of information before donation. One donor mentioned that the duration of the actual apheresis procedure was longer than anticipated (p7), but he felt otherwise well informed. All donors with high PCS scores reported that the donation was better or easier than expected. They experienced minimal pain or other ARs and often resumed normal activities shortly after donation. The responses for the donors with lower scores were more varied and 3 donors experienced unexpected ARs (p3) or more severe ARs than anticipated (p 2, p5).

> "I think people react differently. I felt a little bit low after the donation. It was a strange feeling that I wasn't expecting." (p3)

> "I had quite a lot of headaches. I hadn't necessarily known that they were going to happen. I knew there were going to be side effects but not necessarily to that degree." (p2)

Even though several donors experienced considerable ARs, most donors said they were not worried, as they had been warned about them.

> "It didn't worry me as such. They explained me that it wasn't serious and that the pain would go once the injections had stopped." (p4)

> "I was warned about the side effects. It didn't worry me at all." (p3)

> "Because I knew it was a temporary thing because of the injections and it wasn't a symptom of more severe back disease I sort of carried on as normal and I didn't pay much notice." (p12)

Only one donor commented on feeling worried about the pain he experienced.

"It felt like a pressure in the abdomen. The nurse said it was normal, but I just sort of worried so in the end I didn't go to work for a couple of days." (p1)

7.1.4 Discussion

The results show that pre-donation physical health was very good in general, both for donors with pre-donation SF-36 scores in the lowest and in the highest quartiles. This is what would be expected, given the population average is set at a score of 50 and even the lowest quartile scores ≤ 56 are above average physical health. A close agreement between physical health derived from the SF-36 form (prospectively) and the retrospective interview was observed in all but 1 donor. This donor participated in heavy exercise shortly before filling out the questionnaire. This highlights a possible disadvantage of the form we used, as the SF-36 has a recall period of 4 weeks, which makes it possible to be influenced by recent, transient events (for example having a

cold). However, it may be that the current pre-donation state is more closely linked to the donation experience than long-standing physical health prior to donation. The SF-36 was able to distinguish between "extremely fit" donors or donors with scores in the highest quartile and "fit" donors or donors with scores in the lowest quartile in a quantitative and user-friendly manner. Even more importantly, pre-donation scores correlated strongly with outcomes following donation (as seen in my prospective study); donors with scores in the lowest quartiles experienced considerable ARs whereas donors in the highest quartile reported a significantly better donation experience. This is interesting, given both groups of donors were of above average physical fitness.

Despite experiencing significant ARs, most donors did not feel worried as they felt well prepared. The adequacy of preparation for donation has been shown to influence the donation experience and inadequate donor education may be associated with poorer donation experiences (Pillay et al., 2012). Three of the seven donors with low scores felt the donation was worse than they expected and this group may have benefitted from more detailed information and counselling beforehand. Research in surgery has also confirmed the benefits in recovery when providing detailed information about procedures and their ARs (Devine and Cook, 1983). A pilot study that is proposed in the next chapter suggests a tailored approach to donors with low PCS scores and this includes providing more in-depth information about delayed recovery and potential ARs. Despite sometimes experiencing considerable ARs, donors remained positive about the donation experience and were all willing to donate again in the future. It is possible that the more time lapses, the more positively donors remember their donation experience, possibly because altruistic feelings of having performed a good deed may be more prominent.

7.2 Part II: A thematic analysis of donor resilience

7.2.1 Introduction

The second part of this qualitative study involves an analysis of “resilience factors”, or the ability to bounce back from a profound experience. Previous research has shown that the psychosocial response to donating bone marrow (BM) is usually a positive one (Butterworth et al., 1993). Most donors see donation as worthwhile and most would be willing to donate again in the future. This is often despite experiencing ARs during the donation process. Butterworth reported that donors who developed severe back pain following BM donation, were as likely to experience the donation as positive emotionally than their counterparts who did not experience back pain (Butterworth et al., 1993). PBSC donation is usually tolerated better than BM donation, but is nevertheless associated with common ARs. My prospective study found that both BM and PBSC donors experienced considerable ARs and showed that, even in PBSC donors, physical health was significantly reduced 4 weeks following donation compared to pre-donation. Physical health had returned to pre-donation values at 3 months following donation. Mental health was significantly reduced at 4 weeks in BM donors, but remained high throughout in PBSC donors. All apart from one donor in my study were willing to donate again in the future. This part of the analysis will focus on the factors that may explain these physical and psychological outcomes in our donors, using thematic analysis.

7.2.2 Methods

The full material and method can be found in chapter 2 (section 2.5). A full interview transcript with extracted codes and overarching themes is shown in document S2. An

overview of codes and themes is shown in table S5 appendix 1 (initial draft) and S6 (final draft).

7.2.3 Results

Five themes were identified: intrinsic motivation, determination, relationship with recipient, strong feeling of fairness and ease of decision. Table S6 appendix 1 displays the five themes with their constituent codes. No differences were observed between the donors with low (p1-p7) and high (p8-p14) pre donation PCS scores, therefore no distinction is made between the two groups for the thematic analysis.

7.2.3.1 Theme 1: Intrinsic motivation

Altruism as a personality trait

Most donors were highly motivated in their decision to donate and were driven by an intrinsic commitment. In particular, the central importance of altruism as a personality trait was remarkable and altruistic acts appeared to be fairly typical for several donors.

> "I have always been a very generous person. I thought it would be a good thing to do." (p11)

> "I would donate a kidney as well. I would do it to help others. I think my wife would not be too pleased, but you would still be alive afterwards, right?" (p6)

> "I have been giving blood since I was 18 and grew up with my dad being a regular blood donor. And so, it was just quite a normal thing to join, that kind of made sense." (p2)

> "You have to help others, don't you? If you see someone lying on the street, you wouldn't walk away, would you? And it is not just the individual, it is the whole family.

> It doesn't matter who they are or which race it is. You have to do it for others, without knowing who they are." (p6)

Two donors commented on how guilty they had felt about not being blood donors.

> "I have been a blood donor several years ago. I found it very uncomfortable. I should have persisted really but I didn't. I feel guilty about it." (p1)

> "I feel very guilty about not being a blood donor. I remember it every 6 months and think I need to get a grip!" (p8)

Several donors commented on how they did not expect anything in return, highlighting a true altruistic motivation of joining the register.

> "You don't become a donor to try and get a reward from it or anything. I think you need to keep that boundary between the donor and the recipient." (p10)

> "I was meant to write a card, but I don't want to put an expectation onto the recipient or any kind of thanks." (p2)

> "I didn't do it to get a congratulation or to get a well done. I just wanted to help somebody." (p14)

Opportunity to save someone's life

Participants viewed donation as a chance to save someone's life and an opportunity to show kindness and help another person. Of note, several stated that they felt "honoured" to have been selected as donors.

> "I think it is a great thing and I think it is an honor to be able to donate. And it is wonderful to have that opportunity to make a difference in somebody's life." (p7)

> "At the time of the letter, I felt very blessed, blessed to give someone the chance." (p8)

> "To suddenly have this opportunity to do something that was so positive and hopeful and wasn't connected to what we had been going through. It was an amazing time for me as well. It was really good timing to do something that was so positive." (p2)

> "It a good opportunity so save someone regardless. Who the person is, is irrelevant really" (p13)

Hoping to rely on others' donations if ever in need

Some donor statements implied the relative costs to themselves and benefits (to themselves or the recipient) of donating and expressed hope that should they or their family were in a similar desperate situation others would do the same for them.

> "If anyone in my family needed a donation and there wasn't a family match, I would like somebody else to help my family" (p10)

> "I think it is a bit like giving blood. You give blood because you know one day you hope that if something happened to you someone will be there to help you out" (p7)

> "I asked myself a couple of very simple questions: If this were one of my children, would I not want someone to do whatever they could to save my child? And if that is what I want for my children, I have to do the same for someone else. In this world, you can't get by without helping each other and if we are not able to take that step, why the hell would someone else in your situation do it?" (p3)

> "Maybe someone would do it for me in the future" (p11)

Religious identification and the decision to donate

While many donors reported altruism to be a motivating factor, they also saw themselves as belonging to specific social groups that impacted their decision to donate. Religious beliefs were often cited as a major influence in deciding to donate.

> "And I think, as a Christian, you have to go through these kind of things. It says in the bible: treat people as you want to be treated and I would hope someone would do the same for me." (p7)

> "The only thing necessary for the evil to prevail is for good men to stand by and do nothing" (p7)

> "I am a Christian. I teach girls in a catholic school and teach them to try and save lives" (p8)

Community sense and the decision to donate

Other donors described how being part of a cultural community inspired them to become a donor.

> "I have never been in London before. I live in a small community and there was a young local girl in need of a donor" (p6)

> "I joined because there was an advert in the local paper about a patient who required a donation and I naively though that I could be a match" (p1)

> "Someone in our (Jewish) community was dying from leukaemia. There was an actual need in the community" (p3)

Personal circumstances

Rather than general altruism being the main motivating force, some donors viewed their donation as precipitated by specific personal circumstances. These donors tended to relate to the recipient and have empathic feelings towards them.

> "My son had meningitis and there was nothing I could do. Knowing what it is like to have a sick child, I though, it must be terrible for a parent to be in a similar sort of

situation and not being able to help. I joined because I could potentially help somebody." (p14)

"I was thinking of my children and of how I almost lost my son. I really related to the woman (in need of a transplant), as she might be a mom, she might have children!" (p8)

"One of my high school friends was diagnosed with leukemia, that is the reason I joined" (p13)

"My nephew was diagnosed with leukaemia when he was 3 and a half. He was the reason I am on the register" (p9)

Promotion of donation

The intrinsic motivation to donate was reflected in the finding that many donors remained actively involved in AN recruitment events and fundraising activities.

"I organised an AN recruitment event to about 3000 people in the local area following donation. I have sent e-mails to AN saying that I am happy to be an ambassador, but I haven't heard anything." (p3)

"I have been involved with several fundraising activities for AN" (p6)

"I try to get all my friends to join the register, just for the chance that they may be a match at some point." (p10)

"I have tried to convince many people to join the register. I got loads of my friends signed up. I think it was a very important thing for me to do." (p11)

"I am so passionate about people joining. I tell people that you can also donate via the PBSC method and they are surprised. If that was better communicated, far more people would join." (p13)

7.2.3.2 Theme 2: Determination

Sense of duty

Some donors felt that donating was almost an obligation or duty. Not donating was simply not an option, regardless of the difficulties they might encounter as a donor.

> "Not for a second did I think, do I fancy this? Am I going to do this? That was never a possibility. I couldn't live with myself if I didn't go ahead. I just wouldn't be able to live with myself." (p1)

> "I suffer from needle phobia. It has been impossible doing blood tests in the past. My wife had to take my hand during the donation process. They gave me one or maybe two valiums as well. For this cause, I was willing to take on the challenge of the needle phobia." (p3)

> "I wasn't going to give up" (p7)

Not influenced by other people

Even though most donors felt encouraged and supported by their family or friends in their decision to donate, most donors commented that they made the decision independently, without being influenced by other people. Some family members expressed worries and concerns, but this did not influence the donor's decision to donate.

> "My husband was very worried, but it wasn't going to change my mind. I was going to do it." (p8)

> "My wife was worried about something going wrong, but I have the (donor) card in my wallet and that is my final decision." (p6)

Worries about not being able to donate

When donors were asked about concerns related to the donation process, several responded they were mainly worried about not being able to donate, rather than feeling worried about their own health. They were worried about the possibility of becoming unable to donate due to health reasons, or not being a good match for the recipient.

> "I was concerned that I needed to be in better physical health. I was wondering whether the medical would show anything that would stop me donating. That would have been devastating to me." (p3)

> "I was hoping I would still be able to continue with the injections (despite the tonsillitis), but it was fine in the end." (p7)

> "Knowing that I am not in good physical health at the moment worries me as it is not a good situation for yourself or someone else to be in. You wouldn't be in the best position or best physical condition (in case you can donate again). (p3)

> "My only worry was not being a good enough match for that woman." (p8)

Playing down ARs

Despite the fact that these donors experienced considerable ARs, they did not perceive them as having a large impact after completing the donation.

> Despite experiencing severe headaches up to a week following donation:

> "I think I was quite lucky with the side effects" (p3)

> Despite experiencing considerable pain:

> "I don't feel like it has been a huge cost or anything, not like I donated an organ or anything." (p2)

> "All I had to do was sort of roll up my sleeve and have a needle in my arm for a couple of hours. That was all that was to it." (p1)

"It wasn't bad at all" (p5)

Despite having been advised to go to A&E for pain control:

"It wasn't a bother to me" (p7)

"It wasn't bad at all, I just saw it as a bit of pain that was related to the process" (p7)

7.2.3.3 Theme 3: Development of relationship with recipient

Emotional reactions to donation process

Most donors reported experiencing intense emotions in response to the donation process. Both positive and negative experiences were reported.

"When I found out I was a match, I was excited, but at the same time upset and sad, as it meant there was someone going through this all. So very mixed emotions, but at least knowing that potentially I could help that person outweighed the more sad feelings at the end of the day" (p13)

"I felt low after the donation and went very quiet for several weeks afterwards." (p6)

"At the time of the letter, I felt very blessed, blessed to give someone the chance. After the donation, for the next 4 months, it was like let's hope it has worked and I really wanted to know (the outcome)." (p8)

One donor reacted quite differently and commented that he experienced some closure after the experience.

"Whenever I donated stem cells, I finished in my mind, it was over. And then I had to give more a couple of months later and that was very difficult, because in my mind I had made some closure. I was happy to do it again, but when I finished I thought I am glad this is over." (p11)

Wanting to know the outcome

Most interviewees wanted to know as much as possible about the person who received their cells. Donors showed a special personal interest in their recipients and were concerned about them. Although realising the potential of receiving bad news, all donors asked to be informed about the outcome of the donation for the recipient. One donor commented that knowing less about the recipient would help him cope better with a potential recipient death, whereas another donor commented that having more information relating to the circumstances of a recipient's death might help him manage his grief.

> "I would really like to meet the person and see how much of a difference it has made." (p14)

> "I think I wanted to know more whether it worked or not rather than who it was. Maybe it would upset me more if it was for a small child and if it hadn't worked…" (p12)

> "I would like to know what his health outlook like." (p2)

> "I don't like the unknown, good or bad, I want to know." (p14)

> "If I wouldn't get updates about the recipient, I would end up thinking a lot. I just want to know for better or for worse." (p12)

> "It would be easier to deal with the recipient's death if you knew more about the person. You would want to know whether someone is depending on them." (p6)

Fantasising about recipient

Several donors fantasised about recipients' characteristics and personality traits and some wondered if they shared traits with the recipient beyond their HLA match.

> "I have related a lot to that woman. We were of the same weight and she was one year older than me. And a woman. And I just thought, she might be a mum! She might

> have children. And I was thinking about my children and how I almost lost my son. And I really thought of her. I thought I hope her children are fine." (p8)
>
> "I received a letter from recipient 3 months ago. He sounded like a family person. I think I put myself in the same situation and how important it would have been for my family (to survive)" (p9)
>
> "I was thinking a lot about the recipient, wondering whether it was someone who lived nearby." (p6)
>
> "I was told it was an adult male and a male can be from 16 up until whatever age. I got a thank you card and I was wondering: Is he a 16-18 year-old and is it his mum or someone aged 40 or 50 and his wife wrote the card? You know what I mean? You are left in suspense until you finally meet them." (p6)

Reactions when recipient dies

Given this background, it is not astonishing that donors are affected by recipients' deaths. Only one donor in this cohort was told that his recipient had died. This donor expressed feelings of grief.

> "It was pretty devastating. It is a strange feeling. Somebody passing who you don't even know but somehow you have a major connection. That's why maybe I have been quite a bit upset since I was notified several months ago." (p3)

This donor also commented on the lack of preparedness and the lack of emotional support or counselling following the news.

> "Going through a test is easy but finding out bad news is not. I am not sure I was sufficiently prepared. I was notified by letter and maybe it would have been better to have spoken to somebody. Some degree of counselling would have been good. I understand time and funds are limited, but part of the aftercare for the donors should maybe be looked into." (p3)

He nevertheless explained that he perceived the attempt to save the recipient's life as worth the effort and noted a wish to donate again in the future.

Remaining realistic about possible outcome for the recipient

Even though most donors experienced strong emotions, they often demonstrated a capacity to manage strong feelings and impulses and their thinking remained rational.

> "I gave it a best chance, but it is a shame it didn't work. And I was the best match, if more people would have been on the register, they would have found a better match. So I think it is also a message to try say that we need more donors on the list." (p8)

> "Actually you have given them quite a chance, because if you hadn't done anything their chances of survival would have been depleted even more. (p7)

> "If the recipient wouldn't make it, I could still say that I had done the best I could." (p5) (p10)

> "If I hadn't been on the register, the next one wouldn't have been as good (a match), so the chances of survival would have been even less. I set up in my mind, that they had the best chances" (p10)

> "They talk about guilt and everything, but I don't believe in that. I have done all I can essentially. I gave them an opportunity of a lifetime, an opportunity to survive potentially." (p13)

> "I would take away that I have given them time to spend with their family, even if they wouldn't survive. I certainly wouldn't regret doing it." (p12)

> "The news my donor didn't survive was pretty devastating. But what I did prolonged his life and it was maybe for a bleeping moment, a ray of hope for his family." (p3)

> "I am just a donor, it is not my responsibility (when the recipient dies). I do wish her all the best, but if she would not make it, it is not my fault." (p1)

7.2.3.4 Theme 4: Strong feeling of fairness

Donors who did not always feel supported by work, felt frustrated or upset. They felt it was not right to be treated in this way given the altruistic gesture they had shown.

> "Work was not generous and didn't give me the time off. I was very upset with a catholic school dealing with it so poorly really. The whole value of caring, really…" (p8)

> "My work wasn't supportive. It made me frustrated because I felt I was doing all possible to save somebody's life and they didn't really see it as that." (p10)

> "My old employer was not supportive, that was probably part of the reason why I left them. They acted like they were doing me a favour by giving me the time off. They offered me unpaid leave, I felt that was wrong." (p13)

7.2.3.5 Theme 5: Ease of decision

No conscious motivation

Some donors seemed to have decided to donate "automatically" without careful thought about the potential costs of donation or even their own motivations in becoming a volunteer.

> "Joining the register was as simple as buying a packet of crisps. You buy it and you don't really look at the packet thinking did I really need to buy it, you know, you just open them and eat them. That's it." (p1)

> "It was a no brainer, it is a good cause with not much effort really" (p9)

7.2.4 Discussion

The second part of the qualitative study explored the factors that may explain "donor resilience" or explain why donors are able to remain positive despite sometimes experiencing significant ARs.

I found that most donors were driven by a strong, intrinsic motivation. Character traits such as altruism appeared to be a major determinant in the decision to donate. While intrinsic motivation does not occur in isolation and is in part a response to a public or social role to donate it appeared that many interviewees were motivated by a genuine desire to help others. It has been suggested that donation to strangers may be considered an example of more extreme altruism than that to family members (Switzer et al., 1996). Yet the literature to date remains divided on the existence of a purely altruistic act and one major issue centres on the self-rewards that seem to result from helping behaviour (Simmons et al., 1993). Piliavin and Callero suggest that individuals may obtain specific rewards from donating, such as enhanced self-esteem, greater happiness and a heightened sense of fulfilment and meaning in their lives (Piliavin, 1991). In this context, self-esteem may be self-reinforcing and may lead to future altruism. Nevertheless, most would argue that the possibility that altruism may be self-rewarding in no way belittles the altruism itself. Some donor statements implied the awareness of the relative costs to the donor themselves and benefits (to themselves or the recipient) of donating, what has been called an 'exchange-related motive' (Switzer et al., 1997). Others viewed donation as a chance to save someone's life, help another person and an opportunity to show kindness and help another person. Valued social identities were closely implicated in the decision to become a donor. These identities included religious connections (based on the belief that helping is emphasised by religion) and community sense. Some donors were

motivated by past personal events (such as the illness of a child) and these donors appeared to be motivated by feelings of empathy towards their recipient. Other donors commented on how they almost joined the register “automatically” without giving it much thought. Switzer et al described this kind of motivation as an “idealized helping” motivation (Switzer et al., 1997).

Donors appeared extremely determined in their decision to donate and donation even seemed like a moral duty to some. The decision to donate was largely made without deliberation with family members and friends and several donors commented on how they were not influenced by others in making the decision. The majority of participants in this study were white and these findings contrast with an Asian study, where decisions were often influenced by peers and friends (Holroyd and Molassiotis, 2000). This dedication to donation was also illustrated by the finding that several donors were worried about not being able to donate, more so than expressing worries about potential ARs or risks to their own health. If ARs were experienced, they were perceived as being minimal. This may also be a consequence of the retrospective nature of this study, as donors were interviewed 1 to 1.5 years following donation.

The strong intrinsic motivation and determination observed reflects very low levels of ambivalence. Ambivalence involves feeling unsure about donation and has been extensively studied by Switzer et al (Switzer et al., 1996, Switzer et al., 2014). High ambivalence encompasses the feeling of relief if donors find out they cannot donate, doubts and worries about donating or wishing that the patient was getting the stem cells from someone else. Switzer et al. found that low levels of ambivalence was the best predictor of positive donation-related outcomes (Switzer et al., 1996, Switzer et al., 2003). The same author showed that respondents with lower intrinsic commitment

to join the donor registry (those who did not feel morally obligated to join and those who would not have been disappointed in themselves had they not joined) reported higher ambivalence. Donors who had been encouraged to or discouraged by others from joining the registry reported higher ambivalence as well as donors who believed they were not well informed about the donation process. These results are consistent with the low levels of ambivalence and the generally positive donation experience observed in this study.

Even though donors are not related to the recipients, a strong emotional bond was often observed. In accordance with WMDA guidance, unrelated donors are permitted to find out about the outcome of the donation and to exchange letters anonymously via the donor registries and transplant centres. Two years after donation, anonymity between donors and recipients can be removed if both sides agree and no legal restrictions of the recipient country require on-going anonymity (Wanner et al., 2009). Similar to previous studies (Atkinson, 2005, Wanner et al., 2009), all donors interviewed wanted to know the outcome for the recipient. Only one donor in this cohort received bad news and he experienced significant symptoms of grief as a consequence. These unexpected, intense feelings of grief have been described previously (Butterworth et al., 1992, Wanner et al., 2009). The explanation for this strong affective response may be due to the strong emotional relationship most donors develop with their recipient, even if unknown to them. Another explanation may be that the donor's altruistic act has failed, leaving them disappointed. One might argue that donor centres could avoid such negative consequences for donors by not informing donors about recipients' deaths. However, there is general agreement that donor centres should inform donors who request this information on the health status of their respective recipients. This also applies to information about recipients' deaths (Goldman, 1994). One study also reported that donors preferred the knowledge of

the failure to uncertainty, even if this knowledge caused grief (Butterworth et al., 1992). Donors' hopes regarding the positive outcomes of transplantation may be unrealistic. It is therefore important that registries or collection centres provide realistic information during donation preparation and inform prospective donors openly about the possibility of failure. One author reported that donors who felt poorly informed prior to donation significantly less often consider the message regarding the recipient's death to be helpful and informative (Wanner et al., 2009). The way this information is communicated is important – of note, most donors prefer to be contacted by telephone (Atkinson, 2005). Registries should be encouraged to implement this and the role of trained counsellors in this respect should also be considered. The relevance of personal coping resources and referring donors to their family and friends has also been suggested (Wanner et al., 2009). Some registries have reported that sharing experiences with other donors may be therapeutic and therefore opportunities for donors to meet within a support group may be beneficial. Despite the death of a recipient, most donors in previous studies were happy to have donated and said they would be willing to donate again (Wanner et al., 2009). Even though an emotional bond with the recipient is often developed, this study found that donors seemed able to manage strong feelings and emotions, an important prerequisite to resilience.

A limitation of this qualitative study is the retrospective nature mentioned earlier. Another potential limitation is the epistemological position that was adopted; one of essentially accepting what participants say as a genuine reflection of their experience. For example, donors may not have been consciously aware of rewards gained from the donation process or perhaps not willing to acknowledge such rewards in an interview as thinking of themselves as highly altruistic and presenting themselves to

the world as such. Another limitation lies within the donor recruitment method, as only donors with PCS scores in the highest and lowest quartile were selected. This may limit the ability of its results to be generalized to the rest of the donor population.

This qualitative study identified several donor characteristics, including strong intrinsic motivation, altruism, sense of duty, determination, low levels of ambivalence and the ability to develop a strong emotional relationship with an (unknown/anonymous) recipient whilst being able to manage strong feelings and emotions. These personality traits may explain the resilience that has been observed previously in HSC donors. It should be borne in mind that this study recruited donors who had already donated and thus can be expected to be different from potential donors presenting at recruitment or confirmatory typing (CT) stage. As expected, Switzer et al reported higher levels of ambivalence at earlier stages in the donation process (Switzer et al., 2003, Switzer et al., 2005, Switzer et al., 2013) and identified this as the main risk factor for donor attrition or opting out of the register. The finding that most donors in this cohort joined as a result of an intrinsic commitment, rather than as a result of extrinsic pressures, means that strategies could be considered to create a recruitment context that emphasises the former. Some strategies have already been considered by the NMDP and include creating materials that reinforce the message of intrinsic and long-term commitment to donation and avoiding recruitment settings that may involve high levels of extrinsic pressure to join, e.g. recruitment drives in schools (Switzer et al., 2003). Strategies to enhance commitment at recruitment could also involve a two-stage process, where the decision to join the register needs to be reaffirmed. Other approaches may include making it easier for donors to opt out of the register. Although most of the donor characteristics in this cohort are related to inherent personality traits, several aspects of the donation process may help to build

a “resilient donor population”. Possibilities include raising awareness of potential poor outcomes in the recipient and offering improved counselling services if the recipient dies. Donors who display high levels of ambivalence at CT stage after having been matched to a patient, could be offered ambivalence reducing interventions. One author employed telephone calls to discuss remaining concerns about donation in solid organ donors (Dew et al., 2012). However, any interventions to reduce ambivalence would need to take particular care to strike a balance between reduction of ambivalence and addressing misconceptions without being coercive in encouraging donation.

Chapter 8 - Conclusions

8.1 Summary

This thesis presents a broad investigation of the physical and psychological donation experience and of factors influencing recovery and adverse reactions (ARs) following PBSC and BM donation. It focuses on the association between baseline health-related quality of life (HRQOL) scores and the donation experience and outlines the changes in HRQOL throughout the donation process. A diverse group of activities contribute to its final structure: I have written a review of factors implicated in the donation experience that was subsequently published in a peer-reviewed journal; I have designed and carried out 3 research studies, 2 of which have been published; and I have initiated a significant service development project in-house at Anthony Nolan (see 8.3 below). In this chapter, the outcomes of these studies and projects are summarized. I will also briefly discuss some of the challenges I faced in this work and present future work.

Chapter 1 provides an overview of the literature in the field of the donation experience. It outlines the physical and psychological reactions to the donation process as well as demographic factors influencing the donation experience. Chapters 4 and 5 update this through a large prospective study involving 275 PBSC and 37 BM donors. This study found that the majority of both PBSC and BM donors reported ARs, however ARs were mainly classified as mild. BM donors recovered significantly slower compared to PBSC donors (14.3 versus 5.2 days) and experienced pain for a longer time following donation.

There are few studies that have prospectively examined factors influencing recovery and adverse reactions (Pulsipher et al., 2013, Miller et al., 2008, Nishimori et al., 2002). There are several retrospective studies (table 1.3) investigating the donation experience, but they are often limited by an underreporting of adverse reactions (due to the lack of standardised checklists of donor adverse reactions). Time to complete recovery as a study endpoint has only been previously used by Pulsipher et al (Pulsipher et al., 2013). My study was the first study to investigate the influence of pre-donation HRQOL, the number of dependants, marital status and being a blood donor on the donation experience.

The only demographic factor in my study associated with slower recovery in PBSC donors was higher donor age. Higher age was also associated with increased symptoms of fatigue. Having a higher BMI or having more dependants was associated with headache in PBSC donors. Female PBSC donors were more likely to experience any adverse reaction, in particular pain and fatigue. Both female gender and having a higher number of dependants appeared associated with slower recovery in BM donors.

The key finding of the study is that pre-donation HRQOL markers are strong predictors of time to recovery and ARs. Poorer pre-donation physical health (measured using the physical component summary or PCS score) was associated with longer recovery ($p = 0.017$) and symptoms of pain, fatigue and dizziness in PBSC donors. Poorer pre-donation mental health was associated with longer recovery in BM donors ($p = 0.03$) and pain following PBSC donation ($p = 0.003$). A possible explanation of the finding that MCS scores predicted recovery in BM donors but not in PBSC donors, may be related to the very distinct nature of the two procedures. As BM donation was associated with pain symptoms at later time points, I would speculate that pre-existing symptoms of anxiety or low mood would have a significant

impact on this outcome. I believe that HRQOL markers should be used alongside demographic markers in order to risk stratify the donor population and to help identify donors at risk for poorer outcomes. These donors may benefit from modification of joining policies or different supportive measures or follow-up procedures (see 8.3 Future work below).

To the best of my knowledge this is the first study to show that, even in PBSC donors, physical health is significantly (although minimally) reduced 4 weeks following donation compared to pre-donation. This decline was shown both for PBSC and BM donors ($p < 0.001$ and $p = 0.009$ respectively), but most scores at 4 weeks were significantly lower for BM donors compared to PBSC donors, reflecting the delayed recovery in the former. Mental health measured using the mental component summary or MCS score was significantly reduced at 4 weeks for BM donors, but not for PBSC donors. One earlier study has investigated HRQOL using the SF-36 form pre-donation, 1 week and 4 weeks following donation (Bredeson et al., 2004). This study equally found that BM donation was associated with more physical morbidity and negative effects on HRQOL compared to PBSC donation. This study did not find significant HRQOL changes when comparing pre and 4-week post donation scores in PBSC donors.

My qualitative study in chapter 7 found that there was a good correlation between the pre-donation HRQOL measured using SF-36 scores and information derived through detailed donor interviews. The interviews showed that PBSC donors felt well prepared for the donation and were not generally worried about adverse reactions. Thematic analysis demonstrated that donors exhibited a strong, intrinsic motivation to donate as well as a remarkable determination and low levels of ambivalence. These factors may explain the “donor resilience” or the positive attitude that was observed in donors

despite often experiencing significant adverse reactions. Donors had often developed a strong emotional relationship with their recipient and significant symptoms of grief were observed in cases where the recipient passed away. Raising awareness of potential poor outcomes in the recipient and offering improved counseling services if the recipient dies are strategies that have shown to be beneficial and ought to be implemented by donor registries in order to improve the donation experience.

Chapters 3 and 6 evaluate the factors affecting the frequency with which PBSC (chapter 3) and BM (chapter 6) collections meet the transplant centre's requested dose. This was the first study to examine the influence of the difference between donor and recipient weight. I found that male gender, lower donor age, higher BMI, higher baseline platelet counts and a positive difference between donor and recipient weight were significantly associated with meeting the target yield in PBSC donors. This knowledge could affect future donor recruitment and selection strategies as well as mobilisation regimens in PBSC donors. Improved strategies may limit the numbers of days of apheresis or potential emergency bone marrow harvests procedures; factors associated with increased donor ARs. The most important factors in meeting the transplant centre's requested dose for BM donors were a larger difference between donor and recipient weight and lower volume of BM collected. Larger volumes collected are often associated with high volume aspirations and peripheral blood contamination and hence poorer quality harvests. Improved BM harvest techniques such as using multi-hole aspiration needles may improve the quality of the harvests and reduce the duration of the harvest procedure and number of puncture holes and hence improve the donation experience. Table 8.1 lists the main findings of this thesis.

Table 8. 1 Main thesis findings

Main thesis findings

- Most PBSC and BM donors experience adverse reactions (ARs), although majority of ARs is mild
- BM donors recover significantly slower following donation compared to PBSC donors
- PBSC Donors at risk of delayed recovery or increased donation toxicity
  - Older age
  - Female gender
  - Higher BMI
  - Higher number of dependants
- Physical health (measured using PCS score) is significantly reduced 4 weeks following donation, both for PBSC and BM donors, compared to pre-donation with a return to pre-donation values 3 months following donation
- Mental health (measured using MCS score) is significantly reduced 4 weeks following donation for BM donors (not for PBSC donors) compared to pre-donation with a return to pre-donation values 3 months following donation
- Pre- and 3 month post-donation PCS scores are higher compared to the general population, both in PBSC and BM donors
- When comparing BM and PBSC donors, PCS and MCS scores are significantly lower for BM donors compared to PBSC donors 4 weeks following donation; BM scores at 4 weeks are comparable to scores of patients with chronic medical conditions. PBSC scores at 4 weeks are still comparable with scores of the general healthy population.
- Lower pre-donation PCS scores (especially scores in the lowest quartile) are associated with a delayed recovery and very common adverse reactions (such as pain and dizziness) in PBSC donors; these “lower” scores are still above the average of the general population, illustrating the high fitness levels of donors.
- Lower pre-donation MCS scores (especially scores in the lowest quartile) are associated with pain in PBSC donors and a slower recovery in BM donors

- Donors appear very resilient and are willing to donate again in the future despite often experiencing significant ARs
- Donors are driving by a strong, intrinsic motivation to donate, they display high levels of altruism and low levels of ambivalence
- A strong emotional relationship with the recipient is developed
- Factors associated with reaching target yield in PBSC donors
  - Higher donor weight/BMI
  - Donor heavier than recipient
  - Male gender
  - Younger age
- Factors associated with reaching target yield in BM donors
  - Donor heavier than recipient
  - Lower volume of marrow collected
- Lower harvest volumes in BM donors are associated with higher TNC counts per ml; this is likely due to a reduced contamination with peripheral blood and better harvest techniques.

8.2 Challenges

Inevitably there were many challenges faced in these projects.

Data collection, particularly for the prospective study, required many different information sources. Often several different spreadsheets were required to provide the necessary information and donor and patient paper notes were used to validate much of these data. This proved very time consuming. A single system used for all departments (along with a facility to extract data in an automated fashion) is currently in the development stage at Anthony Nolan and will hopefully be introduced in the near future.

Missing data were also problematic. I went to great lengths to obtain all the relevant information, but there were many key variables that the registry did not reliably hold.

Another challenge was the difficulty in achieving adequate responses to the SF-36 forms. This required several telephone calls and e-mails. The fact that this was all executed by myself led to inevitable "gaps" in donor recruitment, as there was nobody available to cover during periods of leave. Another cause of missing data was the slow introduction of the health care provider form mentioned in chapter 3 (section 3.2.3.1). I was dependant on external companies for the introduction of this form and the delay led to the low response rate to this form during my study period.

Setting up the qualitative study and performing the thematic analysis was another major challenge, as I hadn't been involved with this type of research before. It required a significant amount of reading and assistance from my supervisors within the UCL psychology department.

8.3 Future work: Pilot project "Improving donor recovery following donation"

8.3.1 Background and objectives

Understanding that ARs vary with certain donor characteristics gives AN the opportunity to investigate possible interventions that may result in donors experiencing fewer ARs or reduce the time a donor takes to recover post donation. This would have several clear advantages. Most importantly, the act of donating BM or PBSC for HSCT is a gesture rewarded only by the potential sense of satisfaction derived from a humane act. Hence, care must be taken to optimise donor safety. There may also be benefits to the organisation with regards to safeguarding the overall reputation of HSC donation, but also possible reductions in covering donor loss of earning costs, time spent supporting donors who have not recovered from their donation and associated medical costs. For example, during the financial year of

2013-2014 AN has spent £49,000 on loss of earnings and £11,000 on consultant specialist fees (predominantly post donation) totalling £60,000 over 500 donors.

In initiating this pilot project, I involved our donor relationship advisor and the heads of our donor follow-up and donor provision department in the further development. The objectives of the project are listed in table 8.2.

Table 8. 2 Objectives of the "Improving donor recovery following donation" project

Objectives
Provide donors with tailored information and counselling pre-donation
Provide donors with a tailored follow-up that offers education and a more stringent follow-up of high risk groups
Aim to reduce adverse reactions
Aim to shorten time to complete recovery
Aim to improve donation experience
Aim to reduce costs associated with covering loss of earnings or medical consultations

8.3.2 Pilot project

8.3.2.1 High risk groups

I proposed to change our approach to the high risk donors, but to continue our existing management for the other donors. My study found that PBSC donors with PCS scores in the lowest quartile (scores ≤ 56) recovered significantly more slowly compared to other donors (on average 6 vs 3.4 days); BM donors with MCS scores in the lowest quartile (scores ≤ 46) also recovered significantly more slowly (on average 28.6 vs 11.4 days). These 2 groups are what I consider to be the high risk groups.

The only demographic characteristic implicated in a delayed recovery was older donor age; I found that PBSC donors > 40 recovered significantly slower compared to donors ≤ 40 (6.8 vs 3.9 days). I could not demonstrate this in BM donors, but this may be due to the low number of donors in this group. Several other studies have shown a delayed recovery and increased SARs in older BM donors (Miller et al., 2008, Pulsipher et al., 2013). Although donors > 40 could be included in the intervention group, we decided not to based on the finding that fatigue was the main AR associated with higher donor age and this is likely the cause of a delayed recovery in this group. As the use of pre-emptive analgesia will be one of the key interventions, it will unlikely be effective in this group of donors. Given that we want to standardise interventions within the PBSC and BM group, the inclusion of this group was less practical.

Our registry coordinates on average 500 UK donations per year. 90% of these donors are PBSC donors and 10% BM donors. Approximately 25% of PBSC donors will have PCS scores ≤ 56 and approximately 25% of BM donors will have MCS scores ≤ 46. If we assume a 70% response rate of baseline SF-36 questionnaires, this would mean a total of 79 PBSC and 9 bone marrow donors that would need intervention on an annual basis (table 8.3).

Table 8. 3 Expected numbers of donors to be included in pilot project

Characteristic	Expected number of donors (n)
PCS score ≤ 56 (PBSC)	25 x [(70 x 450)/100]/100 = 79
MCS score ≤ 46 (BM)	25 x [(70x50)/100]/100 = 9

8.3.2.2 Intervention

I did not find any interventional studies in the area of HSC or organ donation reported in the literature and I have based my project proposal on research in general surgery; importantly patient education and pre-emptive analgesia appear to have made a considerable impact on recovery in the surgical field.

Reviews of psychological and educational preparation for surgery strongly support the effectiveness of a variety of interventions, across a variety of procedures, in reduction of post-surgical pain, use of analgesics, psychological distress, days until discharge and overall cost (Devine, 1992, Devine and Cook, 1983, Hathaway, 1986, Anderson and Masur, 1983, Ibrahim et al., 2013, GTA, 2005). A meta-analysis of 49 published and unpublished studies showed that the average hospital stay was reduced by 12%, a mean of 1.25 days (Devine and Cook, 1983). Interventions can be grouped into several types: information about the procedure, cognitive coping strategies, relaxation and hypnosis, reassurance and support. Most reviewers have confirmed the generally beneficial effects for all forms of preparation, but found that information about procedures and their side effects provided the most widespread benefits in recovery.

Other possible interventions for high risk donors may include the use of pre-emptive analgesia, an approach that has proven to be effective in general surgery patients. Mardani-Kivi et al (Mardani-Kivi et al., 2013) described improved pain scores following knee arthroscopy with pre-emptive celecoxib. Another study demonstrated a decreased length in hospital following joint arthroplasty when using pre-emptive analgesia (Duellman et al., 2009). Chern et al reported a significant reduction in pain following BM harvest by infiltrating the harvest site with 10 ml of 0.5% bupivacaine immediately following bone marrow harvest (Chern et al., 1999). The interventions I suggested for our donors are shown in table 8.4.

Table 8. 4 Suggested interventions for high risk groups

Intervention group	Intervention
PBSC (PCS score ≤ 56)	• Detailed medical information and donor education at the time of medical (document S3) explaining the increased recovery time (approximately 1 week) and the increased risk of adverse reactions including fatigue, dizziness and pain • Use of pre-emptive paracetamol (1 g QDS) from the first day of G-CSF up until the day of donation • Stringent donor follow-up: weekly telephone calls if not recovered after 1 week up until full recovery (rather than e-mail follow-up)
BM (MCS score ≤ 46)	• Detailed medical information at the time of medical (document S4) explaining the increased recovery time (approximately 4 weeks) and the increased risk of pain symptoms • Use of paracetamol (1 g QDS) from the day of the bone marrow harvest up until 5 days after donation + supply donor with prescription of co-codamol or codeine • Stringent donor follow-up: for weekly telephone calls up until full recovery (rather than e-mail follow-up)

8.3.2.3 Costing

Table 8.5 outlines the project plan and associated costs of the project. The total annual added cost to the organisation would be estimated around £5100. This excludes staff time as part of the project team (the medical officers and donor relationship advisor) and the external statistical analysis.

Table 8. 5 Project plan and costing. Teams can be either the Donor Provision Team (DP) or the Donor Follow-up Team (FU) within Operations.

Task	Team	Donors (n)	Time Taken	Cost
Work Up process to be altered to introduce SF-36 form for all donors SF36 to be sent to all donors with covering message as soon as day of medical consultation is confirmed SF-36 forms to be e-mailed (preferential) or posted	DP	500	5 mins per donor 42 hours in total annually	£840
Scoring of SF-36 assuming a 70% response rate	FU or DP	350	10 mins per form 60 hours in total annually	£900 (FU) or £1200 (DP)
PBSC donor follow up – phone call if needed + repeat SF-36 at 4 weeks	FU	79	15 mins 20 hours in total	£300
BM donor follow up – weekly phone call up until full recovery + repeat SF36 at 4 weeks	FU	9	25 mins 4 hours in total	£60
Licencing of SF36 forms and scoring software (based on smart survey as interface)	NA		NA	£2999 (price for up to 600 copies)
TOTAL in addition to usual processes				£5100

The potential savings for AN are harder to calculate. First of all, we can only make assumptions of potential improvements regarding the number of days of loss of earnings claimed. Based on the experience in surgery, implementation of providing adequate information beforehand reduced hospital stay by 12%. Additionally, providing pre-emptive analgesia improved hospital stays with on average 15%. It is unknown what the additional value of combining these interventions would be. Also, it is unsure whether these figures can be extrapolated to days off work in our donor population. Even if we would hypothesise this to be x days in PBSC donors and y days in BM donors, we would still not have sufficient information. AN is currently not recording how many days donors claimed and whether the days claimed were for PBSC or BM donors. The only figure available is the total amount of loss of earnings covered for the financial year. We can intuitively expect that the amount claimed by BM donors will be significantly higher compared to PBSC donors, but BM donors only make up 10% of the donor population. In conclusion, an estimate of potential savings with regards to loss of income seems not possible with the current available information.

8.3.2.4 Outcomes

As per our registry's routine donor follow-up, the time to complete recovery will be documented as well as adverse reactions on the first 3 days of G-CSF, on the day of donation, 2-3 days following donation and weekly after donation until full recovery. In addition, records will be kept of the cost of loss of earnings cover and post donation medical costs.

I will continue to be involved with this project and with the initial analysis in 1 year's time.

8.4 Conclusion

This thesis clarifies the donor and collection characteristics associated with poorer donation experiences. This is a first step towards creating targeted strategies concerning donor recruitment, selection, work-up and donor follow-up and will contribute significantly to improving the donor physical and psychological donation experience. Additionally, illuminating donor and collection characteristics that are associated with not reaching the required yield, is important as different approaches for these donors may avoid unnecessary additional procedures and adverse reactions. Such strategies that improve the donation experience will contribute to improved donor outcomes, help to safeguard the reputation of the process and ultimately benefit the general transplant community.

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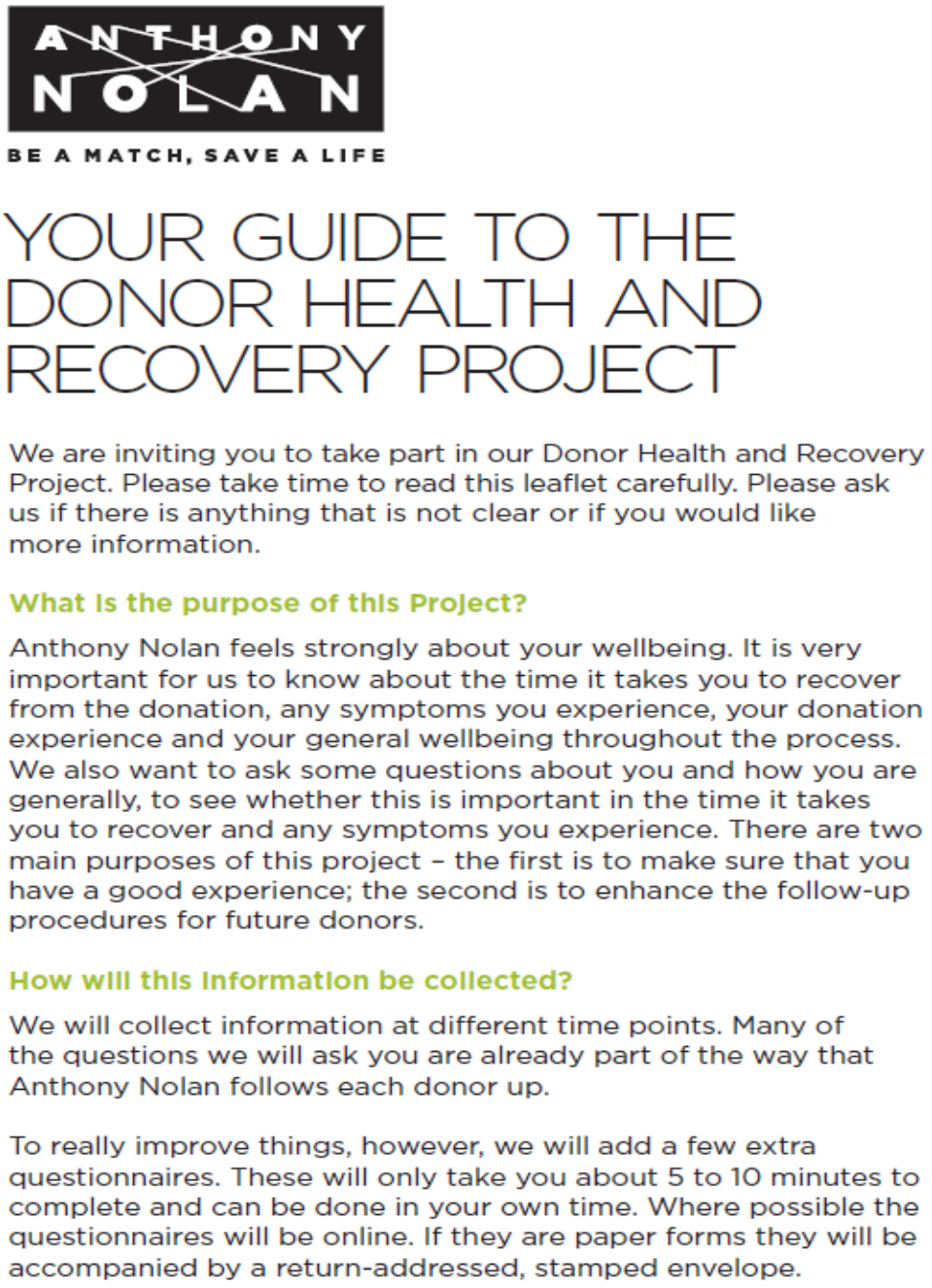
Appendix 1 – Supplemental tables and figures

Figure S 1 Your guide to the donor health and recovery project



These are the times that we ask you to fill in a form:

- Before you start the donation, one questionnaire will be sent to you via email or posted, depending on your preference, asking you about your general health and wellbeing
- 1 week following donation, an email with a link to a short online questionnaire will be sent to you, asking you about possible symptoms you are experiencing
- If you have not fully recovered after a week, you will receive weekly follow-up emails to fill in the same online questionnaire, until you have fully recovered
- 4 weeks following donation, a questionnaire will be sent to you via email or posted asking about your general health and wellbeing, another questionnaire asking about feedback of the whole donation process will be posted to you
- 3 months following donation, a questionnaire will be sent to you asking you about your general health and wellbeing.

Do I have to take part?

No. It is entirely up to you to decide whether or not to take part. You are free to withdraw at any time and without giving a reason. A decision to withdraw at any time, or a decision not to take part, will not affect the standard of care you receive or any other part of your involvement with Anthony Nolan.

Will my taking part in the Survey be kept confidential?

All information that is collected about you during the course of the Survey will be kept strictly confidential. You should be aware that all information will be handled, stored and destroyed in compliance with the Data Protection Act of 1998.

USEFUL CONTACTS

- General switchboard **0303 303 0303**
- Donor provision team **donorprovision@anthonynolan.org**
- Catherine Burlton, donor advocate **0207 4246 644** **catherine.burlton@anthonynolan.org**
- Annelies Billen, medical officer **07788 385331** **annelies.billen@anthonynolan.org**

Reg charity no 803716/SC0388
134OP/0113

Figure S 2 Home care provider form

Donor Name:	DOB:		Homecare Provider ID Number: Anthony Nolan ID Number:			
Date	Drug administered	Dose	Route/Site	Batch no	Time given	Duration of visit
	GCSF					
Female Patient Yes/No **- If Yes pregnancy test to be completed**			**Date:** **Time:**		**Result:**	
Clinical Observations:						
Date / Time	Pre / Post	Pulse	Temp	BP	Respiratory Rate	
Adverse Drug Events (specification + grading 0 - 4 – CTCAE toxicity score):						
Reaction	**Y/N**	**Grade (1-4)**	**Reaction**	**Y/N**	**Grade (1-4)**	
Allergy			Injection Site reaction			
Anorexia			Insomnia			
Bruising			Nausea			
Dizziness			Myalgia			
Fatigue			Pain			
Fever			Rash			
Headache			Vomiting			
Infection			Any other adverse reactions			
Doctor Informed		Medication				

Donor Consent: I confirm that the relevant clinical obeervations and treatment have been explained to me by the nurse and I consent for them to proceed with prescribed treatment. Donor Signature: Date:	
Nurse Name:	Nurse Signature:

Figure S 3 Toxicity guide

ANTHONY NOLAN
BE A MATCH, SAVE A LIFE

ANTHONY NOLAN GUIDE TO ADVERSE EVENTS BASED ON CALGB TOXICITY SCORES

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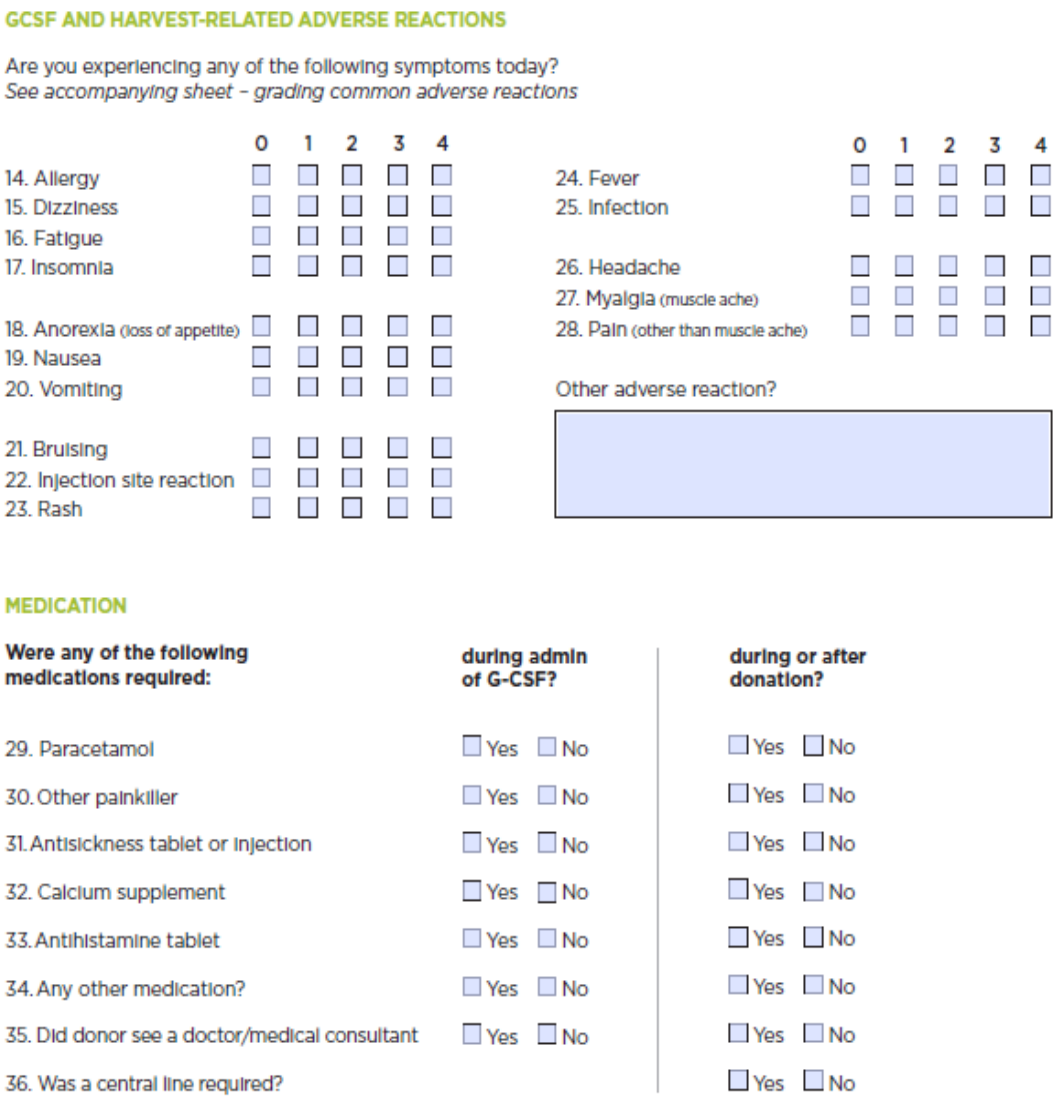
Registered charity number
803716/SC038827

CALGB TOXICITY SCORE	1	2	3	4
Allergy	Brief 'flushing reaction' or rash, mild fever of less than 38oC. No treatment required	Rash or other reaction which requires treatment with antihistamines or other medicine to help relieve symptoms (e.g. paracetamol). Symptoms last less than 24 hours and respond rapidly to medication	More severe or prolonged reaction which is slow to respond to medication OR comes back after initial improvement OR requires admission to hospital	Life-threatening reaction requiring urgent intervention
Anorexia/Loss of appetite	Loss of appetite without alteration in eating habits	Food intake altered without significant weight loss or malnutrition; food supplements required	Significant weight loss or malnutrition (inadequate food or fluid intake; tube or intravenous feeding required)	Life-threatening reaction requiring urgent intervention
Bleeding	Mild without need for transfusion		Requiring transfusion	Catastrophic bleeding requiring major non-elective intervention
Bruising	Localised or in dependent area	Generalised		
Dizziness	Mild unsteadiness or sensation of movement (vertigo)	Moderate unsteadiness or sensation of movement (vertigo); limiting activities other than self-care	Severe unsteadiness or sensation of movement; limiting self-care activities	
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 or more for up to 24 hours	40˚C or more for over 24hrs
Headache	Mild pain	Moderate pain; limiting activities other than self-care	Severe pain; limiting self care activities	
Infection	Mild infection, requiring only symptomatic relief (such as paracetamol, night nurse etc...)	Moderate infection, requiring tablet antibiotics; limiting activities other than self care	More severe infection, requiring treatment with intravenous antibiotics and/or hospital admission; limiting self-care activities	Life-threatening consequences; urgent intervention indicated
Injection site reaction	Tenderness with or without other symptoms (e.g. warmth, skin reddening, itching)	Pain, swelling, or distortion of the skin	Ulcer formation or skin breakdown - requires surgery.	Life-threatening consequences; urgent intervention indicated
Insomnia	Mild difficulty falling asleep, staying asleep or waking up too early	Moderate difficulty falling asleep, staying asleep or waking up early	Severe difficulty falling asleep, staying asleep or waking up early	
Myalgia (muscle ache)	Mild pain	Moderate pain; limiting activities other than self-care	Severe pain; limiting self care activities	
Nausea (feeling sick)	Loss of appetite without alteration in eating habits	Food intake altered without significant weight loss or malnutrition; food supplements required	Inadequate food and/or fluid intake; tube feeding or intravenous feeding indicated	
Pain	Mild pain	Moderate pain; limiting activities other than self-care	Severe pain; limiting self care activities	

Figure S 4 PBSC visit form



GCSF AND HARVEST-RELATED ADVERSE REACTIONS

Are you experiencing any of the following symptoms today?
See accompanying sheet – grading common adverse reactions

	0	1	2	3	4
14. Allergy	☐	☐	☐	☐	☐
15. Dizziness	☐	☐	☐	☐	☐
16. Fatigue	☐	☐	☐	☐	☐
17. Insomnia	☐	☐	☐	☐	☐
18. Anorexia (loss of appetite)	☐	☐	☐	☐	☐
19. Nausea	☐	☐	☐	☐	☐
20. Vomiting	☐	☐	☐	☐	☐
21. Bruising	☐	☐	☐	☐	☐
22. Injection site reaction	☐	☐	☐	☐	☐
23. Rash	☐	☐	☐	☐	☐
24. Fever	☐	☐	☐	☐	☐
25. Infection	☐	☐	☐	☐	☐
26. Headache	☐	☐	☐	☐	☐
27. Myalgia (muscle ache)	☐	☐	☐	☐	☐
28. Pain (other than muscle ache)	☐	☐	☐	☐	☐

Other adverse reaction?

MEDICATION

Were any of the following medications required:	during admin of G-CSF?	during or after donation?
29. Paracetamol	☐ Yes ☐ No	☐ Yes ☐ No
30. Other painkiller	☐ Yes ☐ No	☐ Yes ☐ No
31. Antisickness tablet or injection	☐ Yes ☐ No	☐ Yes ☐ No
32. Calcium supplement	☐ Yes ☐ No	☐ Yes ☐ No
33. Antihistamine tablet	☐ Yes ☐ No	☐ Yes ☐ No
34. Any other medication?	☐ Yes ☐ No	☐ Yes ☐ No
35. Did donor see a doctor/medical consultant	☐ Yes ☐ No	☐ Yes ☐ No
36. Was a central line required?		☐ Yes ☐ No

Figure S 5 BM visit form

HARVEST RELATED ADVERSE REACTIONS

See accompanying sheet – Grading Common Adverse Reactions

	0	1	2	3	4
7. Allergy	☐	☐	☐	☐	☐
8. Anorexia (loss of appetite)	☐	☐	☐	☐	☐
9. Back pain	☐	☐	☐	☐	☐
10. Bleeding	☐	☐	☐	☐	☐
11. Bruising	☐	☐	☐	☐	☐
12. Dizziness	☐	☐	☐	☐	☐
13. Fatigue	☐	☐	☐	☐	☐
14. Fever	☐	☐	☐	☐	☐
15. Harvest site pain	☐	☐	☐	☐	☐

	0	1	2	3	4
16. Headache	☐	☐	☐	☐	☐
17. Infection	☐	☐	☐	☐	☐
18. Insomnia	☐	☐	☐	☐	☐
19. Nausea	☐	☐	☐	☐	☐
20. Rash	☐	☐	☐	☐	☐
21. Throat pain	☐	☐	☐	☐	☐
22. Vomiting	☐	☐	☐	☐	☐
23. Any other pain	☐	☐	☐	☐	☐

24. Other adverse reaction

MEDICATIONS

Were any of the following medications required during, or after donation?

25. Paracetamol	☐ Yes	☐ No
26. Other painkiller	☐ Yes	☐ No
27. Antisickness tablet	☐ Yes	☐ No
28. Antihistamine tablet	☐ Yes	☐ No
29. Any other medication?		

Figure S 6 Day 2 or 3 telephone call form

ANTHONY NOLAN

DONOR EVALUATION PBSC

Donor Name	Donor Number	Date of collection	Date of call

- Have you fully recovered from your donation? Y/N
- Are you back at work and participating in normal activities? Y/N
- Were you discharged the same day?
- Did you require a second day collection?
- Were any medications started following donation?

  Please specify

Collection related adverse reactions

	0	1	2	3	4
Allergy					
Anorexia (Loss of appetite)					
Bruising					
Dizziness					
Fatigue					
Fever					
Headache					
Infection					
Insomnia (difficulty sleeping					
Myalgia (muscle ache)					
Nausea (feeling sick)					
Rash					
Vomiting					
Any other pain					

Other adverse reactions:

Would the donor like to receive recipient progress reports? Y/N

Does the donor want to communicate with the recipient? Y/N

Call donor if something arrives Y/N

Mention surveymonkey – e-mail address verified Y/N – surveymonkey link sent Y/N
Comments: Name: Date:

Figure S 7 SF-36 questionnaire

Your Health and Well-Being

This survey asks for your views about your health. This information will help keep track of how you feel and how well you are able to do your usual activities. ***Thank you for completing this survey!***

For each of the following questions, please tick the one box that best describes your answer.

1. In general, would you say your health is:

Excellent	Very good	Good	Fair	Poor
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

2. <u>Compared to one year ago</u>, how would you rate your health in general <u>now</u>?

Much better now than one year ago	Somewhat better now than one year ago	About the same as one year ago	Somewhat worse now than one year ago	Much worse now than one year ago
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

3. The following questions are about activities you might do during a typical day. Does your health now limit you in these activities? If so, how much?

	Yes, limited a lot	Yes, limited a little	No, not limited at all
a. Vigorous activities, such as running, lifting heavy objects, participating in strenuous sports	☐ 1	☐ 2	☐ 3
b. Moderate activities, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf	☐ 1	☐ 2	☐ 3
c. Lifting or carrying groceries	☐ 1	☐ 2	☐ 3
d. Climbing several flights of stairs	☐ 1	☐ 2	☐ 3
e. Climbing one flight of stairs	☐ 1	☐ 2	☐ 3
f. Bending, kneeling, or stooping	☐ 1	☐ 2	☐ 3
g. Walking more than a mile	☐ 1	☐ 2	☐ 3
h. Walking several hundred yards	☐ 1	☐ 2	☐ 3
i. Walking one hundred yards	☐ 1	☐ 2	☐ 3
j. Bathing or dressing yourself	☐ 1	☐ 2	☐ 3

4. During the past 4 weeks, how much of the time have you had any of the following problems with your work or other regular daily activities as a result of your physical health?

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
a. Cut down on the amount of time you spent on work or other activities	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
b. Accomplished less than you would like	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
c. Were limited in the kind of work or other activities	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
d. Had difficulty performing the work or other activities (for example, it took extra effort)	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

5. During the past 4 weeks, how much of the time have you had any of the following problems with your work or other regular daily activities as a result of any emotional problems (such as feeling depressed or anxious)?

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
a. Cut down on the amount of time you spent on work or other activities	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
b. Accomplished less than you would like	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
c. Did work or other activities less carefully than usual	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

6. During the past 4 weeks, to what extent has your physical health or emotional problems interfered with your normal social activities with family, friends, neighbours, or groups?

Not at all	Slightly	Moderately	Quite a bit	Extremely
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

7. How much bodily pain have you had during the past 4 weeks?

None	Very mild	Mild	Moderate	Severe	Very severe
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6

8. During the past 4 weeks, how much did pain interfere with your normal work (including both work outside the home and housework)?

Not at all	A little bit	Moderately	Quite a bit	Extremely
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

9. These questions are about how you feel and how things have been with you during the past 4 weeks. For each question, please give the one answer that comes closest to the way you have been feeling. How much of the time during the past 4 weeks…

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
. Did you feel full of life?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
. Have you been very nervous?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
. Have you felt so down in the dumps that nothing could cheer you up?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
. Have you felt calm and peaceful?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
. Did you have a lot of energy?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
. Have you felt downhearted and low?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
. Did you feel worn out?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
. Have you been happy?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
. Did you feel tired?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

10. During the past 4 weeks, how much of the time has your physical health or emotional problems interfered with your social activities (like visiting with friends, relatives, etc.)?

All of the time	Most of the time	Some of the time	A little of the time	None of the time
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

11. How TRUE or FALSE is <u>each</u> of the following statements for you?

	Definitely true	Mostly true	Don't know	Mostly false	Definitely false
a. I seem to get ill more easily than other people	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
b. I am as healthy as anybody I know	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
c. I expect my health to get worse	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
d. My health is excellent	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

Table S 1 Univariate analysis of demographic and collection characteristics influencing adverse reactions at different time points following PBSC donation. All time points are defined as the day of donation (D 0), 2-3 days after donation (D2-3) and weekly after donation up until full recovery. The number of cases (n) are displayed for categorical variables; means are given for continuous variables.

End point		Gender (M/F)	BMI	Age	Blood donor (Y/N)	No of dependents (0, 1-2, 3 or more)	Central line (N/Y)	Days of collection (1/2)	Pre-harvest white blood cell count (x 10^9/l)
Allergy D 0	Yes (0)								
	No (264)								
	p-value	NA	NA	NA	NA	NA	NA	NA	NA
Anorexia D 0	Yes (14)	9/5	27.3	31.6	7/7	7/2/1	13/1	12/2	41.9
	No (250)	193/57	26.3	33.1	152/95	132/56/13	241/10	184/66	41.1
	p-value	0.33	0.41	0.54	0.41	0.82	0.46	0.25	0.84
Back pain D 0	Yes (21)	16/5	28.0	32	11/10	12/4/2	18/3	12/9	41.6
	No (227)	176/51	26.3	33.3	138/86	118/52/10	222/6	172/55	42.0
	p-value	0.99	0.087	0.53	0.49	0.58	**0.031**	0.071	0.90
Bleeding D 0	Yes (1)								
	No (261)								
	p-value	NA	NA	NA	NA	NA	NA	NA	NA
Bruising D 0	Yes (16)	8/8	27.7	31.4	12/4	11/3/1	12/4	11/5	41.8
	No (248)	194/54	26.3	31.1	147/98	128/55/13	242/7	185/63	42.0
	p-value	**= 0.028**	0.23	0.54	0.30	0.79	**0.002**	0.57	0.97
Dizziness D 0	Yes (16)	13/3	24.8	35.8	7/8	9/1/2	16/1	13/4	46.2

	No (248)	189/59	26.5	32.9	152/94	130/57/12	238/10	183/64	41.6
	p-value	0.77	0.17	0.20	0.28	0.15	0.53	0.99	0.16
Fatigue D 0	Yes (84)	55/29	25.7	32.3	50/32	44/15/6	80/4	60/24	42.5
	No (180)	147/33	26.7	33.4	109/70	95/43/8	174/7	136/44	41.7
	p-value	**= 0.005**	0.13	0.37	0.99	0.43	0.75	0.55	0.62
Fever D 0	Yes (12)	8/4	26.2	33.1	9/3	5/3/1	11/1	8/4	43.2
	No (252)	194/58	26.4	33.0	150/99	134/55/13	243/10	188/64	41.9
	p-value	0.48	0.90	0.98	0.38	0.76	0.41	0.51	0.70
Headache D 0	Yes (68)	40/28	27.1	33.1	39/27	34/14/8	66/2	46/21	43.3
	No (196)	162/34	26.1	33.0	120/75	105/44/6	188/9	150/47	41.1
	p-value	**< 0.001**	0.10	0.97	0.77	**0.027**	0.73	0.26	0.28
Infection D 0	Yes (0)								
	No (264)								
	p-value	NA	NA	NA	NA	NA	NA	NA	NA
Injection site reaction D 0	Yes (15)	11/4	28.1	31.9	8/7	12/0/0	15/0	11/4	43.1
	No (249)	191/58	26.3	33.2	151/95	127/58/14	239/11	185/64	41.9
	p-value	0.76	0.13	0.35	0.59	**0.037**	0.99	0.99	0.73
Insomnia D 0	Yes (44)	30/14	26.8	34.9	28/16	22/10/2	41/3	34/10	44.3
	No (220)	172/48	26.3	32.7	131/86	117/48/12	213/8	162/58	41.4
	p-value	0.17	0.49	0.14	0.74	0.95	0.40	0.71	0.20
Myalgia D 0	Yes (85)	63/22	25.6	32.6	48/36	43/15/5	84/2	63/23	41.5

	No (179)	139/40	26.8	33.2	111/66	96/43/9	170/9	133/45	42.2
	p-value	0.54	0.054	0.58	0.42	0.69	0.51	0.88	0.68
Nausea D 0	Yes (22)	15/6	26.9	27.8	11/10	16/2/2	20/2	18/4	43.2
	No (241)	185/56	26.4	33.5	146/92	122/56/12	232/9	177/63	41.9
	p-value	0.60	0.57	**= 0.005**	0.49	0.17	0.23	0.61	0.67
Any other pain D 0	Yes (69)	50/19	26.3	31.7	39/30	39/15/6	64/6	50/20	42.4
	No (194)	151/43	26.4	33.5	119/72	100/43/8	189/5	145/48	41.7
	p-value	0.41	0.88	0.17	0.47	0.44	0.073	0.63	0.74
Rash D 0	Yes (1)								
	No (263)								
	p-value	NA	NA	NA	NA	NA	NA	NA	NA
Vomiting D 0	Yes (1)								
	No (263)								
	p-value	NA	NA	NA	NA	NA	NA	NA	NA
Pain summary D 0	Yes (153)	109/44	26.5	32.7	85/66	81/31/13	148/6	110/43	42.5
	No (108)	90/18	26.2	33.5	73/34	56/26/1	103/5	84/24	41.1
	p-value	**< 0.05**	0.53	0.48	0.069	**0.029**	0.77	0.32	0.54
Summary all adverse reactions D 0	Yes (190)	137/53	26.5	33.6	114/73	95/45/13	182/8	140/50	42.2
	No (71)	62/9	26.1	31.4	44/27	42/12/1	69/2	54/17	41.6
	p-value	**< 0.01**	0.54	0.084	0.99	0.091	0.73	0.75	0.75

Allergy D 2-3	Yes (1)								
	No (243)								
	p-value	NA	NA	NA	NA	NA	NA	NA	NA
Anorexia D 2-3	Yes (20)	14/6	27.1	35.2	10/10	6/3/2	118/2	15/5	44.1
	No (223)	172/51	26.3	33	136/84	123/47/11	211/11	164/58	41.9
	p-value	0.58	0.45	0.30	0.34	0.28	0.29	0.99	0.46
Back pain D 2-3	Yes (9)	7/2	27.7	31.2	3/6	5/3/0	9/0	7/2	3/6
	No (230)	175/55	26.4	33.4	140/87	120/47/13	216/13	169/60	140/87
	p-value	0.99	0.42	0.50	0.16	0.62	0.99	0.99	0.16
Bleeding D 2-3	Yes (1)								
	No (240)								
	p-value	NA	NA	NA	NA	NA	NA	NA	NA
Bruising D 2-3	Yes (81)	56/25	27.2	33.2	46/34	41/17/3	71/10	48/33	42.5
	No (162)	130/32	26.0	33.2	100/60	88/33/10	158/3	131/30	41.9
	p-value	0.077	**= 0.05**	0.99	0.49	0.75	**0.001**	**< 0.001**	0.74
Dizziness D 2-3	Yes (24)	18/6	27.0	37.0	14/9	13/4/2	23/1	15/9	41.7
	No (219)	168/51	26.3	32.8	132/85	116/46/11	206/12	164/54	42.1
	p-value	0.80	0.52	**< 0.05**	0.99	0.72	0.99	0.22	0.88
Fatigue D 2-3	Yes (98)	74/24	26.4	36.1	58/39	44/22/6	93/5	69/29	43.2
	No (145)	112/33	26.4	31.2	88/55	85/28/7	136/8	110/34	41.3
	p-value	0.76	0.92	**< 0.001**	0.79	0.38	0.99	0.3	0.28

Fever D 2-3	Yes (3)	2/1	32.8	33.2	½	1/1/1	3/0	3/0	39.5
	No (241)	184/57	26.3	33.2	145/93	129/49/12	227/13	177/63	42.1
	p-value	0.56	**< 0.05**	0.99	0.56	0.15	0.99	0.57	0.68
Headache D 2-3	Yes (24)	17/7	27.6	35.6	16/8	10/5/3	22/2	18/6	44.4
	No (219)	169/50	26.3	32.0	130/86	119/45/10	207/11	161/57	41.7
	p-value	0.46	0.17	0.19	0.66	0.19	0.62	0.99	0.32
Infection D 2-3	Yes (0)								
	No (244)								
	p-value	NA	NA	NA	NA	NA	NA	NA	NA
Injection site reaction D 2-3	Yes (0)								
	No (240)								
	p-value	NA	NA	NA	NA	NA	NA	NA	NA
Insomnia D 2-3	Yes (19)	16/3	26.2	31.7	12/7	9/5/0	18/1	14/5	43.3
	No (224)	170/54	26.4	33.3	134/87	120/45/13	211/12	165/58	41.9
	p-value	0.58	0.82	0.47	0.99	0.45	0.99	0.99	0.64
Myalgia 2-3	Yes (50)	34/16	27.0	34.0	30/19	27/10/4	47/3	38/12	43.4
	No (193)	152/41	26.2	33.0	116/75	102/40/9	182/10	141/51	41.7
	p-value	0.13	0.24	0.48	0.99	0.69	0.74	0.86	0.40
Nausea D 2-3	Yes (17)	11/6	27.0	33.0	9/8	10/3/2	13/4	11/6	41.7
	No (226)	175/51	26.4	33.2	137/86	119/47/11	216/9	168/57	45.6
	p-value	0.24	0.60	0.92	0.61	0.53	**0.008**	0.39	0.23

Any other pain D 2-3	Yes (9)	8/1	28.3	37.3	7/2	5/3/0	8/1	8/1	45.4
	No (234)	178/56	26.3	33.0	139/92	124/47/13	221/12	171/62	41.9
	p-value	0.69	0.20	0.18	0.49	0.60	0.40	0.45	0.45
Rash D 2-3	Yes (2)	1/1	27.7	33.9	1/1	1/1/0	2/0	2/0	62.1
	No (242)	185/57	26.4	33.2	145/94	129/49/13	228/13	178/63	41.8
	p-value	0.42	0.46	0.91	0.99	0.71	0.99	0.99	**0.01**
Vomiting D 2-3	Yes (2)	2/0	27.7	35.9	0/2	0/1/0	2/0	1/1	51.1
	No (242)	184/58	26.4	33.1	146/93	130/49/13	228/13	179/62	41.9
	p-value	0.99	0.70	0.67	0.15	0.24	0.99	0.45	0.24
Pain summary D 2-3	Yes (72)	52/20	27.2	33.5	42/29	35/16/6	69/3	53/19	42.2
	No (171)	134/37	26.1	33.0	104/65	94/34/7	160/10	126/44	42.0
	p-value	0.32	0.067	0.71	0.77	0.33	0.76	0.99	0.89
Summary all adverse reactions D 2-3	Yes (165)	119/46	26.8	34.1	99/64	82/36/9	154/11	116/49	41.7
	No (78)	67/11	25.5	31.2	47/30	47/14/4	75/2	63/14	42.7
	p-value	**< 0.05**	**< 0.05**	**< 0.05**	0.99	0.55	0.24	0.061	0.59
Allergy 1 week	Yes (0)	0/0							
	No (239)	182/57							
	p-value	NA	NA	NA	NA	NA	NA	NA	NA
Anorexia 1 week	Yes (2)	0/2	20.5	35.4	1/1	1/0/1	1/1	0/2	49.5
	No (237)	182/55	26.4	33.3	143/92	126/53/13	229/9	172/65	41.3

	p-value	0.056	**< 0.05**	0.76	0.99	0.056	0.082	0.078	0.47
Back pain 1 week	Yes (5)	3/2	24.4	34.6	2/3	3/0/1	4/1	3/2	49.9
	No (231)	177/54	26.4	33.4	141/88	121/53/13	223/9	167/64	41.1
	p-value	0.34	0.39	0.78	0.38	0.23	0.20	0.62	0.12
Bleeding 1 week	Yes (1)								
	No (238)								
	p-value	NA	NA	NA	NA	NA	NA	NA	NA
Bruising 1 week	Yes (16)	10/6	24.8	34.0	11/5	7/4/1	11/5	10/6	47.3
	No (223)	172/51	26.4	33.3	133/88	120/49/13	219/5	162/61	41.0
	p-value	0.22	0.18	0.77	0.60	0.87	**< 0.001**	0.40	0.12
Dizziness 1 week	Yes (1)								
	No (238)								
	p-value	NA	NA	NA	NA	NA	NA	NA	NA
Fatigue 1 week	Yes (21)	15/6	26.3	37.2	10/11	10/3/3	20/1	14/7	45.4
	No (218)	167/51	26.3	33.0	134/82	117/50/11	210/9	158/60	41.0
	p-value	0.60	0.95	**< 0.05**	0.24	0.12	0.99	0.61	0.16
Fever 1 week	Yes (0)	0/0							
	No (239)	182/57							
	p-value	NA	NA	NA	NA	NA	NA	NA	NA
Headache 1 week	Yes (3)	2/1	24.3	32.2	2/1	2/0/1	3/0	2/1	42.0
	No (236)	180/56	26.4	33.4	142/92	125/53/13	227/10	170/66	41.4
	p-value	0.56	0.43	0.83	0.99	0.13	0.99	0.99	0.96

Infection 1 week	Yes (1)								
	No (238)								
	p-value	NA	NA	NA	NA	NA	NA	NA	NA
Injection site reaction 1 week	Yes (2)	1/1	25.4	30.0	2/0	1/1/0	1/1	1/1	51.1
	No (237)	181/56	26.3	33.4	142/93	126/52/14	229/9	171/66	41.2
	p-value	0.42	0.77	0.61	0.52	0.74	0.082	0.48	0.22
Insomnia 1 week	Yes (3)	3/0	27.9	37.7	½	1/1/0	3/0	3/0	52.5
	No (236)	179/57	26.3	33.3	143/91	126/52/14	227/10	169/67	41.3
	p-value	0.99	0.32	0.42	0.56	0.74	0.99	0.56	0.16
Myalgia 1 week	Yes (6)	3/3	23.4	36.1	3/3	3/0/2	5/1	3/3	48.3
	No (233)	179/54	26.4	33.3	141/90	124/53/12	225/9	169/64	41.2
	p-value	0.15	0.14	0.47	0.68	**0.011**	0.23	0.35	0.16
Nausea 1 week	Yes (2)	1/1	24.2	31	2/0	2/0/0	2/0	1/1	46.9
	No (237)	181/56	26.3	33.4	142/93	125/53/14	228/10	171/66	41.3
	p-value	0.42	0.52	0.72	0.52	0.59	0.99	0.48	0.48
Any other pain 1 week	Yes (6)	4/2	26.0	31.8	3/3	3/1/1	6/0	3/3	44.6
	No (233)	178/55	26.3	33.4	141/90	124/52/13	224/10	169/64	41.3
	p-value	0.63	0.89	0.67	0.68	0.53	0.99	0.35	0.62
Rash 1 week	Yes (1)								
	No (238)								

	p-value	NA	NA	NA	NA	NA	NA	NA	NA
Vomiting 1 week	Yes (239)								
	No (0)								
	p-value	NA	NA	NA	NA	NA	NA	NA	NA
Pain summary 1 week	Yes (9)	5/4	26.2	33.5	4/5	5/1/2	8/1	5/4	46.1
	No (226)	175/51	26.3	33.4	137/86	118/52/12	218/9	165/61	41.2
	p-value	0.22	0.95	0.98	0.32	0.12	0.33	0.27	0.26
Summary all adverse reactions 1 week	Yes (30)	21/9	25.3	36.4	17/12	13/5/3	26/4	20/10	43.9
	No (205)	159/46	26.5	33	124/79	110/48/11	200/6	150/55	41.1
	p-value	0.36	0.21	0.062	0.84	0.43	**0.026**	0.51	0.31
All time points Allergy summary	Yes (2)	2/0	29.1	27.7	1/1	2/0/0	2/0	1/1	51.8
	No (272)	207/65	26.4	33.2	164/105	141/60/15	258/14	199/73	42.1
	p-value	0.99	0.39	0.39	0.99	0.59	0.99	0.47	0.40
All time points anorexia summary	Yes (32)	23/9	27.0	32.9	16/16	13/5/2	29/3	24/8	42.3
	No (242)	186/56	26.3	33.1	149/90	130/55/13	231/11	176/66	42.1
	p-value	0.51	0.40	0.24	0.18	0.78	0.22	0.99	0.96
All time points back pain summary	Yes (40)	32/8	27.2	32.7	19/21	22/9/3	37/3	26/14	43.3
	No (230)	173/57	26.5	33.2	143/84	117/51/12	219/11	170/60	41.9

	p-value	0.69	0.12	0.75	0.079	0.84	0.44	0.25	0.54
All time points bleeding summary	Yes (4)	1/3	26.1	33.6	4/0	4/0/0	1/3	3/1	43.9
	No (270)	208/62	26.4	33.1	161/106	139/60/15	259/11	197/73	42.1
	p-value	**=0.013**	0.90	0.92	0.22	0.35	**< 0.001**	0.99	0.79
All time points bruising summary	Yes (96)	65/29	27.1	33.0	59/35	51/19/5	83/13	60/36	43.1
	No (177)	144/36	25.0	33.2	105/71	92/41/10	176/1	140/37	41.7
	p-value	**= 0.052**	**= 0.062**	0.22	0.70	0.86	**< 0.001**	**0.004**	0.42
All time points dizziness summary	Yes (44)	35/9	26.2	34.6	22/21	26/5/4	43/2	31/14	43.5
	No (229)	174/55	26.5	32.8	142/85	116/55/11	216/12	168/60	41.7
	p-value	0.7	0.71	0.25	0.18	0.17	0.99	0.58	0.41
All time points fatigue summary	Yes (150)	106/44	26.2	34.4	93/59	72/33/11	145/8	105/49	43.0
	No (125)	104/21	26.6	31.6	72/47	71/27/4	115/6	95/25	40.9
	p-value	**= 0.016**	0.40	**= 0.009**	0.99	0.23	0.99	0.055	0.23
All time points fever summary	Yes (14)	10/4	27.3	33.1	9/5	6/4/1	13/1	10/4	42.4
	N (260)	199/61	26.3	33.1	156/101	137/56/14	247/13	190/70	42.1
	p-value	0.75	0.46	0.99	0.99	0.72	0.53	0.99	0.93

All time points headache summary	Yes (82)	51/31	27.0	33.7	62/39	41/17/9	99/3	72/30	42.6
	No (193)	159/34	26.0	32.8	103/67	102/43/6	161/11	128/44	41.9
	p-value	**< 0.001**	0.098	0.43	0.99	**= 0.039**	0.27	0.49	0.68
All time points infection summary	Yes (1)								
	No (273)								
	p-value	NA	NA	NA	NA	NA	NA	NA	NA
All time points injection site reaction summary	Yes (18)	12/6	27.3	30.9	11/7	14/1/0	17/1	12/6	45.0
	No (256)	197/59	26.3	33.3	154/99	129/59/15	243/13	188/68	41.9
	p-value	0.39	0.34	0.28	0.99	0.066	0.99	0.58	0.34
All time points insomnia summary	Yes	51/18	26.4	34.1	43/26	36/16/3	66/3	50/19	42.7
	No	158/47	26.4	32.8	122/80	107/44/12	194/11	150/55	42.0
	p-value	0.62	0.91	0.30	0.89	0.92	0.99	0.99	0.71
All time points myalgia summary	Yes	96/34	26.5	33.1	76/52	69/23/8	125/5	94/37	41.8
	No (143)	112/31	26.3	33.1	88/54	73/37/7	134/9	105/37	42.2
	p-value	0.40	0.71	0.95	0.71	0.39	0.42	0.79	0.72
All time points	Yes (40)	28/12	27.2	31.5	20/20	26/6/4	36/5	31/10	43.9

Nausea summary	No (234)	181/53	26.2	33.4	145/86	117/54/11	224/9	169/64	41.8
	p-value	0.32	0.20	0.24	0.16	0.30	**0.042**	0.85	0.38
Any other Pain all time points	Yes (118)	90/28	26.7	33.2	72/44	66/25/9	111/7	87/32	41.7
	No (155)	118/37	26.0	33.1	92/62	76/35/6	148/7	112/42	42.5
	p-value	0.99	0.41	0.87	0.71	0.44	0.60	0.99	0.64
All time points rash summary	Yes (6)	5/1	27.5	35.2	3/3	4/2/0	5/0	6/0	58.1
	No (268)	204/64	26.4	33.1	162/103	239/58/15	255/14	194/74	41.2
	p-value	0.99	0.20	0.57	0.68	0.790.78	0.99	0.20	**0.014**
All time points vomiting summary	Yes (3)	2/1	27.9	32.9	½	1/1/0	2/1	2/1	51.7
	No (271)	207/64	26.4	33.1	164/104	142/59/15	258/13	198/73	42.0
	p-value	0.56	0.26	0.97	0.56	0.75	0.15	0.99	0.14
All time points pain summary	Yes (181)	133/48	26.7	33.2	115/82	104/41/14	192/8	145/55	42.2
	No (74)	77/17	25.7	33.1	50/24	19/1	68/6	55/19	41.9
	p-value	0.14	0.088	0.52	0.21	0.15	0.22	0.88	0.87

Table S 2 Univariate analysis of HRQOL scores influencing adverse reactions at different time points following PBSC donation. All time points are defined as the day of donation (D 0), 2-3 days after donation (D2-3) and weekly after donation up until full recovery. The number of cases (n) are displayed for categorical variables; means are given for continuous variables.

End point		PCS	MCS
Allergy D 0	Yes (0)		
	No (264)		
	p-value	NA	NA
Anorexia D 0	Yes (14)	58.1	52.8
	No (250)	57.5	54.2
	p-value	0.58	0.40
Back pain D 0	Yes (21)	56.2	51.8
	No (227)	57.6	54.4
	p-value	0.15	0.081
Bleeding D 0	Yes (1)	59.5	51.1
	No (261)	57.5	54.1
	p-value	0.57	0.56
Bruising D 0	Yes (16)	58.4	53.7
	No (248)	57.4	54.1
	p-value	0.36	0.80
Dizziness D 0	Yes (16)	54.2	53.9
	No (248)	57.7	54.1
	p-value	= 0.001	0.94
Fatigue D 0	Yes (84)	57.2	54.1
	No (180)	57.7	54.1
	p-value	0.36	0.94
Fever D 0	Yes (12)	58.0	53.6
	No (252)	57.5	54.1
	p-value	0.64	0.76
Headache D 0	Yes (68)	57.2	52.9
	No (196)	57.6	54.5
	p-value	0.50	0.069
Infection D 0	Yes (0)		
	No (264)		
	p-value	NA	NA
Injection site reaction D 0	Yes (15)	57.7	51.9
	No (249)	57.5	54.2
	p-value	0.88	0.20
Insomnia D 0	Yes (44)	58.3	54.9

	No (220)	57.4	54.0
	p-value	0.21	0.37
Myalgia D 0	Yes (85)	56.8	54.4
	No (179)	57.8	53.5
	p-value	0.085	0.27
Nausea D 0	Yes (22)	57.6	52.8
	No (241)	57.5	54.3
	p-value	0.97	0.30
Any other pain D 0	Yes (69)	57.5	54.9
	No (194)	57.5	53.2
	p-value	0.99	0.73
Rash D 0	Yes (1)	58.6	47.8
	No (263)	57.5	54.1
	p-value	0.76	0.21
Vomiting D 0	Yes (1)	59.5	51.1
	No (263)	57.5	54.1
	p-value	0.57	0.56
Pain summary D 0	Yes (153)	57.1	53.4
	No (108)	57.9	54.9
	p-value	0.14	**< 0.05**
Summary all adverse reactions D 0	Yes (190)	57.2	54.2
	No (71)	58.3	54.0
	p-value	< 0.05	0.83
Allergy D 2-3	Yes (1)	56.3	53.1
	No (243)	57.5	54.0
	p-value	0.72	0.85
Anorexia D 2-3	Yes (20)	57.8	54.2
	No (223)	57.5	54.0
	p-value	0.73	0.92
Back pain D 2-3	Yes (9)	53.3	50.2
	No (230)	57.6	54.2
	p-value	0.34	0.20
Bleeding D 2-3	Yes (1)	61.1	54.2
	No (240)	57.5	54.0
	p-value	0.30	0.98
Bruising D 2-3	Yes (81)	57.4	54.3
	No (162)	57.6	53.9
	p-value	0.73	0.68

Dizziness D 2-3	Yes (24)	55.7	52.6
	No (219)	57.7	54.2
	p-value	< 0.05	0.27
Fatigue D 2-3	Yes (98)	56.4	54.2
	No (145)	58.3	53.9
	p-value	< 0.001	0.74
Fever D 2-3	Yes (3)	59.2	48.6
	No (241)	57.4	54.1
	p-value	0.48	0.14
Headache D 2-3	Yes (24)	57.9	52.3
	No (219)	57.4	54.3
	p-value	0.63	0.13
Infection D 2-3	Yes (0)		
	No (244)		
	p-value	NA	NA
Injection site reaction D 2-3	Yes (0)		
	No (240)		
	p-value	NA	NA
Insomnia D 2-3	Yes (19)	57.1	52.2
	No (224)	57.5	54.2
	p-value	0.75	0.25
Myalgia 2-3	Yes (50)	56.3	53.5
	No (193)	57.8	54.2
	p-value	< 0.05	0.43
Nausea D 2-3	Yes (17)	56.3	52.7
	No (226)	57.6	54.1
	p-value	0.25	0.39
Any other pain D 2-3	Yes (9)	57.9	53.8
	No (234)	57.5	54.1
	p-value	0.80	0.93
Rash D 2-3	Yes (2)	59.6	56.4
	No (242)	57.4	54.0
	p-value	0.54	0.65
Vomiting D 2-3	Yes (2)	53.8	50.8
	No (242)	57.5	54.0
	p-value	0.29	0.53
Pain summary D 2-3	Yes (72)	56.4	53.8

	No (171)	58.0	54.2
	p-value	< 0.005	0.63
Summary all adverse reactions D 2-3	Yes (165)	56.9	54.0
	No (78)	58.9	54.4
	p-value	= 0.001	0.61
Allergy 1 week	Yes (0)		
	No (239)		
	p-value	NA	NA
Anorexia 1 week	Yes (2)	54.5	57.1
	No (237)	57.6	53.9
	p-value	0.20	0.40
Back pain 1 week	Yes (5)	54.2	60.0
	No (231)	57.6	54.1
	p-value	< 0.05	0.19
Bleeding 1 week	Yes (1)	58.8	52.5
	No (238)	57.5	54.0
	p-value	0.71	0.79
Bruising 1 week	Yes (16)	57.1	54.4
	No (223)	57.6	53.9
	p-value	0.62	0.78
Dizziness 1 week	Yes (1)	50.2	61.6
	No (238)	57.6	53.9
	p-value	0.08	0.14
Fatigue 1 week	Yes (21)	55.7	53.3
	No (218)	57.7	54.0
	p-value	< 0.05	0.58
Fever 1 week	Yes (0)		
	No (239)		
	p-value	NA	NA
Headache 1 week	Yes (3)	50.2	61.1
	No (236)	57.6	53.9
	p-value	0.08	0.14
Infection 1 week	Yes (1)	50.1	58.1
	No (238)	57.6	54.0
	p-value	0.069	0.43
Injection site reaction 1 week	Yes (2)	56.3	49.9
	No (237)	57.5	54.0

	p-value	0.61	0.27
Insomnia 1 week	Yes (3)	58.0	52.7
	No (236)	57.5	54.0
	p-value	0.81	0.66
Myalgia 1 week	Yes (6)	53.3	53.3
	No (233)	57.6	54.0
	p-value	0.14	0.77
Nausea 1 week	Yes (2)	49.6	42.7
	No (237)	57.6	54.0
	p-value	0.057	0.091
Any other pain 1 week	Yes (6)	57.8	55.2
	No (233)	57.5	54.0
	p-value	0.88	0.64
Rash 1 week	Yes (1)	54.7	50.1
	No (238)	57.5	54.0
	p-value	0.42	0.45
Vomiting 1 week	Yes (239)		
	No (0)		
	p-value	NA	NA
Pain summary 1 week	Yes (9)	54.5	51.9
	No (226)	57.6	54.0
	p-value	0.19	0.30
Summary all adverse reactions 1 week	Yes (30)	56.1	53.5
	No (205)	57.8	54.0
	p-value	< 0.05	0.66
All time points Allergy summary	Yes (2)	58.5	47.0
	No (272)	57.5	54.2
	p-value	0.70	0.12
All time points anorexia summary	Yes (32)	57.8	53.6
	No (242)	57.5	54.1
	p-value	0.67	0.62
All time points back pain summary	Yes (40)	56.4	52.2
	No (230)	57.7	54.4

	p-value	0.28	0.32
All time points bleeding summary	Yes (4)	58.6	53.0
	No (270)	57.5	54.1
	p-value	0.54	0.66
All time points bruising summary	Yes (96)	57.6	54.1
	No (177)	57.5	54.1
	p-value	0.90	0.96
All time points dizziness summary	Yes (44)	55.4	51.8
	No (229)	57.9	54.4
	p-value	< 0.001	0.10
All time points fatigue summary	Yes (150)	56.8	54.1
	No (125)	58.5	54.0
	p-value	= 0.003	0.88
All time points fever summary	Yes (14)	58.2	52.9
	N (260)	57.5	54.2
	p-value	0.49	0.43
All time points headache summary	Yes (82)	57.3	52.8
	No (193)	57.7	54.8
	p-value	0.43	**= 0.021**
All time points infection summary	Yes (1)	50.1	58.1
	No (273)	57.6	54.1
	p-value	0.073	0.44
All time points injection site reaction summary	Yes (18)	56.7	50.7
	No (256)	57.6	54.3
	p-value	0.41	0.11
All time points insomnia summary	Yes	57.9	54.0
	No	57.4	54.1
	p-value	0.49	0.91
All time points myalgia summary	Yes	56.7	53.5

	No (143)	58.1	54.5
	p-value	= 0.009	0.14
All time points nausea summary	Yes (40)	56.8	54.3
	No (234)	57.6	52.7
	p-value	0.26	0.13
Any other Pain all time points	Yes (118)	57.3	53.7
	No (155)	57.7	54.4
	p-value	0.45	0.36
All time points rash summary	Yes (6)	57.2	53.6
	No (268)	57.5	54.1
	p-value	0.87	0.86
All time points vomiting summary	Yes (3)	56.6	50.9
	No (271)	57.5	54.1
	p-value	0.71	0.17
All time points pain summary	Yes (181)	57.1	53.5
	No (74)	58.6	54.9
	p-value	= 0.02	**= 0.068**

Table S 3 Univariate analysis of demographic and collection characteristics influencing adverse reactions at different time points following BM donation. All time points are defined as the day of donation (D 0), 2-3 days after donation (D2-3) and weekly after donation up until full recovery. The number of cases (n) are displayed for categorical variables; means are given for continuous variables.

End point		Gender (M/F)	BMI	Age	Blood donor (Y/N)	No of dependants (0, 1-2, 3 or more)	Duration of procedure	Volume of BM harvested per kg donor weight
All time points Allergy summary	Yes (0)							
	No (37)							
	p-value	NA	NA	NA	NA	NA	NA	NA
All time points anorexia summary	Yes (6)	5/1	24.1	22.9	2/4	6/0/0	40	19.1
	No (31)	28/3	27.5	33.4	22/8	11/7/4	40.7	14.1
	p-value	0.52	0.056	**< 0.001**	0.14	0.085	0.97	**0.003**
All time points back pain summary	Yes (34)	30/4	26.9	31.7	21/12	16/6/4	40.7	14.9
	No (3)	3/0	28	32.0	3/0	1/1/0	40	15.2
	p-value	0.99	0.64	0.96	0.41	0.64	0.98	0.90
All time points bleeding summary	Yes (12)	10/2	25.8	32.3	8/3	5/1/2	21.5	15.8
	No (25)	23/2	27.5	31.4	16/9	12/6/2	24.0	14.5
	p-value	0.58	0.23	0.80	0.30	0.45	0.45	0.37

All time points bruising summary	Yes (22)	18/4	26.5	31.9	17/5	8/4/3	45.1	16.1
	No (15)	15/0	27.7	31.4	7/7	9/3/1	31.2	13.2
	p-value	0.13	0.37	0.89	0.12	0.59	0.16	**0.032**
All time points dizziness summary	Yes (16)	13/3	26.2	32.3	9/7	8/2/3	42.2	15.8
	No (21)	20/1	27.5	31.2	15/5	9/5/1	39.7	14.2
	p-value	0.30	0.35	0.74	0.33	0.33	0.79	0.25
All time points fatigue summary	Yes (32)	28/4	28.0	31.7	22/9	15/6/4	43.1	15.1
	No (5)	5/0	26.8	31.2	2/3	2/1/0	27.5	13.5
	p-value	0.99	0.53	0.91	0.36	0.74	**0.013**	0.42
All time points fever summary	Yes (2)	2/0	24.9	29.6	2/0	1/0/0	120	14.4
	No (35)	31/4	27.1	31.8	22/12	16/7/4	37.4	14.9
	p-value	0.99	0.47	0.77	0.56	0.72	NA	0.85
All time points headache summary	Yes (4)	3/1	29.1	34.3	3/1	2/1/1	35	14.5
	No (33)	30/3	26.7	31.4	21/11	15/6/3	41.2	15.0
	p-value	0.38	0.26	0.59	0.87	0.79	0.72	0.83
All time points infection summary	Yes (0)							

	No (37)							
	p-value	NA	NA	NA	NA	NA	NA	NA
All time points insomnia summary	Yes (7)	6/1	28.0	31.0	6/1	2/1/2	53.9	14.1
	No (30)	27/3	26.7	31.9	18/11	15/6/2	35.6	15.1
	p-value	0.99	0.45	0.84	0.43	0.19	0.27	0.56
All time points myalgia summary	Yes (2)	2/0	27.4	44.2	2/0	0/0/2	72.5	13.4
	No (35)	31/4	26.9	31.0	22/12	17/7/2	37.9	15.0
	p-value	0.79	0.87	0.068	0.56	**0.002**	0.42	0.60
All time points nausea summary	Yes (7)	7/0	27.2	33.6	5/2	2/2/2	48.3	15.5
	No (29)	25/4	26.8	31.3	18/10	14/5/2	40.1	15.0
	p-value	0.57	0.78	0.60	0.83	0.24	0.58	0.78
Any other Pain all time points	Yes (5)	5/0	25.0	35.0	5/0	2/1/1	70	17.6
	No (32)	28/4	27.2	31.2	19/12	15/6/3	38.1	14.5
	p-value	0.99	0.25	0.43	0.21	0.79	0.48	0.1
All time points rash summary	Yes (1)							
	No (36)							
	p-value	NA	NA	NA	NA	NA	NA	NA
All time points	Yes (2)	2/0	28.9	19.7	2/0	2/0/0	20	12.3

vomiting summary								
	No (35)	31/4	26.8	32.4	22/12	15/7/4	41.5	15.1
	p-value	0.99	0.49	**< 0.001**	0.56	0.50	0.37	0.35
All time point throat pain	Yes (21)	18/3	26.7	32	14/6	9/4/3	43.5	14.8
	No (15)	14/1	27.5	30.3	9/6	8/2/1	38.6	14.9
	p-value	0.63	0.57	0.50	0.57	0.66	0.62	0.95

Table S 4 Univariate analysis of HRQOL scores influencing adverse reactions at different time points following BM donation. All time points are defined as the day of donation (D 0), 2-3 days after donation (D2-3) and weekly after donation up until full recovery. Means are given.

End point		PCS	MCS
All time points Allergy summary	Yes (0)		
	No (37)		
	p-value	NA	NA
All time points anorexia summary	Yes (6)	58.0	47.5
	No (31)	60.5	53.1
	p-value	**0.028**	0.12
All time points back pain summary	Yes (34)	58.5	51.6
	No (3)	58.1	58.2
	p-value	0.87	0.22
All time points bleeding summary	Yes (12)	58.8	52.2
	No (25)	58.2	52.0
	p-value	0.55	0.96
All time points bruising summary	Yes (22)	58.6	52.7
	No (15)	58.3	51.0
	p-value	0.80	0.56
All time points dizziness summary	Yes (16)	59.1	50.0
	No (21)	57.8	54.0
	p-value	0.24	0.15
All time points fatigue summary	Yes (32)	58.6	51.8
	No (5)	57.3	53.7
	p-value	0.52	0.69
All time points fever summary	Yes (2)	54.1	44.9
	No (35)	58.6	52.3
	p-value	0.12	0.32
All time points headache summary	Yes (4)	58.7	51.9
	No (33)	58.4	53.7
	p-value	0.86	0.19
All time points infection summary	Yes (0)		
	No (37)		
	p-value	NA	NA
All time points insomnia summary	Yes (7)	58.7	48.7
	No (30)	58.4	53.1
	p-value	0.83	0.19
All time points myalgia summary	Yes (2)	58.9	52.1
	No (35)	58.4	52.1
	p-value	0.81	0.99

All time points nausea summary	Yes (7)	58.6	52.6
	No (29)	58.0	51.9
	p-value	0.67	0.86
Any other Pain all time points	Yes (5)	58.7	52.2
	No (32)	58.4	52.1
	p-value	0.82	0.17
All time points rash summary	Yes (1)	57.7	52.6
	No (36)	58.5	52.1
	p-value	0.78	0.94
All time points vomiting summary	Yes (2)	59.1	55.8
	No (35)	58.4	51.8
	p-value	0.73	0.46
All time point throat pain	Yes (21)	58.2	53.1
	No (15)	59.2	51.3
	p-value	0.42	0.56

Document S 1 *Qualitative interview schedule*

Before tape is turned on:

- Introduction about interview & questionnaire:
    - Re: possible distress
    - Confidentiality
    - Tape recorded
    - Consent

- Orientation: focus on general health and health perception

Turn tape on:

1. Getting to know the participant (3 minutes)

- Who do you live with? Tell me a bit about your family?
- Siblings
- Children/dependents
- Do you have a partner/married? Boyfriend or girlfriend?
- Social network – friends living nearby

2. Assess how well informed and prepared donor felt (15 minutes)

Ok, let's talk now about your PBSC donation.

- Was the donation like you expected?
- Was it better or worse than expected?
- Did you feel you were given the right information and right amount?
- Amount of contact with AN register since joining – sufficient? Not enough?
- Is this their first and only experience of donation? If no, what others and when?
- If not feeling well prepared - Is there anything we could change in the future (as an organisation) in order to prepare you better?

- How do you feel about the donation now?

3. Explore general physical HRQOL during the donation process and health perception/illness perception (20 minutes)

- How would you rate your health compared to other people of the same age? (before and after donation)
- Do you experience physical limitations (compared to other people of the same age), for example when doing moderate activities or vigorous activities (before and after donation)
  If yes, explore further + impact on social activities/mood/emotional well being
- Have you been experiencing pain symptoms? (before and after donation)
  If yes before donation, explore (how often, how severe, how often, underlying cause etc. + impact on social life/mood/sleep/work)

- How important would you say that "health" is in your life (comparing it to other values such as happiness, wealth, comfortable life, exciting life, world at peace, wisdom, freedom etc.)

- What was your most serious symptom(s) following donation
- How did symptoms affect you? Did you have to take time off work? Social impact? Did you cut down on certain activities afterwards?
- How long did you think the symptoms would last for? Did you feel they were serious?
- How did you influence/control symptoms
- How did you feel in response to symptoms (for example depressed, anxious, afraid, worried, angry, upset, etc.)
- Did you feel supported by work or family?

4. Assess ambivalence (10-15 mins)

- What motivated you in becoming a stem cell donor?
- When/how did donor join the register – how long did it take between initial thought and actually joining
- How certain were you about the decision? Was it a difficult decision? What made it easier? What made it more difficult?
- How important is being a stem cell donor for you?

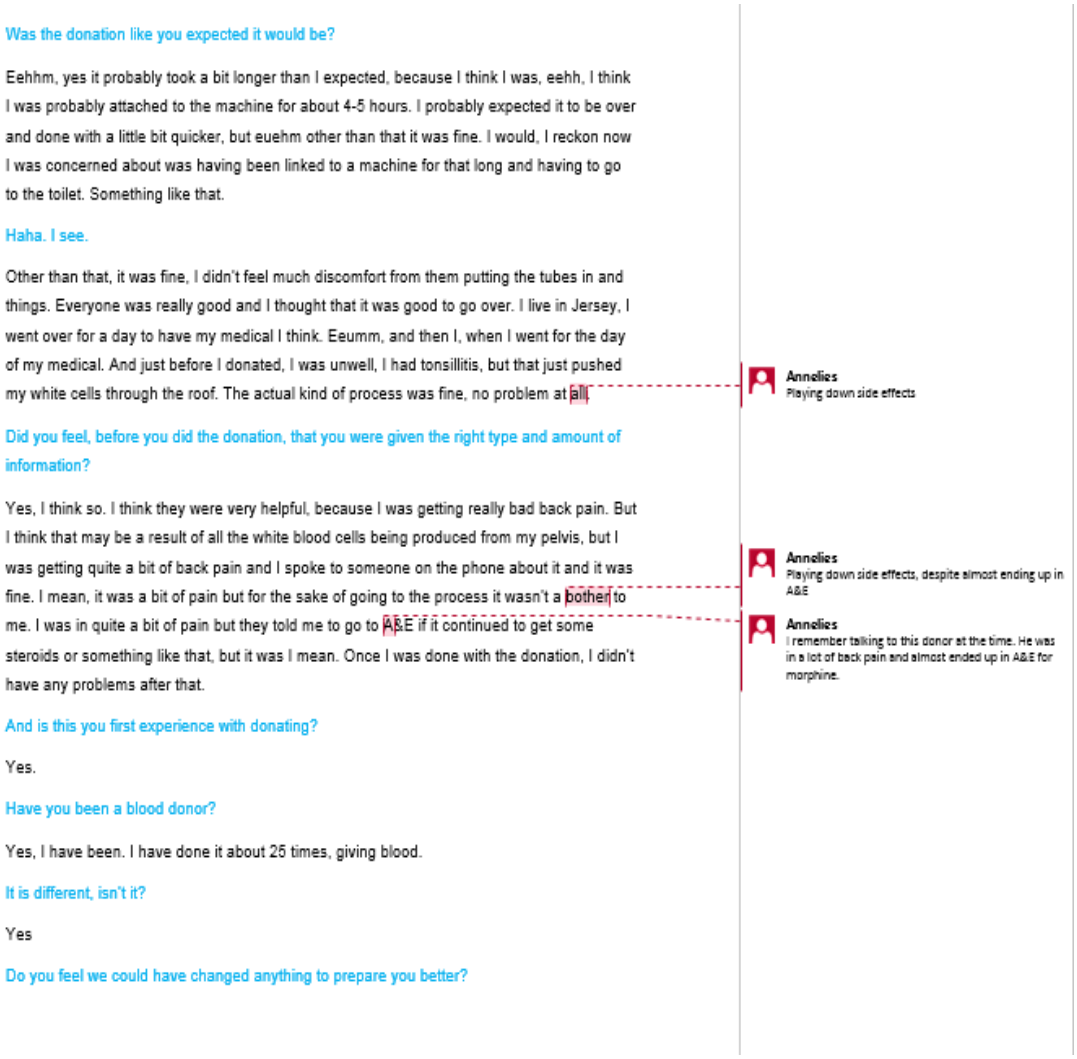
- Who helped you to decide? Consulted family/friends/health professionals? What did they say?
- Did you have doubts or worries about the donation?
  Did you feel there were a lot of risks involved with donating?
  Do you think it is associated with a lot of risks?

Now you have been through it, do you think you would do it again?

If not, why?

End of interview

Document S 2 Example of interview (p7): initial codes and themes are documented on the right side.



Was the donation like you expected it would be?

Eehhm, yes it probably took a bit longer than I expected, because I think I was, eehh, I think I was probably attached to the machine for about 4-5 hours. I probably expected it to be over and done with a little bit quicker, but euehm other than that it was fine. I would, I reckon now I was concerned about was having been linked to a machine for that long and having to go to the toilet. Something like that.

Haha. I see.

Other than that, it was fine, I didn't feel much discomfort from them putting the tubes in and things. Everyone was really good and I thought that it was good to go over. I live in Jersey, I went over for a day to have my medical I think. Eeumm, and then I, when I went for the day of my medical. And just before I donated, I was unwell, I had tonsillitis, but that just pushed my white cells through the roof. The actual kind of process was fine, no problem at all.

Annelies
Playing down side effects

Did you feel, before you did the donation, that you were given the right type and amount of information?

Yes, I think so. I think they were very helpful, because I was getting really bad back pain. But I think that may be a result of all the white blood cells being produced from my pelvis, but I was getting quite a bit of back pain and I spoke to someone on the phone about it and it was fine. I mean, it was a bit of pain but for the sake of going to the process it wasn't a bother to me. I was in quite a bit of pain but they told me to go to A&E if it continued to get some steroids or something like that, but it was I mean. Once I was done with the donation, I didn't have any problems after that.

Annelies
Playing down side effects, despite almost ending up in A&E

Annelies
I remember talking to this donor at the time. He was in a lot of back pain and almost ended up in A&E for morphine.

And is this you first experience with donating?

Yes.

Have you been a blood donor?

Yes, I have been. I have done it about 25 times, giving blood.

It is different, isn't it?

Yes

Do you feel we could have changed anything to prepare you better?

Eeum No I don't think so. I mean, I guess I wasn't too sure what to expect. Because they don't have the machines in Jersey, so you cant really show anyone what it is going to look like and you know, I guess, if you get too much information, you may get a bit concerned, a bit worried. And it is like donating blood. Instead of one blood going out of you, you have one going in and one going out.

And you mentioned the pain. Do you think that was your most serious symptom during the whole process?

Yes, I think so. It was, I mean, I think it was just the fact that I was on antibiotics and then getting the injections. I think my body went into overdrive because of the white blood cells.

Where was the pain exactly?

In my lower back

When did it start?

Eeum, probably a year ago, probably not after the first injection, but after the second.

When did the pain stop?

Eum, it kind of came and went. I don't remember having much pain like when I was travelling over and things. I cant remember, is it 4 days leading up?

Yes that's right

Eeum. It just came and I don't remember having really bad back pain travelling over. But I think it came and went now and again. It wasn't necessarily straight after an injection. It was fine. I think it came in the evenings a few times. It is hard to remember. It was like having a really bad back. My back went into spasms.

What kind of pain killers where you taking?

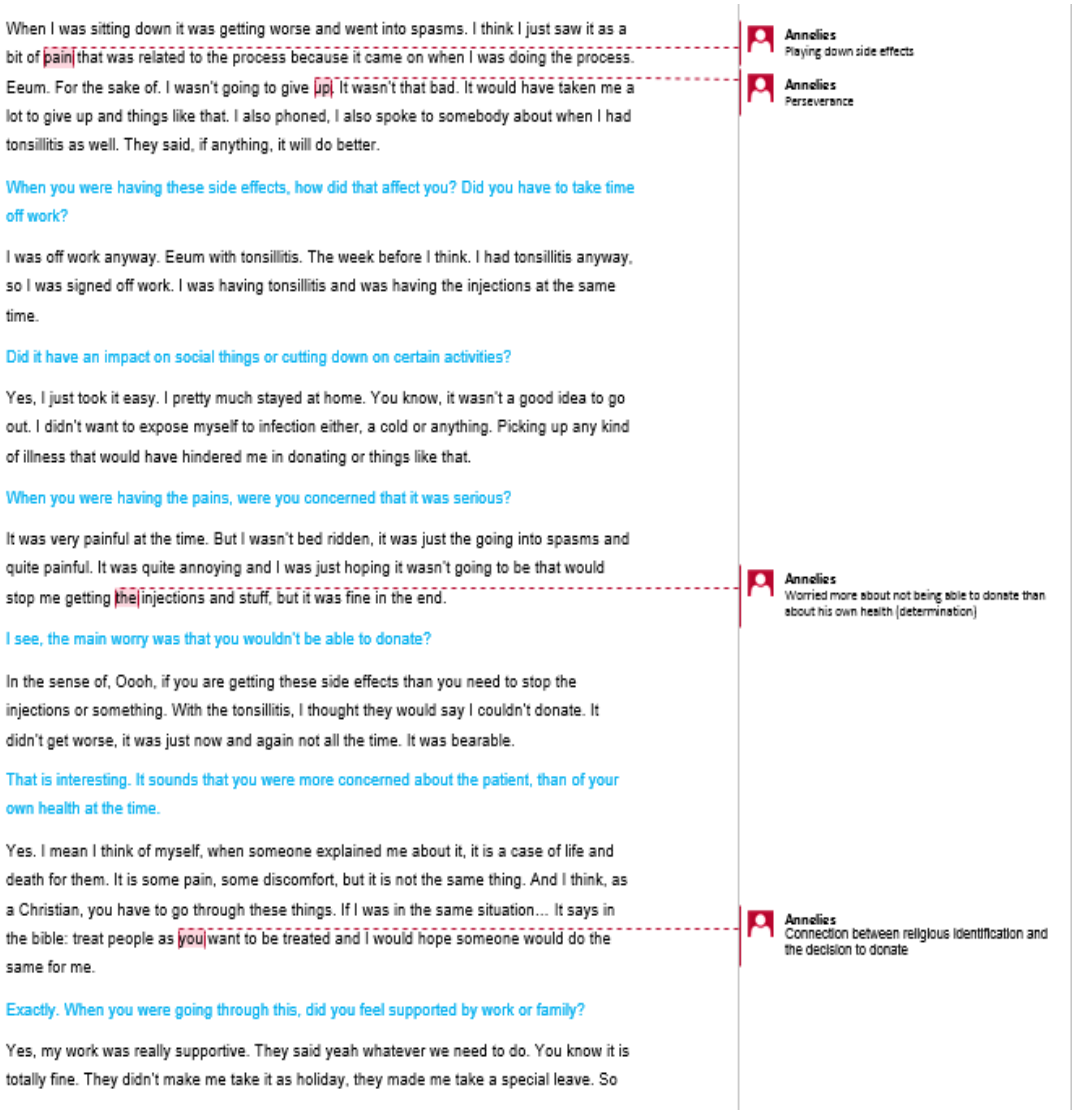
I think I probably took ibuprofen or something like that.

You mentioned you spoke to someone.

Yes, I rang AN. They got a doctor.

I think I may have spoken to you.

Yes I think so. I didn't have to go to A&E, it wasn't that bad. My wife, she was my fiancee, my girlfriend at the time. Eeum, but she suffers with really bad back and spasms. But there is not really that much you can do about it. You have to just rest.


When I was sitting down it was getting worse and went into spasms. I think I just saw it as a bit of pain that was related to the process because it came on when I was doing the process. Eeum. For the sake of. I wasn't going to give up. It wasn't that bad. It would have taken me a lot to give up and things like that. I also phoned, I also spoke to somebody about when I had tonsillitis as well. They said, if anything, it will do better.
When you were having these side effects, how did that affect you? Did you have to take time off work?
I was off work anyway. Eeum with tonsillitis. The week before I think. I had tonsillitis anyway, so I was signed off work. I was having tonsillitis and was having the injections at the same time.
Did it have an impact on social things or cutting down on certain activities?
Yes, I just took it easy. I pretty much stayed at home. You know, it wasn't a good idea to go out. I didn't want to expose myself to infection either, a cold or anything. Picking up any kind of illness that would have hindered me in donating or things like that.
When you were having the pains, were you concerned that it was serious?
It was very painful at the time. But I wasn't bed ridden, it was just the going into spasms and quite painful. It was quite annoying and I was just hoping it wasn't going to be that would stop me getting the injections and stuff, but it was fine in the end.
I see, the main worry was that you wouldn't be able to donate?
In the sense of, Oooh, if you are getting these side effects than you need to stop the injections or something. With the tonsillitis, I thought they would say I couldn't donate. It didn't get worse, it was just now and again not all the time. It was bearable.
That is interesting. It sounds that you were more concerned about the patient, than of your own health at the time.
Yes. I mean I think of myself, when someone explained me about it, it is a case of life and death for them. It is some pain, some discomfort, but it is not the same thing. And I think, as a Christian, you have to go through these things. If I was in the same situation… It says in the bible: treat people as you want to be treated and I would hope someone would do the same for me.
Exactly. When you were going through this, did you feel supported by work or family?
Yes, my work was really supportive. They said yeah whatever we need to do. You know it is totally fine. They didn't make me take it as holiday, they made me take a special leave. So
Annelies
Playing down side effects
Annelies
Perseverance
Annelies
Worried more about not being able to donate than about his own health (determination)
Annelies
Connection between religious identification and the decision to donate

they were good. And any question I had, the nurse who came round was able to answer those and I was able to phone up to AN. And An sent me a lot of information. And I spoke to one of my doctor friends and my mum, because she used to be a nurse. I was kind of.. I guess when I thought about it I was probably surprised that it was going to be giving it through blood. It think about the film, sometimes with AN, it would be good to shake off the stereotype of what giving BM is about. Cause when people think of BM, you know the film seven pounds, I think they take BM from the cork, from the bone. They take it from the bottom of the spine don't they? I think people think about that when thinking about giving BM rather than thinking about a transfusion.

Did you think that was how you were going to donate as well?

Yes, that was what I probably thought. I didn't realise it was going to be like giving blood. When giving blood, there is a bit of discomfort in the beginning with the needles and things. But once this is done it is sitting there and just finishing it. Probably it would be nice to. All I know about the patient is that they are well, but other than that I haven't been told anything. I wouldn't want to know. I do want to know but it doesn't concern me not knowing, euuhm, who they are or anything like that. But just knowing their progress, just knowing it made a long term difference. Because I do know it made a difference at the time...

Annelies
Wanting to know outcome in recipient

When did you hear from your recipient?

I think I got an email or a letter or something like that a number of months afterwards. I cant quite remember. I only got one letter and it said I don't know whether there will be any more contact or something. I cant quite remember. I think when people give the BM it is quite nice to know, but I know there are issues with confidentiality and some patients may not want to share information.

Exactly. Hopefully your recipient will be doing well. But you know it is a very aggressive treatment and some patients don't do very well. Just hypothetically, if you would get news from your recipient that wasn't good, how do you think you would react?

I think it would have been like you have done your best isn't it. And actually you have given them quite a chance, because if you had not done anything their chances of survival would have been depleted even more. But I guess it is a double edged sword. It is nice to know they are well, but if the person passed away or something, then your effort has been in vain. Also, people who don't know may assume the worst. I mean if people don't have any news, they may assume the worst, like something happened.

Annelies
Rational behaviour, realises chances are that outcome wont be good, but he shows good coping behaviour.

Annelies
Not knowing outcome of recipient is worse, better to have news.

Although it doesn't mean anything, it means that we don't know.

But when you ticked that box about wanting to find out about the recipient, was it a difficult decision?

No, it wasn't a difficult decision. I didn't have to think about it much. It is good to know what the outcome is. Cause you know, either way, you are giving someone else a chance of survival. You are giving them a better chance of survival compared to when you hadn't done it.

Exactly. Just slightly changing the topic. If you think back how you felt before donating, how would you have rated your health compared to other people of the same age?

Out of 10 ?

Better or worse or the same?

Better I would say. I am pretty active, I cycle to work every day. I am not overweight, I have a BMI of about 25.

Did you have any physical limitations before donation? When doing moderate or vigorous activities?

No not really

And any pain symptoms?

No

With this back pain, do you remember when you felt back to normal?

I think it was pretty much straight after I think.

After donation, would you still rate your health the same or better?

Yeah, it is pretty good. It has not been that good recently, but that is more because I got a viral infection and I was unwell for 3 weeks and I have a cold at the moment. But that has nothing to do with AN. With my health, I think I am better health than I was. I have lost a bit more weight and things like that. And I cycle a bit further because I have moved house. Yeah, I would say the same or slightly better (compared to before donation).

If you think about health as a value in life, how would you rate it comparing it to other values? And that is comparing it to for example family or friendship or wealth or happiness? How high up would it be?

I think health is really important, but I think you can not have perfect health and have family and things like that. For me for example, my faith comes above everything else, it is my

absolute value for me. My Christian faith is above everything and then probably you know my family are quite important. And wealth would come below health. You could still be very happy and don't have very much. You could still loose your house, your car, you know they are all material things. Your family and relationships are the things that matter. Even your job, your job is important but belief and family are more important than that. For me, my wife and stepdaughter, they are of ultimate importance for me, under my faith. Jobs come and go, you can loose your job, which I have lost in the past when I was made redundant. You know, God always provides for me and for my family. I have that ultimate faith in him. God always provides for me and always will and he always has. I think health is important, but if you think about your health too much you can make yourself unwell. If you think about certain things too much you can make yourself unwell or down. I think you need to be positive about things and I think it is important to look after your health and to be a good steward of your body and not to put too much rubbish in it. I think you have a lot of control over your health. MMm, you know, some illnesses come and go. Some illnesses come without knowing why they come. But more often, people are healthy because they have a healthy life style, some people get illnesses like cancer or something else, in which case there is no real reason, but I think you still need to look after yourself. Did I answer your question?

Annelies
Very religious person

Annelies
Very religious

Completely. Do you remember how long ago you joined the register?

I think it was probably around 2007, it has been a while. It was a bit out of the blue. I think because I moved, it took them a bit to track me down. I think that's why they probably take so many contact details.

In 2007, do you remember what motivated you in becoming a SC donor?

I think there was a drive in Jersey and my girlfriend at the time, wanted to do it. We both went together, we went to give blood and ended up on the register. She couldn't do it because she had low iron counts, in the same way that she couldn't donate blood. Mmm, but I was fit and healthy. I was quite surprised that if I would like to go onto the register now, I wouldn't be allowed to, because I am over 30. Eeum, because is said to other people, maybe your health is better at that stage. Maybe the register is quite big and they want to keep it with young and healthy people. Maybe over the age of 30 the likelihood of illnesses is greater. And health is less likely to be as good.

Yes that and the fact that transplant centres tend to go for younger donors. If they can choose for two equivalent donors and when is 20 and the other 50, they will pick the younger one.


Mm. Is there an age limit when people come off the register?
60. It is still better to have an older donor than no donor.
What is the reason that donors need to come off the register after 2 donations?
Well, it is because we expose people to drugs and some people are even exposed to BM donation for example, and then you are exposed to 2 general anaesthetics. It is a protection we put on our donors.
I understand that if you donated and then you are of the register. I think I am off the register now, is that right?
You are reserved for that patient. It means that if he/she would need you to donate again you would be able to do that. Rather than loosing the opportunity because you have donated to someone else in the meanwhile. You are reserved just to ensure that you can be there for that person in case he/she gets unwell.
How long am I reserved for?
2 years
I guess there is also a bit of human sense to it? If I would have to be taken off the register, because I donated twice to the same patient, it seems a shame, in case my patient would need another donation?
Annelies Billen
Very keen to donate in future
In that case, it would probably be discussed with an ethical committee. We may approve this in rare circumstances, but it would depend on for example how you did with previous donation.
Ah ok.
It would be well thought trough, but it is not impossible.
I know it is all speculation and that kind of situations is very rare.
It is, but it can happen. You mentioned you joined via a hospital drive, but what actually motivated you in becoming a donor?
Eeum, I can't really remember. I think it is a bit like giving blood. You give blood because you know one day you hope that if something happened to you someone will be there to help you out. And then you. I think signing up for AN,it's a real honour to try and save someone's life . If I or someone in my family would be unwell, you would hope that there would be a match for you. I think people need to consider, it is like an organ donation, which I am not,
Annelies
Hope that can rely on others' donations if ever in need

but you think by yourself, once you have passed away, your body is, you know, is no use anymore but it can save someone else's life.

When you joined, how long did it take you between initially thinking about it and joining? Did you decide straight away?

Yeah, I think it is more about someone giving you the opportunity. I think it is more of a positive suggesting it rather than people not wanting to do it. I said at work, I have been a donor and it is not a lot of hassle. I got flown over to the UK, I was put in a travel lodge and I was back the next morning. So I flew out on the Sat night, I was there on the Mon and I flew back on the Tues. They would have changed my flight if I needed to, but I gave it all in one day, so they didn't have to.

How certain were you about joining the register, was that an easy decision?

Yeah yeah.

Did you consult family or friends? Or did you speak to a health professional?

I cant really remember. I think there was something in the paper and I probably just spoke to. I cant even remember if I spoke to my family. It didn't take me very long to decide and I think it was a... It didn't take me very long. I may have spoken to a few people about it. But I don't see it being much different than giving blood. I have already given blood probably a dozen times or something like that. It wasn't much of a big deal to me, being on the register wasn't a big deal. And I thought that you know if I am called up, it may safe somebody's life. It may be a pain if they did the actual extraction eeum procedure that may be painful but I thought to myself for the sake of a bit of pain you can safe somebody's life. That's the bigger thing for me. If somebody in my family was sick, I would hope for someone to do, be there to do the same thing. The only thing necessary for the evil to prevail is for good men to stand by and do do nothing.

Annelies Billen
Strong intrinsic motivation. Easy, quick decision

Annelies
Other altruistic acts (blood donor)

Annelies
Connection between religious identification and the decision to donate

You joined and a couple of years later they contacted you to say you are a match. Do you remember how you reacted at that time?

I think it was good. It is nice to have a medical and find out you are fit and healthy. I think I was really pleased to come up and to be able to make a difference to someone's life.

Do you know what you were feeling?

It was exciting

Any worries or doubts?

I wouldn't say worries or doubts. I guess it was like, I didn't necessarily know much about it, The sent me a lot of information and when I looked at it, I saw that they do most of it by the kind of transfusion rather than the extraction process. And you know the person was pretty good. I think it was good to have a full medical and find out you are fit and healthy. When they send the results and things there is always that moment that you think they might find something. It is good to do that process because even if you are not a match.

And in retrospect, how important has it been for you to be a SC donor?

What do you mean? Has the experience been?

Exactly.

It has been a good experience. If somebody else would think about signing up or you know talk about being donor, I could entirely recommend it. It is not a hard process and for the sake of somebody's life you can make a difference and you can make the ultimate difference in somebody's life.

Have it changed you in a way?

No I don't think so. I think the sense of my lifestyle and the way I think about people and treat people hasn't changed. You know, I treat people as I like to be treated. I think you value of life is, I think my value of life is the same, I think it is a great thing and I think it is an honor to be able to donate. And it is wonderful to have that opportunity to make a difference in somebody's life. I think it has been a difference in the sense that I can speak about the process and I have knowledge about the process. If somebody wants to know, I can give them that information.

Annelies
Strong intrinsic motivation

Annelies
Honor to be able to donate

Is there anything else you would like to mention?

Eeum. I am not a 100% clear whether I will hear more updates. I don't know that at the moment. I cant remember what the letter said. I guess it is not that crucial. And I am not that concerned about knowing who the person is. I am not bothered either way. I don't necessarily know at the moment whether I will get any updates. I don't think I am? But eum, I guess it is difficult for you to answer.

It is very different for everyone and it also depends on the transplant centre where the patient was and how often we are communicating with them. A lot depends on them as well in getting back to us. It is difficult to answer. Sometimes you do hear, but not always.

Normally, if you havent heard anything for a while you wont hear anything?

I think it is less likely.

Ok. That's fine. I mean if something was to happen with the person now, I now it be more about other developments rather anything to do with the donation, because it went quite well. I guess it is that immediate time afterwards. After that, loads of stuff could have happened in the persons life.

And with this information, how will it be used?

It is a qualitative study. I am interviewing 10-15 people or so and I am looking into more detail into certain areas. I am trying to find a bit more information about the donation experience.

Will I be sent the results?

What I can do that if it gets published, to send you the link to the paper? Of course, none of the donors would be identifiable if it gets published.

What do you do exactly?

I am a qualified doctor,a haematologist. I treat patients with leukaemia in the hospital. I have been working for the AN for 2 yrs now as a medical officer and I am also doing some research as well. It is good to see both sides, it has been very interesting.

I see, I guess it is a good way to make people aware. The best way to publish is probably newspapers and things.

Yes sometimes

Good, thanks very much.

No problem at all. Hope you find some good things and that your research goes well. It is really important and I am really glad I am part of the whole process.

Thank you

Table S 5 Themes and codes - first draft

Themes	Codes
Anthony Nolan (AN) ambassador	Altruism as a personality trait Guilt about not being a blood donor Favour to be returned if they would end up to be in similar situation Connection between religious identification and the decision to donate Connection between community sense and the decision to donate Donation precipitated by specific personal circumstances On asking whether they would still be willing to be on the register, even though they weren't a match for the person they originally joined for, responses were the following:
Determination	Not influenced by other people Perseverance Donors worried about not being able to donate, rather than expressing worries about own health Playing down side effects
Relationship with recipient	Very emotional reactions to donation process, both high and low Fantasising about recipient Reactions of grief when finding out recipient has died Wanting to know about outcome and recipient in general Despite strong (emotional) relationship with recipient, very rational behaviour
Strong feeling of rightness/fairness	
Not expecting reward	

Table S 6 Themes and codes - final

Themes	Codes
Intrinsic motivation	Altruism as a personality trait
	Opportunity to save someone's life
	Hoping to rely on others' donations if ever in need
	Religious identification and the decision to donate
	Community sense and the decision to donate
	Donation precipitated by personal circumstances
	Promotion of donation
Determination	Sense of duty
	Not influenced by other people
	Worries about not being able to donate
	Playing down side effects
Relationship with	Emotional reactions to donation process
recipient	Wanting to know the outcome
	Fantasising about recipient
	Reactions of grief when finding out recipient has died
	Remaining realistic about possible outcome for the recipient
Strong feeling of	
fairness	
Ease of decision	

Document S 3 Donor education sheet for higher risk PBSC donors

The stem cells used in peripheral blood stem cell (PBSC) donation come from the bloodstream. A process called apheresis is used to obtain PBSC for transplantation. For 4 days before apheresis, you will be given a medication to increase the number of stem cells released into the bloodstream. This medication will likely cause bone and muscle aches, headaches, fatigue, dizziness, nausea, vomiting, and/or difficulty sleeping. During apheresis, blood is removed through a large vein in the arm or a central venous catheter (a flexible tube that is placed in a large vein in the neck or groin area). The blood goes through a machine that removes the stem cells. The blood is then returned and the collected cells are stored. Apheresis typically takes 4 to 6 hours. Apheresis itself usually causes minimal discomfort, but you may feel dizzy or experience numbness around the lips or cramping in the hands.

Based on previous research within our organisation, we found that some of our PBSC donors were at higher risks of side effects. We think you may be at higher risk based on some of the answers on your “general health and wellbeing” questionnaire.

- You may be more likely to experience the following side-effects, although you will likely experience them as being “mild”. These symptoms may last for a week or sometimes a bit longer.
    - Tiredness
    - Dizziness
    - Pain symptoms
- If you are a woman, you may be more likely to experience pain symptoms
- If you are older than 40, you may experience more tiredness after donation (43% of donors > 40 vs 21% donors ≤ 40 after 1 week of donation)
- You may take longer to recover and to be free of any symptoms; most PBSC donors that are at higher risk take about a week to feel fully back to normal

As an intervention to help you to recover quicker, we ask you to start taking paracetamol on the first day of G-CSF. Please take 1 g every 6 hours up until the day of donation.

Document S 4 Donor education sheet for higher risk bone marrow donors

The stem cells used in bone marrow donors come from the liquid centre of the bone, called the marrow. You will be given general anaesthesia which puts you to sleep during the procedure. Needles are inserted through the skin over the hip bone and into the bone marrow to draw the marrow out of the bone. Drawing the marrow takes about half an hour to an hour. You will usually stay in hospital for 2 nights; you will be admitted to hospital the day before the donation and you will be discharged the day after the donation. The area where the bone marrow was taken out may feel stiff or sore and you may feel tired.

Based on previous research within our organisation, we found that some of our bone marrow donors were at higher risks of side effects. We think you may be at higher risk based on some of the answers on your "general health and wellbeing" questionnaire.

- You may be more likely to experience the following side-effects, although you will likely experience them as being "mild"
    - Pain symptoms
- You may take longer to recover and to be free of any symptoms. Although the time required for bone marrow donors to recover varies, most bone marrow donors that are at higher risk take about 4 weeks to fully recover their strength.

As an intervention to help you to recover quicker, we ask you to start taking paracetamol on the day of donation up until 5 days after donation. Please take 1g every 6 hours. We will also provide you with a prescription of codeine when you leave the hospital in case you would need some stronger painkillers.
We will also keep a closer eye on you after the donation with regular telephone calls up until you have fully recovered. You can also ring us on xxx.