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Donor Selection for Patients Undergoing Allogeneic Hematopoietic Stem Cell Transplantation: Assessment of the Priorities of Canadian Hematopoietic Stem Cell Transplant Physicians

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Donor Selection for Patients undergoing Allogeneic Hematopoietic Stem Cell Transplantation: Assessment of the Priorities of Canadian Hematopoietic Stem Cell Transplant Physicians

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Abstract

Allogeneic Hematopoietic Stem Cell Transplantation is applied in the management of cancer. It involves myeloablative chemoradiotherapy followed by infusion of donor stem cells. The characteristics of the donor stem cells influences transplant outcomes which itself, is dependent on the donor characteristics. The purpose of this thesis was to explore preferences over donor characteristics.

A systematic review was performed to identify all donor characteristics associated with outcome. Eight traditional and 5 non-traditional characteristics were identified. The results of the review were used to inform a survey of the Canadian Bone Marrow Transplant Group which primarily includes transplant physicians. An online survey and conjoint analysis of Canadian Bone Marrow Transplant Group members was performed to define relative importance of donor characteristics. Canadian Bone Marrow Transplant Group members, including transplant physicians caring for adults strongly indicate preference for donors related to recipients (HR 2.97) over the donor's age, gender and cytomegalovirus compatibility.

Word count =149

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Chapter 1: Challenges of Donor Selection in Allogeneic Hematopoietic Stem Cell Transplant

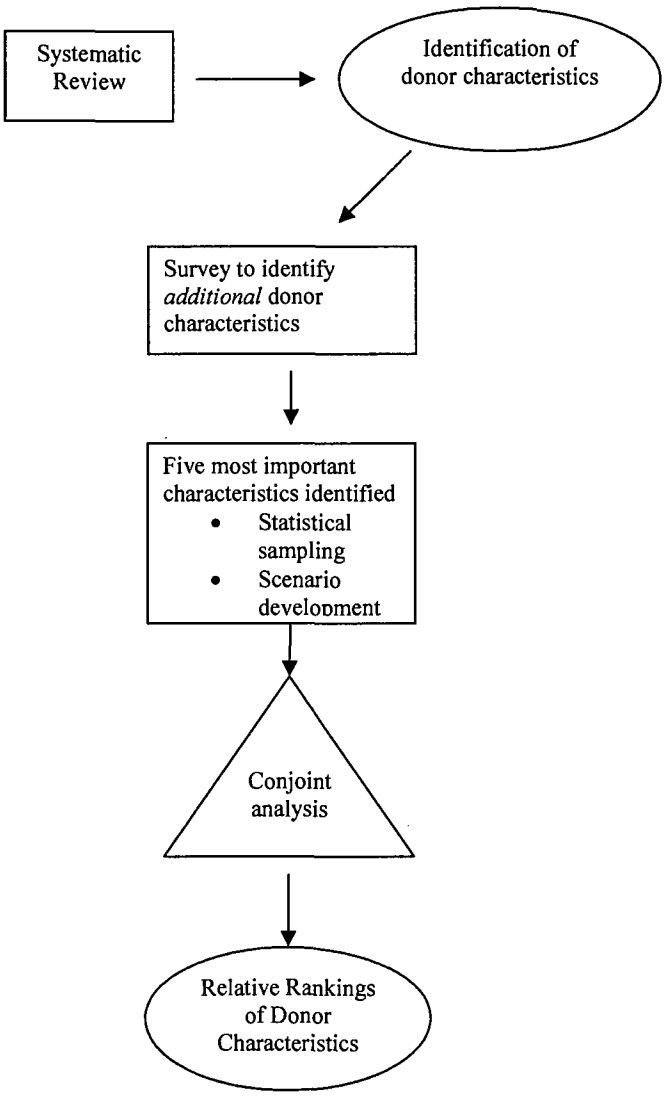
Thesis Overview

There has not been an objective summary or comprehensive study of pertinent donor characteristics in the literature. Although there have been several narrative reviews on this subject, they suffer from selection and individual author biases [1]. Systematic reviews and meta-analyses can provide objective up to date evidence, overcoming some inherent problems with opinions. Further, objective and scientific methods for donor selection can be developed as in other fields of medicine. For instance, the use of clinical decision rules (based on recursive partitioning techniques) in the diagnosis of deep vein thrombosis and ankle fractures have led to better clinical and economical outcomes [2, 3]. The presence of clinical evidence does not always lead to timely practice or practice at all[4].Consequently, the uptake and implementation of such "clinical rules" require an understanding of current beliefs and practices.

A rational starting point is to undertake a systematic review of literature. It will focus on identifying pertinent donor characteristics which will include factors that are well known as well as others that are less defined. Further, it will document the breadth of literature and the quality of the evidence. It will be the first comprehensive review to document and summarize this extensive literature as well as to highlight deficiencies in knowledge. Apart from helping to focus further avenues of research, the systematic review will help inform a subsequent survey and conjoint analysis (as part of this thesis) of all Canadian Hematopoietic Stem Cell Transplant Physicians, providing insight into

Canadian practice patterns. The survey will document the most common donor characteristics considered by Canadian transplant physicians. Identifying the characteristics in a systematic fashion will ensure that all factors will be considered within the survey. Subsequently, a conjoint analysis will be undertaken to determine the relative preferences of donor characteristics of physicians when choosing donors for their transplant patients (Figure 1). The results from this thesis will lay the groundwork to larger projects to help optimize donor selection which will improve the care and outcomes of patients suffering from hematologic malignancies. Future research may include surveys of the international hematopoietic transplant community, large database analyses of donor characteristics and patient outcomes and ultimately a useful validated tool for donor selection.

Figure 1: Schema of thesis proposal



Allogeneic Stem Cell Transplantation

Allogeneic Hematopoietic Stem Cell Transplantation is performed for a variety of hematologic diseases and especially considered in the management of hematologic malignancies[5, 6]. Broadly, it involves the administration of myeloablative doses of chemotherapy with or without radiotherapy as a means of eliminating malignant cells. This is followed by a donor stem cell infusion in order to repopulate the hematopoietic system and elicit an immunomodulatory effect[6].

Donor stem cells in their new transplanted environment will differentiate and proliferate into a new hematopoietic system. The subsequently derived lymphocytes (a subtype of the white blood cells) assist in the elimination of any residual malignant cells that remain after chemotherapy. They perform this function by recognizing a variety, but specific foreign antigens on the malignant cells (graft versus tumor effect) and either directly eliminating them or "tagging" them for elimination by the new immune system. However, these active lymphocytes could also recognize normal host tissue as being foreign and will consequently lead to dysfunction and disease of normal tissue (graft versus host disease). The organs that are primarily affected by graft versus host disease include the gastrointestinal tract, liver and the skin which are potentially fatal [7]. A potent graft versus tumor is generally associated with an equally significant graft versus host disease. The "magic switch" to eliminate graft versus host disease while preserving graft versus tumor effects remains the "holy grail" of hematopoietic stem cell transplant medicine.

The degree of immunomodulation (both graft versus tumor and graft versus host disease) by allogeneic graft is dependent on the histocompatibility between the host and

the donor [5]. The strength/severity of this reaction is determined by a complex system of glycoproteins expressed on cell surfaces; the histocompatibility antigens [8]. Recipient immune cells, more specifically T cells recognize foreign donor antigen (protein) and can reject the graft. Similarly, donor T cells can recognize recipient antigens which can lead to graft versus tumor effects and graft versus host disease. The major determinant of such a reaction is the Major Histocompatibility Antigens and in humans is also known as the Human Leukocyte Antigens (HLA). Incompatibility of Human Leukocyte Antigens between the donor and recipient will result in profound and adverse transplant reactions. Differences in the minor Histocompatibility Antigens (mHAGs), of which there are many account for the remainder of immune reactions when the Human Leukocyte Antigens are compatible.

The Human Leukocyte Antigen genetic region lies on the short arm of chromosome 6 and encodes numerous genes, not all which are involved in immune responses. This genetic region is divided into Class I, II and III, where they contain large number of polymorphic alleles (minor variations of the same gene). Class I (A, B and C) and II alleles (DR, DQ, DP) play a pivotal role in allogeneic hematopoietic stem transplantation where donor-recipient compatibility influences the transplant outcomes. Alleles are inherited from parents, with one set derived from each parent. Consequently there is a 1 in 4 chance that a sibling would have similar Human Leukocyte Antigen alleles (Human Leukocyte Antigen matched). The determination of Human Leukocyte Antigen types has become more accurate with better technology, namely with polymerase chain reaction where exact nucleotide sequences of individual alleles are analyzed. Human Leukocyte Antigens are evolutionary selected and inherited (linkage

equilibrium), and accounts for the identification of certain haplotypes (a set closely linked alleles inherited as a unit) far more commonly than would be expected by chance alone. The probability and availability of a Human Leukocyte Antigen matched unrelated donor is dependent on race and access to technology; for example there is 1 in 7 chance of finding a Human Leukocyte Antigen compatible donor for a Caucasian living in North America [9].

Allogeneic hematopoietic stem cell transplants are associated with high mortality and morbidity. Immediate and short term adverse events result from a crippled immune system and from direct organ toxicities related to the conditioning chemoradiotherapy. Such events include infectious complications from viruses, bacteria and fungi, thrombotic events such as veno-occlusive disease and acute graft versus host disease. Further, there are a multitude of non-hematologic adverse events involving the gastrointestinal, pulmonary and cardiac systems. The transplant related mortality (<100 days) is related to many factors as discussed later, and rates as high as 20% have been reported[12]. Moreover, long term survivors (>5 years) continue to be at variable risk of infections, relapse and are prone to develop secondary malignancies compared to the general population.

According to The Centre for International Blood and Marrow Transplantation (CIBMTR) registry, the most common indications for allogeneic hematopoietic stem cell transplants were leukemia and myelodysplasia (Figure 2)[10]. Worldwide, greater than 1/3 of allogeneic transplants were from unrelated donors while patients with acute leukemias are most likely to be considered for unrelated allografts (Figure 3). The causes of death in the setting of allogeneic transplants are presented below, with up to a third due to relapsed disease (Figure 4).

Figure 2: Indications for Hematopoietic Stem Cell Transplantation in North America 2003[10]

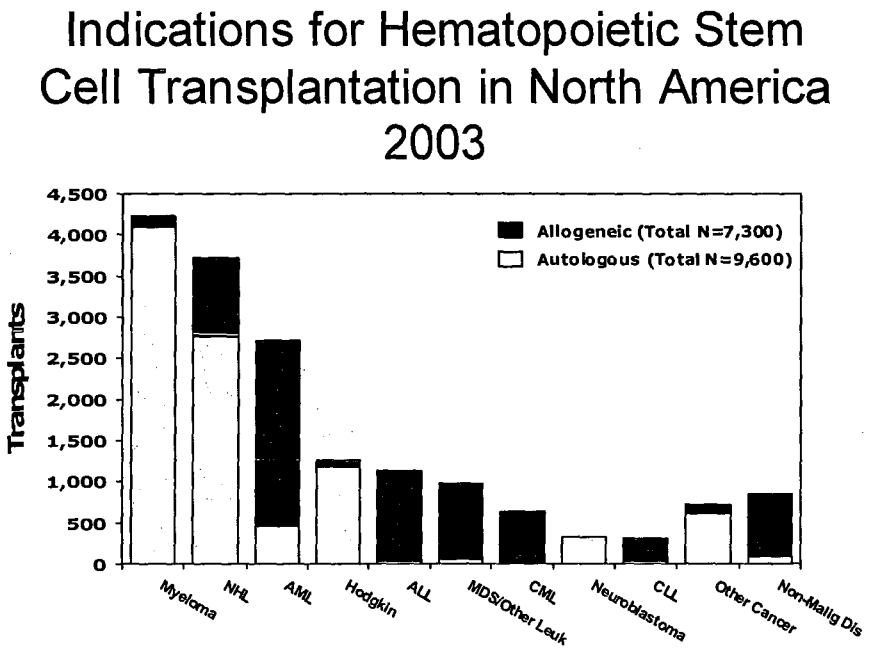


Figure 3: Indications for Allogeneic Hematopoietic Stem Cell Transplants, 2003 Worldwide[10]

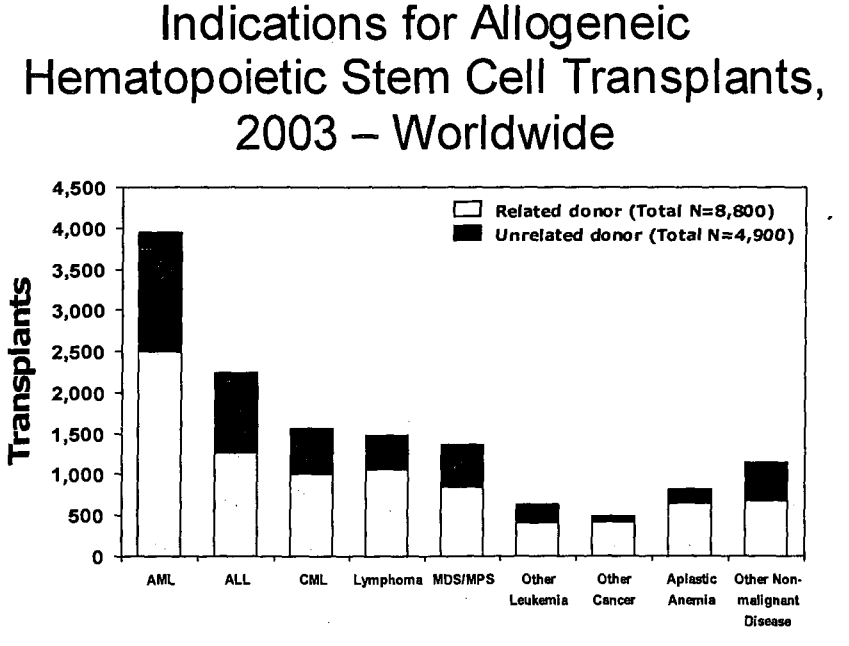
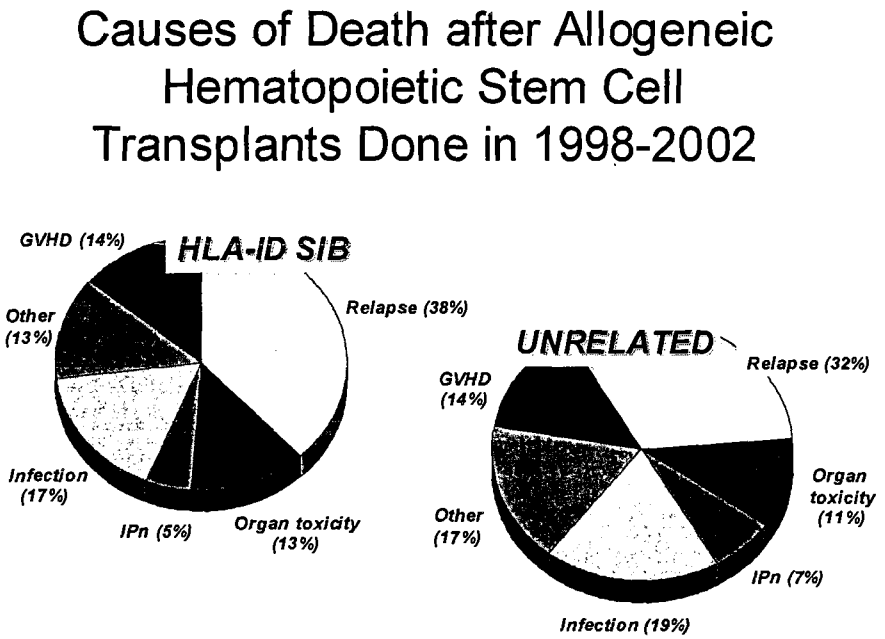


Figure 4: Causes of Death after Allogeneic Hematopoietic Stem Cell Transplants done in 1998-2002[10]



The Dilemma

The allogeneic hematopoietic stem cell transplant process is associated with significant multiple organ toxicities (e.g. lungs, heart, liver, kidneys and gastrointestinal tract) from the chemoradiotherapy that could result in death. Infectious complications due to a temporarily crippled immune system and the potential risk of graft versus host disease contributes to both the high morbidity and mortality associated with transplant process. Frequently, patients and physicians are faced with whether to embark on this high risk intensive therapy while acknowledging the potential for long term disease control and possibly cure. The alternative option, using standard chemotherapy without allogeneic hematopoietic stem cell transplant is association with less toxicity but also

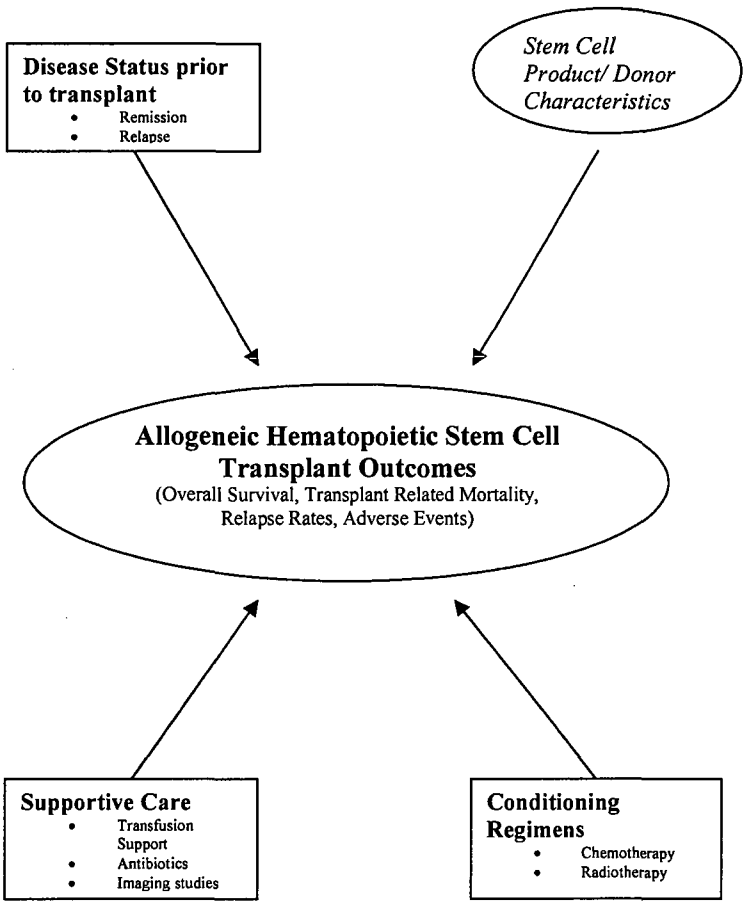
decreased likelihood of cure. For instance, adults with standard risk acute myeloid leukemia have a 5 year survival of <10% without the use of allogeneic hematopoietic stem cell transplant [11]. Gratwohl[12] eloquently summaries this "transplant or not to transplant" dilemma by stating "The conflict in decision-making becomes apparent when long-term results of a large heterogeneous series are considered: roughly 50% of all patients are alive at 5 years, while 50% have died. For a patient, outcome after transplant might look like flipping a coin...." Despite this uncertainty, pre-transplant risk assessment is possible and commonly employed to help with this complex decision making process. Indeed, several investigators have derived scoring systems primarily [13, 14]based on patient related factors.

The outcomes of allogeneic hematopoietic stem cell transplantation are dependent on a variety of factors (see Figure 5). Patient/recipient characteristics such as underlying disease, disease status at the time of transplant as well as concurrent co-morbidities clearly influence transplant outcomes[13, 14]. Furthermore, the transplant conditioning chemoradiotherapy prescribed and post-transplant supportive care also affects the outcome. Recipient factors, conditioning therapies and supportive care have been extensively reviewed and many advances in transplant have been made from this careful study[15-17]. However, the stem cell "product" given as part of the transplant procedure plays a vital role.

The quality of the stem cells is dependent on donor characteristics. Unlike the above characteristics (patient factors and conditioning regimen) comparatively less attention has been focused on the influence of donor characteristics on transplant outcomes. Historically, it is perceived that a matched related donor transplant is superior

to a matched unrelated donor transplant. This relates to the concept of Human Leukocyte Antigen (HLA) compatibility. The Human Leukocyte Antigen compatibility of the donor/recipient pair was paramount in ensuring the potential success of the allogeneic hematopoietic stem cell transplant[18-20]. However, with improved HLA matching techniques this perceived "Human Leukocyte Antigen barrier" may be less important[21, 22]. Consequently, other donor characteristics will be increasingly important and will be increasingly considered.

Figure 5: Factors influencing the Outcomes of Allogeneic Hematopoietic Stem Cell Transplantation



Traditional donor characteristics that have been studied include: Human Leukocyte Antigen compatibility[18, 20], age[14], race[23], gender[24-26], parity (number of pregnancies) [27], Body Mass Index [28], Cytomegalovirus status[29] and Blood Group (ABO) compatibility[30]. These factors have not been consistently evaluated together and there may be other unstudied factors that are important and relevant. The timing of allogeneic stem cell transplant is often critical and consequently the time to donor stem cell procurement matters. Furthermore the monetary cost of donor "activation" is relevant. More recently, research has also focused on whether certain genetic polymorphisms in

the donor influence transplant outcomes[31]. These recent evaluations of a multitude of genetic polymorphisms underscore the increasing importance of other donor related characteristics.

The selection of an allogeneic hematopoietic stem cell transplant donor is complex and there are no clear guidelines or consensus. Differences exist both at the level of the individual physician and institution. The choice of an ideal donor following identification of Human Leukocyte Antigen compatible donors is currently dependent on local belief and judgment. Further, the technology for accessing Human Leukocyte Antigen compatibility continues to improve and "perfect" compatibility/match presents a "moving target". Consequently, the tolerability of Human Leukocyte Antigen mismatches is evolving, especially if other factors are taken into account. The selection of positive donor characteristics may negate poor prognostic characteristics of the disease or the donor's Human Leukocyte Antigen compatibility. Whether a particular negative characteristic can be compensated by other positive characteristic and the degree of such compensation is unknown. There is no obvious "ranking/weighting" system for donor characteristics.

Hematologic malignancies are more prevalent in the older individuals (>50years) and many such patients are considered for allogeneic hematopoietic stem cell transplantation as part of their therapy. The siblings of an older patient will be closely correlated with the patient; they too will be older. Therefore, even if the sibling was Human Leukocyte Antigen matched, there will be concerns with the donor's age. This indirectly implies an increased likelihood of co-morbidities, prior alloimmune sensitization (previous pregnancies and/or blood transfusions) as well as decreased stem

cell collection in the potential donor. Furthermore, the likelihood of malignancy is increased if a family member is involved; this is particular true if the related individual is older. There are 2 prevailing schools of thought: A Related Donor is preferable in an allogeneic stem cell transplant regardless of other factors. A competing view is that a younger (<40 years) unrelated is as "good" a donor and possibly even superior.

Donor Selection Practice

Data from the The Centre for International Blood and Marrow Transplantation (CIBMTR) suggests that over 10,000 allogeneic hematopoietic stem cell transplants are performed worldwide with an increasing dependence on unrelated donors. The reasons for this dependence are unclear, but could either reflect changes in family size or an increasing confidence in the use of unrelated donors[10]. In Canada, approximately 300 allogeneic hematopoietic stem cell transplants are performed annually with a quarter performed for acute myeloid leukemia in first complete remission (most common indication for allogeneic transplant).

There is no robust frequency data on the instances when there is more than one potential Human Leukocyte Antigen (HLA) matched donor to choose from when comtemplating allogeneic hematopoietic stem cell transplants. This absence of knownledge may reflect the moving definition of a Human Leukocyte Antigen (HLA) "matched" donor. However, it has been suggested that a 8/8 (HLA A, B, C and DR) matched donor is necessary to optimize transplant outcomes. Within unrelated donor registries, the "depth" of HLA matching is variable i.e. donors are not initially typed at a

level that is deemed necessary for a transplant. Furthermore, an unrelated donor search is not routinely carried out unless there is an absence of a matched related donor.

The Canadian Unrelated Bone Marrow Donor Registry (UBMDR) also known as One Match co-ordinates the selection of potential unrelated bone marrow donor in all 13 allogeneic hematopoietic stem cell transplant centers in Canada. One Match facilitates the electronic search and contact with the potential donors within Canada, and through the International donor registries has access to donors from across the world. Potential donors with their characteristics (e.g. Human Leukocyte Antigen type, age, gender) are made available to the individual requesting clinical center. Commonly, there are many potential eligible donors and the ultimate choice is dependent on the individual center. In many instances, the choice of donor is subjective. Local opinions (Ottawa Hospital Blood and Marrow Program) would suggest that that in the majority (>75%) of allogeneic hematopoeitic stem cell transplants performed, there were more than one Human Leukocyte Antigen (HLA) matched (8/8) donor to choose amongst.

Donor selection practice of Adult Canadian Hematopoietic Stem Cell Transplant Physicians is currently unknown. Local centre and personal preferences may exist, and are likely influenced by clinical evidence as well as belief. Further, the strength of the individual preferences for certain donor characteristics are unclear: are physicians willing to "trade-off" certain donor characteristics? Understanding the prevailing views on donor selection will help facilitate further research and ultimately improved donor selection criteria.

Objectives and Overview of Methods

1. To identify donor characteristics that are thought to influence Hematopoietic Stem Cell Transplant recipient outcomes.
    - A systematic review of the literature will **identify** both traditional and non-traditional donor characteristics that influence allogeneic hematopoietic stem cell transplant outcomes. **The purpose of the systematic review is to help inform objectives 2 and 3.**

2. To determine donor characteristics which Adult Canadian Hematopoietic Stem Cell Transplant physicians consider clinically important when choosing a donor.
    - A survey will determine which donor characteristics are considered important by Adult Canadian Hematopoietic Stem Cell Transplant physicians. Further, it may identify characteristics not identified in the systematic review.

3. To determine the relative rankings of donor characteristics based on physician preferences.
    - A Conjoint Analysis involving Adult Canadian Hematopoietic Stem Cell Transplant Physicians will determine the relative importance of different donor characteristics.

Chapter 2: Systematic Review

Introduction

Pre-transplant assessment of patients remains critical in the field of allogeneic hematopoietic stem cell transplantation. Indeed, in this unique field of stem cell transplantation consideration has to be given to the potential stem cell donor. Simply stated: Is there an ideal donor? There have been numerous studies reporting outcomes of the patient can be influenced by characteristics of the donor (donor/recipient compatibility) such as donor age, gender and relatedness. However, with the advent of more sophisticated techniques in the field of basic science and genomics, a multitude of potential characteristics (gene polymorphisms) have been reported as important. There may be others which are important but less well characterized. An understanding and appreciation of such characteristics will help facilitate the choice of an ideal donor and optimize the care of eligible patients. The vast literature on donor characteristics has not been systematically reviewed nor quantified.

Systematic reviews are scientific tools which can be used to summarize, appraise, and communicate the results and implications of otherwise unmanageable quantities of research[32]. Whenever the data permits, a summary effect size can be displayed (pooling) using statistical techniques that account for the sample size of the individual studies (meta-analysis). Consequently, it can be argued that systematic reviews may help improve the shortcomings of lack of statistical power in the individual studies. The results of systematic reviews can then be used as a means to inform clinical care through

clinicians, health policy makers, clinical practice guideline authors as well as implementation researchers.

The primary purpose of the thesis is to understand the relative importance Canadian Allogeneic Hematopoietic Stem cell Transplant physicians place on donor characteristics. A survey and conjoint analysis would enable such an assessment as described in Chapters 3 and 4.

A list of donor characteristics would be required to inform the survey and subsequent analysis. This list was generated by conducting a systematic review of literature. Consequently, the purpose of the systematic review is to identify donor characteristics rather than to quantify the degree of association of characteristics and outcomes. However, one illustrative meta-analysis was performed to demonstrate how such an analysis could be accomplished. In this instance, the top donor characteristic (most commonly cited) apart from Human Leukocyte Antigen compatibility was chosen. A meta-analysis of Human Leukocyte Antigen compatibility was not done as there have been substantial reviews in this area, and consequently a meta-analysis of donor relatedness was performed instead. Crude associations for the remaining donor characteristics are displayed as described below.

Methods

Search Strategy

Using the OVID interface, the systematic search strategy included MEDLINE (1966 to 4th week of November 2006), EMBASE[33] (1980 to 4th week of November 2006) and all EBM Reviews (3rd quarter of 2006). Further, a Haynes filter was used to

aid identification of relevant clinical trials[34, 35] (Figure 11). Studies relevant to animals but not humans were excluded. Publications regardless of language or whether they were published as conference proceedings, abstracts or journals were included in the review. Local hematopoietic stem cell transplant physicians were also approached to identify additional relevant studies/trials. References to selected articles were examined by 2 reviewers [Jason Tay (JT) and David Allan (DA)] to identify relevant citations.

Figure 6: Systematic Review Search Strategy

1 (donor$ adj2 (characteristic$ or trait$ or variable$ or factor$ or qualit$)).tw.
2 Age Factors/
3 age factor$.tw.
4 Cytomegalovirus Infections/bl [Blood]
5 (cytomegalovirus adj3 serolog$).tw.
6 ABO Blood-Group System/
7 Blood Group Incompatibility/
8 (blood adj2 incompat$).tw.
9 Histocompatibility/
10 tissue compatibility$.tw.
11 Continental Population Groups/
12 race.tw.
13 Sex/
14 gender.tw.
15 body mass index/
16 (bmi or body mass index).tw.
17 risk$.mp.
18 exp cohort studies/
19 between group$.tw.
20 or/1-19
21 tissue donors/ or living donors/
22 ((tissue or organ or living) adj2 donor$).tw.
23 21 or 22
24 20 and 23
25 exp Stem Cell Transplantation/
26 stem cell transplant$.tw.
27 blood cell transplant$.tw.
28 marrow transplant$.tw.
29 blood transplant$.tw.
30 progenitor cell transplant$.tw.
31 hsct.tw.
32 sct.tw.
33 pbpct.tw.
34 bmt.tw.
35 or/25-34
36 24 and 35

Selection of studies

A structured question format[32] was used to aid the literature search strategy, identifying trials that satisfied the following inclusion criteria: any controlled clinical trials such as randomized controlled trials, cohort studies or case control studies, the

evaluation of donor characteristic(s) as a primary objective of the trial, patients undergoing hematopoietic stem cell transplantation and studies reporting clinically relevant outcomes such as Overall survival (Primary Outcome), Transplant related mortality, Disease Free Survival, engraftment, CMV infections, CMV diseases, non-CMV Infections, graft versus host disease, transfusion requirements, interstitial pneumonitis and veno-occlusive disease. Studies that only reported the results of biochemical tests were excluded from the review.

Definition of Clinical Outcomes

- Overall survival was broadly defined as survival with varying follow-up times as defined by the individual studies. In the field of Hematopoietic Stem Cell Transplant, overall survivals of 2-5 years have been reported.
- Transplant related mortality is defined as within 120 days of hematopoietic stem cell transplantation.
- CMV Infection was defined as recovery of the virus from the throat, urine or blood, seroconversion of a patient or significant increase in CMV viral copies in the absence of any clinical signs or symptoms of disease.
- CMV Disease was defined as symptomatic infection, recovery of virus from a visceral site or histologic evidence of infection.
- Hepatic veno-occlusive disease was broadly defined as weight gain or fluid accumulation, elevated bilirubin and abdominal pain.

- Graft versus host disease, interstitial pneumonitis/fibrosis and engraftment were defined by the individual studies but follow the recommended international guidelines.

Data Collection

Two reviewers [Jason Tay (JT) & David Allan (DA)] independently reviewed the abstracts and applied our trial eligibility criteria. Any discrepancies were documented, discussed and adjudicated by a third party [A Tinmouth (AT)]. The 2 reviewers (JT & DA) assessed trial quality and extracted the data using standardized data abstraction forms and the results entered into Microsoft Excel to aid data processing. Similarly, any discrepancies were documented, discussed and adjudicated by a third party (AT). The methodological quality of observational studies was evaluated by two reviewers (JT & DA) using the Newcastle-Ottawa Scale[36] while the Jadad scale[37] was employed for randomized studies. Consequently, observational studies were judged on 3 broad perspectives: the selection of the study groups; the comparability of the groups; and the ascertainment of either the exposure or outcome of interest for case-control or cohort studies respectively. A maximum of 4 stars can be assigned for selection of study groups, a maximum of 2 stars for comparability of groups and a maximum of 3 stars for ascertainment of outcomes. The Jadad scale uses a validated 5 point system consisting of Description of Study being randomized, Study described as double blind, Description of dropouts and withdrawals as well as a thorough description of randomization and blinding.

Analysis

The primary analysis focused on identifying all donor characteristics studied, while secondary analyses documented the volume of the studies and the clinical outcomes reviewed. Standard frequency plots and statistics were used to summarize the data (means, standard deviations) when appropriate. The clinical effects of various donor characteristics were tabulated and effects were stated as present or absent as demonstrated by the individual studies.

It was not the primary purpose of the systematic review to conduct meta-analyses of all the identified studies. Nevertheless, an illustrative example was performed for the most commonly cited donor characteristic (donor relatedness) other than Human Leukocyte Antigen compatibility which has been extensively reviewed. In this instance, odds ratios (OR) were used as summary measures with 95% confidence intervals when provided by the individual studies. Pooled measures were calculated for the clinical trials using a random effects model. A random effects model was chosen as a conservative measure, as it is possible there may be trials that were clinical trials that may not have been identified by the search strategy or not published. Individual trial estimates and pooled estimates were performed using the Review Manager software (Cochrane Collaboration's Information Management System)[38].

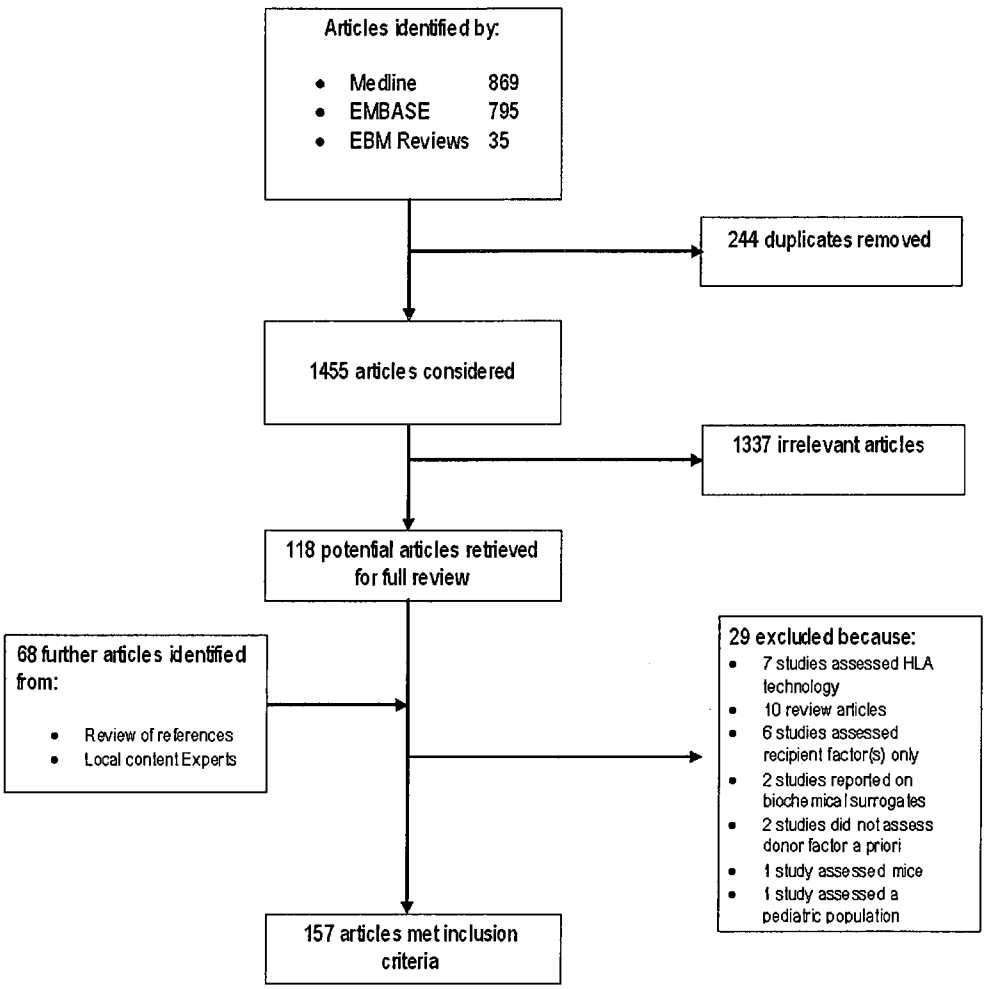
A pragmatic approach was taken, to analyze the best available data using both unadjusted or adjusted (for potential confounding factors) ratios. The Cochrane Q/Chi squared test and Higgins I^2 statistic were also calculated to evaluate heterogeneity. When pooling of the data was inappropriate, either due to availability or marked heterogeneity of studies, crude results were displayed instead. Whenever possible, a funnel plot visual

inspection was used to assess potential publication bias[39-42]. As the purpose of the systematic review was to identify donor factors, further sensitivity analyses were not performed.

Results

We identified a total of 1699 citations and removed 244 duplicates, leaving 1455 citations. One thousand three hundred and thirty seven of 1455 citations were deemed irrelevant. Consequently, 118 citations were retrieved for full review. A further 68 articles were identified from a review of references. Twenty nine articles were excluded (7 studies assessed HLA technology, 10 were review articles, 6 studies reviewed recipient characteristics, 2 studies only reported biochemical surrogates as outcomes, 2 studies did not assess donor characteristics a priori, 1 study assessed the pediatric population while another study reviewed mice (Figure 7).

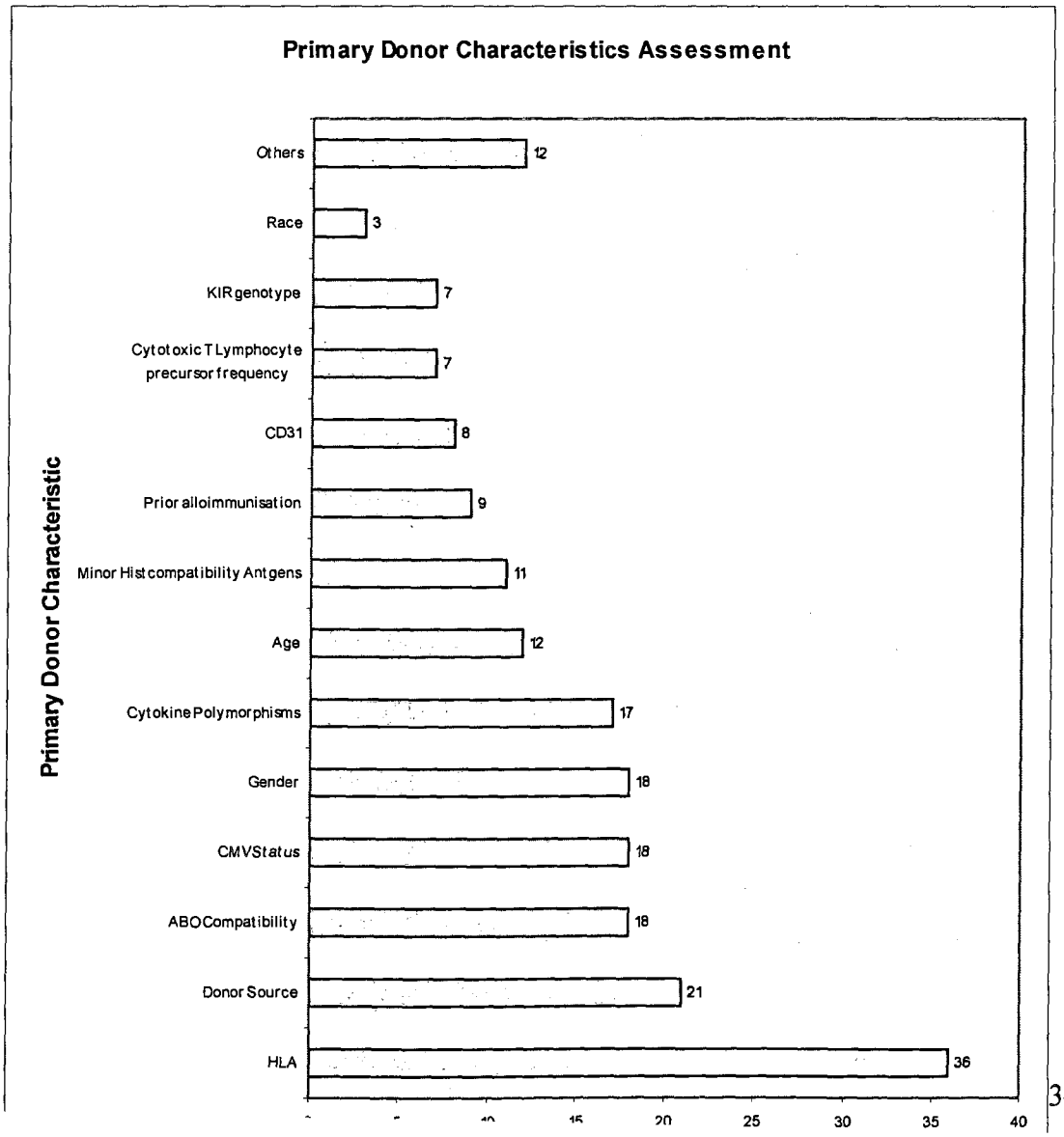
Figure 7: Flow Diagram detailing inclusion and exclusion of studies in Systematic Review



One hundred and fifty seven clinical trials representing 67,750 patients were included in the review (Figure 7). In total, 36 studies addressed HLA compatibility, 21 studies assessed type of donor (relatedness), 18 studies assessed ABO compatibility, 18 studies assessed cytomegalovirus(CMV) compatibility, 18 studies assessed donor gender, 17 studies assessed cytokine polymorphisms, 12 studies assessed donor age, 11 studies assessed minor histocompatibility, 9 studies assessed prior alloimmunisation (such as donor parity), 8 studies assessed CD31 polymorphisms, 7 studies assessed Cytotoxic T

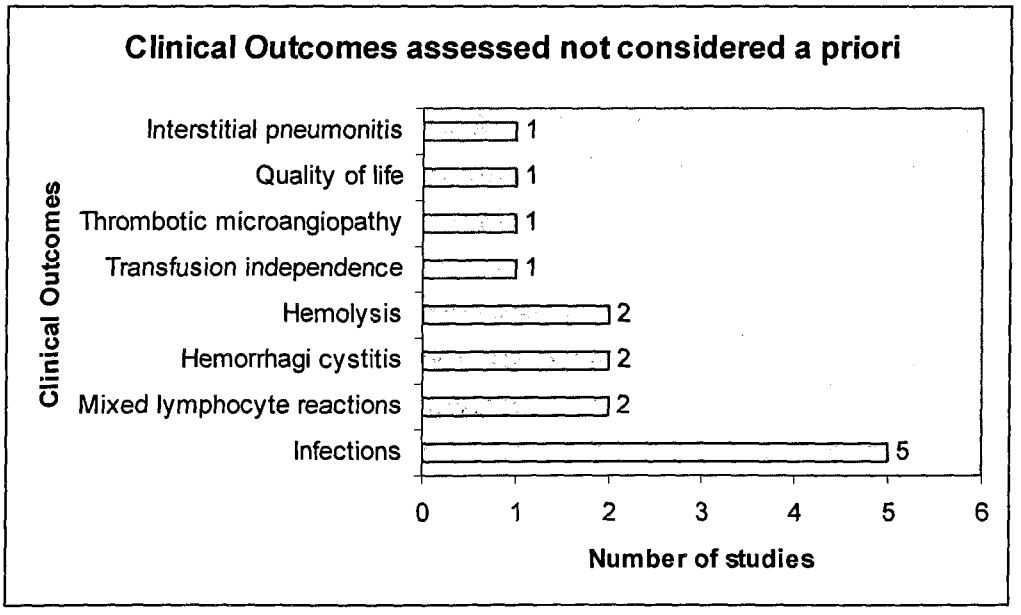
cell precursor frequencies, 7 studies assessed Natural killer-cell Inhibitory receptor(KIR) compatibility and 3 studies assessed donor race (Figure 8). Of the above, there were 21 studies where the primary donor characteristic assessed was not stated, but assessed >1 donor characteristic. Twelve studies assessed a variety of donor variables such as Regulatory T cells, Heat Shock Protein 70, Cytokine levels, Toll like receptors, donor cells alloreactivity, Methyltetrahydrofolate reductase (MTHFR) genotype and aa subsets in Human Leukocyte Antigen Class 1.

Figure 8: Primary Donor Characteristics Assessed by identified studies



One hundred and twenty four studies reported on acute graft versus host disease (aGVHD), 71 reported on Overall survival, 60 studies reported on chronic graft versus host disease (cGVHD), 44 studies reported on relapse, 35 studies reported transplant related mortality, 30 studies reported on engraftment, 28 studies reported on disease/event free survival, 12 studies reported on Cytomegalovirus (CMV) infections/disease, 6 studies reported on graft failure, 5 studies reported on transfusion requirements while 3 studies reported on transplant toxicity. Furthermore, there were 15 studies reporting on a variety of other relevant outcomes not considered a priori within the systematic review (figure 9).

Figure 9: Clinical outcomes assessed by identified studies not considered a priori



Traditional Donor Characteristics

Donor Source

Twenty one studies comprising 19 retrospective cohort studies[43-61] and 2 case control studies [62, 63] assessed the impact of type of hematopoietic stem cell donor on adult transplant outcomes. The study sizes ranged from 28 to 551, representing a total of 4274 patients. The majority for allogeneic transplants were performed for leukemias where a combination of chemotherapy (most frequently Cyclophosphamide) and Total Body Irradiation was used as the conditioning regimen (Table 1).

There were 2 broad categories of donors considered: Related Donors (RD) or Unrelated Donors (URD). Further, they could be subcategorized as Matched or Unmatched as well as haploidentical in the Related Donors category. Consequently, there are 5 subcategories of donors: Matched Related Donors (MRD), Mismatched Related Donors (MMRD), Matched Unrelated Donors (MUD), Mismatched Unrelated Donors and Haploidentical Donors. Table 2 summarizes the number of studies comparing different donor types. Furthermore, there was a study[50] which compared the outcomes of using Mismatched Related Donors (MMRD) with autologous stem cell transplants while another[48] compared Matched Related Donors (MRD) with either Mismatched Related Donors (MMRD) or autologous stem cell transplants.

Table 1: Characteristics of Studies reviewing Donor Source and Transplant Outcomes

Studies	Type of Study	Type of BMT	Population(n)		Gender (M/F)		Mean/Median Age(yrs)		Diagnosis (acute leukemia)		Diagnosis (chronic leukemia)		Diagnosis(others)	
			MRD	*URD*	*MRD*	*URD*	*MRD*	*URD*	*MRD*	*MUD*	*URD*	*MUD*	*MRD*	*URD*
Alyea 2002	Retro cohort	Cy/TBI & T cell depletion(MUD)	120	50	68/52	30/20	43	46	50 (30%)	29 (58%)	22(13%)	11(22%)	48 (28%)	10 (20%)
			MRD	*MUD*	*MRD*	*MUD*	*MRD*	*MUD*	*MRD*	*MUD*	*MRD*	*MUD*	*MRD*	*MUD*
Bacigalupo 1998	Retro cohort	Cy/TBI	36	24	25/11	12/12	36	29			36 (100%)	24 (100%)		
			MRD	*MUD*	*MRD*	*MUD*	*MRD*	*MUD*	*MRD*	*MUD*	*MRD*	*MUD*	*MRD*	*MUD*
Bearman 1994	Case Control	Chemo ± TBI	52	104	58/46	31/21	29.5	29.5	34	17	58	29	12	6
			MRD	*MUD*	*MRD*	*MUD*	*MRD*	*MUD*	*MRD*	*MUD*	*MRD*	*MUD*	*MRD*	*MUD*
Boiron 2001	Retro cohort	Chemo ± TBI	36	22	27/9	16/6	27	31	36	22				
				MMRD		MMRD		MMRD		MMRD		MMRD		MMRD
				14		11/3		21		14				
			MRD	*MUD*										
Carlens 1998	Retro cohort	Cy/TBI or Bu/Cy	334	87	287	264	23 range (1-58)		50%		24%		26%	
			MMUD	*MMRD*										
			2	28										
			MRD	*MUD*	*MRD*	*MUD*	*MRD*	*MUD*	*MRD*	*MUD*	*MRD*	*MUD*	*MRD*	*MUD*
Davies 1994	Retro cohort	Mainly TBI based	221	98	110/112	47/51	23	28.5	105	25	64	57	52	16
			MRD	*MUD*	*MRD*	*MUD*	*MRD*	*MUD*	*MRD*	*MUD*	*MRD*	*MUD*	*MRD*	*MUD*
Davies 2001	Retro cohort	Mainly Cy/TBI	96	45	47/49	28/17	38	35			96 (100%)	45 (100%)		

			MRD	*URD*	*MRD*	*URD*	*MRD*	*URD*	*MRD*	*URD*	*MRD*	*URD*	*MRD*	*URD*
de Brabander 2000	Retro cohort	*not described*	102	39	59/40	23/16	38	31	60	18	27	9	10	7
			MMRD	Auto	MMRD	Auto	MMRD	Auto	MMRD	Auto	MMRD	Auto	MMRD	Auto
deWitte 2001	Retro cohort	not described	20	75	n.s.	n.s.	n.s.	n.s.					all MDS	all MDS
			MMRD	MUD	MMRD	MUD	MMRD	MUD	MMRD	MUD	MMRD	MUD	MMRD	MUD
			58	78	n.s.	n.s.	n.s.	n.s.					all MDS	all MDS
			MRD	*URD*	*MRD*	*URD*	*MRD*	*URD*	*MRD*	*URD*	*MRD*	*URD*	*MRD*	*URD*
Dominietto 2001	Retro cohort	Cy/TBI	270	67	162/108	40/27	33	29	158	11	88	54	24	2
			MUD	MMUD	MUD	MMUD	MUD	MMUD	MUD	MMUD	MUD	MMUD	MUD	MMUD
Drobyski 2002	Retro cohort	Cy/TBI	81	58	42/39	34/24	20	17	46	44	21	12	14	2
				Haplo		Haplo		Haplo		Haplo		Haplo		Haplo
				48		27/21		22		34		9		5
			MRD	*MUD*	*MRD*	*MUD*	*MRD*	*MUD*	*MRD*	*MUD*	*MRD*	*MUD*	*MRD*	*MUD*
Duggan 2002	Case Control	Chemo ± TBI	57	57	36/21	35/22	33	32	41	41	14	14	2	2
			MRD	*MUD*	*MRD*	*MUD*	*MRD*	*MUD*	*MRD*	*MUD*	*MRD*	*MUD*	*MRD*	*MUD*
El-Zimaity 2004	Retro cohort	TBI based	32	24	n.s.	n.s.	n.s.	n.s.	all ALL	all ALL				
				MMRD		MMRD		MMRD		MMRD		MMRD		MMRD
				24		n.s.		n.s.		all ALL				
			URD	*MMRD*	*URD*	*MMRD*	*URD*	*MMRD*	*URD*	*MMRD*	*URD*	*MMRD*	*URD*	*MMRD*
Hows 1986	Retro cohort	Chemo ± TBI	14	14	8/6	3/11	21	17.5	1	1	2	2	11	11

Marks 1993	Retro cohort	TBI based	*MRD* 57	*MUD* 46	*MRD* 26/31	*MUD* 16/30	*MRD* 32.7	*MUD* 30.1	*MRD*	*MUD*	*MRD* all CML	*MUD* all CML	*MRD*	*MUD*
Ochs 1995	Retro cohort	Chemo ± TBI	*RD* 151	*URD* 98	*RD* 85/66	*URD* 52/46	*RD* n.s.	*URD* n.s.	*RD* 62	*URD* 20	*RD* 35	*URD* 40	*RD* 54	*URD* 38
Ottinger 2003	Retro Cohort	not described	*MRD* 138	*MUD* 101	*MRD* 79/59	*MUD* 58/43	*MRD* 40.5	*MUD* 40	*MRD* 31	*MUD* 25	*MRD* 107	*MUD* 76	*MRD*	*MUD*
				MMRD 86		*MMRD* 49/37		*MMRD* 35.5		*MMRD* 30		*MMRD* 56		*MMRD*
Ringden 1995	Case control	Chemo ± TBI	*MRD* 39	*MUD* 39	*MRD* 24/15	*MUD* 24/15	*MRD* 23	*MUD* 28	*MRD* 9	*MUD* 9	*MRD* 13	*MUD* 13	*MRD* 12	*MUD* 12
Seber 1999	Retro cohort	Chemo ± TBI	*RD* 973	*URD* 267	1123	785	45% between 20-40 years; 4%> 50 years		44%		20%		36%	
				Others 668										
Uderzo 2006	Retro Cohort	Chemo ± TBI	*MRD* 314	*URD/Haplo* 195	*MRD* n.s.	*URD/ Haplo* n.s.	*MRD* n.s.	*URD/Haplo* n.s.	*MRD* n.s.	*URD/Haplo* n.s.	*MRD* n.s.	*URD/Haplo* n.s.	*MRD* n.s.	*URD/Haplo* n.s.
van Kraaji 2002	Retro Cohort	Mainly Cy/TBI	*MRD* 159	*URD* 55	*MRD* 101/58	*URD* 36/19	*MRD* 41	*URD* 30	*MRD* 56	*URD* 27	*MRD* 31	*URD* 15	*MRD* 72	*URD* 13

TBI: Total Body Irradiation; Cy= Cyclophosphamide; MRD: Matched Related Donor; URD: Unrelated Donor; Haplo: Haploidentical; RD: Related Donor; MMRD: Mismatched Related Donor

Table 2: Studies comparing different donor sources

Studies		Donor Types			
		Matched Related Donors (MRD)	*Matched Unrelated Donors (MUD)*	*Mismatched Unrelated Donors (MMUD)*	*Mismatched Related Donors (MMRD)*
Alyea 2002		+	X		
Bacigalupo 1998		+	X		
Bearman 1994		+	X		
Boiron 2000		+	X		
Carlens 1998		+	X		
Davies 1994		+	X		
Davies 2001		+	X		
Dominietto 2001		+	X		
Duggan 2002		+	X		
*El-Zimaity 2004**		+	X		
Marks 1993		+	X		
Ottinger 2003†		+	X		
Ringden 1995		+	X		
Total	**13**				
Ochs 1995		+ (RD)	X (URD)		
Seber 1999		+ (RD)	X (URD)		
Total	**2**				
de Brabander 2000		+	X(URD)		
van Kraaji 2002		+	X(URD)		
Uderzo 2006		+	X (URD/Haplo)		
Total	**3**				
deWitte 2001‡			X		+
Hows 1986			X (URD)		+
Total	**2**				
*El-Zimaity 2004**		+			X
Ottinger 2003†		+			X
Total	**2**				
deWitte 2001‡					+
Drobyski 2002			X		X

MRD=Matched Related Donor; MUD=Matched Unrelated Donor; MMUD=Mismatched Unrelated Donor; MMRD=Mismatched Related Donor; Auto=Autologous Stem cell; Haplo= Haploidentical Donor; URD=Unrelated Donor; RD=Related Donor; *, †, ‡ are similar studies; +=comparator

Clinical Outcomes

Clinical outcomes were variably reported by the studies assessing donor relatedness. There were 12 studies reporting Overall Survival [43-45, 48, 50, 52, 54-58, 63], 7

studies reporting on Disease Free Survival[43, 45, 48, 50, 52, 56, 63], 7 studies reporting on Transplant Related Mortality [43-45, 51, 52, 57, 63], 9 studies reporting on Disease Relapse [43-45, 48, 50, 52, 55, 57, 58], 6 studies reporting on neutrophil engraftment [45, 47, 54, 55, 58, 63], 4 studies reporting on transplant toxicities with 2 specifically addressing hemorrhagic cystitis [53, 59], 3 studies reporting on infections [56, 58, 61], 1 study reporting on Cytomegalovirus disease[58] while another study reported on thrombotic microangiopathy [60]. Further, there were 11 studies reporting on Grades III-IV acute graft versus host disease [43-45, 51-55, 57, 58, 63] and 6 studies reporting on extensive chronic graft versus host disease [44-46, 52, 55, 58]. The outcomes reported were predominantly unadjusted for other confounding factors, with only 3 studies [43, 57, 60] reported adjusted values but for variable number of confounding factors (Table 3).

Quality of Studies

On application of the Ottawa Newcastle Scale for study quality assessment, 17 of the 19 cohort studies and both case control studies received the maximum number of stars (*). One study}[54] lost a star (*) for comparability, while the other[61] lost 2 stars(*).

Table 3: Reporting of Clinical Outcomes by studies reviewed Donor source

STUDIES	Study Size	Reported Clinical Outcomes: aGVHD (Grade III-IV)	Extensive cGVHD	OS	DFS	TRM	Relapse	Engraft-ment	Toxicity	TMA	Infections	CMV disease
Alyea 2002		x (x)		x (x)	(x)	(x)	x					
acigalupo 1998		x	x	x		x	x					
Bearman 1994									x			
Boiron 2000		x	x	x	x	x	x	x				
Carlens 1998			x									
Davies 1994								x				
Davies 2001				x	x		x					
Brabander 2000									x			
deWitte 2001				x	x		x					
Dominietto 2001		x				x						
Drobyski 2002		x	x	x	x	x	x					
Duggan 2002		x		x	x	x		x				
El-Zimaity 2004		x							x (HC)			
Hows 1986		x		x				x				
Marks 1993		x	x	x			x	x				
Ochs 1995				x	x						x	
Ottinger 2003		x		(x)		(x)	x					
Ringden 1995		x	x	x			x	x			x	x
Seber 1999									x (HC)			
Uderzo 2006										x (x)		
Van Kraaji 2002											x	
TOTAL		**11**	**6**	**12**	**7**	**7**	**9**	**6**	**4**	**1**	**3**	**1**

AD=acute graft versus host disease; ext cGVHD=extensive chronic graft versus host disease; OS=overall survival; DFS=disease free survival; TRM=transplant related mortality; H Cystitis= Hemorrhagic cystitis; A= Thrombotic Microangiopathy; CMV=Cytomegalovirus; (x) =adjusted point estimate

ABO Compatibility

Number of Studies

Eighteen studies [23, 64-80] (all of which are retrospective cohort studies) assessed ABO compatibility and allogeneic hematopoietic stem cell outcomes. Study sizes ranged from 27 to 6,978 patients, representing a total of 19,428 patients summarized in Table 4

Clinical Outcomes

Pertinent clinical outcomes were variably reported: 13 studies reporting on Overall Survival [23, 68, 70-80], 4 studies reporting on Transplant Related Mortality [70, 74, 78, 79], 5 studies reporting on Disease Free Survival [23, 68, 74, 77, 79], 5 studies reporting on Relapse [74, 75, 78-80], 15 studies reporting on acute graft versus host disease [23, 64, 65, 67, 68, 70-75, 77-80] and 10 studies reporting on chronic graft versus host disease [23, 66, 68, 71, 73, 74, 77-80]. Furthermore, 8 studies reported on neutrophil engraftment [23, 65, 70, 73, 75, 76, 78, 79], 5 studies reported on platelet engraftment [73, 75, 76, 78, 79], 5 studies reporting on red blood cell transfusion needs [69, 70, 73, 78, 79] and 5 studies reporting on platelet transfusion requirements [69, 70, 73, 78, 79]. Data from the majority of studies was unadjusted for other potential confounding variables with only 1 study [65] reporting an adjusted value.

Quality of Studies

Applying the Ottawa Newcastle Scale for Cohort studies, 16 of 18 cohort studies received the maximum number of stars (*). Two studies [73, 78], each lost a star (*) for comparability.

Table 4: Reporting of Clinical Outcomes by Studies reviewing Blood Group (ABO) compatibility

DIES on ABO ›mpatibility		**Reported Clinical Outcomes**									
	Study Size	OS	TRM	DFS	Relapse	aGVHD	cGVHD	Neutrophil engraftment	Platelet engraftment	RBC transfusions	Platelet transfusions
Gale 1987	2036					x					
:igalupo 1988	174					x (x)		x			
kinson 1990	3972						x				
:gglund 1995	291					x					
ayciogIu 1995	199	x		x		x	x				
Mehta 1996	448									x	x
:njamin 1999	292	x	x			x		x		x	x
'er-Taylor 2001	481	x				x	x				
)llman 2001	6978	x		x		x	x	x			
Stussi 2001	173	x				x					
:adros 2002	27	x				x	x	x	x	x	x
Mehta 2002	119	x	x	x	x	x	x				
Stussi 2002	562	x			x	x		x	x		
)ldman 2003	153	x						x	x		
ingden 2004	291	x		x		x	x				
Norel 2003	40	x	x		x	x	x	x	x	x	x
Kim 2005	89	x	x	x	x	x	x	x	x	x	x
:ebach 2005	3103	x			x	x	x				
Total		**13**	**4**	**5**	**5**	**15**	**10**	**8**	**5**	**5**	**5**

D=acute graft versus host disease; cGVHD= chronic graft versus host disease; OS=overall survival; DFS=disease free survival; TRM=transplant related mortality; RBC=red blood cell; (x) =adjusted point estimates

Study Results

Table 5 summarizes the number of studies reviewing ABO compatibility by clinical outcome and the presence or absence of effect of ABO compatibility on a variety of clinical outcomes. Acute graft versus host disease was the most commonly reviewed clinical outcome while Transplant Related Mortality was the least reviewed.

Table 5: Effect of Blood Group (ABO) compatibility on Clinical Outcomes

Studies on ABO compatibility by Outcome	Total number of Studies	*Effect present		†Effect absent	
		Number of Studies	Total number of patients	Number of Studies	Total number of patients
Overall Survival	13	3	1027	10	11502
Transplant Related Mortality	3	1	292	2	208
Disease Free Survival	5	0	0	5	7676
Relapse	5	0	0	5	1009
aGVHD	15	3	909	12	13946
cGVHD	10	0	0	10	15299
Neutrophil engraftment	8	1	174	7	8141
Platelet engraftment	5	1	27	4	844
RBC transfusions	5	3	767	2	129
Platelet transfusions	5	2	67	3	829

At the individual study level: *Effect present suggests a statistically significant association between ABO incompatibility and negative clinical outcomes.†Effect absent suggests no statistically significant association with ABO compatibility and clinical outcome

Nine [23, 68, 71, 73, 74, 76-80] of 13 studies did not find any association between donor/recipient ABO incompatibility and Overall Survival in the context of allogeneic hematopoietic stem cell transplant. Indeed, 2 of the largest studies [23, 80] representing 10,584 of a total 12,529 patients did not demonstrate an association.

Three studies [74, 79] representing a total of 208 patients did not find an association between ABO compatibility and Transplant Related Mortality while 1 study[70] of 292 patients suggest otherwise. All 5 studies [23, 68, 74, 77, 79] that assessed ABO compatibility and

Disease Free Survival did not demonstrate an inferior outcome with ABO incompatibility. The majority of the studies [23, 64, 67, 68, 70, 71, 73, 74, 77-80] (9 of 12 studies), including the largest 3 studies[23, 64, 80] found that aGVHD was not attenuated by ABO incompatibility. Similarly, the proportion of cGVHD nor Relapse was not altered by ABO incompatibility in all 10 [23, 66, 68, 71, 73, 74, 77-80] and 5 [68, 74, 75, 78, 79] studies respectively.

Both neutrophil and platelet engraftments appear not to be altered by ABO incompatibility. Only 1 [65] of 8 studies, representing 174 of 8,315 patients demonstrated an association between ABO incompatibility and slower neutrophil engraftment. Likewise, 1 [73] of 5 studies representing 27 of 871 patients showed that platelet engraftment was delayed using an ABO incompatible donor. Red blood cell transfusion needs of the transplant recipient appear to be increased when using an ABO incompatible donor with 3 [69, 70, 73] of 5 studies representing 767 of 896 patients demonstrating an association. Conversely, platelet transfusion requirements appear not to be affected; 3 [69, 70, 79] of 5 studies representing 829 of 896 patients showing no association.

CMV Compatibility

Number of Studies

Eighteen studies (all of which are retrospective cohort studies) [23, 29, 46, 67, 71, 77, 81-92] assessed CMV compatibility and allogeneic hematopoietic stem cell outcomes. Study sizes ranged from 48 to 6,978 patients, representing a total of 19,796 patients (Table 6).

Clinical Outcomes

Pertinent clinical outcomes were variably reported: 8 studies reporting on Overall Survival [23, 29, 71, 77, 81, 85, 86, 90], 3 studies reporting on Transplant Related Mortality [29, 77, 86], 6 studies reporting on Relapse [23, 29, 82, 85, 86, 90], 12 studies reporting on acute graft versus host disease [23, 29, 67, 71, 77, 83, 85-87, 89, 90, 92] and 9 studies reporting on chronic graft versus host disease [23, 29, 46, 71, 77, 83, 85, 86, 90]. Furthermore, 3 studies reported on neutrophil engraftment [23, 88, 90] and 5 studies reporting on CMV Disease [83-86, 91]. No studies reported on Disease Free Survival. Data from all 18 studies were unadjusted for other potential confounding variables (Table 6).

Quality of Studies

Applying the Ottawa Newcastle Scale for Cohort studies, 17 of 18 cohort studies received the maximum number of stars (*). One study [83], lost 2 stars (*) for comparability.

Table 6: Reported Clinical Outcomes on Studies reviewing Cytomegalovirus (CMV) compatibility

Studies on CMV compatibility		Reported Clinical Outcomes						
	Study Size	aGVHD	cGVHD	CMV Infection	Overall Survival	TRM	Relapse	Engraft-ment
Carlens 1998	451		x					
Carreras 2006	92				x			
Hagglund 1995	291	x						
Jacobsen 1990	163						x	
Jacobsen 1986	54	x	x	x				
Keever-Taylor 2001	503	x	x		x			
Kollman 2001	6978	x	x		x		x	x
Ljungman 2003	7013	x	x		x	x	x	
Meyers 1986	545			x				
Nachbaur 2001	103	x	x	x	x		x	
Nachbaur 2006	48	x	x	x	x	x	x	
Nash 1992	446	x						
Nichols 2002	1760							x
Przepiorka 1999	160	x						
Ringden 2004	291	x	x		x	x		
Sierra 1997	204	x	x		x		x	x
Vij 2003	225			x				
Weisdorf 1991	469	x						
Total		**12**	**9**	**5**	**8**	**3**	**6**	**3**

aGVHD=acute graft versus host disease; cGVHD=extensive chronic graft versus host disease; TRM=transplant related mortality

Study Results

Table 7 summarizes the number of studies reviewing ABO compatibility by clinical outcome with acute graft versus host disease most reviewed and the engraftment the least. Further, Table 7 summaries the presence or absence of effect of CMV compatibility on a variety of clinical outcomes.

Table 7: Effect of Cytomegalovirus (CMV) compatibility on Clinical Outcomes

Studies on CMV compatibility by Outcome	Total number of Studies	*Effect present		†Effect absent	
		Number of Studies	Total number of patients	Number of Studies	Total number of patients
Acute graft vs. host disease	12	0	0	12	16560
Chronic graft vs. host disease	9	4	7673	5	7972
CMV Infection	5	1	545	4	430
Overall Survival	10	3	3371	7	13621
Transplant Related Mortality	4	1	1108	3	6244
Relapse	6	1	163	5	14298
Engraftment	3	1	1760	2	7182
Disease Free Survival	0	-	-	-	-

At the individual study level: *Effect present suggests a statistically significant association between CMV incompatibility and negative clinical outcomes. †Effect absent suggests no statistically significant association with CMV compatibility and clinical outcome

Three [29, 71, 88] of 10 studies, representing 3,371 of 16,992 patients suggest inferior Overall Survival when the allogeneic hematopoietic stem cell donor is CMV incompatible. Transplant Related Mortality appears to be worse in the context of Matched Unrelated Donor Transplants when the donor is CMV incompatible [29]. However, 2 other studies and a stratified analysis of another suggests otherwise [29, 77, 86]. One of 4 studies representing 545 of 975 patients demonstrates an association with CMV incompatibility with the risk of CMV infection [84].

All 12 studies assessing CMV incompatibility with acute graft versus host disease showed no association. However, 4 of 9 studies representing 7673 of 15,645 patients suggest that chronic graft versus host disease may be prevalent [29, 71, 83, 85]. CMV incompatibility does not appear to attenuate relapse as only 1 of 6 studies representing 163 of 14,461 patients suggests an association [82]. Further, 1of 3 studies representing 1,760 of 8,942 suggest prolonged neutrophil engraftment in the context of CMV incompatibility [88].

Gender

Number of Studies

Eighteen studies (all of which are retrospective cohort studies) [23-26, 46, 66, 67, 71, 77, 87, 89, 90, 92-97] assessed gender and allogeneic hematopoietic stem cell outcomes. Study sizes ranged from 40 to 6,978 patients, representing a total of 17,464 patients (Table 8).

Clinical Outcomes

Overall survival was reported by 7 studies [23-26, 71, 77, 97] with 2 and 5 studies reporting on transplant related mortality [25, 77] and disease free survival [25, 26, 77, 90, 96] respectively. Thirteen studies reported on acute graft versus host disease [23, 24, 26, 67, 71, 77, 87, 89, 90, 92, 93, 95, 97] while 10 reported on chronic graft versus host disease [23, 24, 26, 46, 66, 71, 77, 90, 94, 97]. Five studies reported on relapse [23-26, 90] and 2 studies reported on engraftment [23, 90] (Table 8).

Quality of Studies

Applying the Ottawa Newcastle Scale for Cohort studies, 17 of 18 cohort studies received the maximum number of stars (*). One study [96], lost a star (*) for comparability.

Table 8: Reporting of Clinical Outcomes on studies reviewing Gender

Studies on Gender compatibility		Reported Clinical Outcomes						
	Size of study	aGVHD	cGVHD	OS	TRM	Relapse	Engraft-ment	DFS
Bross 1984	136	x						
Storb 1983(1)			x					
Atkinson 1986	40	x						
Zwaan 1989	1915							x
Atkinson 1990			x					
Weisdorf 1991	469	x						
Nash 1992	446	x						
Hagglund 1995	291	x						
Sierra 1997	204	x	x			x	x	x
Carlens 1998			x					
Przepiorka 1999	160	x						
Gratwohl 2001				x	x	x		x
Keever-Taylor 2001	503	x	x	x				
Kollman 2001	6978	x	x	x		x	x	
Randolph 2004	3238	x	x	x		x		
Ringden 2004	291	x	x	x	x			x
Gahrton 2005	1312	x	x	x		x		x
Stern 2006	1481	x	x	x				
Total		**13**	**10**	**7**	**2**	**5**	**2**	**5**

GVHD=acute graft versus host disease; cGVHD=extensive chronic graft versus host disease; TRM=transplant related mortality; OS=overall survival; DFS=Disease free survival

Study Results

Table 9 summarizes the number of studies reviewing Gender compatibility by clinical outcome. Further, Table 9 summaries the presence or absence of effect of CMV compatibility on a variety of clinical outcomes.

Four of 7 studies representing a total of 6,813 of 14,585 patients suggest that overall survival is inferior with gender disparate allogeneic transplants [24-26, 97]. Further, disease free survival was worse in 2 of 5 studies representing 3,227 of 4,504 patients [26, 96]. Transplant related mortality was inferior in one of 2 studies with gender disparity [25]. Engraftment was not affected by gender incompatibility as reported by 2 studies [23, 90]. Acute graft versus host disease was more common in gender disparate transplant in 6 of

13 studies, representing 6653 of 15,549 patients [24, 26, 87, 93, 95, 97]. However, there was no association between chronic graft versus host disease and gender disparity in 8 of 10 studies representing 14,090 of 18,640 patients [23, 46, 71, 77, 90, 94, 95, 97].

Table 9: Effect of Gender on Clinical Outcomes

Studies on Gender compatibility by Outcome	Total number of Studies	*Effect present		†Effect absent	
		Number of Studies	Total number of patients	Number of Studies	Total number of patients
Acute graft vs. host disease	13	6	6653	7	8896
Chronic graft vs. host disease	10	2	4550	8	14090
Overall Survival	7	4	6813	3	7772
Relapse	4	2	4550	2	7760
Disease Free Survival	5	2	3227	3	1277
Transplant related Mortality	2	1	782	1	291
Engraftment	2	0	0	2	7182

At the individual study level: *Effect present suggests a statistically significant association between gender incompatibility and negative clinical outcomes.†Effect absent suggests no statistically significant association with gender compatibility and clinical outcome

Donor Age

Number of Studies

Twelve studies (all of which are retrospective cohort studies) [23, 46, 64, 67, 77, 81, 82, 87, 90, 92, 95, 98] assessed the influence of donor age on allogeneic hematopoietic stem cell outcomes. Study sizes ranged from 40 to 6,978 patients, representing a total of 11,469 patients (Table 10).

Clinical Outcomes

Clinical outcomes were variably reported with 4 studies reporting on Overall Survival [23, 77, 81, 98], 2 studies reporting on Transplant Related Mortality [77, 98], 4 studies reporting of Disease Free Survival [23, 77, 90, 98], 3 studies reporting on Relapse [23, 82, 90], 1 study reporting on neutrophil engraftment [23], 8 studies reporting on acute graft versus host disease [23, 64, 67, 77, 87, 90, 92, 95] and 4 studies reporting on chronic graft versus host disease [23, 46, 77, 90]. Data from all 12 studies were unadjusted for other potential confounding variables (Table 10).

Quality of Studies

Applying the Ottawa Newcastle Scale for Cohort studies, all 12 studies received the maximum number of stars (*).

Table 10: Reporting of Clinical Outcomes by Studies reviewing Donor Age

Studies on Donor Age	Reported Clinical Outcomes							
	Study size	OS	TRM	DFS	Relapse	aGVHD	cGVHD	Engraft-ment
Atkinson 1986	40					x		
Gale 1987	2036					x		
Jacobsen 1990	163				x			
Weisdorf 1991	469					x		
Nash 1992	446					x		
Hagglund 1995	291					x		
Carlens 1998	551						x	
Sierra 1997	204			x	x	x	x	
Kollman 2001	6978	x		x	x	x	x	x
Ringden 2004	136	x	x	x		x	x	
Carreras 2006	92	x						
Mehta 2006	63	x	x	x				
Total		**4**	**2**	**4**	**3**	**8**	**4**	**1**

aGVHD=acute graft versus host disease; cGVHD= chronic graft versus host disease; OS=overall survival; DFS=disease free survival; TRM=transplant related mortality;

Study Results

Table 11 summarizes the number of studies reviewing Gender compatibility by clinical outcome and the presence or absence of effect of CMV compatibility on a variety of clinical outcomes.

Three of 4 studies representing 7,133 of 7,269 patients suggest that an older donor age is associated with inferior overall survival [23, 81, 98]. However, only 1 of 2 studies representing 63 of 199 patients demonstrates that an older donor is associated with more transplant related mortality [98]. Disease free survival appears to be worse with an older donor: 2 of 4 studies representing 7041 of 7381 patients suggest an association [23, 98]. There was no association of donor age on engraftment in the sole study [23].

Acute graft versus host disease was seen to be more frequent in 2 of 6 studies (7,018 of 10,600 patients) [23, 95] while chronic graft versus host disease was more frequent

in only 1 study (6,978 of 7,869 patients) [23]. Similarly, relapse was more frequent in 1 of 3 studies, representing 163 of 7,345 patients [82].

Table 11: Effect of Donor Age on Clinical Outcomes

Studies on Donor age by Outcome	Total number of Studies	*Effect present		†Effect absent	
		Number of Studies	Total number of patients	Number of Studies	Total number of patients
Acute graft vs. host disease	8	2	7018	6	3582
Chronic graft vs. host disease	4	1	6978	3	891
Overall Survival	4	3	7133	1	136
Relapse	3	1	163	2	7182
Disease Free Survival	4	2	7041	2	340
Transplant related Mortality	2	1	63	1	136
Engraftment	1	0	0	1	6978

At the individual study level: *Effect present suggests a statistically significant association between donor age and negative clinical outcomes.†Effect absent suggests no statistically significant association with donor age and clinical outcome

Prior Donor Alloimmunisation

Number of Studies

Nine studies (all of which are retrospective cohort studies) assessed prior donor alloimmunisation (including previous parity) and allogeneic hematopoietic stem cell outcomes [23, 27, 46, 64, 66, 67, 87, 90, 92]. Study sizes ranged from 136 to 6,978 patients, representing a total of 15,083 patients (Table 12).

Clinical Outcomes

Seven studies reported on acute graft versus host disease [23, 27, 64, 67, 87, 90, 92] while 4 studies reported on chronic graft versus host disease [23, 46, 66, 90]. Two studies reported on relapse [23, 90] and 2 on engraftment [23, 90]. Only 1 study reported on overall survival [23] and similarly, another reported on disease free survival [90]. No study reported on Transplant Related Mortality.

Table 12: Reporting of Clinical Outcomes by Studies reviewing prior Donor Alloimmunisation

Studies		Reported Clinical Outcomes					
	Study size	aGVHD	cGVHD	Overall Survival	Relapse	Engraft-ment	DFS
Gale 1987	2036	x					
Flowers 1989	136	x					
Atkinson 1990	3972		x				
Weisdorf 1991	469	x					
Nash 1992	446	x					
Hagglund 1995	291	x					
Sierra 1997	204	x	x		x	x	x
Carlens 1998	551		x				
Kollman 2001	6978	x	x	x	x	x	
Total		**7**	**4**	**1**	**2**	**2**	**1**

aGVHD = acute graft versus host disease; cGVHD = chronic graft versus host disease; OS = overall survival; DFS = disease free survival; TRM=transplant related mortality;

Quality of Studies

Applying the Ottawa Newcastle Scale for Cohort studies, all 9 studies received the maximum number of stars (*). There were no case control studies identified.

Study Results

Table 13 summarizes the number of studies reviewing prior donor alloimmunisation by clinical outcome. Further, Table 13 summarizes the presence or absence of effect of prior donor alloimmunisation on a variety of clinical outcomes.

Five of 7 studies, representing 9978 of 10,560 patients (including the largest study of 6978 patients) did not find an association between acute graft versus host disease and prior donor alloimmunisation [23, 64, 67, 90, 92]. Further, no association with chronic graft versus host disease was demonstrated in 3 of 4 studies, representing 11,154 of 11,705 patients [23, 66, 90]. All other studies assessing prior alloimmunisation and clinical outcomes of overall survival, disease free survival, engraftment and relapse found no association.

Table 13: Effect of prior Donor Alloimmunisation on Clinical Outcomes

Studies on Prior Donor Alloimmunisation by Outcome	Total number of Studies	*Effect present		†Effect absent	
		Number of Studies	Total number of patients	Number of Studies	Total number of patients
Acute graft vs. host disease	7	2	582	5	9978
Chronic graft vs. host disease	4	1	551	3	11154
Overall Survival	1	0	0	1	6978
Relapse	2	0	0	2	7182
Disease Free Survival	1	0	0	1	204
Transplant related Mortality	0	-	-	-	-
Engraftment	2	0	0	2	7182

At the individual study level: *Effect present suggests a statistically significant association between prior donor alloimmunisation and negative clinical outcomes. †Effect absent suggests no statistically significant association with prior donor alloimmunisation and clinical outcome

Donor Race and compatibility

Number of Studies

All three retrospective studies with study sizes ranging from 136 to 6978, representing a total of 9,335 patients assessed the influence of donor race on allogeneic hematopoietic stem transplant outcomes [23, 93, 99].

Clinical Outcomes

Clinical outcomes were variably reported: All 3 studies reporting on acute graft versus host disease, 2 studies reporting on chronic graft versus host disease and overall survival [23, 99], 1 study reported on both relapse and engraftment [23] and another on transplant related mortality [99] (Table 14). No studies reported on relapse or disease free survival.

Table 14: Reporting of Clinical Outcomes by Studies reviewing Donor Race

Studies on Donor Race		Reported Clinical Outcomes					
	Comparisons	aGVHD	cGVHD	Overall Survival	TRM	Relapse	Engraft-ment
Bross 1984	White vs. Nonwhites	x					
Kollman 2001	Race matched vs. Non-matched	x	x	x		x	x
Mielcarek 2005	White/Black/Asian/ Hispanic/Native Indian	x	x	x	x		
Total		**3**	**2**	**2**	**1**	**1**	**1**

aGVHD = acute graft versus host disease; cGVHD = chronic graft versus host disease; OS = overall survival; TRM=transplant related mortality;

Quality of Studies

Applying the Ottawa Newcastle Scale for Cohort studies, all 3 studies received the maximum number of stars (*).

Study Results

Table 15 summarizes the number of studies reviewing donor race by clinical outcome. Further, Table 19 summarizes the presence or absence of effect of prior donor race on a variety of clinical outcomes.

Two of 3 studies including the largest of 6,978 patients found no association between donor race and acute graft versus host disease [23, 93]. Of the 2 studies that assessed the association between chronic graft versus host disease and overall survival, the larger found no association [23]. Transplant related mortality [99] appeared to be associated with donor race while an association was not found with engraftment [23].

Table 15: Effect of Donor Race on Clinical Outcomes

Studies on Donor Race compatibility by Outcome	Total number of Studies	*Effect present		†Effect absent	
		Number of Studies	Total number of patients	Number of Studies	Total number of patients
Acute graft vs. host disease	3	1	2221	2	7114
Chronic graft vs. host disease	2	1	2221	1	6978
Overall Survival	2	1	2221	1	6978
Relapse	0	-	-	-	-
Disease Free Survival	0	-	-	-	-
Transplant related Mortality	1	1	2221	0	0
Engraftment	1	0	0	1	6978

At the individual study level: *Effect present suggests a statistically significant association between donor race and negative clinical outcomes.†Effect absent suggests no statistically significant association with donor race and clinical outcome

Non-Traditional Donor Characteristics

Donor Killer cell immunoglobulin like receptor (KIR) compatibility and Donor KIR genotype

Number of Studies

Three studies (all of which are retrospective cohort studies) assessed donor killer cell immunoglobulin like receptor (KIR) compatibility [100-102] and 4 studies assessed donor killer cell immunoglobulin like receptor (KIR) genotype with allogeneic hematopoietic stem cell outcomes [103-106]. Study sizes ranged from 25 to 374 patients, representing a total of 1,283 patients (Table 16).

Clinical Outcomes

Overall survival and transplant related mortality was reported by all 3 studies that assessed killer cell immunoglobulin like receptor (KIR) compatibility while 2 and 1 study(s) assessing donor killer cell immunoglobulin like receptor (KIR) genotype reported on overall survival[104, 105] and transplant related mortality[106]. Disease free survival was reviewed in 3 studies [100-102], while cytomegalovirus (CMV) reactivation was assessed in 1 study [103]. Acute and chronic graft versus host disease was reported in 1 study assessing killer cell immunoglobulin like receptor (KIR) compatibility [101] and 2 studies assessing donor killer cell immunoglobulin like receptor (KIR) genotypes [105, 106]. Relapse was reviewed by 5 of 7 studies [100-102, 105, 106]. (Table 16)

Quality of Studies

Applying the Ottawa Newcastle Scale for Cohort studies, 6 studies received the maximum number of stars (*) while one study [104]lost a star (*) for comparability. There were no case control studies identified.

Table 16: Reporting of Clinical Outcomes by Studies reviewing KIR

Studies on KIR		Reported Clinical Outcomes						
	Study Size	OS	TRM	DFS	Relapse	aGVHD	cGVHD	CMV reactivation
KIR compatibility								
Beelen 2005	374	x	x	x	x			
Elmaagacli 2005	235	x	x		x	x	x	
Giebel 2003	130	x	x	x	x			
Donor KIR genotype								
Cook 2006	234							x
Cook 2004	220	x						
Giebel 2006	25	x		x	x	x	x	
Verheyden 2005	65		x		x	x	x	
Total		**5**	**4**	**3**	**5**	**3**	**3**	**1**

aGVHD = acute graft versus host disease; cGVHD = chronic graft versus host disease; OS = overall survival; DFS = disease free survival; TRM=transplant related mortality; KIR = Killer Cell immunoglobulin like receptor

Study Results

The 2 most recent studies, representing 609 patients found no association with Overall survival with killer cell immunoglobulin like receptor (KIR) compatibility [100, 101]. Conversely, an earlier study of 130 patients demonstrated suggests that killer cell immunoglobulin like receptor (KIR) compatibility was associated with an inferior overall survival. Likewise, similar associations are noted for transplant related mortality with the 3 studies. Killer cell immunoglobulin like receptor (KIR) compatibility was found to impact on disease free survival in one study [100], but not the other [102]. Neither acute nor

chronic graft host disease was appeared to be attenuated by killer cell immunoglobulin like receptor (KIR) compatibility. However, there is an association with more disease relapse in the 2 most recent studies [100, 101] while the older study did not demonstrate an association [102]. (Table 17)

Table 17: Effect of Donor killer cell immunoglobulin like receptor (KIR) compatibility on Clinical Outcomes

Studies on KIR compatibility by Outcome	Total number of Studies	*Effect present		†Effect absent	
		Number of Studies	Total number of patients	Number of Studies	Total number of patients
Acute graft vs. host disease	1	0	0	1	235
Chronic graft vs. host disease	1	0	0	1	235
Overall Survival	3	1	130	2	609
Relapse	3	2	609	1	130
Disease Free Survival	2	1	130	1	374
Transplant related Mortality	3	1	130	2	609
Engraftment	0	-	-	-	-

At the individual study level: *Effect present suggests a statistically significant association between KIR incompatibility and negative clinical outcomes. †Effect absent suggests no statistically significant association with KIR compatibility and clinical outcome

Overall survival was attenuated by different donor killer cell immunoglobulin like receptor (KIR) genotypes in the 2 studies that evaluated this outcome. Similarly, transplant related mortality appears to be influenced by donor KIR genotype in one and only study. However, no association with disease relapse was identified in study while another suggested there was is an influence. All studies that assessed donor KIR genotypes with allogeneic hematopoietic stem cell transplant found no association with acute or chronic graft versus host disease. (Table 18)

Table 18: Effect of Donor killer cell immunoglobulin like receptor (KIR) genotype on Clinical Outcomes

Studies on Donor KIR genotype by Outcome	Total number of Studies	*Effect present		†Effect absent	
		Number of Studies	Total number of patients	Number of Studies	Total number of patients
Acute graft vs. host disease	2	0	0	2	90
Chronic graft vs. host disease	3	0	0	3	325
Overall Survival	2	2	245	0	0
Relapse	2	1	65	1	25
Disease Free Survival	1	1	25	0	0
Transplant related Mortality	0	-	-	-	-
Engraftment	0	-	-	-	-
CMV Reactivation	1	1	235	0	0

At the individual study level: *Effect present suggests a statistically significant association between donor KIR genotype and negative clinical outcomes.†Effect absent suggests no statistically significant association with donor KIR genotype and clinical outcome

Donor Cytotoxic T and T helper cell frequencies

Number of Studies

Seven studies (all of which are retrospective cohort studies) assessed donor cytotoxic T and T helper cell frequencies with allogeneic hematopoietic stem cell outcomes. Study sizes ranged from 25 to 374 patients, representing a total of 1,283 patients. (Table 19)

Clinical Outcomes

Acute graft versus host disease was reported by all 7 studies that assessed donor cytotoxic T and T helper cell frequencies [107-113]. Two studies looked for an association with chronic graft versus host disease [112, 113] while one study reviewed relapse, disease free survival and engraftment as outcomes [111]. No studies reviewed Overall survival or Transplant elated mortality. (Table 19)

Quality of Studies

Applying the Ottawa Newcastle Scale for Cohort studies, 3 studies [108, 111, 112] received the maximum number of stars (*) while 4 studies lost a star (*) for comparability [107, 109, 110, 113]. There was one study (abstract) that received no stars (*) for outcome [113].

Table 19: Reporting of Clinical Outcomes by Studies reviewing Donor Cytotoxic T and Helper Cell frequencies

Studies on Donor Cytotoxic T and T helper cell frequencies	Reported Clinical Outcomes					
	Study Size	aGVHD	cGVHD	Relapse	Engraftment	Disease Free Survival
Fussell 1994	17	x				
Spencer 1995	48	x				
Weston 1997	42	x				
van der meer 1998	153	x				
Kotlan	16	x	x			
Affaticati 2000	51	x		x	x	x
Sizzano 2006	92	x	x			
Total		**7**	**2**	**1**	**1**	**1**

aGVHD=acute graft versus host disease; cGVHD=extensive chronic graft versus host disease

Study Results

Five of 7 studies representing 249 of 419 patients suggested an association between donor cytotoxic T or Helper cell frequencies and acute graft versus host disease [108, 109, 111-113]. Conversely, the larger of 2 studies reviewing chronic graft versus host disease as an outcome found no association [112]. In the single study that assessed relapse and engraftment, there was no association with donor cytotoxic T or helper cell frequencies, while there appears to be an association with disease free survival in another small study [111].

Table 20: Effect of Donor Cytotoxic T and T Helper Cell frequencies on Clinical Outcomes

Studies on Donor Cytotoxic T and T helper cell frequencies by Outcome	Total number of Studies	*Effect present		†Effect absent	
		Number of Studies	Total number of patients	Number of Studies	Total number of patients
Acute graft vs. host disease	7	5	249	2	170
Chronic graft vs. host disease	2	1	16	1	92
Overall Survival	0	-	-	-	-
Relapse	1	0	0	1	51
Disease Free Survival	1	1	48	0	0
Transplant related Mortality	0	-	-	-	-
Engraftment	1	0	0	1	51

At the individual study level: *Effect present suggests a statistically significant association between donor cytotoxic T and T helper cell frequencies and negative clinical outcomes. †Effect absent suggests no statistically significant association with donor cytotoxic T and T helper cell frequencies and clinical outcome.

CD 31 (PECAM) Compatibility

Number of Studies

Eight studies, 7 retrospective cohort studies [114-120] and 1 case control study [121] assessed the influence of CD31 compatibility on allogeneic hematopoietic stem cell transplant outcomes. Specifically, all 8 studies assessed compatibility at codon 125, while 5 studies assessed compatibility at codon 563/670 [115-117, 119, 120]. Study size ranged from 46 to 301, with total population of 1047. No studies reported on Disease Free survival, Transplant Related mortality, engraftment or relapse. (Table 21)

Clinical Outcomes

Clinical outcomes were variably reported: All 8 studies reported on acute graft versus host disease, chronic graft versus host disease was reported by 2 studies [117, 119] while only 1 reported Overall survival [117]. No other clinical relevant outcomes were assessed.

Table 21: Reporting of Clinical Outcomes by studies reviewing CD31 compatibility

Studies	Reported Clinical Outcomes			
	Study Size	aGVHD	cGVHD	Overall Survival
Behar 1996	46	x		
Nichols 1996	301	x		
Maruya 1998	118	x		
Balduini 2001	150	x		
Grumet 2001	120	x	x	x
Heinemann 2004	163	x		
Cavanagh 2005	64	x	x	
Goodman 2005	85	x		
Total		**8**	**2**	**1**

aGVHD=acute graft versus host disease; cGVHD=extensive chronic graft versus host disease

Quality of Studies

Applying the Ottawa Newcastle Scale for Cohort studies, all 7 studies received the maximum number of stars (*) while the only case control study lost 2 stars (*) for comparability [121].

Study Results

Six of 8 studies that assessed CD31 compatibility at codon 125 did not find an association with acute graft versus host disease [115, 116, 118-121]. These 6 studies including the largest study represented 891 of 1057patients. However, 2 of 5 studies representing 270 of 547 patients suggest that CD31 incompatibility at codon 563/670 was associated with increased risk of acute graft versus host disease [116, 117]. There was no association noted in studies that assessed CD31 compatibility with chronic graft versus host disease or overall survival. (Table 22)

Table 22: Effect of CD31 compatibility on Clinical Outcomes

Studies on Donor Compatibility at CD31 (Codon 125) by Outcome	Total number of Studies	*Effect present		†Effect absent	
		Number of Studies	Total number of patients	Number of Studies	Total number of patients
Acute graft vs. host disease	8	2	166	6	891
Chronic graft vs. host disease	2	0	0	2	194
Overall or Disease Free Survival	1	0	0	1	120
Relapse	0	-	-	-	-
Disease Free Survival	0	-	-	-	-
Transplant related Mortality	0	-	-	-	-
Engraftment	0	-	-	-	-

Studies on Donor Compatibility at CD31 (Codon 563/670) by Outcome					
Acute graft vs. host disease	5	2	270	3	277
Chronic graft vs. host disease	2	0	0	2	194
Overall or Disease Free Survival	1	0	0	1	120
Relapse	0	-	-	-	-
Disease Free Survival	0	-	-	-	-
Transplant related Mortality	0	-	-	-	-
Engraftment	0	-	-	-	-

At the individual study level: *Effect present suggests a statistically significant association between donor CD31 incompatibility and negative clinical outcomes.†Effect absent suggests no statistically significant association with donor CD31 compatibility and clinical outcome

Minor Histocompatibility Antigens (mHAG) Compatibility

Number of Studies

Eleven studies (all retrospective cohort studies) assessed the impact of minor histocompatibility antigens and clinical outcomes after allogeneic hematopoietic stem cell transplant [115, 118, 122-130]. Study sizes ranged from 70 to 577, representing a total of 2,496 patients (Table 23).

Clinical Outcomes

Three of the 11 studies specifically reviewed HA-1, 1 study reviewed HA-1, 2, 3, 4 and 5 while the other reviewed both HA-1 and CD49. Two studies assessed HA-8 while the remaining studies assessed minor histocompatibility antigens such as: CD2, CD42, CD49b, CD54, CD62L, HPA-1, 2, 3, 5, ACC1 and UGT2B17. The clinical outcomes studied were variable with all 11 studies reviewing acute graft versus host disease to no studies reviewing engraftment (Table 23).

Quality of Studies

Applying the Ottawa Newcastle Scale for Cohort studies, 10 studies received the maximum number of stars (*) while one study lost a star (*) for comparability [115].

Table23: Reporting of Clinical Outcomes by Studies reviewing minor histocompatibility antigen (mHAG) compatibility

Studies	mHag assessed		Reported Clinical Outcomes					
		Study Size	OS	TRM	DFS	Relapse	aGVHD	cGVHI
Goulmy 1996	HA-1-5	115					x	
Maruya 1998	CD2, CD42, CD49b, CD54, CD62L	118					x	
Balduini 1999	HPA-1,2,3,5	70					x	
Tseng 1999	HA-1	237					x	
Gallardo 2001	HA-1	215	x	x		x	x	x
Socie 2001	HA-1	100					x	x
Akatsuka 2003	HA-8	577	x			x	x	x
Heinemann 2004	HA-1, CD49	163					x	
Nishida 2004	ACC1	320			x	x	x	x
'erez-Garcia 2005	HA-8	146		x		x	x	
Terakura 2005	UGT2B17	435	x	x	x	x	x	x

iVHD=acute graft versus host disease; cGVHD=extensive chronic graft versus host disease; OS=overall survival; TRM=Transplant related mortality; DFS=Disease free survival

Study Results

Acute graft versus host disease was more frequent in HA-1 incompatible allogeneic transplants with of 4 of 5 studies demonstrating an association [118, 122, 125, 126]. However, the largest of the 5 studies did not concur [124]. In the relevant studies that assessed HA-1, transplant related mortality, relapse and chronic graft versus host disease was not affected with HA-1 incompatibility [125, 126]. (Table 24)

HA-8 incompatibility was associated with increased risk of acute graft versus host disease in both studies reviewing HA-8 [127, 129]. However, overall survival was not influenced by HA-8 compatibility in one study [127], while it was inferior in other when HA-8 was incompatible [129]. The only study that assessed HA-8 compatibility with disease free survival suggests that it was inferior when HA-8 was incompatible [129]. Transplant related mortality, overall survival nor chronic graft versus host disease were influenced by HA-8 compatibility. (Table 24)

The sole study of 70 patients by Balduini et al. assessed Human Platelet Antigens found no association with acute graft versus host disease [123]. Terakura et al. in an analysis of 435 patients found an association between UGT2B17 incompatibility and inferior transplant related mortality, disease free survival and overall survival [130]. However, there was no association between UGT2B17 with either acute or chronic graft versus host disease. Maruya et al. assessed several potential mHags: CD2, CD42, CD49b, CD54 and CD62L. The authors demonstrate increased risk of acute graft versus host disease with incompatibilities in CD49b and CD62L [115]. Nishida et.al. reviewed ACC-1 and found no association with either acute or chronic graft versus host disease [128]. Goulmy et al. found association between HA-3 and acute graft versus host disease [122]. Similarly, Heinemann et al. did not demonstrate any association between CD49 and acute graft versus host disease [118].

Table 24: Effect of minor histocompatibility antigen (mHAG) compatibility on Clinical Outcomes

Studies on mHAG (HA-1) by Outcome	Total number of Studies	*Effect present		†Effect absent	
		Number of Studies	Total number of patients	Number of Studies	Total number of patients
Acute graft vs. host disease	6	5	691	1	237
Chronic graft vs. host disease	2	0	0	2	315
Overall Survival	1	0	0	1	215
Relapse	1	0	0	1	215
Disease Free Survival	0	-	-	-	-
Transplant related Mortality	1	0	0	1	215
Engraftment	0	-	-	-	-
Studies on mHAG (HA-8) by Outcome					
Acute graft vs. host disease	2	2	723	0	0
Chronic graft vs. host disease	2	0	0	2	723
Overall Survival	2	1	577	1	146
Relapse	1	0	0	1	577
Disease Free Survival	1	1	146	0	0
Transplant related Mortality	1	0	0	1	146
Engraftment	0	-	-	-	-

Donor Cytokine polymorphisms

Number of Studies

Seventeen studies assessed the effects of a variety of donor cytokine polymorphisms and allogeneic hematopoietic stem cell transplant outcomes [126, 131-146]. One of the 17 studies was an update of a previous study. Study size ranged from 62 to 953, representing a total of 3,290 patients. (Table 25)

Clinical Outcomes

Various cytokines were assessed are summarized in Table 25. Further, the polymorphisms assessed with a particular cytokine are variable from study to study. Polymorphisms on IL-10 were most frequently studied, and researchers frequently assessed more than one cytokine and/or polymorphisms in their study. Studies that assessed specific cytokine polymorphisms report on a variable number of clinical outcomes with acute graft versus host disease most frequently reported.

Table 25: Reporting of Clinical Outcomes by Studies assessing Donor Cytokine Polymorphisms

Studies	Study size	Polymorphisms assessed													
		IL-1α	IL-1β	IL-1Rα	IL-1R	IL-6	IL-7Rα	IL-10	IL-10Rβ	IL-18	TNF-α	TNF-β	TNFR2	IFN-γ	Fas
Takahashi 2000	62	x						x							
Cavet 2001	80					x		x			x			x	
Cullup 2001	99				x										
Socie 2001	100					x		x			x	x		x	
Dickinson 2002	242							x							
Ishikawa 2002	462										x		x		
Jordlander 2002	196							x			x				
Cullup 2003	115	x													
MacMillan 2003	90	x	x	x											
Stark 2003	104												x		
Cardoso 2004	157									x					
Keen 2004	182							x			x				
Mullighan 2004	160		x		x	x								x	x
Karabon 2005	93					x		x							
Lin 2003/2005	953		x		x	x		x	x						
Shamim 2006	195						x								
Total	**3290**	**3**	**3**	**1**	**3**	**5**	**1**	**8**	**1**	**1**	**5**	**1**	**2**	**3**	**1**

IL = Interleukin; TNF = Tumor Necrosis Factor; IFN = Interferon

Quality of Studies

Applying the Ottawa Newcastle Scale for Cohort studies, 10 studies received the maximum number of stars (*) while one study [31] lost 2 stars (*) for comparability and another lost a star (*) for comparability [136].

Study Results

All studies that assessed donor cytokine polymorphisms on IL-1α, IL-1β, IL-1Rα, TNF-β, IFN-γ and IL-18 did not demonstrate an influence on the incidence of acute graft versus host disease. Three of 5 studies, including the largest found no association between donor polymorphisms on IL-6 and acute graft versus host disease [126, 132, 144]. Similar disparate results were seen with polymorphisms on Il-10, TNF-α and TNFR2, where 2 of 7 [31, 131], 2 of 5 [131, 135] and 1 of 2 [135] studies respectively found an association with acute graft versus host disease. However, single studies on polymorphisms on Fas and IL-18 appear to demonstrate an association with acute graft versus host disease [126, 142].

The majority of studies that assessed a variety of cytokine polymorphisms and chronic graft versus host disease found no association. However, individual studies on polymorphisms IL-1α, IL-10, TNFR2 and Fas suggest that they may attenuate chronic graft versus host disease. Overall Survival, transplant related mortality and relapse were variably associated with several cytokine polymorphisms as seen in Table 26.

Table 26: Effect of Donor Cytokine Polymorphisms on Clinical Outcomes

Studies on Donor cytokine polymorphism by Outcome	Total number of Studies	*Effect present		†Effect absent	
		Number of Studies	Total number of patients	Number of Studies	Total number of patients
IL-1α					
Acute graft vs. host disease	2	0	0	2	205
Chronic graft vs. host disease	1	1	115	0	0
Overall Survival	2	1	90	1	115
Relapse	1	0	0	1	115
Transplant related Mortality	1	0	0	1	90
IL-1β					
Acute graft vs. host disease	3	0	0	3	1243
Chronic graft vs. host disease	1	0	0	1	160
Overall Survival	1	1	90	0	0
Transplant related Mortality	1	1	90	0	0
IL-1Rα					
Acute graft vs. host disease	1	0	0	1	90
Overall Survival	1	0	0	1	90
Transplant related Mortality	1	0	0	1	90
IL-1R					
Acute graft vs. host disease	3	1	99	2	1153
Chronic graft vs. host disease	1	0	0	1	160
IL-6					
Acute graft vs. host disease	5	2	253	3	1173
Chronic graft vs. host disease	2	0	0	2	240
IL-10					
Acute graft vs. host disease	7	2	342	5	1424
Chronic graft vs. host disease	2	1	62	1	80
Transplant related Mortality	1	1	182	0	0
TNF-α					
Acute graft vs. host disease	5	2	524	3	376
Chronic graft vs. host disease	2	0	0	2	142
Relapse	1	1	462	0	0

Disease Free Survival	0	-	-	-	-
Transplant related Mortality	1	1	182	0	0
TNF-β					
Acute graft vs. host disease	1	0	0	1	100
TNFR2					
Acute graft vs. host disease	2	1	462	1	104
Chronic graft vs. host disease	1	1	104	0	0
Relapse	1	1	462	0	0
IFN-γ					
Acute graft vs. host disease	3	0	0	3	340
Chronic graft vs. host disease	2	0	0	2	240
IL-10Rβ					
Acute graft vs. host disease	1	1	953	0	0
IL-18					
Acute graft vs. host disease	1	0	0	1	157
Fas					
Acute graft vs. host disease	1	0	0	1	160
Chronic graft vs. host disease	1	1	160	0	0
IL-7Rα					
Overall Survival	1	1	195	0	0
Transplant related Mortality	1	1	195	0	0

IL = Interleukin; TNF = Tumor Necrosis Factor; IFN = Interferon

Meta-Analysis on the influence of Donor Type and Allogeneic Hematopoietic Stem Cell Transplantation Outcomes

Overall survival was not improved in allogeneic hematopoietic stem cell transplants using Related Donors (RD) versus Unrelated Donors (URD) with an Odds Ratio OR 1.12 (95%CI 0.63-1.96). Even when the analysis was restricted to cohort studies that assessed Matched Related Donors (MRD) with Matched Unrelated Donors (MUD), there was no statistical difference in overall survival OR 1.07 (95%CI 0.48-2.36) (Table 39). Similarly, Disease Free Survival was not improved when Related Donors (RD) were compared with Unrelated Donors (URD) OR 0.62 (95%CI 0.38-1.01). However, transplant related mortality was improved when Related Donors (RD) were used instead of Unrelated Donors (URD) OR 0.52 (95%CI 0.33-0.82). Engraftment of stem cells was similar with either Related Donors (RD) or Unrelated Donors (URD) with OR 1.79 (95%CI 0.68-4.70) while disease relapse was more common with transplants using Related Donors(RD) compared to Unrelated Donors (URD) with an OR 1.66 (95%CI 0.95-2.89), although not statistically significant.

Acute graft versus host disease is less common with allogeneic hematopoietic stem cell transplants using Related Donors (RD) compared with Unrelated Donors (URD) with an OR of 0.46 (95%CI 0.23-0.88). Moreover, the effect size is similar when only cohort studies and studies that compared Matched Related Donors (MRD) to Matched Unrelated Donors (MUD) were analyzed giving an OR of 0.37 (95%CI 0.20-0.69). The proportion of chronic graft versus host disease was decreased with the use of a Related Donors (RD) over an Unrelated Donors (URD), with an OR of 0.43 (95%CI

0.13-1.16). Transplant toxicity was less pronounced with Related Donor (RD) with an OR of 0.35 (95%CI 0.21-0.56). Both Infections and Cytomegalovirus (CMV) disease were similar with either Related Donors (RD) or Unrelated Donors (URD) with OR of 0.98 (95%CI 0.46-2.10) and 1.07 (95% 0.35-3.29) respectively. Thrombotic microangiopathy was reported to be less common with a RR of 0.528 (p=0.029) in RD transplants in one study.

Table 27: Forest Plot of Clinical Outcomes (1) comparing Matched Related Donors (MRD) with Matched Unrelated Donors (MUD)

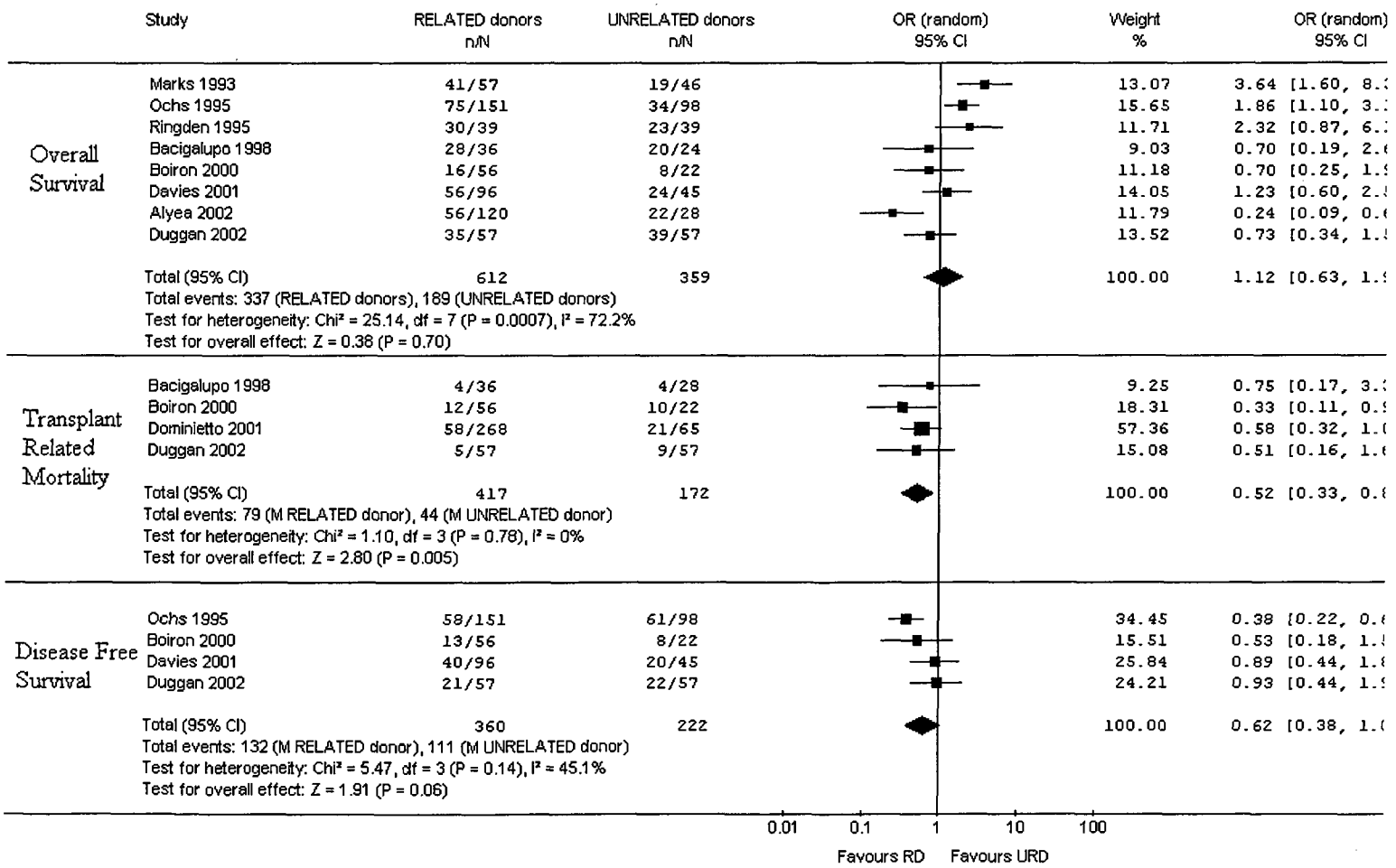


Table 28: *Forest Plot of Clinical Outcomes (2) comparing Matched Related Donors (MRD) with Matched Unrelated Donors (MUD)*

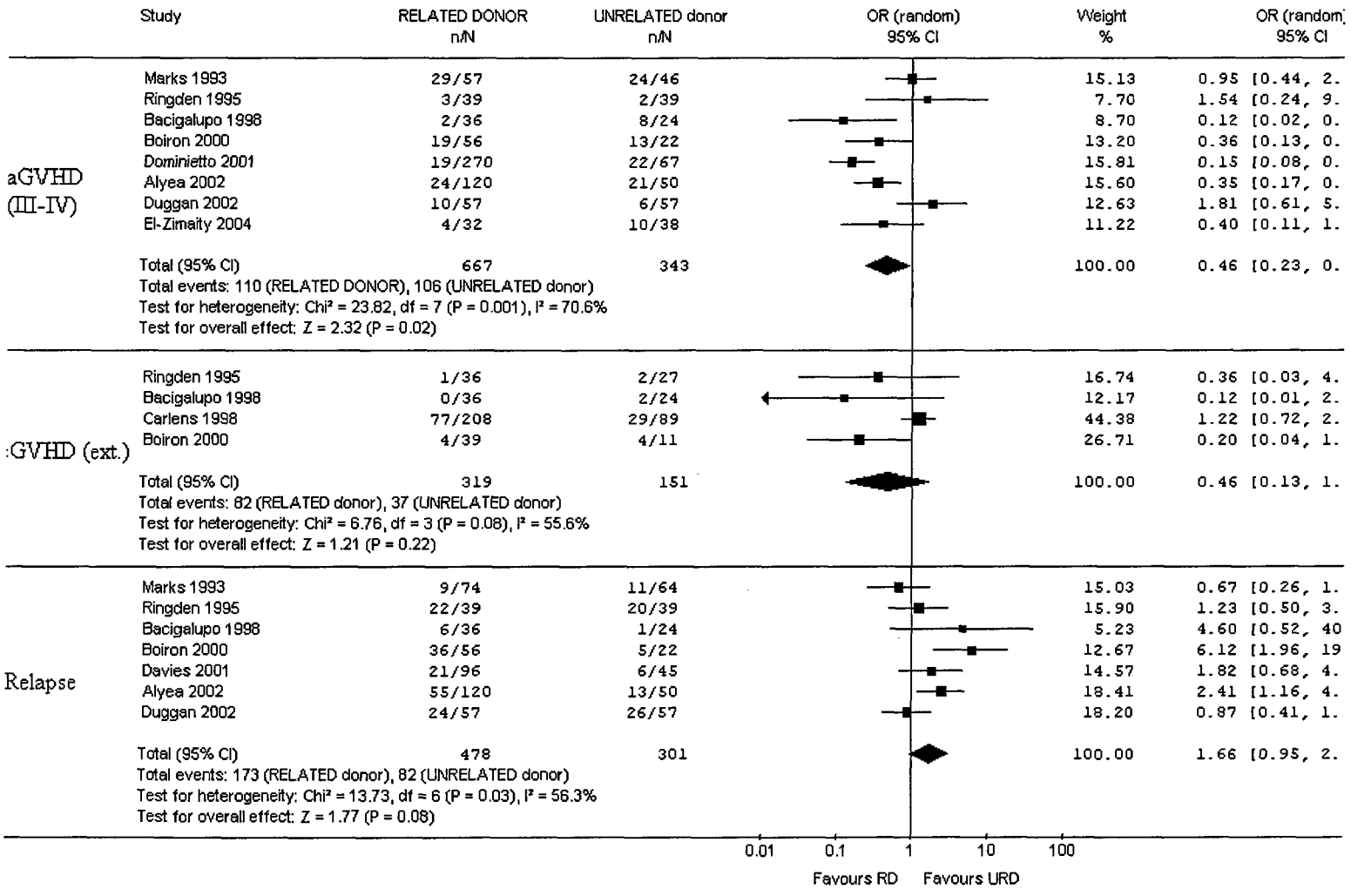
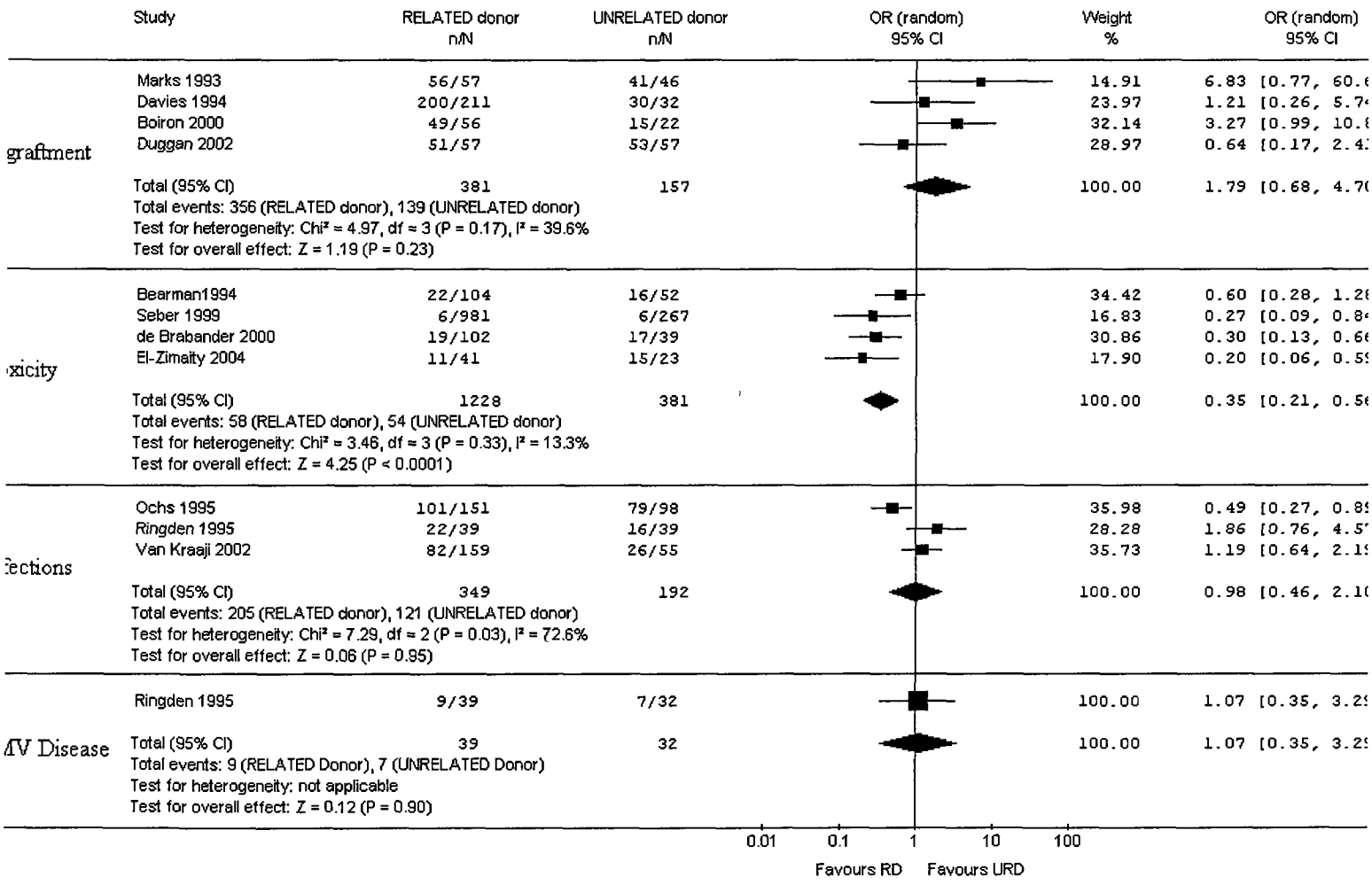


Table 29: *Forest Plot of Clinical Outcomes (3) comparing Matched Related Donors (MRD) with Matched Unrelated Donors (MUD)*



On inspection of a funnel plot on overall survival (Figure 10), there appears to be no obvious asymmetry. Further, the p value of Egger's test is p>0.05 (Table 30). Taken together, there appears to no evidence to support the presence of publication bias.

Figure 10: Funnel Plot assessing Publication Bias

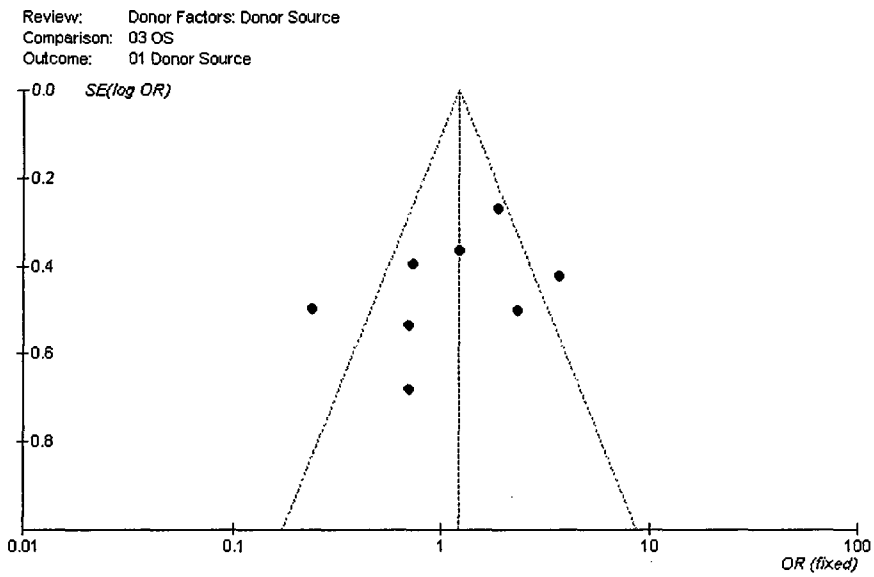


Table 30: Egger's test for Publication Bias

Egger's regression intercept

Intercept	-2.83262
Standard error	2.46073
95% lower limit (2-tailed)	-8.85380
95% upper limit (2-tailed)	3.18856
t-value	1.15113
df	6.00000
P-value (1-tailed)	0.14674
P-value (2-tailed)	0.29348

Discussion

A broad range of donor characteristics were identified that may potentially influence the outcome of allogeneic hematopoietic stem cell transplant. Broadly they could be considered as either traditional or non-traditional. Traditional factors such as Human Leukocyte Antigen (HLA) compatibility, Cytomegalovirus (CMV) compatibility, Blood group (ABO) compatibility, Gender Compatibility, Donor Source and Age were most commonly reviewed. However, non-traditional characteristics are increasingly reviewed, with the bulk of the literature focusing on a variety of donor cytokine polymorphisms.

Clinical outcomes that require less follow-up such as acute graft versus host disease are more frequently reported than survival and relapse data. Indeed, there appears to be a paucity of data on survival in the majority of studies reviewing non-traditional donor characteristics. This may reflect the lack of maturity of data, and any firm conclusions about its impact on "hard" clinical outcomes are absent. It is also plausible that many of the non-traditional factors are primarily studied by basic and translational scientists without easy access to clinical data.

There were no randomized controlled trials identified in this review reflecting the paucity of strong epidemiologic evidence for any donor characteristic that may influence allogeneic hematopoietic stem cell transplant outcomes. The majority of the studies identified were retrospective cohorts likely derived from clinical databases where "data-mining" was performed. Importantly, many of the clinical outcomes reviewed in the individual studies were not adjusted for possible confounding factors. Even when adjustments were made, the adjustments varied from study to study. Perhaps this reflects

a lack of standardized set of clinical factors that should be considered and routinely accounted for in statistical analysis. Further, it is possible that authors may have used similar or overlapping datasets for analysis within their published manuscript. For instance, the European Group for Blood and Marrow Transplant (EBMT) and the Centre for International Blood and Marrow Transplant Research (CIBMTR) are North American, European registries that routinely receive clinical data from member institutions. Consequently, any published data from any of these member institutions may also be reviewed at the registry level and later analyzed collectively and published. It would be difficult to account for this potential duplicate reporting. Nevertheless, this systematic review still provides the broadest currently available overview of the transplant "landscape".

In the illustrative meta-analysis of Donor Type, neither overall survival nor free survivals were inferior when a matched unrelated stem cell donor was used instead of a related stem cell donor. This finding is consistent with the notion that chronic graft versus host disease occurs more commonly in the unrelated setting, but the proportion of disease relapses is less compared to the related setting as described in Chapter 1. Multiple meta-analyses of all the 13 most common donor characteristics could be performed. However, given the heterogeneity of the data it is likely that any pooling of data would be questionable. This is particularly highlighted by the donor cytokine polymorphisms where multiple cytokines were studied, with different polymorphisms for each cytokine and with variable clinical outcomes reported.

Clinical outcomes after allogeneic hematopoietic stem cell transplants are varied and dependent on a variety of factors. Donor characteristics play a role, however the

degree of importance is inter-dependent on other recipient, transplant and disease factors. For example, improved Human Leukocyte Antigen (HLA) matching of allogeneic hematopoietic stem cell transplants translates to better outcomes and clinicians will begin to place more emphasis on other factors that may further improve outcomes of the transplant. Thus, clinical improvements in one area will highlight the relative importance of another.

In summary, there are numerous donor characteristics that may influence clinical outcomes after allogeneic stem cell transplantation. Adding to this complexity are newer and novel characteristics such as donor killer cell immunoglobulin like receptor (KIR) genotypes/polymorphisms that are being explored. However, the available literature does not allow one to comprehensively evaluate their relative importance. Nevertheless, it is still possible to consider simple characteristics such as age and donor source when choosing an appropriate donor. Non-traditional donor characteristics remain experimental and likely not easily assessable to clinical practice. It remains unclear how transplant physicians choose donors given this broad and heterogeneous literature.

Chapter 3: Survey of Current Canadian Attitudes

Introduction

In the previous chapter, a systematic review of literature identified all pertinent donor characteristics (Table 31). Characteristics can be broadly segregated into 2 categories. First, traditional characteristics include factors such as age, gender and donor relatedness. Secondly, non-traditional characteristics consist of a heterogeneous group of factors (such as, cytokine polymorphisms and minor histocompatibility antigen mismatches) which are novel and of uncertain significance. Further, these novel donor characteristics are primarily available through specialized laboratories and may not be used in routine practice.

Table 31: Donor Characteristics that influence Allogeneic Stem Cell Transplant Outcomes

Traditional Donor Characteristics	Non-traditional/Novel Donor Characteristics
Relatedness	Minor histocompatibility antigen compatibility (including CD31)
Age	Cytokine polymorphisms
Gender	Natural killer cell receptor polymorphisms
CMV compatibility	Regulatory T cell frequency
ABO compatibility	Cytotoxic T cell frequency
Prior alloimunization	
HLA compatibility	
Race	

The clinical practice of allogeneic hematopoietic stem cell transplantation consists of identifying an "ideal" donor to optimize the outcomes of this process. However, in

most instances an "ideal" donor may not be available and the choice will be between alternate donors with divergent characteristics. Thus, Canadian transplant physicians are frequently faced with choosing between such potential donors.

Rationale for Survey

Canadian Hematopoietic Transplant centers rely on local expertise to help choose allogeneic hematopoietic stem cell transplant donors. Local expertise includes professionals such as physicians, nurses, lab technologists and administrators. Their collective opinions help to ensure timely access to an optimal donor. Nevertheless, it is unclear which donor characteristics are considered important by such experts. Further, it is unknown whether novel donor characteristics are routinely considered by local experts. Indeed, the non-availability of novel technology may influence individual experts' opinions/choice.

The Canadian Bone Marrow Transplant Group (CBMTG) consists of physicians, nurses, laboratory technologists as well administrators. Importantly, the choice of donor may not necessarily be performed by physicians alone. For instance in Ottawa, a well trained transplant nurse practitioner performs this duty (personal communication). A survey of all Canadian Bone Marrow Transplant Group (CBMTG) members would provide insight into current practices and will provide valuable information for comparative purposes.

It is unclear whether there may be other characteristics that one considered important but not identified by the systematic review. For instance, the clinical and financial cost of "activating" an unrelated donor may influence the choice of donor. A

survey of Canadian Bone Marrow Transplant Group (CBMTG) members will identify such "gray" donor characteristics. Furthermore, it is also uncertain whether non-traditional but novel characteristics are in routine use. Moreover, it may suggest whether current practice is in keeping with evidence.

Finally, the relative importance of donor characteristics that are routinely considered in clinical practice is unknown. This survey will allow identification of the characteristics which are considered the most important. However, it will not allow the assessment of their relative importance of factors – this will be assessed further in the next chapter of the thesis.

Survey Objectives

Primary objective:

- To identify donor characteristics most frequently considered being important by Canadian Bone Marrow Transplant Group (CBMTG) members.

Secondary objectives

- To identify donor characteristics not identified in the systematic review but considered important by Canadian Bone Marrow Transplant Group (CBMTG) members.

- To document the proportion of respondents who considered any novel/non-traditional characteristics as amongst the most important donor characteristics considered in routine practice.
- To document whether donor characteristics chosen vary by demographics of the Canadian Bone Marrow Transplant Group (CBMTG) member.

Methods

Survey Population

Canadian hematopoietic stem cell transplant physicians who care for adults is the primary focus of the survey as transplant physicians are generally the individuals who choose bone marrow donors. However, physicians and other Canadian Bone Marrow Transplant Group (CBMTG) members who work exclusively in the laboratory who help choose donors and physician trainees will also be included. Survey respondents will be limited to Canadian Bone Marrow Transplant Group (CBMTG) members that are actively involved in the care of adult patients undergoing allogeneic stem cell transplant.

There are 13 Adult Bone Marrow Centers and 5 Pediatric Bone Marrow Centers in Canada. Canadian experts involved in allogeneic stem cell transplants are part of the Canadian Bone Marrow Transplant Group (CBMTG). Consequently, Canadian Hematopoietic Stem Cell Transplant Physicians as well as nurses, technologists and administrators who care for adults were identified through the Canadian Bone Marrow Transplant Group member roster. The Canadian Bone Marrow Transplant Group (CBMTG) membership roster is an efficient means to identify Health Care Professionals

who are involved in Allogeneic Hematopoietic Stem Cell Transplant. The Canadian Bone Marrow Transplant Group (CBMTG) membership roster was obtained via the Canadian Bone Marrow Transplant Group (CBMTG) Data Manager and is up to date as of March 2007 (personal communication).

There may be Canadian allogeneic transplant experts that are not part of the Canadian Bone Marrow Transplant Group (CBMTG). However, the Canadian transplant community is relatively small but collegial. Consequently, non-members are the minority and such members are less likely to be involved in patient care (Stem cell transplantation requires much collaboration, and individual practice is highly unlikely).

Sample size is an important issue in the design of any survey. In the conduct of this survey, saturation sampling was employed. This is not a sampling technique per se but an attempt to conduct a population census. Saturation sampling is commonly employed in settings such as universities, corporations, government agencies and professional associations [147]. This technique eliminates coverage error as every member of the population is invited to participate in the survey. In this case, all allogeneic hematopoietic stem cell transplant physicians caring for adults and relevant health care professionals are the target population. As previously stated, such individuals are most likely members of the Canadian Bone Marrow Transplant Group (CBMTG). Consequently, no "sampling" actually takes place and no sample size calculation was performed.

Survey Design

There are several means of conducting surveys: Traditional methods such as paper based mailings ("slow mail") and telephone surveys. More recently, with the advent of the World Wide Web, internet (email) based surveys are increasingly common. Indeed, there are advantages and disadvantages to both Traditional and Internet based methods. Further, a combination of both strategies (mixed mode surveys) could also be undertaken.

An internet based survey was chosen over other methods (e.g. telephone or paper based mailing) as it was deemed more cost effective as well as time efficient. Paper based mailings require multiple steps to ensure optimal responses. Firstly, the postal service has to ensure that the mailings are received at either end. On filling out responses to the survey, the individual has to "take time" to return the mailing. Even with prepaid return envelopes, the respondent needs to ensure that the envelope is mailed. This requires more effort on the respondents' part than sending an email. Consequently, a relatively lengthy response period is expected with mail surveys together with a higher potential of non-response. Telephone surveys require optimal time management from both parties (the interviewer and respondent). Canadian Bone Marrow Transplant Group (CBMTG) members are inherently busy individuals and are unlikely to answer "research" related calls during regular working hours; it is intrusive. Further, it would be ethically wrong to potentially interrupt clinical work (caring for patients) by CBMTG members during working hours. Finally, it would be more difficult to contact such individuals after hours even if an "after-hours" contact number was obtained.

It would be highly unlikely that Canadian Bone Marrow Transplant Group (CBMTG) members do not have emails given the internet age and the focus of the profession. Indeed, only 3 of 128 members on the Canadian Bone Marrow Transplant Group (CBMTG) roster did not either provide or have an email address [personal communication with the Canadian Bone Marrow Transplant Group (CBMTG)]. Further, members would likely access work related emails when there are no immediate patient care concerns resolving any ethical concerns regarding interrupting clinical care. Finally, the cost of an internet based survey is negligible (see below). Consequently, the internet would provide the optimal medium for the survey and reminders.

The survey was conducted using Survey Monkey - an easy-to-use tool for the creation of online surveys [148]. There are many online survey tools but Survey Monkey's primary strength is its intuitive Web interface, which makes it easy for most individuals to create surveys and export collected data. It has advanced features, like the ability to branch questions based on response and exporting to different formats, including hypertext markup language (HTML), concurrent version systems (CVS) and structured query language (SQL). Furthermore, the software has a free limited account that stores 100 responses. Given the potential need for more than 100 responses, a "Professional" account was purchased for a cost of US$19.95 per month which allows up to 1,000 responses. If that amount is exceeded, a small extra fee is charged (US$0.05) per response. Further with a "Professional" account, the user can create unlimited surveys with an unlimited number of questions. Finally, the results from the "Professional" account can be stored on the web and/or exported to standard software e.g. Microsoft Excel for analysis.

The internet survey interface and content was piloted amongst the thesis supervisors and local hematologists (5) to ensure its graphic appeal, content clarity and ease of response[149]. Relevant changes were made to web content, color, font size and grammar to optimize the survey [150].

Survey Content

The survey content consists of four (4) sections: Section 1 of the survey invites Canadian Bone Marrow Transplant Group (CBMTG) members to respond to the survey, emphasizing the importance of their opinion. The attractive "cover page/letter' which includes relevant organizational logos aims to elicit respondent interest (Figure 1, Appendix 1). Section 2 aims to collect the Canadian Bone Marrow Transplant Group (CBMTG) members' demographic and practice profiles which includes profession, age range of patients cared for, member's age category, gender, member's years in practice, province of practice, number of transplant physicians at centre and a estimate of number of allogeneic transplant recipients in a year (Figure 2, Appendix 1). Results from Section 2 of the survey will allow subgroup analyses of the responses i.e. whether the responses vary by the demographics of the respondent, fulfilling 1 of 3 secondary objectives of the survey.

Section 3 lists the donor characteristics identified by the systematic review (previous chapter) and invites the respondent to consider if there are any donor characteristics that should be added to the list (Figure 3, Appendix 1). Importantly, it also invites the respondent to select in no particular order his/her top 5 donor characteristic that he/she uses in clinical practice which may include any other donor characteristic not

identified by the systematic review. Further, it will be clear from the responses whether novel donor characteristics are among the top 5 characteristics. Consequently, Section 3 (Figure 3, Appendix 1) of the survey focuses on the primary objective of the survey as well as addressing 2 of 3 secondary objectives. Finally, Section 4 thanks the respondent for his/her time and allows for any additional comments (Figure 4, Appendix 1).

Improving Response Rates and Dealing with Non-Response

Survey response is dependent on 3 major factors: the importance of the survey n to the people who receive it, the design of the survey and the length of the survey[150].

Using Survey Monkey, the graphical design was maximized and custom invitations were used to help improve response rates. The survey spans just five web pages, and when piloted took less than 5 minutes to complete. The survey addresses important transplant questions, aiming to understand Canadian practice patterns. Further, the Canadian Hematopoietic stem cell community is small but collegial, potentially enhancing response rates. Finally, the respondents were engaged with a final question of whether they would like the results of this survey.

The survey design (by Survey Monkey) can help prompt and require the respondent to answer the most pertinent question within the survey. In this case an answer to section 3 (Figure 3, Appendix 1) of the survey was required. It could be argued that potential respondents could be "turned off" by such an approach and may abandon the survey. However, it is believed that Canadian Bone Marrow Transplant Group (CBMTG) members are a motivated and interested survey population. Further, the

responses to section 3 form the basis to Chapter 4 of this thesis: it is imperative that optimal responses are received.

Potential respondents to the survey were reminded by email to complete the survey (maximum of 3 times, excluding the first email invitation). The survey emailing occurred prior to the summer holiday period of 2007 potentially improving response rates. No financial or gift incentives were offered to improve responses as it was deemed ethically challenging and has not been shown to improve response rates of online surveys[151, 152].

Results

A total of 125 emails [identified through the Canadian Bone Marrow Transplant Group (CBMTG) CBMTG registry] were sent to potential respondents (Table 32). There were 7 incorrect email addresses, while 9 CBMTG members opted out of the survey giving a maximum number of potential responses of 109.

Three reminders were sent, approximately 2 weeks apart after the initial emailing. There were 79 responses comprising 59 full responses ,12 partial responses and 9 individuals opting out of the survey. The responses to the survey decreased with each successive mailing: 54 responses with the 1st mailing and none with the 4th and final mailing. Table 3 details the demographic information from all respondents.

Table 32: Flow Diagram of Survey responses of Current Canadian Attitudes

Total emails sent	125
Incorrect or undeliverable emails	7
Total potential Responses	118
Responses after 1st email	54
Responses after 2nd email	17
Responses after 3rd email	8
Responses after 4th email	0
Respondents who opted out of the survey	9
Total Responses	79 (59 Full responses)
Response Rate	**67% (79/118)**
Response (Full) Rate	**50% (59/118)**

Table 33: Respondent Demographics of Survey on Current Canadian Attitudes

	All CBMTG members	Nurses	Physicians caring for Adults	Physicians caring for Children	Laboratory Technologist	Others
Total Responses	79	19	33	8	7	4
Complete	59	16	30	8	3	3
Incomplete	21 (12 partial)	3	3	0	4	1
Age Range (All respondents)						
<30	1(1 %)	0 (0%)	1 (3%)	0 (0%)	0 (0%)	0 (0%)
30-40	15 (21%)	3 (16%)	9 (27%)	0 (0%)	1 (14%)	2 (50%)
40-50	33 (46%)	11 (58%)	12 (36%)	4 (50%)	5 (71%)	1 (25%)
>50	22 (31%)	5 (26%)	11 (33%)	4 (50%)	1 (14%)	1 (25%)
Province of Practice						
Years in Practice						
<5	18 (25%)	7 (37%)	6 (18%)	0 (0%)	3 (43%)	2 (50%)
5-10	12 (17%)	1 (5%)	8 (24%)	1 (13%)	0 (0%)	2 (50%)
10-15	16 (23%)	5 (26%)	6 (18%)	2 (25%)	3 (43%)	0 (0%)
>15	25 (35%)	6 (32%)	13 (39%)	5 (63%)	1 (14%)	0 (0%)
Gender						
Male	37 (52%)	0 (0%)	28 (85%)	7 (88%)	1 (14%)	1 (25%)
Female	34 (48%)	19 (100%)	5 (15%)	1 (13%)	6 (86%)	3(75%)
Number of Transplant Physicians at Centre						
1-3	30 (42%)	11 (58%)	8 (24%)	6 (75%)	4 (57%)	1 (25%)
4-6	24 (34%)	4 (21%)	17 (52%)	2 (25%)	1 (14%)	0 (0%)
>6	17 (24%)	4 (21%)	8 (24%)	0	2 (29%)	3 (75%)
Number of transplants/year						
<20	15 (21%)	5 (25%)	5 (15%)	3 (38%)	2 (29%)	0 (0%)
20-40	31 (44%)	9 (47%)	17 (52%)	1 (13%)	2 (29%)	2 (50%)
>40	25 (35%)	5 (26%)	11 (33%)	4 (50%)	3 (43%)	2 (50%)
Province of Practice						
British Columbia	6 (8%)	0 (0%)	3 (9%)	2 (25%)	1 (14%)	0 (0%)
Alberta	8 (11%)	4 (21%)	4 (12%)	0 (0%)	0 (0%)	0 (0%)
Manitoba	5 (7%)	0 (0%)	4 (12%)	1 (13%)	0 (0%)	0 (0%)
Ontario	29 (41%)	7 (37%)	14 (42%)	2 (25%)	4 (57%)	2 (50%)
Nova Scotia	5 (7%)	2 (11%)	2 (6%)	1 (13%)	0 (0%)	0 (0%)
Quebec	11 (15%)	3 (16%)	4 (12%)	2 (25%)	1 (14%)	1 (25%)
Saskatchewan	7 (10%)	3 (16%)	2 (6%)	0 (0%)	1 (14%)	1 (25%)

Primary Objective

To identify donor characteristics most frequently seen to be important by Canadian Bone Marrow Transplant Group (CBMTG) members.

The most frequently chosen donor characteristic by Canadian Bone Marrow Transplant Group (CBMTG) members was Donor Relatedness followed by Gender, Cytomegalovirus (CMV) compatibility, and Age. Forty out of 59 complete respondents (68%) cited all four of these characteristics within their top 5 whilst 57 of 59 (97%) cited at least 3 of the 4 most common characteristics. The next two most frequently cited characteristics were ABO compatibility and prior alloimmunization.

Table 34: Frequency that a Donor Characteristic was identified as one of the 5 Most Important

Donor Characteristics	N=59 (%)
Donor Relatedness	**58 (98%)**
Gender	**54 (92%)**
CMV compatibility	**53 (90%)**
Age	**51 (86%)**
ABO compatibility	**34 (58%)**
Prior Donor alloimmunisation	30 (51%)
Minor histocompatibility antigens	5 (8%)
Donor race	3 (5%)
Cytokine polymorphisms	1 (2%)
Natural Killer Cell receptor polymorphisms	1 (2%)
Availability of Donor	1 (2%)

Psychological fitness	1 (2%)
Size/Weight	1 (2%)
Family history of malignancy	1 (2%)
Allergies	1 (2%)
Cytotoxic T cell precursor frequency	0 (0%)
Regulatory T cell frequency	0 (0%)
Length of storage of Stem Cells	0 (0%)
Travel history	0 (0%)
Sexual History	0 (0%)

Secondary Objectives

To identify donor characteristics not identified in systematic review but considered important by CBMTG members.

Table 35 lists other Donor Characteristics considered by CBMTG members, but not identified by the previous chapter's systematic review. Eight donor characteristics were identified, where 6 were mentioned once by 6 separate CBMTG members whilst 2 characteristics (family history of malignancy and allergies) were mentioned by one CBMTG member. From this list of donor characteristics, donor availability, size/weight, psychological fitness were considered once by 3 separate CBMTG members to be among their top 5 donor characteristics. Both donor family history of malignancy and allergies was considered by 1 CBMTG member to be among their top 5 donor characteristics. Length of storage of stem cells, travel history and sexual history although considered by some CBMTG members, were not among their top 5 donor characteristics.

Table 35: Donor Characteristics considered by CBMTG members not identified by Systematic Review.

Other Donor Characteristics	Times Cited to be among top 5 donor characteristics N (%)
Availability of Donor	1 (2%)
Psychological fitness	1 (2%)
Size/Weight	1 (2%)
Family history of malignancy	1 (2%)
Allergies	1 (2%)
Sexual History	0 (0%)
Length of storage of Stem Cells	0 (0%)
Travel history	0 (0%)

To document whether novel/non-traditional characteristics are among the top donor characteristics considered in routine practice.

Of the novel donor characteristics identified by the systematic review, only 2 were chosen by respondents among the top 5. Specifically, Cytokine polymorphisms and Natural Killer Cell Receptor polymorphisms were both chosen by one respondent (Table 34).

To documenting whether donor characteristics chosen vary by demographics of the Canadian Bone Marrow Transplant Group (CBMTG) member.

Table 36 summarizes the frequency and likelihood that a specific donor characteristic was considered by all CBMTG members and by profession. The top 4 donor characteristics considered by all professions by frequency were age, gender, donor relatedness and CMV compatibility. The percentages of respondents who cited all four of

these were 9 of 15(60%) for nurses, 24 of 30(80%) for physicians treating adults, 6 of 8(75%) for physicians treating children and 1 of 3(33%) for others. However, the 5th most frequent donor characteristic considered varied by profession: Physicians were more likely to consider prior donor alloimmunisation than ABO compatibility compared to other CBMTG members. Nevertheless, the difference between the 2 choices among physicians caring for adults was marginal (60% vs. 53% respectively). Finally, no Canadian Bone Marrow Transplant Group (CBMTG) members considered Cytotoxic T cell frequencies, regulatory T cell frequencies, length of storage of stem cells, travel history and sexual history as among their top 5 donor characteristics.

Table 36: Donor Characteristics considered by CBMTG members' profession by frequency

Donor Characteristics Considered	**Nurses**	**Physicians caring for Adults**	**Physicians caring for Children Only**	**Non-Clinical CBMTG members (Laboratory Technologist & Others)**
Total Complete Responses	15	30	8	6
Age	**14 (93%)**	**25 (83%)**	**8 (100%)**	**4 (67%)**
Gender	**14 (93%)**	**29 (97%)**	**6 (75%)**	**5 (83%)**
Donor Relatedness	**15 (100%)**	**30 (100%)**	**8 (100%)**	**5 (83%)**
CMV compatibility	**11 (73%)**	**30 (100%)**	**8 (100%)**	**4(67%)**
ABO compatibility	**11 (73%)**	16 (53%)	2 (25%)	**5 (83%)**
Prior Alloimmunization	5 (33%)	**18 (60%)**	**5 (63%)**	2 (33%)
Minor histocompatibility	4 (27%)	0 (0%)	0 (0%)	1 (17%)
Race	0 (0%)	1 (3%)	2 (25%)	0 (0%)
Minor histocompatibility antigens	4 (27%)	0 (0%)	0 (0%)	1 (17%)
Cytokine polymorphisms	0 (0%)	0 (0%)	0 (0%)	1 (17%)
Natural Killer Cell receptor polymorphisms	0 (0%)	0 (0%)	1 (13%)	0 (0%)
Availability of Donor	1 (7%)	0 (0%)	0 (0%)	0 (0%)
Psychological fitness	0 (0%)	1 (3%)	0 (0%)	0 (0%)
Size/Weight	0 (0%)	0 (0%)	0 (0%)	1 (17%)
Family history of malignancy	0 (0%)	0 (0%)	0 (0%)	1 (17%)
Allergies	0 (0%)	0 (0%)	0 (0%)	1 (17%)

When donor characteristics were reviewed by number of years CBMTG members have been in practice, Donor age, gender, relatedness and CMV compatibility were most important (Table 37). The percentages of respondents who cited all four of these were: 8 of 14(57%) for CBMTG members in practice <5 years, 8 of 10(80%) for CBMTG members in practice 5-10 years, 9 of 14(64%) for CBMTG members in practice 10-15 years and 16 of 21(76%) for CBMTG members in practice >15 years.

Table 37: Donor Characteristics considered by CBMTG members by years in practice

Donor Characteristics Considered	<5years	5-10 years	10-15 years	>15 years
Total Complete Responses	14	10	14	21
Age	**11 (79%)**	**9 (90%)**	**13 (93%)**	**18 (86%)**
Gender	**13 (93%)**	**9 (90%)**	**13 (93%)**	**19 (90%)**
Donor Relatedness	**14 (100%)**	**9 (90%)**	**14 (100%)**	**21 (100%)**
ABO compatibility	**12 (86%)**	**6 (60%)**	5 (36%)	**11 (52%)**
CMV compatibility	**11 (79%)**	**10 (100%)**	**11 (79%)**	**21 (100%)**
Prior Alloimmunization	6 (43%)	5 (50%)	**9 (64%)**	10 (48%)
Minor histocompatibility	2 (14%)	0 (0%)	3 (21%)	0 (0%)
Race	0 (0%)	0 (0%)	1 (7%)	2 (10%)
Cytokine polymorphisms	0 (0%)	0 (0%)	1 (7%)	0 (0%)
Natural Killer Cell receptor polymorphisms	0 (0%)	0 (0%)	0 (0%)	1 (5%)
Availability of Donor	0 (0%)	0 (0%)	0 (0%)	1 (5%)
Psychological fitness	0 (0%)	0 (0%)	0 (0%)	1 (5%)
Size/Weight	1 (7%)	0 (0%)	0 (0%)	0 (0%)
Family history of malignancy	0 (0%)	1 (10%)	0 (0%)	0 (0%)
Allergies	0 (0%)	1 (10%)	0 (0%)	0 (0%)

When donor characteristics were reviewed by number of transplants at the CBMTG member's centre of practice, Donor age, gender, relatedness and CMV compatibility remain the most important (Table 38). Specifically, the percentages of respondents who cited all four of these were: 7 of 11(64%) for CBMTG members working in a centre with <20 transplants, 16 of 26(62%) for CBMTG members working in a centre with 20-40 transplants and 18 of 22(82%) for CBMTG members working in a

centre with >40 transplants. The 5th most important characteristic by frequency was either donor alloimmunization or ABO compatibility.

Table 38: Donor Characteristics considered by CBMTG members by number of allogeneic hematopoietic stem cell transplants at centre of practice

Donor Characteristics Considered	<20 transplants	20-40 transplants	>40 transplants
Total Complete Responses	11	26	22
Age	**10 (91%)**	**20 (77%)**	**21 (95%)**
Gender	**10 (91%)**	**24 (92%)**	**20 (91%)**
Donor Relatedness	**11 (100%)**	**26 (100%)**	**21 (95%)**
ABO compatibility	4 (36%)	**18 (69%)**	**12 (55%)**
CMV compatibility	**8 (73%)**	**23 (88%)**	**22 (100%)**
Prior Alloimmunisation	**7 (64%)**	13 (50%)	10 (45%)
Minor histocompatibility	1 (9%)	3 (12%)	1 (5%)
Race	1 (9%)	1 (4%)	1 (5%)
Cytokine polymorphisms	0 (0%)	1 (4%)	0 (0%)
Natural Killer Cell receptor polymorphisms	1 (9%)	0 (0%)	0 (0%)
Availability of Donor	0 (0%)	0 (0%)	1 (5%)
Psychological fitness	1 (9%)	0 (0%)	0 (0%)
Size/Weight	0 (0%)	1 (4%)	0 (0%)
Family history of malignancy	0 (0%)	0 (0%)	1 (5%)
Allergies	0 (0%)	0 (0%)	1 (5%)

Discussion

Allogeneic Stem cell transplantation is a complex process which involves many stakeholders. Donor selection remains a relatively understudied area in the transplant process, but is of utmost importance to optimize transplant outcomes. This is the first survey to identify donor characteristics considered important by Canadian Bone Marrow Transplant Group (CBMTG) members. No similar surveys have been performed or planned in Canada [personal communication at the Canadian Bone Marrow Transplant Group (CBMTG) meeting, Feb 2008]. Furthermore, a Medline search (at the time of writing) using the OVID interfaces using the search concepts: survey, stem cell transplant

and bone marrow transplant did not identify any published articles addressing donor characteristics.

The survey achieved a response rate of 67% with a full response rate of 50%, which compares well with other online surveys[153]. Incomplete responses by a few Canadian Bone Marrow Transplant Group (CBMTG) members may reflect a misunderstanding of the survey, disinterest or survey fatigue. Further, the survey was only piloted among hematologists. Consequently, its content and clarity could be argued to be not entirely appropriate for other Canadian Bone Marrow Transplant Group (CBMTG) member professions. Indeed, Laboratory Technologists were most likely to not complete the survey. Nevertheless, the majority of respondents (83%) completed the survey in its entirety. Unfortunately, details on non-respondents were not available as the provided email list of Canadian Bone Marrow Transplant Group (CBMTG) members (roster) does not have the necessary information for confidentiality purposes.

The previous chapter identified the majority of donor characteristics considered in the transplant process, while Canadian Bone Marrow Transplant Group (CBMTG) members suggested several others. Importantly, none of the suggested donor characteristics were novel/non traditional i.e. they do not involve the use of sophisticated laboratory testing. Indeed several of the suggested characteristics are of pragmatic value such as availability of the donor. In this instance, the rapidity in acquiring the donor stem cells may influence patient outcomes. Delaying transplants while waiting to find the ideal donor can result in adverse outcomes; the clinical opportunity for transplant may pass by. Most malignancies have a genetic and possibly an inherited component. Consequently, a

family history of malignancies in any donor may influence one's choice: donor stem cells could in theory harbor the potential for malignant transformation in its new host.

The majority of Canadian Bone Marrow Transplant Group (CBMTG) members considered the following donor characteristics: relatedness, age, gender, and cytomegalovirus (CMV) compatibility. These chosen characteristics are traditional donor characteristics. However, it is less clear what can be considered the 5th most common characteristic: it was either Blood Group (ABO) compatibility or prior donor alloimmunisation. This may reflect the relative lack of evidence for the characteristic's superiority resulting in similar number of respondents choosing either: there is clinical equipoise.

Importantly, none of the novel/non-traditional characteristics were considered by Canadian Bone Marrow Transplant Group (CBMTG) members. Indeed, the most frequent novel donor characteristic considered (minor histocompatiblities) only accounted for 5% of Canadian Bone Marrow Transplant Group (CBMTG) members' choice. The relevance of this finding is unclear, as this could reflect unavailability of such specialized tests or true belief of their relative (un)importance. Further, when the survey results were reviewed within the context of small and larger volume centers or the experience of the Canadian Bone Marrow Transplant Group (CBMTG) members, novel donor characteristics remain infrequently considered.

Several limitations of this survey deserve mention. First, asking individuals to list in order their preferences does not take into account real life scenarios. Further, it does not account for relative preferences i.e. the acquired data may be ordinal but it is difficult to elicit cardinal scale of such preferences. This task will be addressed in the following

chapter. Secondly, this survey only reflects the opinion of Canadian Bone Marrow Transplant Group (CBMTG) members who replied to the survey. There may be other health care professionals including physicians who practice allogeneic stem cell transplantation but are not members of the Canadian Bone Marrow Transplant Group (CBMTG). The Canadian Bone Marrow Transplant Group (CBMTG) membership roster is up to date as of March 2007; there may also be new members that would be missed by this survey. However, it is also possible that some Canadian Bone Marrow Transplant Group (CBMTG) members no longer work in the area of hematopoietic stem cell transplant and elected not to respond to the survey. Thirdly, it could be argued that the responses to the survey do not account for cluster effects i.e. Canadian Bone Marrow Transplant Group (CBMTG) members at each transplant centre are likely to have the same opinion. Unfortunately, the design of the survey did not permit the analysis of such effects. Nevertheless, it is important to note that the results of the survey were fairly homogenous. Finally, it was not possible to clearly identify the 5th most considered donor characteristic by Canadian Bone Marrow Transplant Group (CBMTG) members where Blood Group (ABO) compatibility and prior alloimmunisation were deemed similar (58% vs. 53%).

In summary, 4 donor characteristics [relatedness, age, gender and cytomegalovirus (CMV) compatibility] were considered by the majority of respondents to be most important. The donor characteristics' relative importance will be studied in the following chapter.

Chapter 4: Conjoint Analysis of Canadian Bone Marrow Transplant Group (CBMTG) members

Introduction

Allogeneic hematopoietic stem cell transplant is a complex process which includes choosing the ideal stem cell donor. Stem cell donors have variable characteristics that can influence transplant outcomes: Chapter 2 summarizes the clinical literature and highlights deficiencies in knowledge. Subsequently, Canadian Bone Marrow Transplant Group (CBMTG) members were surveyed via the internet (Chapter 3) to identify additional donor characteristics that are considered important but were not identified by the systematic review. Furthermore, the survey identified donor characteristics that were deemed most important in the allogeneic stem cell transplant process.

Canadian Bone Marrow Transplant Group (CBMTG) members which include allogeneic hematopoietic stem cell transplant physicians may have differing preferences towards donor characteristics. The process by which Canadian Bone Marrow Transplant Group (CBMTG) members choose eligible donors is unclear and their relative preference unknown. This chapter attempts to study Canadian Bone Marrow Transplant Group (CBMTG) members' perceived relative importance of donor characteristics.

Objectives

The primary objective of this chapter is to define the relative importance that Canadian Bone Marrow Transplant Group (CBMTG) members place on the donor characteristics most commonly identified in Chapter 3

Methods to elicit preferences

There are a variety of methods that can be used to determine preferences which includes qualitative analysis, contingent valuation and conjoint analysis.

Qualitative analysis

Qualitative analysis simply involves asking which option is preferable or valuable without specific evaluation of their relative importance.

Contingent valuation

Contingent valuation improves upon this by asking for an absolute value which the respondent would place on the service/option. With its theoretical foundation in economics, contingent valuation techniques include methods to obtain utility values for goods (standard gamble or time trade-off) and methods to determine monetary values for goods (willingness to pay). The former techniques are often applied to health states rather than service options. The latter techniques are best applied to commodities that are marketed and have an explicit money value in exchange. However, health care and in particular allogeneic hematopoietic stem cell transplant from health care professionals' perspective does not necessarily have an explicit monetary value. Specifically, there is neither monetary value with respect to donor characteristics nor are such characteristics health states.

Conjoint Analysis

Conjoint analysis (CA) is a survey method of data collection and analysis originally developed in mathematical psychology and marketing and has close theoretical links to multi-attribute utility theory [154]. It has been extensively and successfully employed in market research, transportation as well as environmental economics. Furthermore, this technique is increasingly used in a variety of health related studies e.g. [155-162]. The basic premise of this technique is that any service or good can be described by its attribute/characteristic and the extent to which the individual values a good or service depends on the levels of these attributes/characteristics. It allows the estimation of the marginal rates of substitution, relative importance of each attribute and the trade-offs between the attributes [163, 164]. It has been also shown that this technique demonstrates good reliability and validity [165].There are a variety of commercial software available to aid in conduct of CA, notably by Sawtooth, SPEED and SAS.

There are several different CA techniques which can be used to elicit individual preferences. Classical methods involve asking respondents to rate and/or rank all (full-profile) profiles which consist of the chosen attributes under study. The scoring by the respondents is then analyzed to determine the relative contribution (part-worth) of each attribute to the overall utility score of the profile. This assumes that the overall utility is the total sum of the part-worths.

Types of Conjoint Analysis

Full-Profile Conjoint Analysis

The full-profile conjoint analysis allows the respondent to assess all products in full profile (all attributes at once). When respondents are faced with too much information, they routinely use simplification strategies to help with the decision process. Consequently, academics argue whether the results are representative of real-life choices. Indeed, it has been suggested that this approach is useful to measure up to 6 attributes. Variations of the full profile conjoint analysis include single concept or pairwise designs. In the former, the task focuses on probing the acceptability of a profile rather than on the differences between competitive profiles. The measurement of interactions between attributes is possible by including all combinations of levels from 2 or more attributes. However, the interactions can only be measured in a limited sense given that many attributes are being evaluated together.

Adaptive Conjoint Analysis

This method facilitates the measurement of more attributes than is possible with full profile conjoint analysis. It is possible to evaluate up to 30 attributes with this method. This method must be administered by computer (as offered by Sawtooth) and the interview process "adapts" to the respondents' answers as the survey progresses. Further, this method uses a main effects model i.e. the part-worths are measured in an all else equal scenario which implies an assumption of no interaction between attributes. The 1st part of this analysis involves the respondent ranking attributes in terms of preference.

This is followed by rating the importance of the difference between the 2 highest ranked attribute.

Choice-Based Conjoint Analysis

Traditional Full Profile and Adaptive Conjoint Analysis results in part-worth preference scores at the individual level based on their ranking and/or rating. This is not the case with choice based conjoint analysis (CBCA) where the results can be analyzed at the individual, aggregate or group level which allows assessment of the relative preference for specific attributes within the group of interest.

In choice based conjoint analysis (CBCA) respondents are shown a set ($\geq$2) of profiles in full (all attributes displayed) and asked to choose one as opposed to ranking and/or rating them. It can be argued that this more closely reflects real-life scenarios, but on the other hand may encourage respondent simplification compared with traditional Full Profile conjoint analysis questions.

It has been noted that most respondents are not likely to provide enough information with ratings and/or rankings to allow accurate measurements of interactions at an individual level; thus favoring an aggregate analysis of choice data. However, others argue that individuals have unique preferences and that aggregate data (assuming homogeneity) cannot be as accurate as individual-level models.

Choice based conjoint analysis (CBCA) has become the most popular form of conjoint analysis [166]. The Choice Based conjoint analysis exercise involves presenting potential respondents with a number of hypothetical discrete scenarios. For example, within each scenario a respondent could be given two potential options (A and B). Each

scenario considers the same set of donor characteristics but with different levels within each characteristic. For each scenario, respondents are asked to choose between 2 options. Respondents are provided with a set of different hypothetical scenarios choosing a single option within each scenario.

In this thesis, the options relate to 2 potential allogeneic hematopoietic stem cell donors. Each scenario considers the same set of donor characteristics but with different levels within each characteristic. For each scenario, respondents are asked to choose between the two potential allogeneic hematopoietic stem cell transplant donors. Ultimately, respondents are provided with 5 different hypothetical scenarios and allowed to compare the hypothetical scenarios by choosing between them (see below).

Conjoint analysis is commonly and increasingly used in health care research given its ability to compare high quality data. Importantly, it allows health care researchers to determine the relative value that "consumers" place on attributes of a service/good.

Steps in Conjoint Analysis

There are several steps in involved in the conduct of a conjoint analysis study [164].

First, it involves identifying the characteristics of interest, also known as attributes. These attributes/characteristics are factors that are of interest to researcher. Specifically, the attributes describe or define the desirability of a "good" under study. For example, the appeal of a particular credit card may depend on attributes such as credit limit, annual interest rate, ancillary benefits and perceived prestige of the card. From a health care context, the appeal of a hospital may depend on attributes such as distance

from patient, wait times and availability of specialists. Certainly, one could include many potential attributes that define desirability. However, with increasing numbers of included attributes the conjoint analysis could become unmanageable as a result of respondent fatigue.

Secondly, levels are assigned to these characteristics. The levels assigned may be of ordinal, cardinal or categorical scale. These levels should be plausible, feasible as well as capable of being traded-off from each other. Using the credit card example from above, credit limits could have 2 levels such as $10,000 or $20,000. In this case, the levels are cardinal. The credit card categories (3) could be American Express, Visa and MasterCard. Again, it is possible to consider multiple levels per attribute. However, this would also result in increasing complexity of the conjoint analysis and respondent fatigue potentially resulting in poor response rates. Importantly, an attempt should be made to balance the number of levels across attributes as both psychologic and algorithmic effects may bias results: attributes with more levels tend to receive more importance. However, there is an argument for the conjoint task to mimic reality rather than balancing levels while sacrificing realism.

Thirdly, scenarios are then produced which describe possible combinations given the number of characteristics and levels chosen. Again using the credit card example, the researcher could inquire whether a VISA card with $10,000 credit limit with 5% interest rate is preferred over an AMEX card with $20,000 credit limit but with 10% interest rate. Pragmatically, using all possible combinations (full factorial design) is rarely possible as there will be limit to the number of scenarios that a respondent can cope with. For example, if there were 4 attributes with 3 levels, there would be 3^4 i.e.81 possible

scenarios. Non-statistical options exist that help limit scenarios to a manageable number include such as removing dominant, dominated or unrealistic options. Statistical sampling techniques are preferred and include fractional factorial designs which are used to limit the combinations to a manageable level. Such designs assume that some or all interactions between attributes are insignificant, and are consequently dropped from analysis. Essentially, it allows an efficient subset of possible combinations and provides enough information to estimate utilities.

Following scenario production, a typical exercise asks respondents to choose between 2 potential options (pairwise choice) within each scenario. In particular, the description of each question covers the same set of attributes but with different levels or descriptions within each attribute. Consider the following example:

If you were in the market to purchase a PC today and the following were the only alternatives, which would you choose?

• Dell	• Sony
• 4 GHz Processor	• 2 GHz Processor
• 2GB RAM	• 512 MB RAM
• 19 Inch Display	• 15 Inch Display
• $1,400	• $1,000

The pair-wise choices within each scenario are randomly assigned using the combinations identified by the orthogonal design. Essentially, the respondent compares the hypothetical scenarios through ranking, rating or by choosing. In the above PC example, the respondent would be choosing between 2 alternatives. Studies with up to 6 pair-wise choices/questions have been shown to be reliable, although more choices can

be used [167]. Commonly, an additional pair-wise choice is included where one choice is dominant (all attributes preferred) over the other to measure consistency, reliability of the experiment as well as comprehension.

The collected data is subsequently analyzed using regression techniques; the appropriate method is determined by the type of data collected- in this case a random effects logit model. Conjoint analyses allow the estimation of a utility function which describes the mathematical relationship between the service/good attribute and the respondent preferences. Specifically, the derived coefficients from the regression analysis would then indicate the relative importance of each attribute [164]. However, respondents must be willing to trade between characteristics-otherwise the results of the regression analysis may be biased leading to false interpretations.

Methods: Choice Based Conjoint Analysis

In this section, the methods used in the Choice based conjoint analysis (CBCA) of donor characteristics will be outlined.

Choice of Attributes

Originally, it was expected that four or five attributes (donor characteristics) would be used in this conjoint analysis. Six attributes would be too many for the conjoint analysis, requiring too many discrete choices to be made within the exercise. Although the top 4 (by frequency) donor characteristics were apparent (relatedness, CMV compatibility, age and gender), the 5th was difficult to define: The donor characteristics

Blood group (ABO) compatibility and prior alloimmunisation were chosen by 58% and 51% of respondents in the survey (Chapter 3) respectively.

Thus it is difficult to choose between Blood group (ABO) compatibility and Prior donor alloimmunisation. A Monte Carlo simulation with 5000 replications was conducted to assess whether, if number of respondents from the survey presented in Chapter 3 was doubled, either Prior donor alloimmunisation or Blood group (ABO) compatibility would clearly become the 5th preferred characteristic or whether either could replace Donor age as the 4th most preferred characteristic. For the 1st analysis, it was assumed that if either Blood group (ABO) compatibility or Prior donor alloimmunisation was preferred by 20% more than the other, then it would be clearly the 5th preferred attribute. Simulating a double of the number of respondents found the probability of this to be very low: 0.3% for Blood group (ABO) compatibility and 0% for Prior donor alloimmunisation. Further, the probability that either of the contenders for the 5th donor characteristic might surpass the 4th donor characteristic if the sample size was doubled was estimated to be 0%.

Given the low response rate and the difficulty identifying the 5th donor characteristic, it was decided that 4 attributes would be used to facilitate the conjoint analysis as this balances the number of scenarios to be developed, number of respondents required and the precision of the eventual result.

Levels per Attribute

Donors can either be related (share common parents) or unrelated (2 levels). It is possible that half-siblings may be available, but this scenario is infrequent. Consequently, it was deemed by the student, supervisors and local transplant experts that the attribute

relatedness should only have 2 levels. It is expected that based on tacit knowledge as well as the previous chapter's meta-analysis that related donors are preferred over unrelated donors.

An individual's cytomegalovirus (CMV) serologic status can only be biologically positive or negative. Consequently, 4 possible combinations exist between a transplant donor's and recipient's cytomegalovirus (CMV) status; for example cytomegalovirus (CMV) negative recipient with cytomegalovirus (CMV) negative donor is preferred over cytomegalovirus (CMV) negative recipient with cytomegalovirus (CMV) positive donor. With cytomegalovirus (CMV) positive recipients, the preferred donor cytomegalovirus (CMV) status is less clear although registry data would suggest that a cytomegalovirus (CMV) positive donor should be chosen. Consequently, the described scenario (see below) involves that recipient being CMV negative. Accordingly, 2 alternatives exist for the donor's cytomegalovirus (CMV) status: either cytomegalovirus (CMV) positive or cytomegalovirus (CMV) negative.

The gender of a donor can either be female or male. Certainly, transgender individuals exist but they remain the minority. Traditionally, it has been argued that a male donor is preferred over a female donor as this relates to the possibility of allo-immunization. Simplistically, the immune system of a woman can become sensitized to fetal antigen(s) when she is pregnant. This primed immune system is more likely to result in adverse transplant outcomes if she was employed as a donor.

Younger donors are preferred over older donors; the rationale has been explained in Chapter 1. Age can be defined as a categorical (age groups) variable or as a continuous variable. Following discussions with supervisors and local transplant experts, it was

deemed that 40 years would be the "cut-off" to define older or younger donors. This was based on tacit knowledge of local transplant physicians and is keeping with national perceptions. Two levels for the attribute age were chosen in order to balance levels across attributes as discussed in the previous section.

Scenario Development

With 4 attributes with 2 levels each, there could be 2^4 i.e.16 possible scenarios. Due to the high number of possible scenarios, an orthogonal fractional factorial design was implemented using the SPEED 2.1 software (Hague Consulting Group, 2002). Orthogonal design is the most commonly used design strategy in health economics[168].The SPEED 2.1 software sampled the different combinations of attributes and their levels, while ensuring that all combinations are represented. This produced pairs of attributes; the attribute pairs were then used to produce clinical scenarios.

In this case, the number of scenarios presented in the conjoint analysis was reduced to 10 (5 pariwise comparisions), thereby diminishing the risk of cognitive exhaustion or disinterest. However, it is important to recognize that the orthogonal design assumes that the different attributes are independent of each other. Consequently, attribute estimates would be uncorrelated. Nevertheless, this allows the effect estimation of the individual attribute.

Description of Scenarios

The scenarios were developed with aid of the supervisors. The scenarios were also carefully reviewed to ensure realism, clarity and relevance by means of a review by the local transplant physicians (Ottawa Hospital, General Campus). In particular, the

clinical vignette suggests that an allogeneic stem cell transplant is being contemplated for a hypothetical individual with acute myeloid leukemia in 1st remission:

> *"An allogeneic hematopoietic stem cell transplant is being considered for a 30 year old male with acute myeloid leukemia in 1st remission (not M3/promyelocytic leukemia). The patient is CMV negative. The decision to proceed with a hematopoietic stem cell transplant is deemed most in keeping with the patient's, families' and physicians' goals.*
>
> *There are 2 potential HLA (by high resolution) matched donors available to choose from:"*

The clinical condition was chosen as this represents the most common indication for an allogeneic hematopoietic stem cell transplant [10]. Given that the outcomes of M3/promyelocytic leukemias in remission are excellent, individuals with M3 AML are not routinely considered for transplant. A 30 year CMV negative male was considered by the student, supervisors and local transplant physicians as a reasonable hypothetical individual upon which to build the scenarios. Five scenarios were developed where they differ only by the potential donors offered. Specifically, the donor characteristics were varied from scenario to scenario (rationale described in previous section). One of the choices could be considered a dominant scenario as all the characteristics of one donor was superior to the alternative (*i.e.* all the attributes for one scenario can be considered "better" than the other). Responses to this scenario can be analyzed to determine whether respondents understood the conjoint analysis concept and that the eventual responses can be considered consistent and valid.

Survey Design

As with the survey, the target audience will be the Canadian Bone Marrow Transplant Group (CBMTG) which will include the majority if not all Adult Canadian Transplant Physicians. Again, the Survey Monkey software was used to facilitate the dissemination of the questionnaire and collection of responses. The rationale for the use of the online format and the choice of online software was discussed and justified in the previous chapter.

The online conjoint analysis content consists of 8 web pages and is represented by Figures 1 to 8 in Appendix 2. Page 1 explains the rationale of the conjoint analysis and invites Canadian Bone Marrow Transplant Group (CBMTG) members to complete the online task (figure 1, appendix 2). In particular, it aims to elicit Canadian Bone Marrow Transplant Group (CBMTG) member's interest with an easy use web interface while emphasizing the importance of their opinion. Page 2 aims to collect potential respondents' demographic profile: profession and whether they care for adults, children or both. Pages 3 to 7 display pairwise hypothetical scenarios (5) where the respondent was asked to choose the preferred allogeneic stem cell donor with varying characteristics. One of the choices in Scenario 3 (Figure 5, appendix 2) is dominant, where one of the hypothetical donors has all the preferred characteristics. Finally, page 8 thanks the respondent for his/her time and allows for any additional comments.

Size of Study Population

A pre-specified sample size calculation was not performed; as the survey attempted to include the entire population of Canadian Bone Marrow Transplant Group (CBMTG) members (no sampling as such takes place). However, a small number of

respondents would affect the precision of our estimates. However, if a "sample" size calculation is deemed necessary, it has been suggested that the minimum sample size could be:

$$\frac{nta}{c} \geq 500$$

Where n= number of respondents

t= number of tasks

a= number of alternatives per task

c= largest number of levels for any one attribute

In this context, there were 5 tasks, 2 alternatives per task and the largest number of levels for any attribute was 2. Correspondingly the required number of respondents could be 100. However, conjoint analyses are based on decision theory rather than hypothesis testing and it has been deemed inappropriate to "calculate" a sample size. Instead, several authors have suggested a "sample size" between 30-100 [166].

Sample size calculations allow one to potentially detect a meaningful, statistically significant result when an experiment is carried out. In this case, the conjoint analysis attempts to elicit strength of preferences as opposed to detect statistical significance. Consequently, a formal sample size calculation could be argued to be less important. The uncertainty of such preferences can still be displayed by confidence intervals.

Analysis

For the conjoint analysis, a multilogit model was chosen given the repeated measurements of data from the same individuals. The multilogit model is an extension of binary models such as logit or probit models where there are 2 alternatives. The multilogit model is applied when respondents are asked a series of choice sets; meaning that more than one observation, is collected from each individual. In this case, there are repeated measurements of data from the same individuals; each respondent had 5 pair-wise choices.

The "discrete" choice model is based on the assumption of utility maximizing behaviour of individuals. Given that an individual i chooses among J alternatives that produces different utilities, the utility function U_{ij} consists of an observable part V_{ij} and random elements ϵij:

$$U_{ij} = V_{ij} + \epsilon_{ij}$$

The probability that individual i chooses alternative k is given by:

$$Pr_{ik} = Pr\,(U_{ik} > U_{im}); \quad \forall m \neq k$$

The analysis of the data was performed with the aid of SAS version 9.1 within the Market Research application using the Discrete Choice Analysis sub-application. The multilogiit model is given by:

$$\text{Utility, } U = \exp(V) = \exp\,(\beta_1 X_1 + \beta_2 X_2 + \ldots + \beta_k X_k) + \text{error}(\varepsilon)$$

In this case, the function to be estimated will be of the form:

$$U = \exp(\beta_1 \text{Relatedness} + \beta_2 \text{Age} + \beta_3 \text{CMV} + \beta_4 \text{Age} + \beta_5 \text{Gender}) + \text{error}(\varepsilon)$$

where U is a binary variable related to choosing a given scenario (where 1 = choosing a given scenario and 0 = not choosing a given scenario), β_k indicates how much a unit change in the independent variable makes in terms of the cumulative probability of the dependent variable and ε is the error term due to differences between respondents and differences amongst observations.

The logit model is derived from the assumption that the error terms of the utility functions are independent and identically Gumbel distributed[171]. The logit model follows random utility theory and assumes that the decision maker is an individual (disaggregate) and that the decision maker has a perfect discrimination capability. This implies that the decision maker would always choose the "alternative" that maximizes utility. Furthermore, the model assumes that the odds of choosing one alternative over another do not depend on other alternatives in the choice set: Independence from Irrelevant Alternatives (IIA). This is illustrated by the following example [169] (Red bus/Blue bus paradox): "*Commuters initially face a decision between two modes of transportation: car and red bus. Suppose that a consumer chooses between these two options with equal probability, 0.5, so that the odds equal 1. Now suppose a third mode, blue bus, is added. Assuming bus commuters do not care about the color of the bus, consumers are expected to choose between bus and car still with equal probability. But IIA implies that this is not the case: the probability of commuters that take each of the three modes equals one*

third". Finally, the logit model does not explicitly account for correlations in unobserved utility over repeated choices by each respondent.

There are other available models such as Nested Logit model, Probit model and Generalized extreme model. All these models are also based on random utility theory and each have their inherent strengths and weaknesses.

There were no continuous variables in this analysis and dummy variables were used for the categorical attribute levels. In this case, the variable donor relatedness was binary and coded 1 for "yes" and 0 for "no". Similarly, age <40 was coded as "1" while age ≥40 was coded as "0" while CMV negative donors were coded as "1" and cytomegalovirus (CMV) positive donors as "0". Finally, male donor gender was assigned "1" and female assigned as "0". Hazard ratios were calculated (exponentiating the coefficients e^{β} of each attribute of the regression model) as a measure of how much the presence/absence of each the donor characteristic affects the risk of a respondent choosing a given scenario.

Finally, the relative importance of one donor attribute over another was calculated by dividing the corresponding regression coefficient over another to demonstrate the strength of the respondents' preferences. In economic theory, this is known as Marginal Rates of Substitution (MRS) and represents the "rate" at which consumers are willing to give up units of one good in exchange for more units of another good.

Results: Conjoint Analysis

A total of 125 potential respondents [identified using the Canadian Bone Marrow Transplant Group (CBMTG) CBMTG registry] were emailed via the Ottawa Hospital

email system using the Survey Monkey interface. There were 11 invalid email addresses or undeliverable emails. Further, 1 respondent opted out of the survey, leaving 113 potential respondents to the conjoint analysis (Table 39). The majority (85%) of respondents of the conjoint analysis were also respondents to the previous survey (Chapter 3). There were 7 respondents from the conjoint analysis that did not reply to the survey in Chapter 3, while there were 32 respondents from the survey that did not reply to the conjoint analysis.

Table 39: Flow Diagram of responses from Conjoint Analysis

Total emails sent	125
Incorrect or undeliverable emails	11
Total potential Responses	114
Responses after 1st email	27
Responses after 2nd email	7
Responses after 3rd email	2
Responses after 4th email	5
Responses after 5th email	5
Respondents who opted out of the survey	1
Total Responses	**47 (44 Full responses)**
Response (Full) Rate	**39% (44/114)**

In contrast to the survey, the responses in the conjoint analysis decreased between the 1st and 3rd emailing but was higher for the 4th and final mailing. This could be accounted for when the 3rd emailing was sent during the 2007 summer holidays, where

numerous Canadian Bone Marrow Transplant Group (CBMTG) members were away. The 4th emailing was sent following the summer vacation, and responses expectedly improved. Table 40 summarizes the demographics of the respondents:

Table 40: Canadian Bone Marrow Transplant Group (CBMTG) respondent demographics from conjoint analysis

Total CBMTG respondents with full responses	44
Physicians caring for adults	23 (52%)
Physicians caring for children	4 (9%)
Nurses	8 (18%)
Laboratory Technologists	4 (9%)
Others	5 (11%)

The combination with the highest frequency (chosen by 52% of respondents) was Donor B (as opposed to Donor A), Donor C (as opposed to Donor D), Donor G (as opposed to Donor H) and Donor J (as opposed to Donor I). The other possible combinations were less frequently chosen, where the next most frequently chosen combination comprised 16% of all responses (B,C,G, I).

Importantly, Donor E is always chosen over Donor F in Scenario 3 where all the characteristics of Donor E are dominant over Donor F adding credence that the survey was understood by the respondents.

When the frequency analysis was limited to only Physicians who care for Adult patients, the combination with the highest frequency (B,C,G,J) was also Donor B (as opposed to Donor A), Donor C (as opposed to Donor D), Donor G (as opposed to Donor

H) and Donor J (as opposed to Donor I). However, this combination now accounts for 48% (10/21) of all responses from Physicians who care for Adult patients. In contrast the responses from other CBMTG members were more heterogeneous.

Table 41: Frequency of all possible combinations of responses from CBMTG members to the randomly paired choices

All possible combinations of responses of pair-wise CA scenarios	N (%)
A,C,G,I	0 (0%)
A,C,G,J	1 (2%)
A,C,H,I	0 (0%)
A,C,H,J	1 (2%)
A,D,G,I	0 (0%)
A,D,G,J	0 (0%)
A,D,H,I	1 (2%)
A,D,H,J	0 (0%)
B,C,G,I	**7 (16%)**
B,C,G,J	**23 (52%)**
B,C,H,I	0 (0%)
B,C,H,J	1 (2%)
B,D,G,I	4 (9%)
B,D,G,J	2 (5%)
B,D,H,I	3 (7%)
B,D,H,J	1 (2%)
Total	44 (100%)

In scenario 1 (Donor A vs. B), the "trade-off" was between an unrelated male donor with a related female donor. The majority of all CBMTG respondents chose Donor B (93%), preferring a related female donor over an unrelated male donor (Table 4).

Scenario 2 (Donor C vs. D) presents a "trade-off" between an older CMV negative donor with a younger, but CMV positive donor. In this case, 75% of all CBMTG respondents preferred an older CMV negative donor over a younger CMV positive donor (Donor C over D) (Table 42).

Scenario 4 involves a "trade-off" between Donor G (older but related donor) and Donor H (Younger but unrelated donor). The majority of Canadian Bone Marrow Transplant Group (CBMTG) respondents chose Donor G (84%) over donor Donor H, favoring a related donor state over an older donor state (Table 42).

Scenario 5 involves a "trade-off" between Donor I (CMV positive but male donor) and Donor J (CMV negative but female donor). The majority of Canadian Bone Marrow Transplant Group (CBMTG) respondents (66%) preferred Donor J over Donor I, suggesting a preference of a cytomegalovirus (CMV) negative state over male gender (Table 42).

Scenario 3 was a dominant scenario where Donor E was always preferred by all Canadian Bone Marrow Transplant Group (CBMTG) respondents over Donor F. Finally, similar trends are noted, when the data was analyzed within Canadian Bone Marrow Transplant Group (CBMTG) member sub-groups (Table 42).

Table 42: Frequency of respondent choices from pair-wise scenarios

	Scenario 1		Scenario 2		Scenario 4		Scenario 5	
	Donor A	Donor B	Donor C	Donor D	Donor G	Donor H	Donor I	Donor J
	Age < 40 years CMV positive *Unrelated* *Male*	Age < 40 years CMV positive *Related* *Female*	*Age > 40 years* *CMV negative* Unrelated Female	*Age < 40 years* *CMV positive* Unrelated Female	*Age > 40 years* CMV negative *Related* Male	*Age < 40 years* CMV negative *Unrelated* Male	Age < 40 years *CMV positive* Related *Male*	Age < 40 yea *CMV negativ* Related *Female*
All respondents	3(7%)	41(93%)	33(75%)	11(25%)	37(84%)	7(16%)	15(34%)	29(66%)
All Physicians	1(4%)	25(96%)	18(69%)	8(31%)	21(81%)	5(19%)	7(27%)	19(73%)
Physicians caring for adults	1(5%)	20(95%)	14(67%)	7(33%)	17(81%)	4(19%)	7(33%)	14(67%)
Nurses	1(11%)	8(89%)	8(89%)	1(11%)	8(89%)	1(11%)	3(33%)	6(67%)
Laboratory Technologists	1(17%)	5(83%)	4(67%)	2(33%)	5(83%)	1(17%)	3(50%)	3(50%)
Others	0 (0%)	3 (100%)	3 (100%)	0 (0%)	3 (100%)	0 (0%)	2 (67%)	1 (33%)

The orthogonal fractional factorial design did not provide scenarios where either relatedness or cytomegalovirus (CMV) status was compared to a combination of other desirable characteristics. Thus, in the 4 scenarios where respondents were asked to trade between desirable characteristics, respondents were asked to trade either donor relatedness or cytomegalovirus (CMV) negative status with either age or gender. It is clear that the majority of respondents strongly favored cytomegalovirus (CMV) status and relatedness over age and gender, thus reducing the trading between characteristics.

This, unfortunately has turned out to be a weakness of the study design as the unwillingness to trade could not be foreseen in advance. This has lead to the statistical analysis which follows providing unintuitive results. For example in Scenario 1, the unwillingness to trade donor relatedness for a male donor can falsely be interpreted as a preference for a female donor.

Figure 11 summarizes the SAS output for all responding Canadian Bone Marrow Transplant Group (CBMTG) members (n=46) and suggest that the model has the following form:

$$U = \exp(\beta_1 \text{Relatedness} - \beta_2 \text{Age} + \beta_3 \text{CMV} - \beta_4 \text{Gender}) + \text{error}(\varepsilon).$$

Figure 11: SAS Output for MultilLogit Regression

Model Fit Statistics

Criterion	Without Covariates	With Covariates
-2 LOG L	731.963	657.652
AIC	731.963	665.652
SBC	731.963	678.334

Testing Global Null Hypothesis: BETA=0

Test	Chi-Square	DF	Pr > Chi-Square
Likelihood Ratio	74.3110	4	<.0001
Score	62.1364	4	<.0001
Wald	51.5076	4	<.0001

Analysis of Maximum Likelihood Estimates

Variable	DF	Parameter Estimate	Standard Error	Wald Chi-Square	Pr > Chi-Square	Hazard Ratio	Label
Age (Younger)	1	-1.10036	0.23640	21.6660	<.0001	0.333	Age
Gender (Male)	1	-0.92429	0.18276	25.5774	<.0001	0.397	Gender
Relatedness (Yes)	1	1.08876	0.18553	34.4392	<.0001	2.971	Relatedness
CMV (Negative)	1	-0.16601	0.21023	0.6236	0.4297	0.847	CMV

Donor relatedness, age and gender significantly affect the odds of choosing a given scenario with p values of <0.001. On the contrary, cytomegalovirus (CMV) status was not significantly associated with choosing a given scenario (p=0.4297).

The results as indicated by the calculated hazard ratios, suggest that donor Relatedness had the greatest impact on choice of a scenario (HR=2.971). Donor Gender (male) decreased the odds (HR=0.397) of choosing a given scenario while cytomegalovirus (CMV) status (negative) decreased the odds (HR=0.847) of choosing a given scenario. (Table 43)

Table 43: Summary of logit model for responses from Canadian Bone Marrow Transplant Group (CBMTG) members

Attribute	Coefficient	Standard Error	Wald $\chi 2$ p Value*	Hazard Ratio
Age	**-1.10**	**0.24**	**<0.0001**	**0.333**
Gender	**-0.92**	**0.18**	**<0.0001**	**0.397**
Relatedness	**1.10**	**0.18**	**<0.0001**	**2.971**
CMV	**-0.17**	**0.21**	**0.43**	**0.847**

Table 44 summarizes the "implied" relative importance (Marginal Rate of Substitution) Canadian Bone Marrow Transplant Group (CBMTG) members place on the studied donor characteristics. For example, the multinomial logit model would suggest that Canadian Bone Marrow Transplant Group (CBMTG) members value a donor <40 years of age 1.19 (-1.10/-0.92) more than a donor who is male.

Table 44: Marginal Rates of Substitution (MRS) of each donor characteristic with all other donor characteristics (all CBMTG members).

		ß2*		
ß1*	Age (Younger)	Gender (Male)	Relatedness (Yes)	CMV (Negative)
Age (Younger)	**1**	**1.19**	**-1.01**	**6.63**
Gender (Male)	**0.84**	**1**	**-0.85**	**5.57**
Relatedness (Yes)	**-0.99**	**-1.18**	**1**	**-6.56**
CMV (Negative)	**0.15**	**0.18**	**-0.15**	**1**

* MRS = ß1/ ß2

The above analysis was repeated for Physicians caring for Adults (n=23). The corresponding results were similar to that of all Canadian Bone Marrow Transplant Group (CBMTG) members, and summarized in Tables 45 and 46.

Table 45: Summary of logit model for responses from CBMTG members (Physicians caring for adults)

Attribute	Coefficient	Standard Error	Wald $\chi 2$ p Value*	Hazard Ratio
Age	**-0.15**	**0.23**	**0.51**	**0.861**
Gender	**-0.49**	**0.20**	**0.01**	**0.614**
Relatedness	**1.18**	**0.24**	**<0.0001**	**3.240**
CMV	**0.61**	**0.21**	**0.0042**	**1.848**

Table 46: Marginal Rates of Substitution (MRS) of each donor characteristic with all other donor characteristics (Physicians caring for adults).

		ß2*		
ß1*	**Age**	**Gender**	**Relatedness**	**CMV**
Age	**1**	**0.31**	**-0.13**	**-0.25**
Gender	**3.27**	**1**	**-0.41**	**-0.80**
Relatedness	**-7.87**	**-2.41**	**1**	**1.93**
CMV	**-4.07**	**-1.24**	**0.52**	**1**

* MRS = ß1/ ß2

Discussion

The process of allogeneic stem cell transplantation involves choosing the most appropriate donor. Although Human Leukocyte Antigen (HLA) compatibility remains of utmost importance, there may be many other donor factors that are considered in the selection process. As described in Chapter 1, the improvement of Human Leukocyte Antigen (HLA) matching allows for better selection of transplant donors. Consequently, other donor characteristics will become more important in the donor selection process. The preferences of Canadian Bone Marrow Transplant Group (CBMTG) members, in particular transplant physicians who for care for adults is unknown. This chapter attempts to understand the strength of their preferences by utilizing conjoint analysis.

Apart from Human Leukocyte Antigen (HLA) compatibility, the 4 most commonly considered donor characteristics (relatedness, age, gender and CMV compatibility) was studied as part of a conjoint analysis. It is apparent that Canadian Bone Marrow Transplant Group (CBMTG) members have strong preference for donor relatedness and cytomegalovirus (CMV) compatibility. This is reflected by their choices

as summarized in Table 42: Donor relatedness and CMV compatibility were nearly always preferred when "traded-off" against the gender and age.

The unwillingness of the Canadian Bone Marrow Transplant Group (CBMTG) members to trade-off their strong preferences for donor relatedness and cytomegalovirus (CMV) compatibility resulted in a counter-intuitive result from the conjoint analysis. It was expected that donor relatedness was preferred and the conjoint analysis result supports this notion. However, the conjoint analysis suggests that Canadian Bone Marrow Transplant Group (CBMTG) members prefer older donors who are female which is counter-intuitive. Preferences for a cytomegalovirus (CMV) positive donor, which again is counter-intuitive was less clear from the conjoint the analysis as the result was not statistically significant given the small sample size.

Given the illogical result of Canadian Bone Marrow Transplant Group (CBMTG) members' preference for older female donors, the analysis was also repeated using the multiprobit model instead of logit. The probit model, unlike the logit model does not make any assumptions regarding irrelevant alternatives. Nevertheless, the results of the probit model reveals similar results (see Appendix 2), suggesting that the regression models are consistent. Certainly other modeling techniques could be applied; however it is likely that similar results would be obtained given the unwillingness of Canadian Bone Marrow Transplant Group (CBMTG) members to trade off certain donor characteristics.

Conjoint analysis is based on mathematical theory rather than behavioral theory, where one investigates the process by which individuals evaluate one option at a time and state a preference for each option. However, in reality individuals often consider multiple options and choices. Further, the individuals often defer decisions and conjoint analysis

does not formally account for such factors. Importantly, the attributes studied within a conjoint analysis should be plausible and amenable to being "traded-off" against each other. Consequently, scenarios could arise where individuals are unwilling to "trade-off" certain attributes. For instance using the above credit card example, consumers may chose an American Express card irregardless of all other credit card attributes. This unwillingness to trade of such attributes could lead to misleading conjoint analysis results.

There are other notable limitations to the results of the conjoint analysis: Firstly, the full response rate for conjoint analysis was 39%. It is possible that the preferences for respondents may be different from that of non-respondents, unless Canadian Bone Marrow Transplant Group (CBMTG) members respond "randomly". However, it is notable that 85% of respondents of the conjoint analysis were also respondents to the previous survey (Chapter 3) where the full response rate was 54%.

Secondly, the clinical scenarios were hypothetical and "force" Canadian Bone Marrow Transplant Group (CBMTG) members to consider a specific transplant scenario: a 30 year old male patient with acute myeloid leukemia in 1st remission who is cytomegalovirus (CMV) negative. In reality, there could be multiple other transplant scenarios which could include different patient age, disease, disease stage and cytomegalovirus (CMV) status. Furthermore, it is possible that only one stem cell donor exists, consequently there may be limited options for the transplant team. It is expected that with a different clinical scenario, Canadian Bone Marrow Transplant Group (CBMTG) members would prefer a younger, related male donor who is cytomegalovirus (CMV) negative. However, the strength of their preferences may be different. A specific

scenario allows the investigator to focus the respondent to a specific clinical issue and allows for a potentially meaningful analysis. A larger available sample size may allow for a variety of clinical scenarios while balancing respondent disinterest and fatigue.

Thirdly, it could be argued that the order of clinical scenarios may influence the choice of the respondent. However, the dominant scenario (Scenario 3) was chosen by all the respondents implying that the conjoint task was understood. Furthermore, is has been shown that the order of scenarios within the conjoint analysis task does not influence results [170].

Finally, the marginal rates of substitution would have yielded important information regarding the relative values Canadian Bone Marrow Transplant Group (CBMTG) members place on the 4 studied donor characteristic. Indeed Tables 44 and 46 demonstrate how this could be accomplished. However, given the counter-intuitive results described above; it would be inappropriate to draw any definitive conclusions from this portion of the analysis.

The majority of Canadian Bone Marrow Transplant Group (CBMTG) members were unwilling to "trade-off" donor relatedness and CMV negativity, limiting the results of the conjoint analysis. This unwillingness to "trade" could not have been foreseen in advance. Nevertheless it is clear that Canadian Bone Marrow Transplant Group (CBMTG) members, including allogeneic hematopoietic stem cell transplant physicians who care for adults strongly value relatedness over donor age, gender and cytomegalovirus (CMV) compatibility.

Chapter 5: Concluding Remarks and Future Directions

Hematologic Malignancies are a heterogeneous group of diseases that comprise 10% of all cancers. The basic premise of hematologic malignancies is that there is dysregulation of the individual's immune system. This allows "unchecked" proliferation of malignant cells. Indeed, the most aggressive cancers are considered to be "blood" based malignancies e.g. acute leukemias and Burkitt's lymphoma.

Chemotherapy is the mainstay of treatment where it preferentially targets cells which high proliferative index (cancers). Although the application of higher doses of chemotherapy may facilitate higher tumor cell kill, it is limited by eventual bone marrow failure (see Chapter 1). Consequently, cures of hematologic malignancies are rare with conventional chemotherapy alone. Allogeneic Hematopoietic Stem Cell Transplantation (also known as Bone Marrow Transplant) remains the only potentially curative therapy for a variety of hematologic malignancies with remarkable progress in this field since the first successful stem cell transplant in 1972.

Hematopoietic Stem cell Transplantation allows the application of high doses of chemotherapy with or without radiation, facilitating maximal tumor cell kill. Further, the use of an allogeneic donor harnesses the activity of a foreign immune system to recognize and "kill" tumor cells (graft versus tumor effect). However, concurrent graft versus host disease may occur where the foreign immune system "attacks" the host's normal tissues (e.g. gut, liver and skin) resulting in morbidity and even death. The outcomes of allogeneic transplants are dependent on 4 broad factors: Disease status, Conditioning Chemotherapy, Supportive Care and Donor Characteristics. A successful allogeneic

hematopoietic stem cell transplant requires the careful selection of an "ideal" donor. This thesis focuses on donor selection, where it aims to understand how Canadian Allogeneic Hematopoietic Stem Cell Transplant Physicians select an "ideal" donor.

There are a multitude of donor characteristics that are known to influence the outcomes of allogeneic hematopoietic stem cell transplants. Most importantly, Human Leukocyte Antigen (HLA) compatibility between the recipient and donor is considered the dominant characteristic in this field (Chapter 1). However, there are other important donor characteristics. These non-human leukocyte antigen (HLA) characteristics may be broadly considered to be either traditional characteristics or non-traditional/novel (requires the use of more sophisticated laboratory analysis). Unsurprisingly, traditional characteristics have been reviewed extensively while novel characteristics are less studied (Chapter 2). With progress in human leukocyte antigen (HLA) matching, these non-human leukocyte antigen (HLA) donor characteristics would be further scrutinized, with a view that optimizing them would improve transplant outcomes.

Chapter 2's systematic review is the first to comprehensively identify all clinically relevant donor characteristics that influence adult allogeneic hematopoietic stem cell transplant outcomes. This review identified traditional donor characteristics and a heterogeneous group of novel donor characteristics. Unsurprisingly there were more identified studies within the traditional characteristics, while there were relatively fewer studies assessing novel donor characteristics

Randomized controlled clinical trials are considered by many researchers as the strongest level of evidence; there were no randomized controlled trials (RCTs) identified by the systematic review. The majority of studies were retrospective cohort studies,

predominantly based on institutional databases. Overall, the quality of studies was good when the Newcastle-Ottawa Scale was employed to assess study quality. Hematologic malignancies remain relatively rare diseases, where allogeneic hematopoietic stem cell transplants remain part of a treatment strategy. Further, pertinent transplant outcomes (e.g. overall survival, relapse, graft versus host disease) are relatively slow to accrue. Consequently, randomized controlled trials (RCTs) are logistically difficult to organize in this field. An example of a potential randomized controlled trial (RCT) would be to compare an "older" human leukocyte antigen (HLA) matched related donor with a "younger" matched unrelated donor (rationale discussed in Chapter 1).

All the identified studies by the systematic review sought to demonstrate an association between a variety of transplant outcomes and the donor characteristic(s) under review. Although most studies "controlled" for other relevant factors that may influence transplant outcomes, there were many that did not. Furthermore, the "adjusted" odds/hazard ratios were adjusted for a heterogeneous group of variables. There was no consistent set of variables that were routinely "adjusted" for, potentially biasing the results of the studies. Consequently, it is inherently difficult to compare outcomes across studies. Perhaps in the future, the transplant research community should insist that the results of such association studies be adjusted for a defined set of variables. This would markedly enhance the validity of the studies. More importantly, this would allow more robust systematic reviews/meta-analysis to be conducted.

An example of a meta-analysis was also carried out (Chapter 2) to demonstrate how data could be "pooled" to arrive at summary measures. In this instance, the use of a related donor compared with an unrelated donor results in an increased incidence of

disease relapse but less incidence of graft versus host disease. Importantly, the overall survival outcomes were not significantly different between a related or unrelated donor. This result could suggest that with better human leukocyte antigen (HLA) matching techniques, the difference between a human leukocyte antigen (HLA) related or unrelated donor is less pronounced.

Canadian health care professionals involved in Adult Allogeneic Hematopoietic Stem Cell Transplantation is relatively small and is represented by 13 Transplant centers. These professionals consisting of physicians, nurses, laboratory technicians and others are highly collegial; they are members of the Canadian Bone Marrow Transplant Group (CBMTG). The Canadian Bone Marrow Transplant Group (CBMTG) is involved in the education, conduct of clinical trials, guidelines and organizing meetings for the Canadian Bone Marrow Transplant community.

Commonly, there may be more than one potential stem cell donor available. The selection of an ideal donor for transplant is a complex process where physicians are primarily involved in the selection process. However, other key members of the transplant team may also play a role. It is unclear which donor characteristics are considered important in clinical practice. Further, it is unknown whether novel donor characteristics are commonly considered in practice. It is not known what relative value, Canadian allogeneic hematopoietic stem cell transplant physicians will place on the different donor characteristics. Finally, the survey suggests that novel donor characteristics are not used in routine clinical practice; no novel characteristics identified by the systematic review were among the top 5 characteristics considered important by Canadian Bone Marrow Transplant Group (CBMTG) members.

A conjoint analysis was carried amongst Canadian Bone Marrow Transplant Group (CBMTG) members as detailed in Chapter 4. Conjoint analysis with its foundation in mathematical psychology and economics, is a method that has been used to estimate relative values individuals place on goods or services. Indeed, it has been increasing used in health care where it has been used in a variety of health related studies demonstrating reliability as well as validity.

In chapter 4, the conjoint analysis aimed to describe the relative importance Canadian Bone Marrow Transplant Group (CBMTG) members place on 4 donor characteristics apart from human leukocyte antigen (HLA) compatibility. This analysis was facilitated by the preceding survey in Chapter 3; the 4 most important donor characteristics were represented in the conjoint analysis. A hypothetical clinical scenario was developed and used to allow Canadian Bone Marrow Transplant Group (CBMTG) members to choose between donors with differing donor characteristics. There could have been a total of 16 possible combinations of donor characteristics leading to 8 discrete choice scenarios, but an orthogonal fractional design was employed to reduce the number of choice scenarios to 5 (Chapter 4).

It was clear from the conjoint analysis that a related donor was strongly preferred by Canadian Bone Marrow Transplant Group (CBMTG) members (hazard ratio (HR) 2.97). However, the results for donor age, gender and CMV compatibility were counter-intuitive where Canadian Bone Marrow Transplant Group (CBMTG) members appeared to prefer older female donors. These results occurred because Canadian Bone Marrow Transplant Group (CBMTG) members were not willing to trade-off attributes: a requirement for conjoint analysis to give meaningful results. Specifically, the majority of

respondents favored donor relatedness and cytomegalovirus (CMV) compatibility over gender and age. Thus, it was not possible to properly and adequately analyze differences in donor gender and age. The unwillingness to trade could not have been foreseen in advance and lead to the main limitation of the conjoint analysis.

Several lessons were learnt from the conduct of this thesis: Firstly, in the absence of any randomized controlled trials there is no strong evidence (Level 1) that any donor characteristic influences allogeneic hematopoietic stem cell transplantation. Nevertheless, numerous observational data would lend support for previously described associations. Secondly, novel characteristics although increasingly studied academically, remain infrequently considered by the Canadian Hematopoietic Stem Cell Transplant community. Thirdly, although conjoint analyses are useful tools in health care research, there are limitations when respondents are unwilling to "trade-off" attributes. Finally, a related donor (apart from human leukocyte antigen (HLA) compatibility) remains the foremost consideration by the Canadian Hematopoietic Stem Cell Transplant community.

There will be several avenues for future study in this area: Formal meta-analyses of each individual donor characteristic that would influence transplant outcomes can be carried out. A more comprehensive survey and conjoint analyses can be performed to illicit preferences of health care professionals involved in adult hematopoietic stem cell transplantation. Potential survey populations explored include the transplant communities in the U.S. (American Bone Marrow Transplant Registry and National Bone Marrow Donor Program), Europe (European Society of Hematology) and Australia/Asia. Canadian database studies (e.g. use of the Ottawa Hospital BMT database) could be carried out to look for associations between donor variables and outcomes. Ultimately,

the derivation and validation of a clinical prediction rule will formally lead to an optimal strategy to help choose the "best" adult allogeneic hematopoietic stem cell transplant donor.

Appendix 1: Survey of CBMTG members (web pages)

Figure 1: Section 1 (Survey invitation)

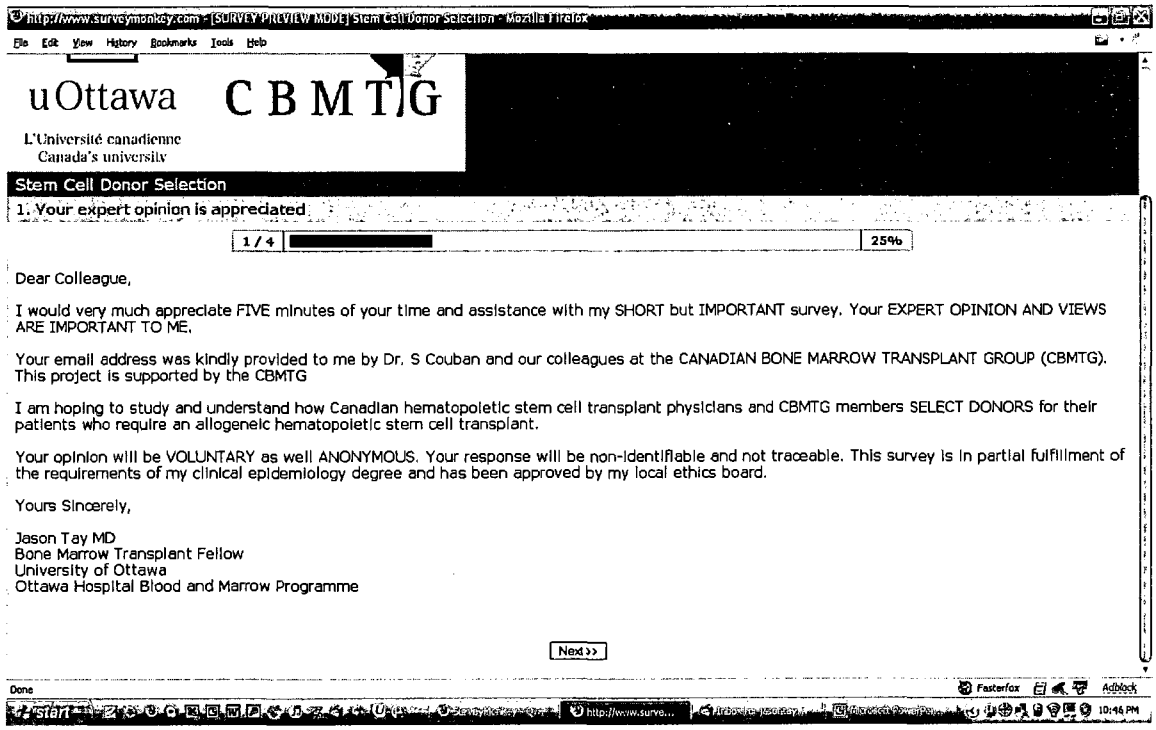


Figure 2: Section 2(Respondent Demographics)

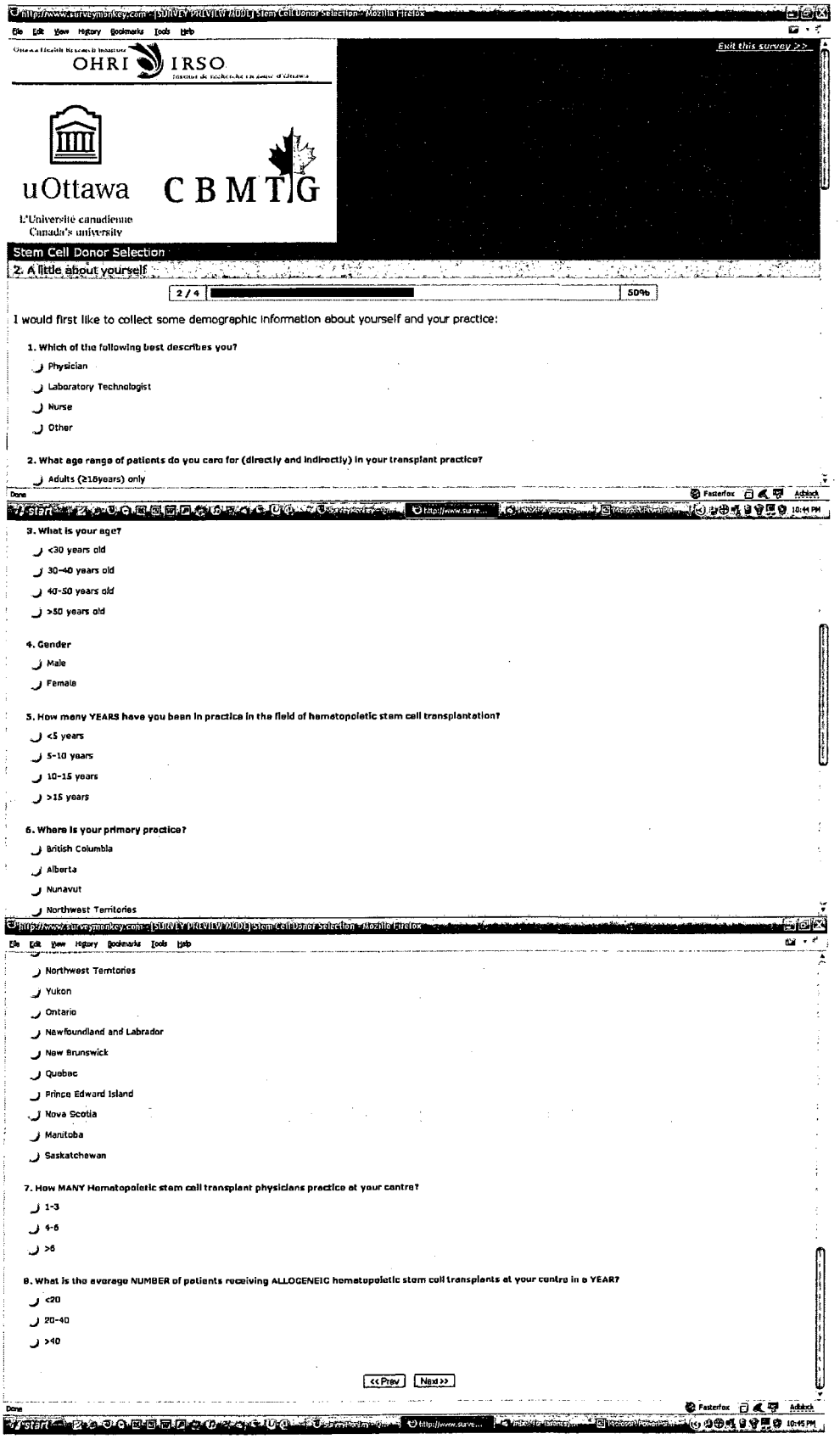


Figure 3: Section 3 (List of Donor Characteristics)

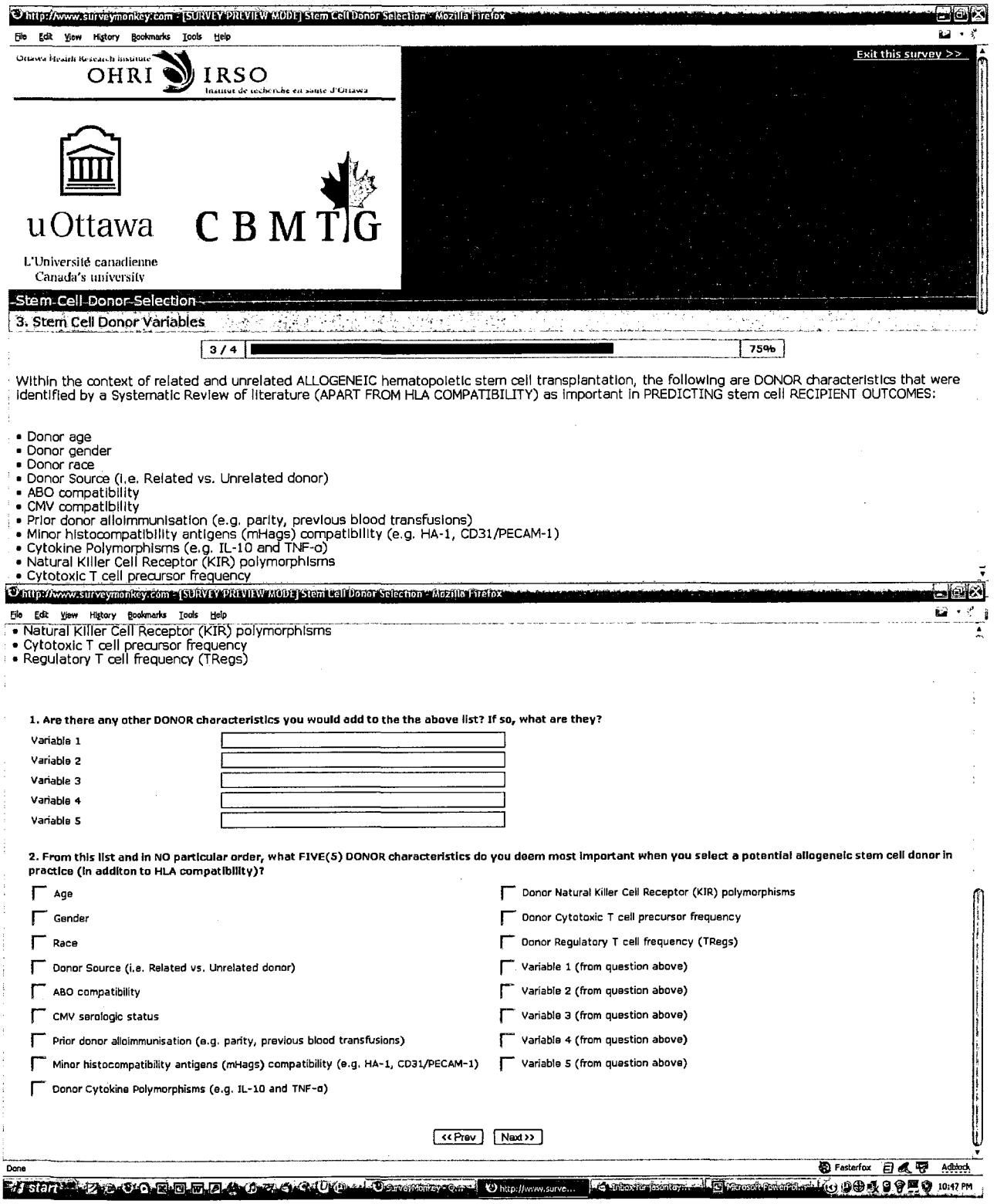
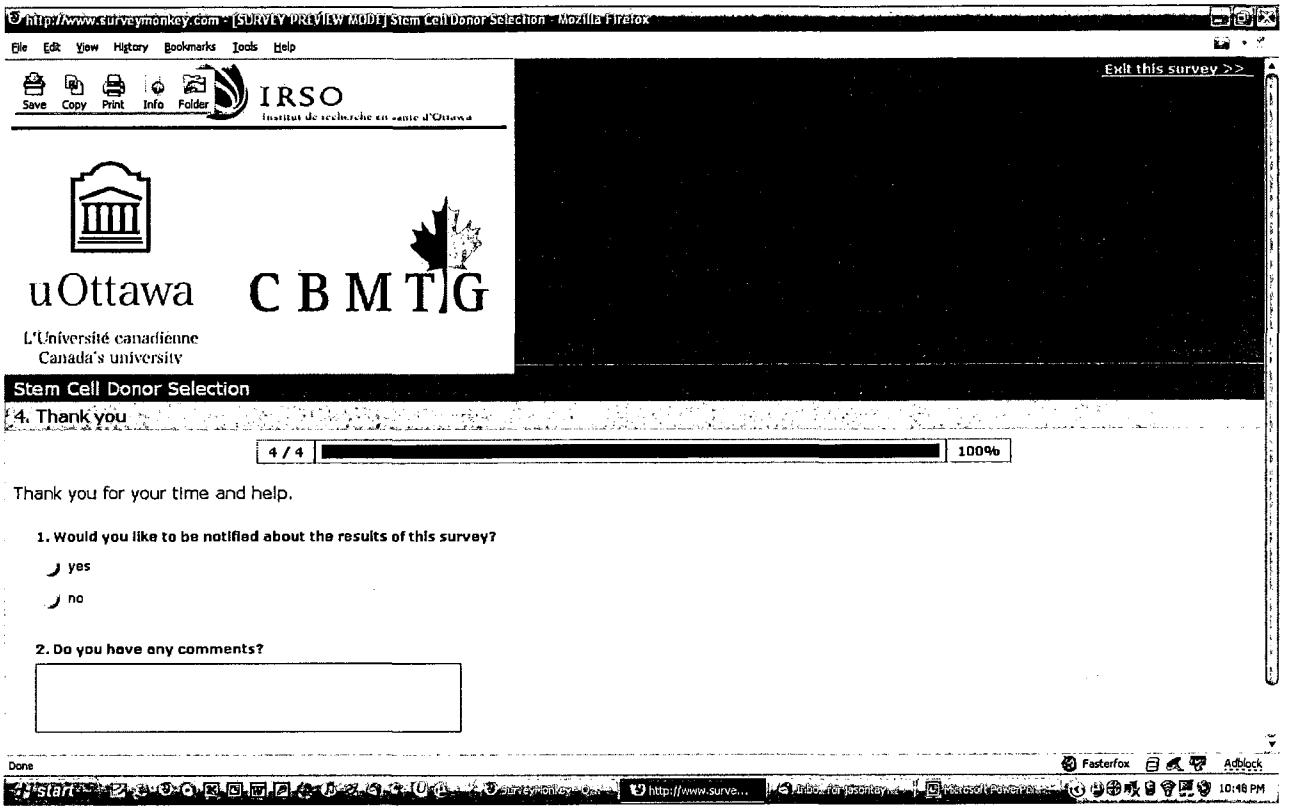


Figure 4: Section 4(Thank you Note)



Appendix 2: Conjoint Analysis of CBMTG members (web pages)

Figure 1: Invitation-Page 1

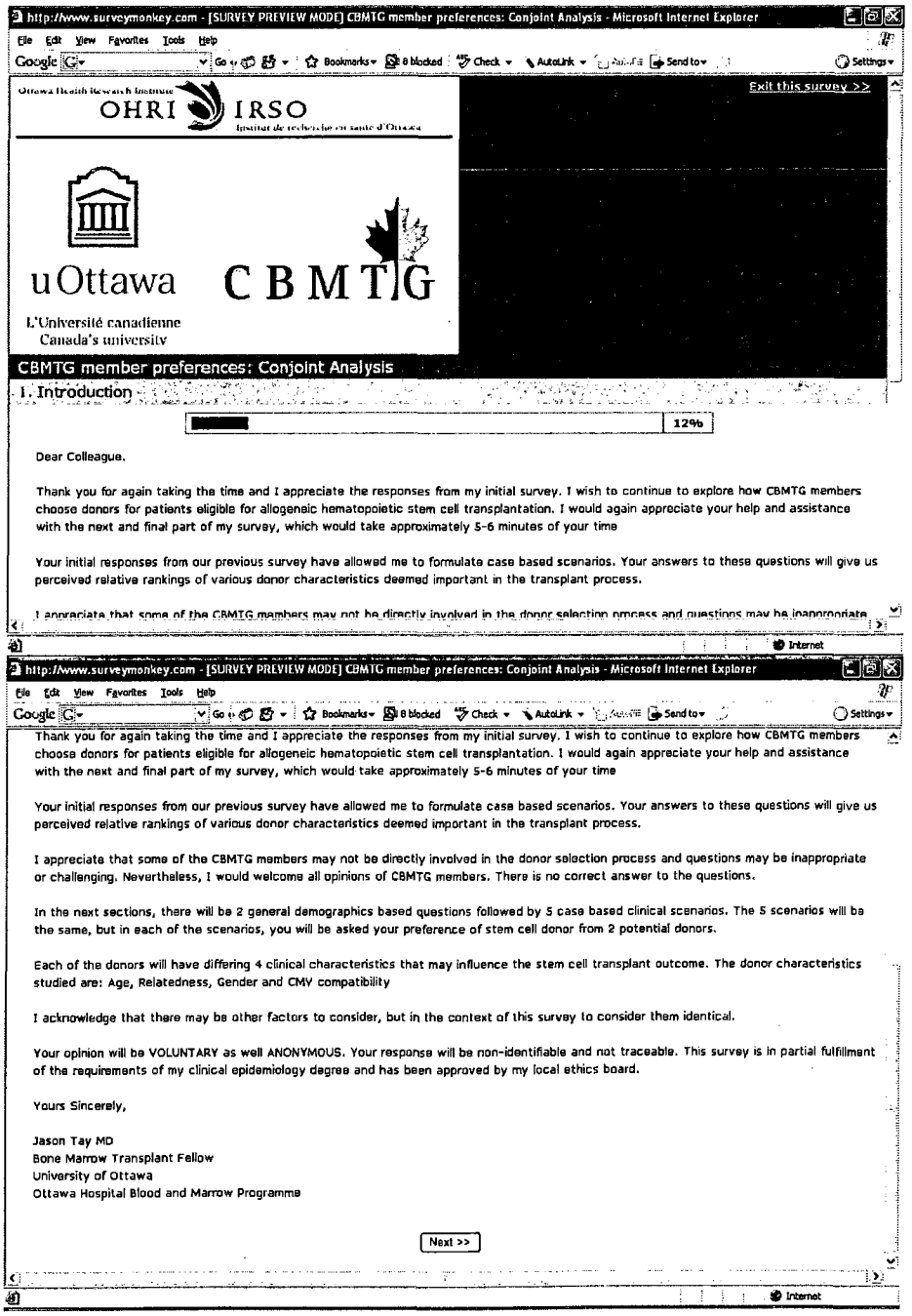


Figure 2: Demographics-Page 2

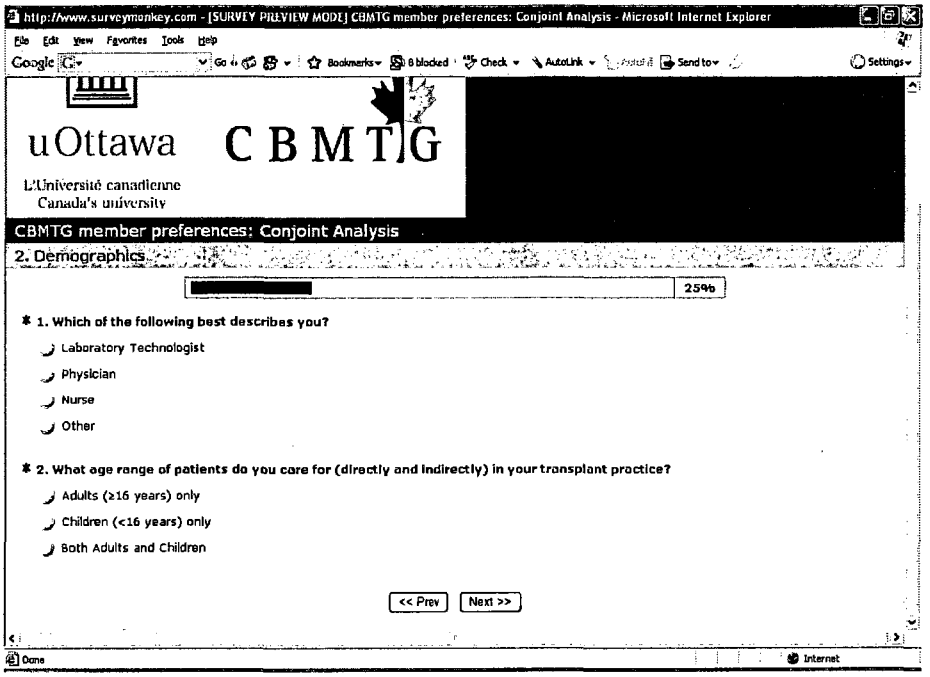


Figure 3: Clinical Scenario1-Page 3

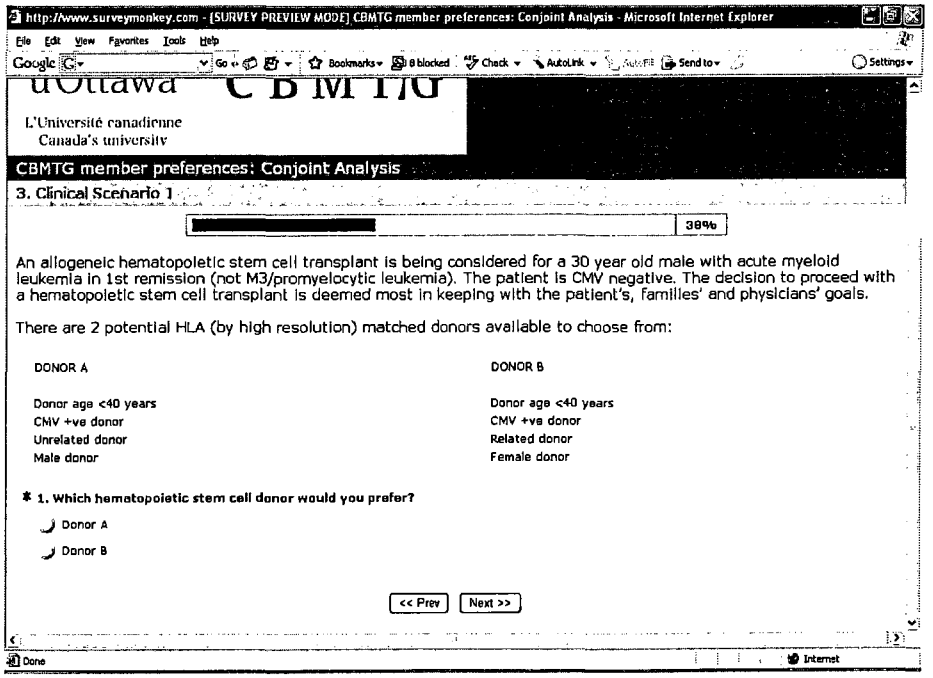


Figure 4: Online Conjoint Analysis-Page 4

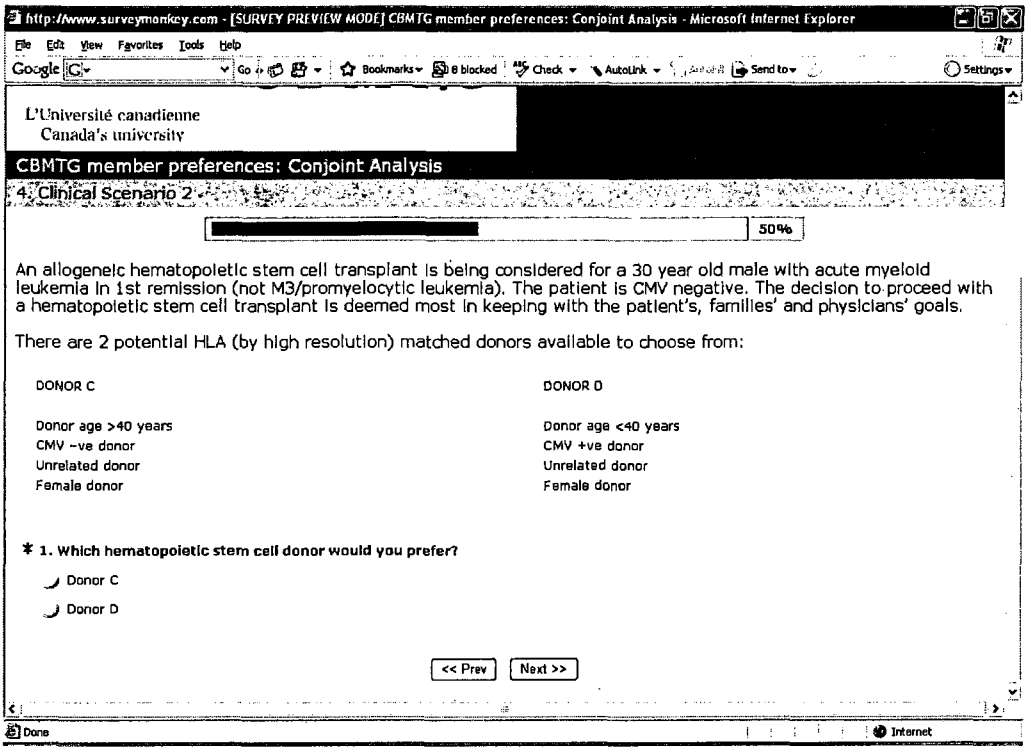


Figure 5: Online Conjoint Analysis-Page 5

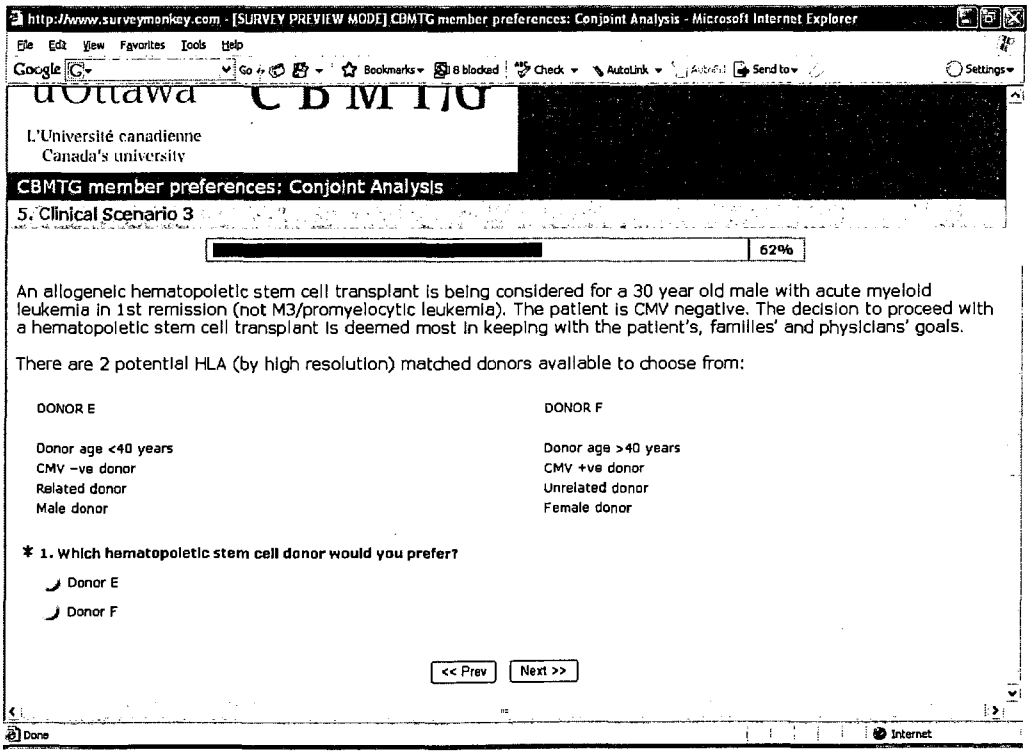


Figure 6: Online Conjoint Analysis-Page 6

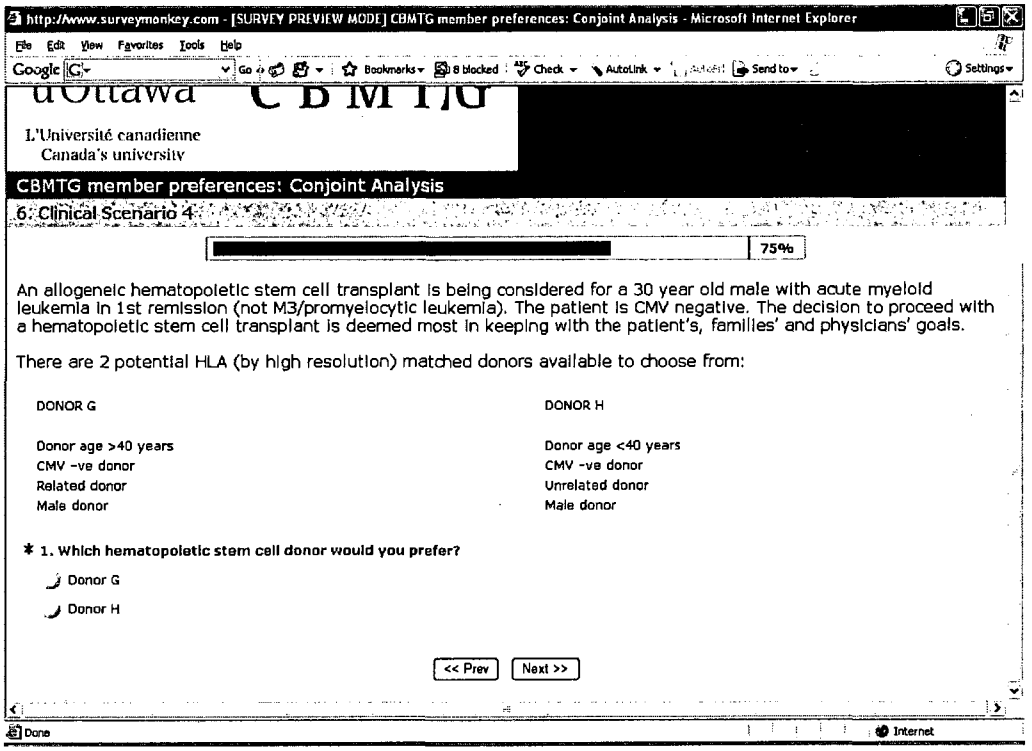
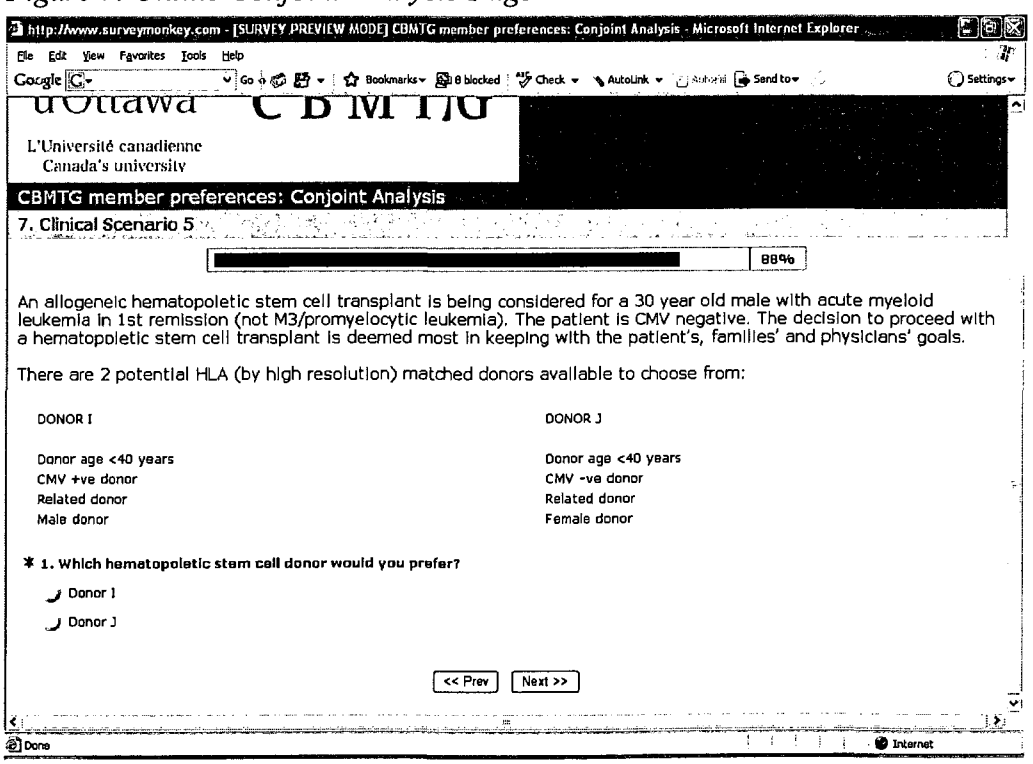


Figure 7: Online Conjoint Analysis-Page 7



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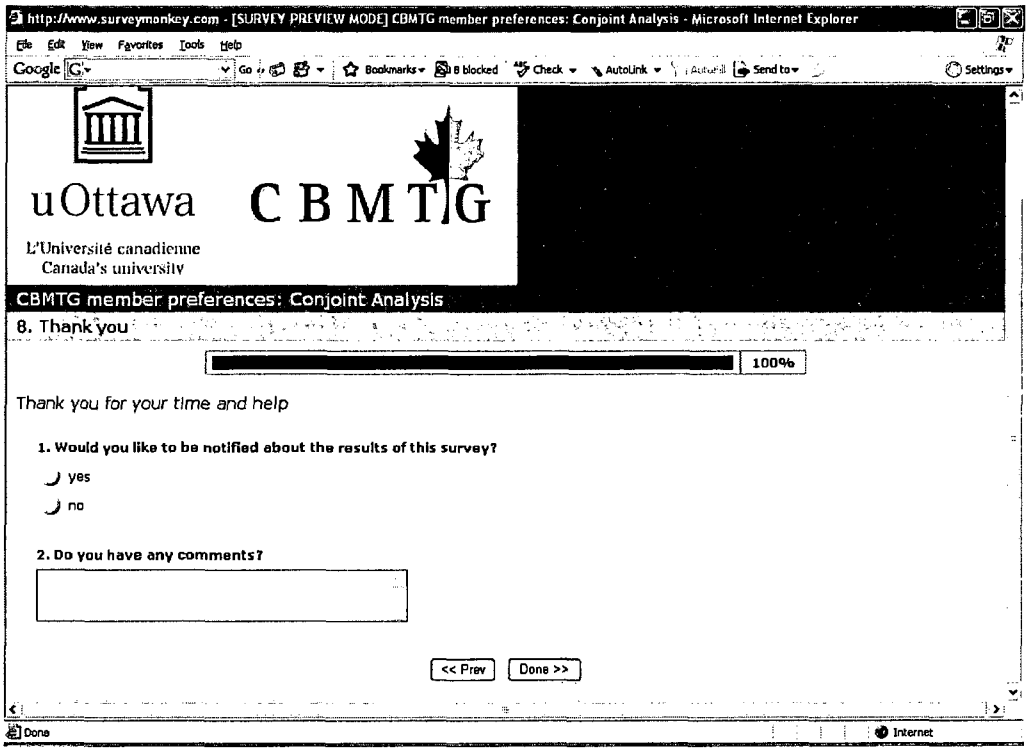

Appendix 3

Summary of probit model for responses from CBMTG members

Attribute	Coefficient	Standard Error	Wald $\chi 2$ p Value*	Hazard Ratio
Age	**-1.19**	**0.22**	**<0.0001**	**0.30**
Gender	**-0.91**	**0.16**	**<0.0001**	**0.40**
Relatedness	**1.19**	**0.16**	**<0.0001**	**3.29**
CMV	**-0.03**	**0.19**	**0.86**	**0.97**

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