An observational study investigating the objective and subjective impact of a structured gynaecology service for women who have undergone allogeneic haematopoietic stem cell transplant.

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Abstract

Hypothesis
The hypothesis for this study is that the provision of consultative gynaecological care and the delivery of gynaecological information to women undergoing allogeneic stem cell transplant will mean a better informed and better satisfied female transplant population. The specific aims of the study were:

1. To determine the type of information women have been given about vaginal GVHD, sexuality and fertility before they had their transplants.

2. To discover the kind of information women would like to receive about these issues before and after HSCT.

3. To assess if a gynaecology service designed especially for women undergoing HSCT is helpful with early detection and treatment of vaginal graft versus host disease.

4. To assess if a gynaecology service designed especially for women undergoing HSCT is beneficial when fertility and sexuality issues arise.

5. To discover whether the gynaecology services being provided meet the emotional, psychosocial and physical needs of the woman undergoing allogeneic stem cell transplantation.

Method
This is a retrospective observational study in which women were recruited in the following groups:

- Eligible women from Wellington Hospital who had an allogeneic haematopoietic stem cell transplant (HSCT) from 1999 to July 2004 and had no exposure to a gynaecology service.

- Eligible women from Wellington Hospital who had an allogeneic HSCT from 1 August 2004 who had exposure to a gynaecology service for HSCT recipients.
Eligible women from the Royal Melbourne Hospital, Australia who had an allogeneic HSCT after January 1999. This group had been exposed to a gynaecology service. This group was split into two cohorts following the date lines of the Wellington cohorts. The first cohort was transplanted between 1999 and July 2004 and the second was transplanted after 1st August 2004.

This was a questionnaire-based study that asked questions about gynaecology services, genital graft versus host disease, sexuality and fertility. There was a response rate of 63% with 72 women signing consent and completing the questionnaire.

**Conclusion**

The results of the study showed that the provision of a gynaecology service for women pre and post HSCT was important in diagnosing and treating genital GVHD and for addressing post HSCT issues around sexuality and fertility. Significant numbers of women had problems with genital GVHD and sexuality post HSCT and better resolution of symptoms was seen in the cohorts that had exposure to gynaecology services. Women who were under the care of a structured and comprehensive HSCT related gynaecology programme were more informed and satisfied than women who did not have access to such a programme.

The study results showed that the information and education about genital GVHD, sexuality and fertility currently provided for women needs to be significantly improved and a combination of written material and verbal information developed and made available.
Preface

This research-based thesis would not have been possible had it not been for the women who participated in the study. The questionnaire asked women about very personal and intimate issues. They responded openly and enthusiastically and were very encouraging of the research. I hope that the results of this study will serve to improve the information and services provided for this very special group of women.

Grateful thanks must go to my supervisors Associate Professor John Carter and Associate Professor David Ritchie. They have helped me to get to this point, despite very busy work schedules, by providing direction, encouragement, critically reviewing trial documentation and being very patient. This thesis would not have been completed without their advice and support.

I would like to thank Yvonne Panek-Hudson for encouraging and supporting me, for her critical reading of material and for being a contact point for Melbourne participants. Her passion for her job and for the women that she supports is inspiring. This research could not have been done without her.

I would also like to thank the following people: Professor Jeff Szer for his support of my study and for helping me to introduce the study to the Melbourne participants, Dr Gordon Purdie for his statistical advice, Dr Dalice Sim for guiding me through and helping me understand the statistical aspects of this study, Monica O’Reilly for generously allowing me to read her Masters’ thesis and Teresa Maguire for her diligent proof reading of this thesis.

Thanks must go to the large support team of colleagues and friends who have helped and supported me to get through this occasionally torrid journey. They have listened, cajoled, assembled study packs and have been there for me when I have needed them.

Grateful thanks also go to the Wellington Division, Cancer Society of New Zealand and the Genesis Oncology Trust for their generous financial support of
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<td>BM</td>
<td>Bone marrow</td>
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<td>BMT</td>
<td>Bone marrow transplant</td>
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<td>DLI</td>
<td>Donor lymphocyte infusion</td>
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<tr>
<td>FSH</td>
<td>Follicle stimulating hormone</td>
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<tr>
<td>GI</td>
<td>Gastrointestinal</td>
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<td>GVHD</td>
<td>Graft versus host disease</td>
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<td>GVL</td>
<td>Graft versus leukaemia</td>
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<td>HLA</td>
<td>Human leukocyte antigen</td>
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<td>HREC</td>
<td>Health Research Ethics Committee</td>
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<td>HRT</td>
<td>Hormone replacement therapy</td>
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<td>HSCT</td>
<td>Haematopoietic stem cell transplant/ation</td>
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<td>LH</td>
<td>Luteinising hormone</td>
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<tr>
<td>PBSC</td>
<td>Peripheral blood stem cells</td>
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<td>RIC</td>
<td>Reduced intensity conditioning</td>
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<td>SFQ</td>
<td>Sexual functioning questionnaire</td>
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Background

Introduction
This research-based thesis is investigating the impact that the involvement of a haematopoietic stem cell transplant (HSCT) specific gynaecology programme has for women undergoing this procedure. The study hypothesis is that the provision of consultative gynaecological care and the delivery of gynaecological information to women undergoing allogeneic stem cell transplant will mean a better informed and better satisfied female HSCT population. The specific aims of the study are:

1. To determine the type of information women have been given about vaginal graft versus host disease (GVHD), sexuality and fertility before they had their transplants.

2. To discover the kind of information women would like to receive about these issues before and after HSCT.

3. To assess if a gynaecology service designed especially for women undergoing HSCT is helpful with early detection and treatment of vaginal graft versus host disease.

4. To assess if a gynaecology service designed especially for women undergoing HSCT is beneficial when fertility and sexuality issues arise.

5. To discover whether the gynaecology services being provided meet the emotional, psychosocial and physical needs of the woman undergoing allogeneic stem cell transplantation.

In this chapter I will give a brief introduction to allogeneic HSCT as a treatment modality for both malignant and non-malignant conditions. I will then give a brief introduction to GVHD while the rest of the chapter reviews the literature around female genital GVHD and about sexuality and fertility issues for women post HSCT.
There is a large body of work regarding sexuality and fertility in women who have been diagnosed and treated for breast and gynaecological cancers. My literature review presented in this thesis focuses on women undergoing allogeneic HSCT and only refers to solid tumours if there is no HSCT literature in a particular area.

**Haematopoietic Stem Cell Transplantation**

Haematopoietic stem cell transplantation, also commonly known as bone marrow transplantation (BMT), has been a treatment available to patients for approximately fifty years. Georges Mathé in France and E. Donnell Thomas in Seattle, USA, performed the first BMTs in the 1960s on patients with end stage acute lymphoblastic leukaemia (Appelbaum, 2007; Jansen, 2005). HSCT was initially used for patients with haematological malignancies, who had exhausted all other treatment options available to them. It has progressed rapidly to become a treatment and cure for various haematological conditions both malignant and non-malignant (Devine & DeMeyer, 2003; Wingard, 2007). Despite advances in this therapy, the process of HSCT is a major undertaking that has significant morbidity and mortality associated with it.

There are two main types of HSCT: autologous and allogeneic. Autologous HSCT is where haematopoietic stem cells are collected from the recipients (patients) themselves, stored and re-infused at a later date after high dose chemotherapy (with or without radiotherapy) has been administered. Allogeneic HSCT is where stem cells are collected from another person, usually a matched sibling or unrelated donor, and infused into the recipient after immunosuppressive conditioning therapy has been administered (Devine & DeMeyer, 2003). The critical difference between autologous and allogeneic HSCT is the immunological differences that exist between an allogeneic donor and the treated recipient. This is the fundamental cause of GVHD (see below) and therefore my research project and the following introduction and discussion concerns allogeneic HSCT only.

The aim of allogeneic HSCT in both malignant and non-malignant conditions is to cure the patient by eradicating their bone marrow and immune system and
replacing them with genetically different but Human Leukocyte Antigen (HLA) matched haematopoietic stem cells from another person (Devine & DeMeyer, 2003). The process of HSCT begins in most cases with the administration of moderate to high doses of chemotherapy, with or without radiotherapy. This is known as conditioning and is administered to the recipient over a two to eight day period depending on the regimen used. The aims of conditioning are to eradicate the underlying disease, to suppress the recipient’s immunity to prevent graft rejection and to create microenvironmental “space” for the donor haematopoietic stem cells to engraft (Devine & DeMeyer, 2003; Gratwohl, 2008; Schmit-Pokorny, 2007; Wingard, 2007). The haematopoietic stem cells collected from the donor are infused at the end of conditioning on a day universally known as Day 0. After Day 0 it takes approximately 10 – 28 days for the new stem cells to engraft and generate new mature leukocytes. During this time the recipient is at risk from life threatening infection, bleeding and organ damage from the high doses of therapy used (Schmit-Pokorny, 2007).

Once the new stem cells begin to grow (engraft), the patient’s blood counts start to normalise. Patients become independent of blood and platelet transfusions and most infective complications usually start to resolve. From about this time, the patient is at risk from a condition called graft versus host disease (GVHD) in which the transplanted lymphocytes see their new environment as foreign and start to attack it (Anders & Barton-Burke, 2007).

Figure 1: Timeline of haematopoietic stem cell transplant
**Graft Versus Host Disease**

GVHD is a common complication of allogeneic HSCT occurring in 30 – 80% of patients depending on a number of risk factors (see Table 1) (Abinun & Cavet, 2007; Anders & Barton-Burke, 2007; Antin & Yolin Raley, 2009; Devergie, 2008; Filipovich et al., 2005). It is caused by interactions between T-cells in the donor graft and antigen presenting cells in the recipient. The T-cells recognise the new HSCT recipient as foreign and initiate an immune attack that results in damage to various organs in the body (Anders & Barton-Burke, 2007; Devergie, 2008). GVHD has traditionally been divided into two types: acute and chronic. Acute GVHD has historically been defined as GVHD that occurs prior to 100 days post HSCT while chronic GVHD has been defined as GVHD occurring after 100 days post HSCT. The two forms of GVHD are however very different syndromes and with a greater understanding of GVHD pathophysiology, this separation of acute and chronic GVHD by date is now less commonly used. Acute GVHD typically occurs shortly after engraftment and generally affects the skin, gastrointestinal (GI) tract and the liver (Abinun & Cavet, 2007; Anders & Barton-Burke, 2007; Filipovich, et al., 2005; Vogelsang, Lee, & Bensen-Kennedy, 2003). Chronic GVHD generally occurs later in the post HSCT period, usually presenting within three years post HSCT. It has features resembling spontaneously occurring autoimmune disorders such as scleroderma, primary biliary cirrhosis, Sjögren syndrome, chronic immunodeficiency, immune cytopenias and bronchiolitis obliterans. It may affect any organ system but most commonly affects the liver and biliary canilculi, skin, conjunctiva, oral/buccal mucosa and the glandular structure of the GI tract (Filipovich, et al., 2005; Vogelsang, et al., 2003).
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<td>HLA disparities between donor and recipient</td>
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<td>Use of peripheral blood stem cells (PBSC) versus bone marrow (BM)</td>
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<td>Matched unrelated donor (MUD)</td>
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<td>Increased donor and recipient age</td>
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<td>Female donor to male recipient</td>
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<td>Cumulative blood transfusions</td>
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<td>Donor Lymphocyte Infusion (DLI)</td>
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<td>Grade II or above acute GVHD for the development of chronic GVHD</td>
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The incidence of chronic GVHD is rising in part due to the increasing use of donor peripheral blood stem cells (as opposed to bone marrow) as a stem cell source, the older age of recipients, the use of donor lymphocyte infusions and the increased use of mismatched and unrelated donors (Flowers & Deeg, 2009; Vogelsang, et al., 2003). Compared to acute GVHD, chronic GVHD in allogeneic PBSC recipients may be more protracted, less responsive to therapy and may have more involvement with the female genitalia (Flowers et al., 2002; Vogelsang, et al., 2003).

**Pathophysiology**

Current thinking about the development of GVHD is that it is a three-step process. The first step is the effect of the conditioning therapy causing tissue damage that results in the release of large amounts of inflammatory cytokines. The second step is T-cell activation – the donor T-cells interact with recipient antigen presenting cells and this leads to T-cell expansion. The third step is the cellular and inflammatory effector stage where there is the generation of cytotoxic effectors that may lead to end-organ damage (Deeg & Flowers, 2009; Devergie, 2008).

The pathophysiology of chronic GVHD is poorly understood in comparison to acute GVHD (Vogelsang, et al., 2003). One hypothesis arises from the similarity of chronic GVHD to some autoimmune diseases. It suggests that chronic GVHD may be largely mediated by autoimmune T-cells (donor T-cells that recognise antigens shared by both donor and recipient which persist due to
impaired mechanisms of regulation) causing tissue damage by direct infiltration and dysregulation of various cytokines. The thymus is a target in the setting of acute GVHD and for those patients that have had preceding acute GVHD, the suggestion is that the damaged thymus may lead to chronic GVHD by failing to delete autoreactive T-cells and failing to produce immunoregulatory T-cells (Bhushan & Collins, 2003; Vogelsang, et al., 2003).

**Graft Versus Leukaemia Effect**

GVHD is a negative consequence of allogeneic HSCT but it is in fact closely linked with the graft versus leukaemia (GVL) effect that is in part responsible for the success of an allogeneic HSCT. The study of allogeneic HSCT has revealed that donor lymphocytes are able to attack any residual malignant cells and are able to induce a remission. This discovery forced a change in thought from an HSCT just being a rescue of the recipient’s bone marrow post high dose conditioning to a procedure that has an immunotherapeutic effect (Weiden et al., 1979). The GVL effect has allowed the introduction of reduced intensity conditioning (RIC) transplants that rely on the GVL effect rather than the high dose conditioning regimen to eliminate the malignant cells. RIC transplants have a lower toxicity profile meaning that those of older age and with co-morbidities have greater access to this therapy. Despite the lower toxicity profile of RIC HSCTs, the incidence of acute and chronic GVHD remains comparable to myeloablative HSCT (Abinun & Cavet, 2007; Anders & Barton-Burke, 2007; Devergie, 2008).

**GVHD of the Female Genital Tract**

**Background**

GVHD (both acute and chronic) can affect the female genital tract. It may affect any part of the vulva or vagina causing alopecia, pain, excoriation, atrophy, inflammation, adhesion and stenosis (da Silva Lara et al., 2010; Lafond et al., 2011; Spinelli et al., 2003; Stratton et al., 2007; Zantomio et al., 2006). It has the potential to have a profound impact on a woman’s quality of life and sexual functioning post HSCT both in the short- and long-term. Evidence shows that early detection and treatment are essential to minimise the impact of genital GVHD by preventing progression (Spinelli, et al., 2003; Zantomio, et
al., 2006), however women seldom self report issues about sexual functioning to their physicians meaning that genital GVHD often goes undiagnosed and untreated. Genital GVHD is not well described in the literature, which may mean that the true incidence is unknown and that the best treatment for this condition is still uncertain (Stratton, et al., 2007).

Corson et al (1982) were the first to describe genital GVHD. They described five women from a group of 175 patients from the Seattle Fred Hutchinson BMT programme who were the first to be treated with allogeneic HSCT. These five women had developed chronic GVHD post HSCT and went on to develop genital complications 170 – 805 days post HSCT. Symptoms included loss of pubic hair, vaginal inflammation, vaginal adhesions, labial and vaginal atrophy and complete stenosis of the vagina.

Following the Seattle report there was a paucity of literature addressing genital GVHD until 1990. Schubert et al (1990) studied 44 women post allogeneic HSCT to determine the aetiology and frequency of gynaecological abnormalities in long-term survivors. Thirty-five of these women had abnormal gynaecological findings including tissue atrophy, loss of pubic hair, small uterine and cervical size, vaginal stenosis and atrophic vulvovaginitis.

Between 1990 and 2003 the literature about genital GVHD largely consisted of case reports (Anguenot et al., 2002; DeLord, Treleaven, Shepherd, Saso, & Powles, 1999; Gossett, Montz, & Bristow, 2002; Hayes & Rock, 2002; Jain & Henry, 2001; Louis-Sylvestre, Haddad, & Paniel, 2003; Yanai, Shufaro, Or, & Meirow, 1999). There were, however, brief mentions of genital GVHD in HSCT textbooks (Bradbury, 1994; Caudell, 1997). In 2003 Spiryda et al presented the largest case series of the time about women treated for genital GVHD. Later that year Spinelli et al published the results of a retrospective study done at their institution. They studied the medical notes of 213 women who received allogeneic stem cell transplants between April 1980 and November 1999 in order to evaluate the incidence and severity of genital tract GVHD. The study showed that almost 25% of their patient population appeared to have genital involvement with GVHD with a subset of these patients having severe disabling genital GVHD. Since that time case reports have continued to
appear in the HSCT literature (Costantini et al., 2004; da Silva Lara, et al., 2010; Norian & Stratton, 2008; Rodolakis, Thomaskos, Harhalakis, Iconomou, & Antsaklis, 2007; Tauchmanovà et al., 2004). Recently, however, more has been published regarding the diagnosis, treatment and outcomes of genital tract GVHD (Costantini, Di Capua, Bosi, & Spinelli, 2006; da Silva Lara, et al., 2010; Stratton, et al., 2007; Zantomio, et al., 2006). These initial reports and more detailed findings are now reflected in the more frequent appearance of medical and nursing guidelines on the education of women regarding the onset and impact of genital GVHD.

**Incidence**

Female genital GVHD has been reported in 25 – 47.5% of long term survivors of allogeneic stem cell transplantation (Spinelli, et al., 2003; Zantomio, et al., 2006) however the literature suggests that this problem has been underreported (Anguenot, et al., 2002; Spiryda, Laufer, Soiffer, & Antin, 2003; Stratton, et al., 2007; Tauchmanovà, et al., 2004; Zantomio, et al., 2006).

Gynaecological complications after treatment for cancer have been described prior to the availability of allogeneic HSCT as a treatment modality. Shortening of the vagina, vaginal stenosis and adhesions have been well reported in the radiation therapy literature in women who have had pelvic radiation therapy for gynaecological cancers (Abitol et al. 1972 and Pitkin et al. 1965) cited in Bergmark, Ävall-Lundqvist, Dickman, Henningson, & Steineck, 1999; Grigsby et al., 1995; Lancaster, 2004). Ovarian failure had been documented in patients who had received chemotherapy for Hodgkins Lymphoma and for autoimmune disorders (Chapman et al, 1979 and Warne et al, 1973 cited in Corson et al., 1982). Ovarian failure is a common occurrence in women who have had high dose chemotherapy or radiation therapy as part of the conditioning regimens prior to autologous and allogeneic HSCT (Grigg, McLachlan, Zajac, & Szer, 2000; Meirow & Nugent, 2001; Spiryda, et al., 2003). However, post HSCT ovarian failure does not appear to be the main cause of genital symptoms in women who have undergone allogeneic HSCT. In a study done by Stratton et al (2007), the commonest cause of vullovaginal symptoms in the post HSCT population was chronic GVHD. In their study, all
patients who had symptoms of genital GVHD had active chronic GVHD in other body systems such as the skin, eyes and mouth. Spinelli et al (2003) report that 73% of the women in their study who were diagnosed with genital GVHD had concurrent chronic GVHD in other organ systems. Zantomio et al (2006) report that 90% of their cohort of women with genital GVHD had other organ involvement with GVHD with 62% of patients classed as having extensive GVHD. Spiryda et al (2003) reported a case series from their institution. They found that although there was a relationship between active chronic GVHD in other organ systems and genital GVHD, the severity of genital lesions did not correlate with the severity of chronic GVHD occurring in other organs. Some women had severe genital lesions with only mild chronic GVHD at other sites.

Costantini et al (2004) found in their case series of eight women that seven had chronic GVHD involving the oral mucosa. This was a small series, however other authors have seen the combined involvement of oral and genital GVHD. Zantomio et al (2006) found that of the 29 women with genital GVHD, 79.3% of them had evidence of concurrent oral chronic GVHD and Stratton et al (2007) found that 89.7% of their patients with genital GVHD also had oral GVHD. The mucosal linings of the mouth and vagina both consist of epithelium which is non-keratinised, stratified and squamous (Standring, 2005). It would appear that there may be a link between these two sites of chronic GVHD. In their report from the chronic GVHD pathology working group, Shulman et al (2006) bundle together the oropharynx and the vulva as having the same histologic appearances on biopsy as each other in the context of chronic GVHD. It may be advisable for clinicians who see chronic GVHD present in a woman’s mouth, to investigate her sexual functioning and genitalia more thoroughly in order to instigate treatment early if genital GVHD is found.

**Presentation and Assessment of Genital GVHD**

Women may present to their medical provider with a number of symptoms. The most common symptom appears to be dyspareunia and difficulty with penetration followed by vaginal dryness and pelvic pain. Other symptoms may include vulval pain, vulval pruritis and burning with micturition (Anguenot, et
al., 2002; Corson, et al., 1982; Costantini, et al., 2004; DeLord, et al., 1999; Hayes & Rock, 2002; Jain & Henry, 2001; Norian & Stratton, 2008; Rodolakis, et al., 2007; Schubert et al., 1990; Spinelli, et al., 2003; Spiryda, et al., 2003; Stratton, et al., 2007; Tauchmanovà, et al., 2004; Yanai, et al., 1999). One case of asymptomatic genital GVHD was described – at a routine annual gynaecological visit the internal examination was unable to be performed presumably due to atrophy. Further examination at a later date revealed atrophic external genitalia, vaginal stenosis and a foreshortened vagina (Gossett, et al., 2002).

Schubert et al in 1990 found that women rarely talked about their post HSCT sexual difficulties to medical professionals. They found that patients didn’t seek out professional help for their problems as they often assumed that this was an unavoidable post HSCT complication and that treatment options were limited. This has been supported by the literature which describes cases where women have presented late with considerable pathology and advanced stenosing lesions which often required surgical intervention (Anguenot, et al., 2002; Corson, et al., 1982; Costantini, et al., 2004; DeLord, et al., 1999; Gossett, et al., 2002; Hayes & Rock, 2002; Jain & Henry, 2001; Norian & Stratton, 2008; Rodolakis, et al., 2007; Yanai, et al., 1999).

Gynaecological examination of women with gynaecological symptoms post HSCT may reveal dryness, stenosis, foreshortening and occlusion of the vagina; fusion of the labia; vulval alopecia and atrophy; pain, erythema, excoriation and ulceration of the vulva and vagina; and loss of tissue elasticity (Anguenot, et al., 2002; Corson, et al., 1982; Costantini, et al., 2004; DeLord, et al., 1999; Gossett, et al., 2002; Hayes & Rock, 2002; Jain & Henry, 2001; Louis-Sylvestre, et al., 2003; Norian & Stratton, 2008; Rodolakis, et al., 2007; Schubert, et al., 1990; Spinelli, et al., 2003; Spiryda, et al., 2003; Stratton, et al., 2007; Tauchmanovà, et al., 2004; Yanai, et al., 1999; Zantomio, et al., 2006). However the spectrum of GVHD findings may be skewed due to the prevalence of more severe cases of genital GVHD in the published case reports. Few series have collected prospective data, and until recently, many HSCT centres did not
offer planned gynaecological assessment and advice as part of their routine practice.

Time from HSCT to presentation varies greatly with a range of 1 to 201 months post HSCT. It is difficult to tease out the time to onset of symptoms because, as mentioned previously, many women present late once they have advanced symptomatology (Anguenot, et al., 2002; Corson, et al., 1982; Costantini, et al., 2004; DeLord, et al., 1999; Gossett, et al., 2002; Hayes & Rock, 2002; Norian & Stratton, 2008; Rodolakis, et al., 2007; Spinelli, et al., 2003; Spiryda, et al., 2003; Stratton, et al., 2007; Tauchmanovà, et al., 2004; Yanai, et al., 1999; Zantomio, et al., 2006). The average time to presentation appears to be approximately 10 months (Spiryda, et al., 2003).

**Diagnosis and Staging**

Diagnosis of genital GVHD largely relies on clinical examination. In the first instance, differential diagnoses such as infections (yeasts, bacteria, viruses (human papilloma virus) or other gynaecological pathogens) and oestrogen deficiency need to be excluded (Couriel et al., 2006). The symptoms of genital GVHD and those of menopausal genital changes, both natural and induced, may be similar (Spiryda, et al., 2003; Stratton, et al., 2007). On physical examination however, the differences are quite marked and distinctive.

The genital changes of menopause, whether natural or induced, are due to decreased oestrogen levels. The vaginal mucosa becomes dry and pale and the vaginal walls become thin and smooth as the rugal folds become less pronounced. The vagina also becomes shortened and narrowed (Farage & Maibach, 2006; Mehta & Bachmann, 2008; H. D. Nelson, 2008; Norian & Stratton, 2008; North American Menopause Society, 2007; Spinelli, et al., 2003). In genital GVHD the vagina is reddened and inflamed in mild cases progressing to narrowing of the vagina, thickening of the mucosa, reduction in vaginal elasticity, adhesions, and stenosis or complete vaginal closure (Norian & Stratton, 2008; Spinelli, et al., 2003; Spiryda, et al., 2003; Zantomio, et al., 2006). Vaginal adhesions and synechiae are not features of menopause (Spiryda, et al., 2003).
Vaginal adhesions and synechiae are features of vaginal toxicity post radiation therapy (Abitol et al (1972) and Pitkin et al (1965) cited in Bergmark, et al., 1999; Grigsby, et al., 1995; Lancaster, 2004), however once the acute toxicity phase post radiation therapy has passed the vagina may appear chronically pale with a thin, atrophic mucosa. Narrowing and shortening of the vaginal vault may occur but this is generally associated with fibrosis and loss of elasticity (Grigsby, et al., 1995). This is in marked contrast to the chronically inflamed vagina in a woman with genital GVHD (Norian & Stratton, 2008; Spinelli, et al., 2003; Spiryda, et al., 2003; Zantomio, et al., 2006). The radiation doses used in conditioning regimens (12 gray) for HSCT (Gratwohl, 2008) are considerably lower than those used in the treatment of gynaecological cancers (80 – 120 gray) (Grigsby, et al., 1995) therefore it is unlikely to be a radiation effect causing genital complications in this group of women.

Several authors recommend that histological confirmation of GVHD involvement in the genital area should be done, especially in the absence of involvement of chronic GVHD in other organs (Couriel, et al., 2006; da Silva Lara, et al., 2010; Shulman et al., 2006). Biopsy of the affected area is possible, however the vulvovaginal area may be so painful that taking a biopsy may be inappropriate or too difficult (Stratton, et al., 2007). Biopsies, when taken, are often consistent with mucocutaneous chronic GVHD (Shulman, et al., 2006; Spiryda, et al., 2003; Stratton, et al., 2007). Biopsies may show ulceration of the vaginal mucosa, fibrosis of the submucosa, collagen and fibrin deposition, perivascular lymphohistiocytic infiltration, apoptotic cells present in the basal layer, sclerosis and vacuolar degeneration of the basal layer (Anguenot, et al., 2002; Costantini, et al., 2004; da Silva Lara, et al., 2010; Jain & Henry, 2001; Spiryda, et al., 2003; Stratton, et al., 2007; Yanai, et al., 1999). Interpretation of any biopsy requires an experienced HSCT pathologist to be able to interpret them accurately as it is often difficult to distinguish some features of acute GVHD from chronic GVHD. There are also no uniform minimum criteria for the histological diagnosis of GVHD and histologic grading systems for affected organs have not been prospectively validated (Shulman, et al., 2006).
There is no prospectively validated scoring or grading system for genital GVHD though scoring systems have been devised by authors writing and researching the topic. Spinelli et al (2003) made the first attempt at a three step scoring system when undertaking their retrospective study. Zanomio et al (2006) and Stratton et al (2007) have also gone on to develop their own in-house scoring systems (see Table 2).

Table 2: Genital GVHD scoring systems

<table>
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<tr>
<td>Minimal/Grade I</td>
<td>Vulval redness</td>
<td>Genital tract discomfort and/or discharge</td>
<td>Generalised erythema and oedema of vulval structures</td>
</tr>
<tr>
<td></td>
<td>Pain on touching the labia</td>
<td>Inflammatory redness of the vaginal and/or vulval mucosa</td>
<td>Patchy erythema of mucosa and glandular structures of vulval vestibule</td>
</tr>
<tr>
<td></td>
<td>Small areas of vulval denudation (plaques)</td>
<td>Genital tract discomfort and/or discharge</td>
<td>Erythema around openings of vestibular (Bartholin’s and Skene’s) glands</td>
</tr>
<tr>
<td>Moderate/Grade II</td>
<td>Extensive areas of vulval denudation with or without leukokeratosis and introital stenosis</td>
<td>Desquamative or erosive inflammatory change of the genital mucosa</td>
<td>Erosions of mucosal surfaces of the vulva</td>
</tr>
<tr>
<td></td>
<td>Vaginal adhesions or complete vaginal closure</td>
<td>Fibrinous exudates</td>
<td>Fissures in vulval folds (eg, interlabial sulci; fourchette)</td>
</tr>
<tr>
<td></td>
<td>Vaginal adhesions</td>
<td>Reduction in vaginal elasticity</td>
<td>Agglutination of the clitoral hood</td>
</tr>
<tr>
<td></td>
<td>Concentric fibrous banding of the vagina</td>
<td></td>
<td>Introital stenosis</td>
</tr>
<tr>
<td></td>
<td>Reduction in vaginal capacity</td>
<td></td>
<td>Vaginal synechiae</td>
</tr>
<tr>
<td></td>
<td>Vaginal stenosis or occlusion</td>
<td></td>
<td>Haematocolpus or complete vaginal closure</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Fasciitis or spasticity of levator sling</td>
</tr>
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The National Institutes of Health (NIH) proposed a new global assessment of chronic GVHD severity. This grading system has been proposed as an
appropriate means to standardise inclusion criteria for clinical trials and also as an indication for initiation of systemic immunosuppression treatment (Filipovich, et al., 2005). The portion of their scoring system related to genital tract GVHD has the following structure:

Score 0 – no symptoms

Score 1 – symptomatic with mild signs on examination and no effect on coitus and minimal discomfort with gynaecologic exam

Score 2 – symptomatic with moderate signs on examination and with mild dyspareunia or discomfort with gynaecologic exam

Score 3 – symptomatic with advanced signs (stricture, labial agglutination or severe ulceration) and severe pain with coitus or inability to insert vaginal speculum (Filipovich, et al., 2005).

There are similarities between each of these grading systems but there are also significant differences. The Spinelli system focuses mainly on the vulval symptomatology in the minimal and moderate categories while the Zantomio system includes the whole genital tract. The NIH grading system uses very subjective phraseology, for example it uses the word “symptomatic” but has no description of what this means, making it more difficult to allocate a score to a patient. The Zantomio and Stratton systems are more descriptive and prescriptive than the Spinelli and NIH systems. The development of these grading systems has encouraged thought into the grading of genital GVHD. There however needs to be further discussion within the international HSCT community towards developing a single validated scoring system so that there is consistency of grading allowing better and more consistent research to be undertaken in this under-recognised post HSCT complication.

**Treatment**

It is important that, when a diagnosis of genital GVHD is made, treatment is instituted immediately. Delayed therapy risks escalation of the pathological changes and reduced likelihood of therapeutic success (Hayes & Rock, 2002).
Treatment for genital GVHD may be divided into four categories:

- Immunosuppressive therapy, both topical and systemic
- Oestrogen therapy, both topical and systemic
- Vaginal dilatation either by the use of vaginal dilators or with sexual intercourse

The type of treatment required might depend on the stage at which the genital GVHD is diagnosed, though there are many now that would say that surgery should be able to be avoided if correct treatment is instituted in a timely manner (Stratton, et al., 2007; Zantomio, et al., 2006).

When premature menopause has been demonstrated, the use of systemic hormone replacement therapy (HRT) is a key initial therapeutic intervention (Anguenot, et al., 2002; Corson, et al., 1982; DeLord, et al., 1999; Gossett, et al., 2002; Schubert, et al., 1990; Stratton, et al., 2007; Zantomio, et al., 2006). Stratton et al (2007) noted that the addition of HRT to the treatment regimens for genital GVHD resulted in vaginal and vulval lesions healing more rapidly and that friable, atropic vulval mucosa became thicker with improved elasticity. For those women that were treated with topical steroid without HRT, the lesions healed but the vulval mucosa remained friable and thin. There is however some discussion in the literature as to whether HRT should be cyclical (given as cycles often with a break off therapy incorporated) or whether it should be continuous (given on a daily basis without any breaks). Some authors have voiced the concern that cyclical HRT may contribute to hematocolpus because it encourages the cyclic shedding of the endometrium (Stratton, et al., 2007; Tauchmanovà, et al., 2004). They suggest using sequential or continuous HRT however Tauchmanovà et al (2004) commented that for some young women the lack of a monthly bleed, like their contemporaries, had a psychological impact meaning that they felt less feminine. If this is an issue for young women then cyclical HRT should be introduced. Anguenot et al (2002) felt the sequential
use of HRT may contribute to the formation of hematocolpus in those patients who had vaginal synechiae. Schubert et al (1990) recommended using daily oestrogen therapy with medroxyprogesterone acetate added on the first fourteen days of each month. Couriel et al (2006) caution that although there is anecdotal evidence that topical and systemic oestrogen therapy has a beneficial effect on genital GVHD, there need to be prospective controlled studies done to prove it.

In the non-HSCT population, there are no clear guidelines regarding the best HRT strategy for women with premature ovarian failure, as there is a lack of randomised controlled trials. Oestrogen replacement should be accompanied by progestogen therapy as this affords some endometrial protection for women with an intact uterus. HRT should be continued until the woman reaches the age at which menopause usually occurs. No studies have been done to directly compare various hormonal therapies or the route of administration in women with spontaneous premature ovarian failure, let alone those who have undergone an HSCT (L. M. Nelson, 2009; Panay & Kalu, 2009; Tauchmanovà et al., 2007). Panay and Kalu (2009) have discovered that many young women prefer to use cyclical HRT as this often allows a monthly bleed like their peers even though it is an induced withdrawal bleed rather than a natural period. Some women prefer a no-bleed regimen meaning that they take a continuous combined HRT regimen. The choice for this is ultimately up to the woman and what she prefers. Both Panay and Kalu (2009) and Nelson (2009) say that the combined oral contraceptive pill should not be used in young women as HRT as it contains more synthetic steroid hormone than is needed for physiological replacement.

Mild Genital GVHD
Early or mild genital GVHD may be defined as redness and inflammation of the vulva/vaginal region and genital tract discomfort with or without discharge or pain on touching the labia, depending on which grading system is being used (Spinelli, et al., 2003; Stratton, et al., 2007; Zantomio, et al., 2006) (See Table 2, page 13). Treatment for this group of patients should include the use of topical high potency glucocorticoids and oestrogen creams with the use of twice
weekly vaginal dilatation by using either vaginal dilators or sexual intercourse (Anguenot, et al., 2002; Bradbury, 1994; Corson, et al., 1982; Couriel, et al., 2006; Lönnqvist & Brune, 1999; Spiryda, et al., 2003; Stratton, et al., 2007; Zantomio, et al., 2006). The use of a water-soluble lubricant should be used when undertaking vaginal dilatation whether this be in the form of sexual intercourse or the use of dilators (Couriel, et al., 2006). Couriel et al (2006) also recommend that mechanical and chemical irritants be avoided and that the use of an emollient cream to the vulva may help to alleviate itching and irritation.

Moderate Genital GVHD

Moderate genital GVHD may be defined as erosive or desquamative inflammatory changes to the genital mucosa, introital stenosis, fibrinous exudates and fissures in vulval folds (Spinelli, et al., 2003; Stratton, et al., 2007; Zantomio, et al., 2006) (See Table 2, page 13). Treatment for this group of patients should include treatment as for the mild/early group but topical calcineuron inhibitors such as Cyclosporin and Tacrolimus should be added to the regimen (Couriel, et al., 2006; Spiryda, et al., 2003; Stratton, et al., 2007; Zantomio, et al., 2006). There should also be a greater emphasis on vaginal dilatation to prevent the formation of strictures. Vaginal dilatation should be undertaken once or twice daily and the resumption of sexual relations should be encouraged (Zantomio, et al., 2006).

Severe Genital GVHD

Severe genital GVHD may be defined as the presence of vaginal adhesions, reduction in vaginal capacity, vaginal stenosis or occlusion and agglutination of the clitoral head (Couriel, et al., 2006; Spinelli, et al., 2003; Stratton, et al., 2007; Zantomio, et al., 2006) (See Table 2, page 13). Surgery has been seen as the treatment of choice along with the use of topical steroids, topical calcineuron inhibitors and dilators in those patients with severe stenosing disease of the vagina (Anguenot, et al., 2002; Corson, et al., 1982; Costantini, et al., 2004; Costantini, et al., 2006; Louis-Sylvestre, et al., 2003; Spinelli, et al., 2003; Spiryda, et al., 2003). Surgery involves dissecting the adhesions or fibrous bands within the vagina. This can be done digitally or may require the use of scissors or a blade (Anguenot, et al., 2002; Hayes & Rock, 2002;
A vaginal dilator is usually inserted and left in situ for between 12 and 72 hours. An intensive vaginal dilator programme, in combination with topical and systemic therapy follows this. There is however no consistency in the literature as to the programme that should be followed by women post-operatively. Regimens include the dilator being in situ overnight, being in situ for at least 12 hours a day or being used for an unspecified period of time three to five days per week. Following the initial postoperative period, maintenance use of dilators is encouraged once again with wide variation in the literature as to how and when they are used (Corson, et al., 1982; Costantini, et al., 2004; Costantini, et al., 2006; Rodolakis, et al., 2007; Spiryda, et al., 2003; Yanai, et al., 1999).

Two cases have been described in the literature where women underwent total hysterectomy and either single or bilateral salpingo-oophorectomy due to symptoms associated with genital involvement with GVHD (Anguenot, et al., 2002; Gossett, et al., 2002). This is major surgery, which according to Zantomio et al (2006) and Stratton et al (2007) should be able to be avoided in most cases of genital GVHD. In an audit undertaken by Zantomio et al (2006), 31% of the 29 women audited had severe genital GVHD. None of these women required surgery to alleviate symptoms. Similarly, 24% of 33 cases evaluated by Stratton et al (2007) had severe genital GVHD with only one woman progressing to surgery largely because she developed hematocolpos and couldn’t be assessed frequently. In managing and treating genital GVHD Zantomio et al (2007) have five steps to follow:

1. Check that patients have been compliant with topical and systemic hormone therapy that was instituted soon after HSCT.
2. Glucocorticosteroid therapy is instituted topically high into the genital tract. Hydrocortisone acetate 100mg/g mucoadherant rectal foam is used at a dose of 1g. It is administered vaginally daily for 4 – 6 weeks and tapered according to response.
3. Topical cyclosporin solution is added if the response to steroids is suboptimal. Cyclosporin 100mg is diluted in 20ml of 0.9% saline and
installed high in the vagina for 15 minutes daily for 4 – 6 weeks and tapered according to response.

4. Prophylactic dilator insertion or sexual intercourse twice weekly.

5. Therapeutic dilator insertion twice daily for patients with established vaginal narrowing. Once satisfactory vaginal capacity has been achieved then a prophylactic programme is used as in Step 4.

Patients should be put on a programme to prevent recurrence once improvement is seen in their genital GVHD. This is especially important in patients with active GVHD in other organ systems, as the inflammatory processes associated with chronic GVHD are still ongoing (Anguenot, et al., 2002; Costantini, et al., 2004; Zantomio, et al., 2006). Prevention of recurrence should include a programme of regular vaginal dilatation either using dilators or by undertaking sexual activity. This should be combined with the use of topical and systemic oestrogen (Zantomio, et al., 2006).

It is rare for patients to have vulvovaginal symptoms as the only manifestation of chronic GVHD, however cases have been reported in the literature (DeLord, et al., 1999; Spinelli, et al., 2003; Spiryda, et al., 2003; Zantomio, et al., 2006). Couriel et al (2006) suggest that if the genital area is the only organ system involved then local treatment with steroid creams, with or without some topical immunosuppression such as cyclosporin, may be enough to treat the symptoms.

**Surveillance and Prevention**

Early recognition and treatment of genital GVHD is a key concept in the care of women post HSCT. Genital GVHD has a profound impact on a woman’s quality of life post HSCT. The symptoms associated with genital GVHD may lead to an inhibition of sexual intimacy and a complete inability to have sexual intercourse. This may put added strain on a relationship that has had to endure the rigours of a life-threatening illness and the aggressive treatment of allogeneic HSCT (Costantini, et al., 2004; Norian & Stratton, 2008; Zantomio, et al., 2006). Recognition of symptoms and prompt treatment may assist in the return of well-being post HSCT and may improve the quality of life in long-term survivors (Rodolakis, et al., 2007; Schubert, et al., 1990; Zantomio, et al., 2006). In addition to the impact on a woman’s quality of life, the presence of
severe genital GVHD may preclude cervical screening for dysplasia potentially putting the woman’s life at risk from an undiagnosed second malignancy (a known risk in the post HSCT population) (Kolb et al., 1999 cited in (Costantini, et al., 2004; Spiryda, et al., 2003).

The literature is very clear that regular gynaecological examination should be undertaken with all women who are having an allogeneic HSCT in order to detect the presence of genital GVHD. Early detection means better treatment outcomes for this group of patients (Corson, et al., 1982; Costantini, et al., 2004; Gossett, et al., 2002; Hayes & Rock, 2002; Louis-Sylvestre, et al., 2003; Norian & Stratton, 2008; Rodolakis, et al., 2007; Spinelli, et al., 2003; Tauchmanovà, et al., 2007; Zantomio, et al., 2006). Stratton et al (2008) and Zantomio et al (2006) however stress the importance of a structured and systematic approach to detection, treatment and follow-up. This kind of programme is multi-disciplinary, involving the HSCT physicians, gynaecologists and the HSCT coordinators/specialist nurses. Genital GVHD is a relatively rare presentation in gynaecology practices so it is important that the gynaecologists involved in the care of these women are fully aware of, and familiar with, the gynaecological manifestations of genital GVHD and the treatment that needs to be undertaken (Costantini, et al., 2004; Gossett, et al., 2002).

Zantomio et al (2006) have developed a surveillance programme for genital GVHD. Pre HSCT, education is given to women about the symptoms of both genital GVHD and oestrogen deficiency (if they have not gone into premature menopause with their previous therapy). A baseline sexual function assessment is also taken at this time. Within the first three months post HSCT, patients begin topical oestrogen and systemic oestrogen according to age. A self-surveillance programme is also begun at this time. At three months post HSCT and at three monthly intervals for the next 18 months, a formal gynaecological review is undertaken, looking for signs and symptoms of genital GVHD. A review of sexual function and/or self-surveillance and hormone therapy is also done at these times. After 18 months post HSCT, these reviews are done six monthly, moving to annually once the woman is three years post HSCT. If genital GVHD has been diagnosed however, gynaecological review is more
frequent. At six months post HSCT, Zantomio et al (2006) suggest adding androgen replacement such as transdermal 1% testosterone cream or tibolone (Livial®) if there are symptoms of androgen deficiency. Cervical screening is performed annually.

It is imperative, during initial discussions about the potential treatment of an allogeneic HSCT, that women are informed of the risk of genital GVHD (Costantini, et al., 2004). Once the decision has been made to go ahead with a HSCT then education of women about the use of HRT and oestrogen creams and the use of vaginal dilation is very important, as these are the mechanisms to help prevent the occurrence of severe genital GVHD. Good education about the signs and symptoms of genital GVHD is vital, along with instructions about what to do if such symptoms occur (Costantini, et al., 2004; Spinelli, et al., 2003; Zantomio, et al., 2006).

Summary
Genital GVHD is an under recognised and underreported post HSCT complication. It may have a profound impact on a woman’s quality of life, both in the short- and long-term. A greater body of literature about this issue is being generated but this still largely consists of case reports. A handful of retrospective studies have been conducted but as yet there are no prospective, randomised studies looking into the best ways of evaluating, treating and preventing this potentially disabling condition. In combination with the lack of prospective data, women are often reluctant to talk about gynaecological issues affecting them and medical and nursing personnel often do not ask. Greater education about this condition needs to be provided for patients undergoing HSCT and also for the medical and nursing staff involved in their care. It is also important that structured surveillance programmes are developed with the involvement of gynaecologists, HSCT physicians and specialist nurses. With greater numbers of people surviving HSCT due to better supportive care, and with the increasing incidence of chronic GVHD, the incidence and relative impact of female genital GVHD will both increase. HSCT providers have a duty of care to their patients to ensure that they are fully aware of this
potentially disabling condition and that services are provided to evaluate and treat it.

**Sexuality and Haematopoietic Stem Cell Transplantation**

The diagnosis and treatment of cancer is a potentially life-threatening event. There has been a presumption that once a person has been diagnosed with such a disease they will lose interest in sexuality as all thoughts and energy will be focused on fighting the disease. The likelihood of long-term survival and cure is now higher with improved cancer therapies and supportive care. Improved patient outcomes have resulted in an increase in emphasis on quality of life issues including sexuality (Graziottin, 2007; Hordern, 2008; Lamb, 1995; Molassiotis, 1998; Tierney, 2004).

Issues with sexuality and sexual function are one of the most common quality of life concerns for survivors of HSCT. Both males and females are affected, but it appears women are impacted more by this post HSCT complication with up to 80% of women post HSCT reporting long-term sexual problems compared with 50% of male survivors. It appears that many women never fully recover from the effect of HSCT on their sexuality (Humphreys, Tallman, Altmaier, & Barnette, 2007; Syrjala, Kurland, Abrams, Sanders, & Heiman, 2008; Syrjala et al., 1998; Watson et al., 1999; Wingard, Curbow, Baker, Zabora, & Piantadosi, 1992; Yi & Syrjala, 2009).

The concept of sexuality has been variously defined and debated in the literature with some feeling that definitions of sexuality are too narrow and tend to focus solely on the act of sexual intercourse (Hordern, 2008; Krebbs, 2008; Quinn, 2009). Weiss (cited in Quinn, 2009) states that:

> Sexuality is about connecting our head with our gut through our heart. It is about genuinely caring for ourselves, finding ecstasy in simply being alive, and giving creative voice to our ideas and feelings. It is about bridging physical pleasures with spiritual awareness and serenity.

The World Health Organization (WHO) (2006) offers a broad working definition of sexuality that was developed through a consultative process. This
definition has often been quoted in the literature about sexuality post cancer treatment however most of this literature still tends to focus on genital or functional sexuality (Hordern, 2008). The definition states:

Sexuality is a central aspect of being human throughout life and encompasses sex, gender identities and roles, sexual orientation, eroticism, pleasure, intimacy and reproduction. Sexuality is experienced and expressed in thoughts, fantasies, desires, beliefs, attitudes, values, behaviours, practices, roles and relationships. While sexuality can include all of these dimensions, not all of them are always experienced or expressed. Sexuality is influenced by the interaction of biological, psychological, social, economic, political, cultural, ethical, legal, historical, religious and spiritual factors (World Health Organization, 2006, p. 5).

Defining sexuality is very individualised with sexuality meaning different things to different people. Southard and Keller (2009) conducted a study where they asked participants to define what sexuality meant to them. Definitions were varied but women in particular defined sexuality around themes such as body image, remaining desirable to partners despite body changes that may have occurred, the ability to be a woman, maintaining femininity, love, sex and intimacy. There has been a move away from viewing sexuality in a functional and genital way to recognising a woman’s sexuality as a broad, individualised experience that shifts and changes over a woman’s lifetime. It is dependent on biological events as well as personal and relationship variables (Brandenburg & Bitzer, 2009; Graziottin, Serafini, & Palacios, 2009; Hordern, 2008). Despite this, much of the literature still views sexual function and the act of sex as sexuality (Hordern, 2008).

During an allogeneic HSCT, high doses of therapy are given causing nausea and vomiting, pain, fatigue, premature ovarian failure, skin changes, alopecia and changes in body habitus due to GVHD. These physical changes impact on body image and also cause psychological changes such as anxiety, loss of self-esteem, relationship stress, role changes and uncertainty. All these changes impact on a woman’s sexuality by altering her ability to maintain femininity, feel desirable, be able to share intimately with her partner, to communicate effectively and to feel passionate and sexy (Quinn, 2009; Southard & Keller, 2009; Tierney, 2004, 2008; Wingard, et al., 1992).
The impact of HSCT on a woman’s sexuality is something that needs to be discussed with patients by medical and nursing staff both pre and post HSCT. An evaluation of changes in sexuality needs to be undertaken encompassing the broad concept of sexuality as described by WHO, not just looking at sexual activity (Quinn, 2009; Tierney, 2008). The Sexual Response Cycle is one tool used in evaluating sexual function. Unfortunately this does tend to focus very much on the sexual act rather than concepts such as body image, intimacy, touch, communication, self-worth and love which describe sexuality as a whole (Krebbs, 2008; Quinn, 2009; Tierney, Facione, Padilla, Blume, & Dodd, 2007). It is important to remember however, that there are no universally accepted definitions to describe “normal” sexual activity or function. Sexual function is often described in terms of dysfunction and tends to be rather subjective. One individual’s definition of normal may be quite different to another’s and may depend on factors such as age, sex, number of partners, cultural perspective, frequency of sexual activity and sexual orientation (Brandenburg & Bitzer, 2009; Potter & Johnston, 2011).

**Female Sexual Function**

The Sexual Response Cycle is a model that was developed to assess sexual function (Masters & Johnson, 1966). It consists of four phases: excitement, plateau, orgasm and resolution.

The excitement phase develops from stimulation from either a physiological or mental/emotional source. The stimulation is important, as it will lead the person onto the next phase of the cycle. If the stimulation is adequate, then the intensity of the response increases. The reverse holds true – if the stimulation does not find favour or is inadequate, then the excitement phase might be prolonged or even terminated. This phase, along with the resolution phase, have the longest durations of the cycle.

The next phase in the Sexual Response Cycle is the plateau phase. This leads directly on from the excitement phase and is where sexual tensions are intensified to reach an extreme level, which will then lead onto orgasm. The duration of this phase depends on the stimulation used and the motivation of the
person to achieve orgasm. If the stimulation and the drive aren’t present, the person may not achieve orgasmic release.

The orgasmic phase is the shortest part of the Sexual Response Cycle and encompasses the few seconds in which the vasoconstriction and myotonia that have developed from the previous phase are released. In women, the awareness of orgasm is focused around the pelvic area specifically concentrated in the clitoris, vagina and uterus. The intensity and duration of the female orgasm varies widely and is subjectively experienced by the individual.

The resolution phase is where the person involuntarily relaxes after their orgasm. Women have the physiological ability to return to the orgasmic phase from the resolution phase if the correct stimuli are applied. Men have a slower physiologic ability to respond to restimulation.

The Sexual Response Cycle as developed by Masters and Johnson appears to be more descriptive of sexual function in men rather than in women. The model implies that women progress through the sexual act in a linear fashion, however research and self reporting from women have shown that desire does not always precede arousal and that for example, stimulation of the breast and genitalia may be unwelcome prior to arousal but become desirable afterwards (Basson et al., 2004; Pitkin, 2009). The Sexual Response Cycle may be a useful tool for understanding sexual dysfunction however it must be remembered that normal female sexual function involves more than just the genital and pelvic organs involved in sexual intercourse. Basson (2001) researched female sexual response and then went on to develop a sexual response cycle for women that is more circular and intimacy based. Basson and colleagues felt that the cycle developed by Masters and Johnson did not take in the key roles of emotional intimacy and sexual stimulation as well as other variables such as social, psychological and physical factors. Though organs such as the vagina, clitoris, labia and vulva are important for women during sex, the central nervous system and a number of areas of the brain are also important, as are sex steroids and hormones. (Krychman, 2008; Pitkin, 2009; Tierney, 2005; Tierney, et al., 2007).
Female Sexual Dysfunction

Sexual dysfunction may be defined as a group of disorders that are characterised by psychological and physiological changes that adversely impact on sexual desire and sexuality, causing psychological distress and/or stress within relationships. Sexual dysfunction is characterised by disturbances in the Sexual Response Cycle and for women is divided into four domains: sexual desire, arousal, orgasm and sexual pain (American Psychiatric Association, 2000).

Sexual desire disorder is where there is absent or diminished desire, feelings of sexual interest and fantasies that are needed to develop an interest in achieving sexual arousal and pursuing sexual activity. Low sexual desire is one of the most difficult aspects of sexual dysfunction to treat because of a complex interaction of beliefs or values and psychological and relationship factors (Basson, et al., 2004; Potter & Johnston, 2011; Tierney, 2005).

Female sexual arousal disorder is the absence of feelings of sexual excitement and sexual pleasure. Arousal includes both subjective excitement (an awareness and appreciation of erogenous stimulation) and physiological responses (evidenced by vaginal lubrication, engorgement of the vaginal canal and cutaneous flushing). It is important to note that a physiological response may occur without sexual excitement (Basson, et al., 2004; Potter & Johnston, 2011; Tierney, 2005).

Female orgasmic disorder is an inability to achieve orgasm, a marked delay in achieving orgasm or a marked diminishment in the intensity of orgasmic sensation (Basson, et al., 2004).

Sexual pain disorder is where either one or a combination of sexual stimulation of the genitalia, complete or partial vaginal entry and orgasm may be a painful rather than a pleasurable experience for a woman (Basson, et al., 2004; Potter & Johnston, 2011).

It is likely that for women who have had an allogeneic HSCT, sexual dysfunction is related to more than one problem and is a complex interaction between various physiological and psychological variables (Tierney, 2004).
Physiological factors relate to the disease and treatment with an HSCT and may include:

- Chemotherapy – prior to and with HSCT.
- Radiation therapy – prior to and with HSCT.
- Damage to the hypothalamic-pituitary-gonadal axis.
- Premature menopause.
- Chronic GVHD (particularly genital GVHD).
- Medications – steroids, drugs with anti-cholinergic effects, sedatives.
- Dry mouth.
- Changes in body habitus – weight loss or gain, alopecia, scars, skin changes (Hughes, 2008; Krebbs, 2008; Wingard, et al., 1992; Yi & Syrjala, 2009).

Psychological and psychosocial factors contributing to sexual dysfunction are difficult to separate completely from physiological issues as many of these have a basis in biological effects, but have emotional and cognitive consequences (Yi & Syrjala, 2009). Psychological and psychosocial issues contributing to sexual dysfunction include:

- Fears related to: pain, discomfort, worry whether arousal and orgasm are still possible, relapse or death.
- Altered body or self-image.
- Embarrassment or shame.
- Grief.
- Pre-existing patterns of sexual behaviour.
- Pre-existing relationship issues.
- Financial problems (Hughes, 2008; McKee & Schover, 2001; Schover, 1999; Yi & Syrjala, 2009).

The incidence of sexual dysfunction is higher in patients who have received an allogeneic HSCT compared with patients who have had standard chemotherapy or an autologous HSCT (Zittoun et al., 1997). It is also higher in patients who have chronic GVHD (Watson, et al., 1999). Approximately 25 – 33% of people
report long-term problems with sexual dysfunction that may be ongoing for many years (Heinonen et al., 2001; Hughes, 2008; Syrjala, et al., 1998; Tierney, 2005). Women post HSCT have more problems with sexual dysfunction than women in the general population and also experience more sexual dysfunction than men (Heinonen, et al., 2001; Humphreys, et al., 2007). Women, however, are more likely to report sexual dysfunction (Watson, et al., 1999). It is important to remember that while sexual dysfunction for women post HSCT might be relatively common, the level of dysfunction and the reaction to the dysfunction will differ from patient to patient. It is therefore important to individually tailor treatment interventions based around the issues that the recipients themselves raise (Krebbs, 2008).

Assessment of Sexual Dysfunction

The causes of sexual dysfunction are multi-factorial; assessment therefore needs to be multi-pronged, encompassing physiological, sociological and psychological factors (Tierney, 2005). Yi and Syrjala (2009) stress that for the post HSCT patient reporting sexual difficulties, a full medical examination should be done as there are many frequently occurring concurrent complications such as hypothyroidism, diabetes and loss of muscle mass due to steroids that may impact on sexual function.

Assessment of sexuality and sexual function, however, should not wait until problems exist. It is important that a pre HSCT baseline sexual function assessment be done with both the HSCT recipient and their partner (Yi & Syrjala, 2009). There are advantages of talking about sexuality early in the treatment journey – it emphasises to the patient and their partner that sexuality is an important issue and that the treating team is interested in them as a whole person not just as someone with a disease. It also legitimises the topic, allowing it to be talked about at future visits (Anderson & Lamb, 1995; McKee & Schover, 2001). Humphreys et al (2007) found in their study that those patients who had discussions about sexuality with their health care team prior to HSCT had improved sexual functioning at three years post HSCT compared with those patients who had not had any pre HSCT sexuality discussions. Talking about sexuality early on may prevent some sexual difficulties by just providing some
information about the potential problems that might be experienced throughout treatment. It also means that any changes can be tracked over time and that timely and appropriate treatment can be instituted (Potter & Johnston, 2011; Yi & Syrjala, 2009).

A number of assessment tools have been developed to assess sexual dysfunction, however many of these have not been designed for women with cancer. Of those that are cancer focused, most have been designed for women with gynaecological cancers (Krebbs, 2008; Yi & Syrjala, 2009). Yi and Syrjala (2009) feel that using a standardised assessment tool is important as it makes it easier for both the patient and the health care professional to start a conversation about sexuality. To this end they developed a sexual functioning questionnaire (SFQ) and tested it on cancer survivors plus matched non-cancer controls and also on 200 HSCT patients pre and post HSCT. The final version of the SFQ is a well validated and gender specific questionnaire that asks questions about recent sexual activity, sexual desire, arousal, orgasm, intimacy and problems. It has high re-test reliability when comparing patients pre and post HSCT.

Krebbs (2008) found that to provide an effective sexual assessment and, if necessary, an intervention, then a combination of assessment methods needs to be used to investigate the changes to the patient’s sexuality and sexual functioning. The methods used may depend on the level of expertise of the healthcare professional, the time available and the willingness of the patient to engage in the assessment. The assessment may be brief or intensive but should be conducted in a manner that is sensitive, non-judgemental and avoids medical jargon. It is also very important to include both patients and partners, to discuss sexuality before, during and after treatment, to ask questions about all areas of sexuality not just sexual function and to be mindful of cultural sensitivities (Krebbs, 2008; Potter & Johnston, 2011). The initial steps in any sexuality assessment are to legitimise and normalise it by making it a part of any nursing or medical assessment. To begin a discussion about this topic one might say to the woman and her partner that it is common for HSCT recipients to experience less interest in sexual activity for several months post the HSCT and then go on
to ask if she has resumed sexual activity. If the response to this question is “yes” then further questioning about any difficulties can be undertaken. If the response is “no” then information can be provided about resuming sexual activity (Krebbs, 2008; Tierney, 2005).

**Interventions**

Intervention for sexual impairment post HSCT should begin pre HSCT with education about the effect that treatment might have on sexuality and sexual function. Discussion needs to include information about the potential for impairments in sexuality, fertility, and libido, information about premature menopause and difficulty in achieving orgasm as well as discussion about changes in body image (McKee & Schover, 2001; Potter & Johnston, 2011; Tierney, 2005). Most intimacy and sexual activity does not occur in a vacuum therefore the sexual partner is an important part of these discussions. These pre HSCT discussions serve to:

- Emphasise that sexuality is a legitimate and important concern.
- Identify to the HSCT recipient that the healthcare professional is a resource for any queries or problems around sexuality or sexual issues.
- Allow better adaptation of the recipient and their partner to changes that may occur post HSCT.
- Alert patients and their partners to plan for a return to intimacy and sexual activity post HSCT so that years don’t pass by without anything happening (Tierney, 2005; Yi & Syrjala, 2009).

There are a variety of interventions that are available for the treatment of sexual dysfunction. It is important to remember that the level of dysfunction or impairment, the impact of the impairment and the reaction to it will differ from patient to patient. It is therefore important to tailor any intervention to that patient and base it on the specific issues and concerns raised by that patient (Krebbs, 2008). A combination of interventions is likely to be the most beneficial but there have been no studies done to confirm this approach in the post HSCT population (Yi & Syrjala, 2009).
Education and Counselling

The provision of information and education about sexuality issues associated with HSCT is very important and may be all that is needed for addressing many women’s concerns (McKee & Schover, 2001; Potter & Johnston, 2011). Many women are uninformed about the normal anatomy of the sexual organs so education needs to start with this and go on to discuss the impact that HSCT will have on sexuality both in a physical and emotional sense (Krychman, 2008; Potter & Johnston, 2011; Schover, 1999). Information provided should include:

- Written material such as books and pamphlets.
- Visual material such as DVDs and links to websites.
- Verbal information provided by the healthcare team. This may include referral to appropriate counselling services (Katz, 2005; McKee & Schover, 2001; Potter & Johnston, 2011).

Written information is helpful to women as they are able to refer back to this time and again without having to engage their healthcare team. Written material should include information about normal sexual anatomy and function, the impact that HSCT will have on sexuality and relationships, information about the resumption of sex post HSCT, some solutions to common issues and a list of resources that women can call on (Krychman, 2008; McKee & Schover, 2001; Potter & Johnston, 2011).

DVDs are available from sexual health organisations and there are also many legitimate websites that are a useful resource for information about sexuality. This medium once again allows women to explore solutions to their concerns in their own time and in the privacy of their home environment (Krychman, 2008; McKee & Schover, 2001).

Open discussion with the healthcare team about the challenges that HSCT can pose to intimate relationships is vital. This needs to include how to manage numerous powerful and conflicting emotions as well as how to adjust to the physical changes that may impact on sexual function (Potter & Johnston, 2011; Yi & Syrjala, 2009). Discussions about sexuality should occur from the first
meeting to discuss HSCT and continue through the peri- and post HSCT periods. When the healthcare team raises sexuality during HSCT discussion it emphasises to the patient and their significant others that this is an important issue and allows recognition of the healthcare team as a resource for sexuality information (McKee & Schover, 2001; Potter & Johnston, 2011; Tierney, 2004; Yi & Syrjala, 2009).

Most women who have concerns about sexuality do not require extensive psychological or counselling input. They usually just need information about the impact of HSCT on their sexuality and suggestions for re-engaging in intimacy and sexual activity (Schover, 1999; Yi & Syrjala, 2009). Often, sympathetic understanding of the woman’s issues and evaluation of their concerns may in itself be therapeutic (Hughes, 2008). There are a few patients however that may benefit from more specialist input in the form of counselling or sexual therapy. General counselling may be beneficial to help deal with anxiety, depression and body image issues resulting from the HSCT and may also be useful in helping to improve communication between the woman and her partner. Counselling may be especially helpful for single women who experience significant anxiety regarding their desirability to prospective partners and worry about when to talk about their cancer history. They often express fears that they will be found undesirable, be lacking when it comes to their partners’ sexual expectations or be worried that they will never find another partner (Potter & Johnston, 2011; Yi & Syrjala, 2009). Sex therapy may be required if in-depth interventions are needed to address sexual communication and technique (Krychman, 2008; McKee & Schover, 2001; Potter & Johnston, 2011).

It must be remembered that the woman’s partner may need some assistance in adjusting to his or her partner being a sexual being again. Some partners have been intimately involved in caring for the woman during and post HSCT (such as assisting with toileting and showering) and it may be hard to switch from seeing the woman as a patient to a sexual being. Other issues for the partner being reluctant to engage in sexual intimacy may be:
● Emotional and physical exhaustion from being the primary caregiver.
● Fears about causing the woman pain or discomfort.
● Fears about disease relapse.
● Guilt about a lack of fulfilment of their own sexual needs or desires.
● Guilt about not being able to accept the physical changes that may have occurred to their partner (such as skin pigmentation, alopecia, weight gain etc).
● Guilt about the relationship or sexual activity not being the same as prior to diagnosis (Hawkins et al., 2009).

Behavioural and Lifestyle Changes

Behavioural and lifestyle changes may improve overall quality of life and sexual function in women post HSCT. Obesity, weight gain or loss and physical activity all contribute to negative body image and impact on sexuality. To try and mitigate these effects, women should be encouraged to achieve and maintain a healthy weight, have a balanced diet, engage in regular physical activity and minimise the use of alcohol and tobacco (Krychman, 2008; Potter & Johnston, 2011).

Some women feel betrayed by their bodies after the diagnosis and treatment of a malignancy. Their bodies may look and feel different post HSCT so before engaging in sexual activity with another, they may need to get to know and accept their bodies again and learn what locations and types of touch feel good (Potter & Johnston, 2011). Women should be given permission to explore masturbation and the use of vibrators until they are comfortable with their physical responses. Armed with this information, they are better able to communicate to their partners what kind of stimulation they enjoy (Hughes, 2008; Potter & Johnston, 2011; Yi & Syrjala, 2009). Some consideration also needs to be given about other ways that women can increase their sexual satisfaction beyond traditional intercourse (Yi & Syrjala, 2009). For women not yet ready to engage in this way then she and her partner can explore sexual expression through massage, fondling and caressing, cuddling, sexual fantasies, erotica and showering or bathing together (Hughes, 2008; Krychman, 2008; Potter & Johnston, 2011). Fatigue is a considerable problem post HSCT and
resumption of sexual activity may have to be more carefully thought out in this context (Cooke, Grant, & Eldredge, 2007). Scheduling sexual and intimate time when the woman is least tired may be one solution for this but this does sacrifice a degree of spontaneity that may be difficult to adjust to (Hughes, 1996).

Yi and Syrjala (2009) found in their clinical practice that a communication and intimacy based approach to facilitating a return to satisfying sexual activity has been very successful. They, along with Potter (2011), suggest addressing fears around restarting sexual activity with couples first and then encouraging them to progress gradually with perhaps scheduling specific times for “dating” and intimacy without intercourse. Potter (2011) stresses that there is no such thing as perfect sexual function and there is no “quick fix” in the setting of sexual dysfunction. The media may lead patients and their partners to believe that sexual dysfunction is able to be fixed with commercially available magic bullets in the form of drugs like Viagra® and Cialis® when in actual fact restoration of emotional and sexual intimacy generally requires dedicated time and effort. Some couples may need to accept that sexual satisfaction may never be achieved to the same level as prior to diagnosis and treatment (Yi & Syrjala, 2009).

Physical Examination
A physical examination and laboratory testing may be undertaken to diagnose sexual dysfunction as abnormal findings may suggest specific causes for this. Palpation of the thyroid and measuring thyroid function in recipients with low libidos may indicate hypothyroidism, a common post HSCT complication especially with the use of radiation therapy in the conditioning regimen (Krychman, 2008; Potter & Johnston, 2011). A genital examination should be performed by a gynaecologist in all women post HSCT, looking for signs of GVHD and postmenopausal atrophy (Norian & Stratton, 2008; Potter & Johnston, 2011; Spinelli, et al., 2003; Zantomio, et al., 2006).

Poorly controlled pain, nausea, bowel or urinary symptoms may be barriers to resuming normal sexual function and need to be dealt with. Failure to
acknowledge the impact that these symptoms have on sexuality may cause frustration for both the woman and her partner (McKee & Schover, 2001).

Pharmacologic Interventions
A small number of pharmacologic interventions may be employed in certain circumstances to allow the woman to resume satisfying sexual activity. These may be divided into hormonal and non-hormonal therapies. Before any pharmacological intervention is instigated however, a thorough review of the woman’s current medication should be undertaken and adjustments made, if possible, to any medications that may contribute to sexual dysfunction (Potter & Johnston, 2011; Tierney, 2004). A large number of prescription medications can contribute to sexual dysfunction. Verhulst and Reynolds (2009) conducted a search of a reputed clinical pharmacology database and found 736 prescription medications that decreased libido and 57 medications associated with orgasm dysfunction. Anti-depressants, sedatives and mood stabilisers very commonly affect sexual function causing diminished desire and arousal, and orgasm problems. Anti-hypertensives, opiates and an antiemetic called Metoclopramide are commonly used during and after HSCT and are implicated in sexual dysfunction (Verhulst & Reynolds, 2009). Anticholinergic medications may cause oral and vaginal dryness that may result in difficulty with kissing and other forms of oral intimacy as well as sexual intercourse (Hughes, 2008). Recreational drugs such as alcohol, nicotine and opiates also contribute to sexual dysfunction so evaluation of the woman’s use of these substances is also important (Verhulst & Reynolds, 2009).

Before any pharmacologic intervention is commenced, it is important to discuss the risks and benefits of the medication and once therapy has started, to monitor the patient to minimise side effects (Potter & Johnston, 2011).

Hormonal therapy in the treatment of sexual dysfunction, both topical and systemic, can be used for women who have gone into premature menopause due to the conditioning regimen given prior to HSCT. This treatment has been described in the genital GVHD section of this chapter and will not be further addressed.
Non-hormonal pharmacotherapy for women experiencing sexual dysfunction is fairly limited and is largely still experimental. Non-medicated, non-hormonal vaginal lubricants and moisturisers are the most common non-hormonal preparation available. Vaginal dryness is very common post HSCT so Yi and Syrjala (2009) recommend all women to use lubricants during sexual activity until experience tells them whether continued use of them is warranted. There are several over-the-counter preparations available but women should use water based rather than petroleum-based lubricants as these can interfere with helpful vaginal bacteria and may disrupt the bacterial balance. When using lubricants, reapplication may be needed during sexual intercourse so the bottle or tube should be kept close at hand (Krychman, 2008).

Androgen therapy using oral or transdermal testosterone preparations is controversial and is yet to be recommended by the US Food and Drug Administration (FDA). There is some evidence that testosterone replacement is helpful for low desire in oestrogen replete menopausal women but the paucity of clinical trials means that concerns about safety and effectiveness cannot be fully addressed (Krychman, 2008; Potter & Johnston, 2011).

**The Healthcare Team and Sexuality**

Many quality of life studies in the HSCT population indicate that problems associated with sexuality and sexual function are some of the most prevalent long-term complications of treatment (Humphreys, et al., 2007; Syrjala, et al., 2008; Syrjala, et al., 1998; Yi & Syrjala, 2009). These are significant issues for a growing population of people surviving HSCT. Unfortunately healthcare workers are very reluctant to discuss sexuality and sexual function with their patients. Humphreys et al (2007), in their study looking at sexual function in HSCT patients, found that less than 50% of healthcare workers discussed sexuality issues post HSCT other than the effect of conditioning on fertility. This is backed up by a study done by Hawkins et al (2009) in the general cancer population. They found that 20% of the study participants had sexuality discussed with them but the rates of discussion varied across cancer types with only 9% of haematology patients having some kind of sexuality discussion. Of
those patients who had sexuality discussions, only 37% felt that they were satisfied with the discussion.

The cancer literature has begun to explore the reasons for this lack of discussion with patients about sexuality and intimacy in the context of cancer treatment. A variety of personal and professional reasons are given for not addressing these issues:

- Lack of knowledge and adequate training in this area.
- Fear of embarrassing or offending the patient.
- Personal discomfort in talking about intimate issues.
- Belief that cancer survivors may be too ill or are not interested in sex.
- Age of the patient (significantly older or younger than the healthcare professional).
- Fear about “opening a can of worms” if there are issues such as sexual assault or difficult relationships in the patient’s background.
- Presence of a third party in the consult.

The emphasis of care for HSCT patients may be so focused on getting through the HSCT and on curing the patient that sexual functioning is ignored. This means that the topic of sexuality is not routinely included and as a result, patients are not receiving holistic care focusing on all aspects of human functioning (Katz, 2005). The failure to address sexuality issues also means that patients are not fully informed about the effects of HSCT (Marks, Friedman, Carpini, Nezu, & Nezu, 1997). When signing consent for HSCT, the patient is signing to say that they have been fully informed about the procedure and that they understand the risks and benefits of HSCT. If approximately 50% of patients are not receiving information about post HSCT sexuality in the pre HSCT period, then there are a considerable number of women signing consent without being aware of the up to 80% chance of sexuality problems
Talking about sexuality is something that many medical professionals feel uneasy about. Healthcare providers can easily become more comfortable and knowledgeable with talking about sexuality issues with their patients if they are willing to invest in a little time and to use a few relatively simple strategies (Brandenburg & Bitzer, 2009; Katz, 2005; Potter & Johnston, 2011; Schover, 1999). The literature recognises the limited amount of training that health professionals get in this area but states that there are now a number of resources available such as literature reviews, workshops, textbooks, dedicated journals and an increasing number of conferences dealing with quality of life issues (Katz, 2005; Schover, 1999).

Several authors, aware of the difficulty for health professionals to talk about sexuality, have developed communication models to help with discussion. These models assist with asking patients about sexuality, help to provide information about the impact of treatment and also offer strategies to enhance sexual satisfaction in the face of treatment changes (Hordern, 2008; Potter & Johnston, 2011). Schover (1999), Brandenburg et al (2009) and Potter (2011) believe that all health professionals, whether using formal assessment tools or not, can engage patients in discussion about sexuality in a sensitive manner and that with more frequent discussion about these issues, there will be increased comfort and skill. Several authors recommend that routine screening for quality of life issues be undertaken with each visit to the treatment centre. This may be done using a survey that is completed at each visit or a face-to-face meeting with a dedicated health professional assessing quality of life including sexuality (Katz, 2005; Potter & Johnston, 2011; Schover, 1999).

**Summary**

Many women enjoy satisfying sexual relationships post HSCT, however problems with sexuality and sexual function are significant long-term complications with up to 80% of women experiencing some kind of difficulty (Humphreys, et al., 2007; Syrjala, et al., 2008; Watson, et al., 1999; Wingard, et al., 1992; Yi & Syrjala, 2009). The literature shows that, despite this being a
significant post HSCT complication, the education and information provided by health professionals is on the whole non-existent or sub-standard (Humphreys, et al., 2007; Tierney, 2005; Yi & Syrjala, 2009). This lack of suitable information and a reluctance to talk about sexuality issues with patients impacts on patients’ quality of life and also raises questions about the quality of informed consent (Humphreys, et al., 2007; Marks, et al., 1997; Quinn, 2009; Tierney, 2005; Yi & Syrjala, 2009). There are now many resources available to educate health professionals about communicating with, and educating patients about, sexuality issues (Katz, 2005; Schover, 1999). The literature is very clear that sexuality information should be provided to patients in the pre HSCT period and that ongoing assessment and education about sexuality and sexual function needs to continue for many years post HSCT (McKee & Schover, 2001; Potter & Johnston, 2011; Tierney, 2005; Yi & Syrjala, 2009).

**Fertility After Haematopoietic Stem Cell Transplant**

Infertility is a major complication for women undergoing HSCT. Many are young women of childbearing age and with more people surviving HSCT, the inability to have one’s own children is a significant quality of life issue, one that has been poorly addressed by the HSCT community (Carter et al., 2006; Hammond, Abrams, & Syrjala, 2007; Loren et al., 2011; Nakayama et al., 2009; Schover, 2005; Tichelli, Schwarze, & Socie, 2008).

Infertility may be functionally defined as the failure to conceive after one year of intercourse without the use of contraception (Lee et al., 2006). The well-recognised gonadotoxic effects of chemotherapy and radiation therapy cause either temporary or permanent ovarian failure resulting in infertility in most of the female HSCT population. The exact mechanisms of damage are not well described, however women with ovarian failure have substantial increases in levels of follicle stimulating hormone (FSH) (10 – 20 times above normal) and lutenising hormone (LH) levels (three times above normal)(Lutchman Singh, Davies, & Chatterjee, 2005; Meirow & Nugent, 2001; Nakayama, Milbourne, Schover, Champlin, & Ueno, 2008).
Non cell cycle specific drugs such as alkylating agents are known to be the most toxic to primordial follicles in the ovaries. Cyclophosphamide is an alkylating agent and a very common component of myeloablative conditioning regimens (Lutchman Singh, et al., 2005; Meirow & Nugent, 2001) (Nakayama, et al., 2008). Radiation therapy is generally detrimental to the ovaries with the degree and persistence of damage depending on the radiation dose and patient age with older women sustaining more damage to the ovaries than their younger counterparts (Meirow & Nugent, 2001). Wallace et al (1989), cited in Meirow (2001), estimate that approximately half of the primordial follicles in an ovary are lost at a radiation dose of 4 gray. The standard dose of radiation in most myeloablative conditioning regimens is between 10 - 14 gray (Gratwohl, 2008) therefore there is the possibility of destruction of all the follicles in the ovaries, rendering the woman infertile.

Despite the high rate of permanent treatment induced ovarian failure with conditioning regimens for HSCT, spontaneous pregnancies have been reported post HSCT. Most of these are in women who have had minimal treatment with chemotherapy (most notably patients with aplastic anaemia) and in those aged 15 – 30 at the time of HSCT (Carter, et al., 2006; Chatterjee & Kottaridis, 2002; Loren, et al., 2011; Milroy & Jones, 2010). If pregnancy does occur then data indicates that the outcome is likely to be favourable with no increased risk of stillbirth or miscarriage (Carter, et al., 2006). There may be complications with the pregnancy such as maternal hypertension and possible pre term labour and delivery resulting from distortion of the uterine cavity due to radiation therapy or GVHD, however there is conflicting evidence in the literature regarding this (Carter, et al., 2006; Chatterjee & Kottaridis, 2002; Milroy & Jones, 2010; Salooja et al., 2001).

Even though conception is possible post HSCT, it is likely that these women have sustained damage to their primordial follicles during HSCT and will go into earlier menopause than their peers. Girls are born with approximately 2 million follicles in the ovary. Follicles are naturally lost over time and when the number of follicles falls below a certain threshold, then menopause will occur. Many young women may have larger reserves of follicles going into HSCT and
even though their ovaries will have sustained damage with the chemo-radiation, they may not lose fertility completely (Meirow & Nugent, 2001).

**Incidence**
The true incidence of infertility in women post HSCT is unknown but in one series 100% of women were rendered infertile after receiving a common conditioning regimen containing busulphan and cyclophosphamide chemotherapies (Grigg, et al., 2000). The true magnitude of infertility post HSCT will always be difficult to determine as there is a lack of complete data on pre and post HSCT fertility status, a lack of standardisation of diagnostic criteria for ovarian failure, poor understanding of the pathophysiology of ovarian failure post HSCT, a lack of detailed information from survivors regarding their desire to conceive post HSCT and no registry of recipients’ offspring (Carter, et al., 2006; Chatterjee & Kottaridis, 2002).

The two major BMT registries in the world have collected data about pregnancies in HSCT survivors. Salooja et al (2001) from the European Group for Blood and Marrow Transplantation (EBMT) reported 312 pregnancies from 232 patients (both male and female HSCT recipients) for an overall conception rate of 0.6%. In this cohort, there were 74 women who had an allogeneic stem cell transplant and who had 94 pregnancies that resulted in 78 live births. The Centre for International Blood and Marrow Transplant Research (CIBMTR) collected data on recipients’ pregnancies between 2002 and 2007. During this time, the registry was notified of 83 pregnancies in women who had been transplanted. Of these, 12 of the pregnancies were with women who had undergone myeloablative HSCTs however, the majority of pregnancies (49) were in women who were transplanted for severe aplastic anaemia and therefore had minimal exposure to chemotherapeutic agents (Loren, et al., 2011). Unfortunately the CIBMTR doesn’t collect conception data on its survivors anymore so it will be difficult to tell if the use of non-myleoablative conditioning regimens has any impact on the rate of pregnancy post HSCT.

The rates of permanent ovarian failure and infertility post cancer treatment vary and depend on a number of factors. These include:
• The dose of the chemotherapy or radiation therapy.
• The dose intensity of the chemotherapy or radiation therapy.
• The disease that is being treated.
• The age of the woman (with those over 30 at the time of HSCT more likely to become infertile).
• Pre treatment fertility status (Lee, et al., 2006; Nakayama, et al., 2008).

Diagnosis
Diagnosis of treatment induced ovarian failure is complex as there are no established standard criteria (Chatterjee & Kottaridis, 2002). Cessation of menses is the most common symptom of ovarian failure often accompanied by postmenopausal symptoms of oestrogen deficiency such as hot flushes and vaginal dryness (Nakayama, et al., 2008). However, cessation of menses, though a convenient marker for ovarian function, is not synonymous with infertility just as a regular menstrual cycle is not necessarily synonymous with fertility. Despite the return of cyclic menstruation, there may be a decrease in the number of primordial follicles in the ovary as a result of damage by the conditioning regimen. This may result in a lower chance of future conception and a higher risk of early menopause (Lee, et al., 2006; Lutchman Singh, et al., 2005; Meirow & Nugent, 2001). It is impossible to predict the functional lifespan of the chemotherapeutically damaged ovary and therefore the reproductive potential of these women. Some work has been done on attempting to measure the ovarian reserve however once again, most end up relying on menstrual status as a surrogate marker (Lutchman Singh, et al., 2005; Nakayama, et al., 2008).

When signs of potential ovarian failure are seen in a woman, then a simple blood test measuring gonadatrophins and oestrodial can be done. These are reliable markers of ovarian function and repeated levels of these will determine what is happening and are useful when following up women with ovarian failure (Nakayama, et al., 2008). Chatterjee et al (2002) suggest a multipronged approach to diagnosing treatment induced ovarian failure. They recommend the following:
Clinical presentation – cessation of menses and the presence of menopausal symptoms.

Biochemical markers such as FSH, LH and oestrodial as well as assessing pituitary gonadal function.

Ultrasound of the ovaries looking for any follicular activity.

Options to Preserve Fertility

There are not a lot of options for the preservation of fertility for women undergoing HSCT. On the whole they are invasive and largely investigational (Loren, et al., 2011). The ideal fertility preservation technique would be a type of non-invasive medical therapy that could be initiated in an ill HSCT patient at very short notice. Unfortunately, no such fertility preservation option currently exists for women (Milroy & Jones, 2010). However, the area of oncofertility or the use of reproductive technology for cancer patients is a new and rapidly growing area largely due to patient advocacy groups. Improving access to both standard and investigational techniques for fertility preservation prior to HSCT is very important and can have long lasting impact on quality of life post HSCT (Loren, et al., 2011).

Embryo preservation is the most widely accepted and available option for fertility preservation. Other options include oocyte cryopreservation, ovarian tissue preservation and hormonal inhibition (Chatterjee & Kottaridis, 2002; Lee, et al., 2006; Lutchman Singh, et al., 2005; Nakayama, et al., 2008; Tichelli, et al., 2008). These will be discussed further below.

Embryo Preservation

Embryo preservation is a well-recognised and established treatment to preserve fertility in women undergoing cancer treatment. Despite this, there are some limitations. The process requires that ovaries be stimulated for 2 – 3 weeks with hormone injections. Oocytes are then harvested and fertilised in vitro resulting in embryos. The embryos are then cryopreserved for future use. The whole process may take up to eight weeks and there is therefore a significant delay in starting the HSCT, which may be detrimental to patient outcomes. The oocytes require fertilisation, which means that the woman must have a male partner who
is willing and able to fertilise, or else there must be the willingness to use a sperm donor. This method of fertility preservation is also only available to post-pubertal women (Chatterjee & Kottaridis, 2002; Lee, et al., 2006; Lutchman Singh, et al., 2005; Nakayama, et al., 2008; Tichelli, et al., 2008).

Oocyte Cryopreservation
The cryopreservation of unfertilised oocytes is another option for fertility preservation especially for women who do not have a partner or who have religious or ethical objections to embryo cryopreservation. Oocytes are harvested after hormone stimulation for 2 – 3 weeks and are then cryopreserved. They are thawed later and fertilised in vitro once the woman and her partner are ready to start a family. Once again there are limitations to this technique: time is required to harvest the oocytes thereby delaying the start of conditioning and once again, this option is only available to post-pubertal women. The rate of live births from this procedure is approximately 2 – 6.6% (Chatterjee & Kottaridis, 2002; Lee, et al., 2006; Lutchman Singh, et al., 2005; Nakayama, et al., 2008).

Ovarian Tissue Cryopreservation
This is a largely experimental procedure in which the ovarian cortex, rich in primordial follicles, is removed prior to starting treatment and is cryopreserved for future use. Once treatment is completed then the tissue is thawed and transplanted back into the woman to restore ovarian function. The advantages to this procedure are that it can be offered to pre-pubertal girls, ovarian stimulation is not needed therefore there is not a significant delay to starting conditioning therapy and fertilisation takes place at the time when conception is desired. Collection of tissue however requires a surgical procedure exposing the woman to a general anaesthetic. At the time of writing only two live births have eventuated from this technique. There is also a risk of ischaemia of the transplanted tissue resulting in the loss of the ovarian tissue and therefore chance of fertility (Chatterjee & Kottaridis, 2002; Lee, et al., 2006; Lutchman
Singh, et al., 2005; Nakayama, et al., 2008; Rizzo et al., 2006; Tichelli, et al., 2008).

**Hormonal Inhibition**

The use of gonadotrophin releasing hormone (GnRH) analogues has been used experimentally as a way of protecting women from treatment induced ovarian failure by suppressing the pituitary-gonadal axis. This has resulted in a higher rate of spontaneous resumption of menses than historical controls in some series. It is hypothesised that a greater number of viable follicles remain post treatment, potentially leaving the woman fertile. There have been varying results in the literature and more study is needed before this can become an accepted clinical practice (Chatterjee & Kottaridis, 2002; Lee, et al., 2006; Milroy & Jones, 2010; Nakayama, et al., 2008).

Nakayama et al (2008) have developed a comprehensive strategy for fertility preservation that I think can be used in any HSCT centre. It involves:

- Risk assessment – age of the woman, disease status, gonadal toxicity of treatment, number of children and whether there is a desire to start or add to the family.
- Provision of information – there needs to be frank discussion about the impact of treatment on fertility, fertility preservation options, alternative options, survival expectancy, success rates of HSCT and fertility preservation, and the cost of this. The woman needs to be referred to patient advocacy resources and provided with written information about treatment-induced infertility.
- Confirm the desire for parenthood post HSCT.
- Referral to appropriate specialists for fertility preservation. Referral may also need to be made for counselling for women who are very distressed about the reduced chances of having children.

**Infertility – a Quality of Life Issue**

The loss of fertility is a significant quality of life issue for HSCT survivors, one that may remain a concern for many years post HSCT. While the focus of the woman may have been initially on successfully getting through the HSCT
process, following recovery this may be redirected towards attempting to return to some kind of normality. This may be in deciding to start a family and realisation of the loss of fertility may be very distressing (Hammond, et al., 2007; Lee, et al., 2006; Quinn, 2009). For some, the loss of fertility has been described as more distressing than getting diagnosed with the cancer itself (Nakayama, et al., 2008).

Concern about fertility issues tends to be more of a problem for young women who were childless prior to HSCT (Hammond, et al., 2007; Nakayama, et al., 2009). Infertility concern was also significantly higher in HSCT survivors compared with sibling/friend controls with the feeling that infertility impacted on emotional health and influenced partner/spouse relationships (Hammond, et al., 2007).

Research shows that, despite having been treated for a malignancy, 75% of people who were childless at the time of the survey wanted children in the future. Many of these felt that the experience of cancer increased the value placed on family and would make them better parents. Biological parenthood was the most important goal for most, however adoption and the use of third party gametes was also acceptable (Schover, 2005).

Hammond et al (2007) found in their cohort that 12% of patients had been unsuccessful in building a family through adoption or infertility treatment. Adoption is a potential choice for parenting but there is a high demand for healthy infants and there is a struggle to adopt even if there is no history of malignancy. A history of malignancy may be seen as a contraindication for adoption with some adoption agencies viewing cancer as an incurable illness and pose the question as to whether parents are able to provide a stable home (Nieman et al., 2006; Schover, 2005).

For women presenting post HSCT with ovarian failure and who have not had any fertility preservation, then donor gametes from either a sibling or an unrelated donor, may be the only option available for starting a family (Chatterjee & Kottaridis, 2002; Grigg, et al., 2000).
The Healthcare Team and Fertility

As already discussed, loss of fertility is an important quality of life issue in HSCT survivors. Discussion about fertility has often not been emphasised in the area of HSCT as the focus of the healthcare team has been on eradicating the disease and extending the patient’s life (Nakayama, et al., 2009). Many patients consider that getting information about the impact that HSCT conditioning will have on their fertility is highly important. However, in a study done by Nakayama et al (2009), only 38% of people reported having had such discussions and of those, a large percentage rated the information that they had been given as less than satisfactory. Doctors have a responsibility to inform patients that the conditioning therapy may permanently impair their fertility (Lee, et al., 2006). In addition, as the methods for preserving fertility for females undergoing cancer treatment improves, it is even more important for the healthcare team to describe the available options before treatment is started so that patients can decide if they want to further explore any of these options (Nakayama, et al., 2009). Any discussion must be carefully documented and should be part of the informed consent process prior to HSCT (Chatterjee & Kottaridis, 2002).

Nakayama et al (2009) conducted a study with women who had undergone HSCT that investigated the importance of receiving fertility information at various time points throughout their treatment. It was a questionnaire based study in which 196 women responded (response rate of 40.2%). The results suggested that women wanted fertility information at all time points – at diagnosis, during pre HSCT therapy, at the time of HSCT and post HSCT. Even though women wanted information throughout the course of treatment, it was felt that due to the nature of conditioning regimens and the relative paucity of fertility options for women post HSCT, that fertility information should be emphasised pre HSCT as much as possible.

Loren et al (2011) take this one step further. They recommend that not only fertility preservation information be provided pre and post HSCT but also that women should be provided with family planning and contraception counselling. There is the possibility that pregnancy can occur post HSCT (Carter, et al.,
Discussion about fertility issues associated with HSCT should be undertaken at the earliest opportunity so that, for appropriate patients who are interested, referral to fertility specialists can be done as soon as practicable. Most fertility preservation options for women require timing with the menstrual cycle so expeditious referrals may avoid missing fertility preservation opportunities (Lee, et al., 2006; Nakayama, et al., 2008). It is up to the medical team to assist the woman to fully consider the fertility preservation options open to her and also to consider what a delay in starting treatment might mean for her future health. The team must also determine whether the woman is in fact well enough to tolerate the medications and the procedures required for fertility preservation. The medical team also have a responsibility to ensure that patients do not have unrealistic expectations about their prognosis, the success rates of fertility preservation and should also offer the option of declining fertility preservation (Lee, et al., 2006; Milroy & Jones, 2010). However, it must not be assumed that, despite a poor prognosis, a woman has given up the desire to have children (Nakayama, et al., 2009).

There are many resources about treatment related infertility available to patients through such organisations as the Cancer Society of New Zealand and The Leukaemia and Blood Foundation, as well as many reputable on-line resources. Patients may not be aware of these or may not be able to access them in a timely fashion when confronted with a new diagnosis. Research has not been done on exploring the ideal format for providing education about infertility and fertility preservation options however it is important for the healthcare team to be aware of and to be able to refer patients to the appropriate information resources that are currently available (Lee, et al., 2006; Nakayama, et al., 2009).

Pre HSCT discussions about the potential for infertility are vital however it is very important to keep offering information during, and for many years post, HSCT. Hammond et al (2007) found that repetition of this information is
needed for long-term survivors who may have forgotten, have not processed or not fully understood the information given. This is reinforced by the research undertaken by Nakayama et al (2009) showing that women found that it was important to have fertility information provided at many time points across the treatment trajectory.

Having said that it is important for the healthcare team to engage women about fertility issues, unfortunately it has been shown that many women are not receiving any information or that the information is not of a satisfactory level (Nakayama, et al., 2009). The reasons for the healthcare team not discussing treatment related infertility are many and include:

- A lack of recognition of the importance of fertility to cancer survivors.
- Discussions about immediate or potentially life threatening complications taking priority over fertility preservation discussions.
- An assumption that the cost of fertility preservation will be too much for the patient and their family.
- Emotional discomfort about the topic.
- Lack of knowledge about fertility preservation options.
- A lack of time in the clinical setting.
- A failure to ask women about any fertility concerns and women not bringing up the topic themselves (Lee, et al., 2006).

Summary
Treatment induced infertility is a post HSCT problem that may have significant impact on a woman’s quality of life post HSCT. It is important that information be provided to women about treatment-induced infertility and the options for fertility preservation at the earliest opportunity, so that if the woman’s clinical situation is appropriate and they are willing, referral can be made to infertility specialists. Research has shown that, despite not knowing what the ideal format for the provision of information is, that information about the risks of infertility, fertility preservation and family building options needs to be provided pre, during and post HSCT.
Methods

**Introduction**
The involvement of a multidisciplinary team is essential in delivering high quality care to women post allogeneic haematopoietic stem cell transplantation (HSCT). The aim of this study is to formally evaluate the provision of a structured gynaecology service for women undergoing HSCT and will examine the outcome of this approach to manage these under recognised and complex problems for female survivors of HSCT. It will also assess the informational needs of women in order that better resources might be made available to women if unmet needs are demonstrated. This chapter will describe the research process that was undertaken in order that the study be realised. It will state the study objectives and discuss the research design, the study population, trial documentation and the ethical approval process.

**Study Objectives**

**Hypothesis**
That the provision of consultative gynaecological care and the delivery of gynaecological information to women undergoing allogeneic stem cell transplant will mean a better informed and better satisfied female HSCT population.

**Objective**
To investigate the impact that the involvement of an HSCT specific gynaecology programme has for women undergoing allogeneic stem cell transplantation.

**Aims**
1. To determine the type of information women have been given about vaginal GVHD, sexuality and fertility before they had their transplants.
2. To discover the kind of information women would like to receive about these issues before and after HSCT.
3. To assess if a gynaecology service designed especially for women undergoing HSCT is helpful with early detection and treatment of vaginal graft versus host disease.
4. To assess if a gynaecology service designed especially for women undergoing HSCT is beneficial when fertility and sexuality issues arise.
5. To discover whether the gynaecology services being provided meet the emotional, psychosocial and physical needs of the woman undergoing allogeneic stem cell transplantation.

It is not the intent of this study to measure physical improvement in genital GVHD care as the participant numbers are too small to study this; rather it is looking at the information and care provided to women.

**The Study Population**

The study population consisted of women from Wellington Hospital and The Royal Melbourne Hospital who had had an HSCT between the 1st January 1999 and the 21st October 2009 and who were currently alive as at the 21st April 2010. The study sample was drawn from the BMT databases at Wellington Hospital and at the Royal Melbourne Hospital. The study population formed the basis of four groups:

1. Women from Wellington who were transplanted between the 1st January 1999 and the 31st July 2004. They had not had any routine gynaecology input pre or post allogeneic HSCT.
2. Women from Wellington who were transplanted after the 31st July 2004 who had the input of a newly instigated gynaecology service for those undergoing allogeneic HSCT.
3. Women from Melbourne who were transplanted between 1st January 1999 and the 31st July 2004 and who had access to a dedicated HSCT gynaecology service.
4. Women from Melbourne who were transplanted after the 31st July 2004 and who had access to a dedicated HSCT gynaecology service.
The Wellington Blood and Cancer Centre at Wellington Hospital had no routine gynaecology input for women undergoing HSCT until August 2004. There was no HSCT related gynaecology service in any HSCT centre in New Zealand at that time and Wellington is the only centre that has routine input from a consultant gynaecologist at the current time (personal communications, July 2007 and July 2011). The study compares a Wellington cohort who had not been exposed to any gynaecology input and another Wellington cohort who had been exposed to a newly developed service. The Melbourne cohorts were introduced as a further comparison as they had involvement with a long-running and comprehensive gynaecology service for this group of women.

The following eligibility criteria for entry into the study were developed:

- **Inclusion criteria**
  - Age ≥ 16 years.
  - Female.
  - Received an allogeneic haematopoietic stem cell transplant at Wellington Hospital, New Zealand or the Royal Melbourne Hospital, Australia after 1st January 1999 and at least six months prior to the mail out of study packs.
  - Ability to understand and the willingness to sign a written informed consent document.

- **Exclusion criteria**
  - Age < 16 years.
  - Male.
  - Inability to understand and sign a written informed consent document.

**Research Design**

This study is a retrospective observational study using a survey to elicit the information from consenting participants. An observational study involves the investigator collecting data from a population without seeking to intervene or change anything about what the study participants have experienced. The
investigator plays a more passive role as observer rather than a more active role as experimenter (Graham, 2010; Koepsell & Weiss, 2003; Martin, 2005).

A retrospective survey is a survey of a defined population and involves questioning participants about past and present experiences, attitudes and behaviour (Bowling, 2005; Martin, 2005). I elected to use a retrospective design for this study mainly for logistic reasons as this kind of study can usually be conducted relatively quickly and cheaply in large populations because the events being studied have already occurred. Retrospective studies however are particularly vulnerable to recall bias. Recall bias arises when there is selectivity in the recalling of experiences in relation to the questions being asked. Extra care is needed with the design of the data collection tool in order to minimise this kind of bias (Bowling, 2005; Hennekens & Buring, 1987).

**The Questionnaire**

The aims of this study are to evaluate the provision of a structured gynaecology service for women undergoing HSCT and to assess the informational needs of women in the areas of genital GVHD, sexuality and fertility. I made an educated assumption that women who had undergone an HSCT were the best source of information in relation to the study aims and that as questionnaires are good for collecting information about beliefs, attitudes, opinions, expectations and satisfaction with healthcare that this was the correct tool with which to collect the data (Bowling, 2005).

I was not able to find any research in the literature in which patients’ perceptions about the value of gynaecology services for HSCT patients and about the information provided around genital GVHD, sexuality and fertility had been studied. It was necessary therefore, to develop a questionnaire investigating these issues. Subsequent to the development of my own questionnaire, a survey was published looking at the informational needs of women undergoing HSCT in the areas of fertility and premature menopause (Nakayama, et al., 2009).

I did some research on how to develop a questionnaire and conduct a mail survey (please see the section “Background to Developing the Questionnaire”
later in this chapter). I proceeded to develop the questionnaire and gave it to my supervisors and colleagues to evaluate. Questions were changed, added and removed at this time. The same group of people reviewed the questionnaire again and then I gave it to some non-medical people for their opinion on ease of navigation and whether questions were easily understood. Once feedback indicated that the questionnaire was useable, it was submitted to the ethics committees for approval. Further changes were made at the request of both committees. It was then submitted again for approval and this was received (see Appendices Four and Five). The pretesting of the questionnaire was done with a group of 14 women from Melbourne who had all had allogeneic HSCTs. Of the 14 questionnaires sent out, six were returned (response rate of 43%). It was obvious from all six responses that there was some difficulty negotiating through the questionnaire so changes were made to the order of some of the questions. There were also some questions that needed the choice of answers to be clarified. These changes were made and four questions were added about whether any women had received information post HSCT about genital GVHD. The questionnaire was reviewed again by my supervisors and colleagues and then was re-submitted for approval to the ethics committees. Ethics approval was received (see Appendices Six and Seven) and the study could now formally begin.

**Trial Documentation**

There were a number of documents that had to be developed for the study in addition to the questionnaire. The following documentation was developed and approved by each site’s ethics committee:

- A study protocol.
- Patient information sheets for each site.
- Consent forms for each site.
- Letters of introduction for each site.
- A database for:
  - Documenting study packs sent and received.
  - Collation of the study questions.
A copy of each of these documents (except the database) may be found in the appendices.

**Ethical Approval**

Ethical approval was obtained from the Central Regional Ethics Committee in Wellington and the Health Research Ethics Committee (HREC) in Melbourne. Approval was sought from two ethics committees because this was an international study with participants from both New Zealand and Australia. Each ethics committee is responsible for research activity done in its local area and cannot approve research conducted in another country. The following section documents the complexity of receiving ethical approval for an international study and the lengthy process required to achieve this.

As part of the application process for ethical approval in Wellington, consultation was undertaken with Māori to explore issues of cultural safety for any of the study participants who self identified as Māori. The feedback received noted that the study topic was very personal and that Māori people often find it hard to discuss this kind of thing in any forum but that it was more usual to talk about these things face to face (kanohi ki te kanohi) as this gives an opportunity for trust and respect to develop. The suggestion was made that if there was a poor response from Māori, I should consider kanohi ki te kanohi as a strategy to increase the numbers of Māori participants. The study questionnaire did not request ethnicity data from participants and as I had an overall response rate from the two Wellington cohorts of 89%, I didn’t pursue this line of data collection.

My initial application to the Central Regional Ethics Committee was approved (see Appendix One) subject to the following conditions:

1. To add the option to nominate the participant’s general practitioner to some of the answers on the questionnaire.

2. To clarify the return address for the questionnaire and note that envelopes should be marked confidential so that they would not be opened by anyone other than myself.
3. To add further information to the application form about the storage of data and length of time the data was to be kept before destruction.

Changes were made as suggested and the study was resubmitted for ethical approval. This was received on the 16\textsuperscript{th} August 2007 (see Appendix Two).

My initial application to the HREC in Melbourne was submitted after ethical approval had been received from the Central Regional Ethics Committee in Wellington. The HREC responded with a number of changes that needed to be made to the application itself and to the trial documentation (see Appendix Three). Changes were made as suggested and resubmitted to the committee. There had been a number of delays but approval was finally received from the Melbourne HREC on the 2\textsuperscript{nd} March 2009 (see Appendix Four).

The changes made to the protocol and questionnaire in order to satisfy the Melbourne HREC requirements necessitated approval from the Central Regional Ethics Committee in Wellington. Approval for this was received from this committee on the 29\textsuperscript{th} May 2009 (see Appendix Five).

The pretesting phase of the study was initiated and completed. Once analysis of these questionnaires had been made, changes were made to the questionnaire. Requests for approval of the changes were made to both ethics committees. Approval was received from the Melbourne HREC on the 17\textsuperscript{th} March 2010 (See Appendix Six) and from the Central Regional Ethics Committee in Wellington on the 7\textsuperscript{th} April 2010 (See Appendix Seven).

Annual reports about the conduct of the study have been submitted to each ethics committee as per the committee guidelines.

**The Consent Process**

Written informed consent was a requirement for all participants in the study. Study information sheets and consent forms were based around the requirements for each ethics committee. This meant that there needed to be a separate consent form for each site (see Appendix Thirteen and Fourteen). In each study pack there were two copies of the consent form. For women wanting
to participate in the study, they completed both consent forms, keeping one for their records and forwarding one to me with their questionnaire.

All participants were anonymous and were given a sequential identification number. The number identified the participant and was included on the questionnaire. No other identifying data was collected on the questionnaire.

The Wellington participants received a code number as follows: W/99/001 as the first questionnaire with subsequent sequential numbering (W/99/002, W/99/003 etc) for those women transplanted between the 1st January 1999 and the 31st July 2004 and W/04/001 as the first questionnaire with subsequent number (W/04/002, W/04/003 etc) for those women transplanted on or after the 1st August 2004.

The Melbourne participants received a similar code as follows: M/99/001 as the first questionnaire with subsequent sequential numbering (M/99/002, M/99/003 etc) for those women transplanted between 1st January 1999 and the 31st July 2004 and M/04/001 as the first questionnaire with subsequent numbering (M/04/001, M/04/003 etc) for those women transplanted on or after the 1st August 2004.

The consent covered the use of any results in any reports or publications resulting from the research. Reassurance was made that all data would be anonymous and that any one individual would not be able to be identified in any report or publication.

All data has been kept in a locked filing cabinet or in a password protected computer in a locked office. As per ethics committee instructions, no data will be destroyed until 10 years after the study has closed.

**Statistical Considerations**

Statistical advice was obtained from Dr Gordon Purdie and Dr Dalice Sim. Dr Purdie gave advice about the numbers of study participants required and ways to try to eliminate recall bias. Minimising recall bias was achieved in two ways:
• Recommending that participants have had their HSCT no longer ago than 1999. This is the time that the Melbourne gynaecology service was instituted. It was felt that recollection about the information given and the events that may have occurred may be not as clear for women who were transplanted prior to 1999 compared with those women who received their HSCT more recently.

• The Melbourne cohort was split into two groups. The first group were those who were transplanted from the years 1999 – July 2004 and the second group were those who were transplanted from August 2004 onwards. The gynaecology service in Wellington started in August 2004 and splitting the Melbourne cohort along the same date lines as the Wellington cohorts allowed examination of whether differences that were found were a consequence of the change in service delivery or a differential recall because of the time difference of these women. Comparing the women from Melbourne pre (after 1st January 1999) and post 2004 will give a measure of the differential recall because of the time difference. If the difference in Wellington was greater than this time effect difference then it could be concluded that it is likely to be a consequence of the change in service delivery.

To assemble the data, an Excel spreadsheet was developed. Questions in the questionnaire were assigned a numerical value (eg: no = 0, yes = 1) and each participant’s response to each question was then entered into the spreadsheet. All statistical analyses were performed using SPSS version 18.0.

Analysis of the data was done with the assistance of Dr Dalice Sim. Initial data analysis was done using descriptive statistics. Data was analysed across the whole participant population and also between the individual cohorts. The Pearson chi-squared test was used to evaluate whether there was an association between two categoric variables. Values of $P < 0.05$ indicated statistical significance.

**Conducting the Research**
Once ethical approval had been received from both sites, the research was able to begin. Printing of all the trial documentation was done and the study packs were assembled. Each study pack contained:

- A letter of introduction. Each site had its own letter of introduction. The Wellington cohort had a letter of introduction written by myself as the Principal Investigator (See Appendix Nine). The Melbourne site had a letter written by Professor Jeff Szer from the Royal Melbourne Hospital (See Appendix Ten). This was a requirement from the Melbourne HREC.
- An ethics committee approved “Patient Information Sheet”. Each site had its own information sheet as each of the ethics committees had slightly different requirements for these (See Appendices Eleven and Twelve).
- Two ethics committee approved consent forms. Each site had its own consent form as each of the ethics committees had slightly different requirements for these (See Appendices Thirteen and Fourteen). Both forms were to be completed by the participant then one was enclosed with the questionnaire and sent to the Principal Investigator. The second consent form was to be kept by the participant for her own records.
- An ethics approved questionnaire. The same questionnaire was used for both sites (See Appendix Fifteen).
- A prepaid addressed envelope in which to return the completed consent form and the completed questionnaire.

My collaborator in Melbourne, Yvonne Panek-Hudson, drew up a list of the eligible Melbourne patients from the HSCT database at the Royal Melbourne Hospital. This cohort consisted of women who had an HSCT between the 1st January 1999 and the 21st October 2009. The cohort was then divided into two, following statistical advice, with one cohort consisting of women who had an HSCT from 1st January 1999 to 31st July 2004 and the second cohort consisting of women who had an HSCT from 1st August 2004 to 21st October
2009. The two Melbourne cohorts would have the same time period of their transplants as the Wellington cohorts, and this would therefore minimise the impact of recall bias. Study packs were posted out to the Melbourne cohorts on the 21st April 2010.

The Wellington cohorts were drawn up from the Bone Marrow Transplant Database at Wellington Hospital. The first cohort consisted of women who had been transplanted between the 1st January 1999 and the 31st July 2004 and had not had any routine gynaecology input as part of their HSCT care. The second cohort consisted of women who had been transplanted between the 1st August 2004 and 21st October 2009 and who had been involved with the newly established gynaecology service for these women. Study packs were posted out to these women on the 30th April 2010.

Reminder post cards were developed as a means to increase the response rate for the study (Dillman, 2000). These cards reminded women that they had been sent out a study pack for this study and encouraged them to participate. It also gave contact details so that another study pack could be posted out to them if the previous one had never made it to them or had been misplaced (see Appendix Sixteen). Reminder postcards were posted out to the Wellington cohorts on the 28th July 2010 and to the Melbourne cohorts on the 5th August 2010. The decision was made to close the study to accrual on the 30th September 2010.

Women were encouraged to return the blank questionnaire in the supplied pre-paid envelope if they were not interested in participating in the study. If potential study participants notified me of their intention not to participate in the study, I removed their name from the follow-up mail list and they were therefore not bothered further. Studies have shown that those who actively decide not to participate in a study are unlikely to respond to follow-up requests to participate (Dillman, 2000).

As part of the ethical requirements for conducting the study, women were asked if they would like to receive a summary of the study once it was completed. Women indicated whether they did or did not want a summary report on their consent forms. A summary report will be written in lay terms and submitted to
both ethics committees for approval before being mailed out to those who requested it.

**Background to Designing the Questionnaire**

Mail questionnaires are a commonly used and relatively cost-effective method of collecting data from potential study participants. They are particularly useful when data is required from large numbers of people who live over a widely dispersed geographical area (Alreck & Settle, 2004; Bowling, 2005; Dillman, 2000). A questionnaire mailed to a potential participant allows that person to complete the questionnaire at a time and place of their choosing. Each questionnaire is presented in the same way, has identical questions for each participant and the same instructions and tasks for each participant, thereby eliminating the chance of introducing interviewer bias (Alreck & Settle, 2004; Bowling, 2005). A structured questionnaire involving the use of fixed questions has the ability to collect unambiguous and easy to count answers giving quantitative data for analysis (Bowling, 2005). One disadvantage of the structured questionnaire is that the available responses to a question might not be comprehensive enough for the respondent and may lead to the respondent being ‘forced’ to select an answer that didn’t fully represent her view (Bowling, 2005). To avoid this being a problem in the study questionnaire, I put an ‘other’ option in the multi-selection answers. This allowed women to write down an answer more representative of their view.

The most significant problem with mail questionnaires is a known low response rate. Non-response can be attributed to refusal to participate, moving away from the documented address, death or illness (Bowling, 2005). It is rare to get a response rate over 30% in a mail survey however some surveys have elicited response rates of up to 90% (Alreck & Settle, 2004; Dillman, 2000). A low response rate leads to a non-response bias. Whether a questionnaire is completed, set aside and forgotten or thrown away immediately depends in part on the individual’s attitudes, opinions and interest in the topic being surveyed about. As a result, there is the potential for some types of people to be
overrepresented in the sample and others underrepresented and this may lead to biased results (Alreck & Settle, 2004; Bowling, 2005; Dillman, 2000).

Other types of bias that can be problematic with mail questionnaires are:

- **Recall bias** – relates to selective recalling of past events and experiences by the study participants.
- **Reporting bias** – refers to the study participants’ failure to reveal the information requested perhaps due to embarrassment, the sensitive nature of the question or to a lack of motivation.
- **Measurement bias** – occurs when questions have been worded or presented in such a way that inaccurate or uninterpretable answers are obtained from the survey population (Dillman, 2000).

Mail questionnaires need to be pre-tested to make sure that the questionnaire can be followed and understood and that the questions are eliciting the right kind of information. This is important, as there is no opportunity to go back to the participant to probe for more detailed or slightly different information (Alreck & Settle, 2004; Dillman, 2000).

As there was no contact with the potential study participant, it was very important that the questionnaire be constructed carefully, that the instructions were clear to all participants and that questions or sections contingent on an earlier question or section, be kept to a minimum to prevent confusion (Alreck & Settle, 2004). To this end I researched Alreck and Settle (2004), Bowling et al (2005) and Dillman (2000) who had very practical information as to how I should construct my questionnaire. The books helped in the following ways:

- **Structuring of questions** – how to use closed and open ended questions, how to structure a question to get an interpretable answer, avoidance of bias from unequal comparisons and encouragement to use simple words and terminology.
• Constructing the questionnaire – constructing the questionnaire as a booklet with columns for easier navigation, recommendations on the font size and style to use, when to use bolding and shading, the order of the questions and how to direct people through the questionnaire.

• Pretesting – what should be done and how the pretesting can be evaluated to improve on the finished product.

• Implementing the questionnaire – tips to try and elicit a higher response rate.

Summary
In this chapter I have described the actual research process or method that was undertaken in order that my study be realised. It stated the study objectives and discussed the research design, the study population, trial documentation and the ethical approval process. It also described the research that was undertaken in order to design a functioning questionnaire for use in the study. The following chapter will present the results from the study.
Results

Introduction
This chapter presents the results of the questionnaire divided into the sections outlined in the questionnaire. Initially demographic data will be presented followed by data about HSCT related gynaecology services. Data about genital GVHD, sexuality and fertility issues in this patient population will then given.

Participant Characteristics
There were a total of 139 women who met eligibility criteria (see Methods chapter, page 52) for the study. No contact information was available for eleven women, one questionnaire was returned as it had gone to the wrong address, one woman was found to have died after the questionnaire was mailed out and eleven women returned their questionnaires blank indicating that they did not wish to participate in the study. On statistical advice, these twenty-four women were deemed ineligible to be included in the statistical analysis thus leaving a total potential participant pool of 115 women (See Figure 2).

The women were divided into four cohorts depending on where and when they had their HSCT. They were divided as follows:

- A Wellington cohort that was transplanted between 1st January 1999 and 31st July 2004. This cohort was known as W99.
- A Wellington cohort that was transplanted between 1st August 2004 and 21st October 2009. This cohort was known as W04.
- A Melbourne cohort that was transplanted between 1st January 1999 and 31st July 2004. This cohort was known as M99.
- A Melbourne cohort that was transplanted between 1st August 2004 and 21st October 2009. This cohort was known as M04.
There were 72 questionnaires returned that had analysable data. All questionnaires were anonymous and relied solely on self-reporting by participants. No data could be checked and verified against participants’ medical records, as ethics committee approval had not been obtained for this. The age range of participants at the time of consent was 24 – 73 years of age with a mean of 48 years (SD 10.93 years). The age at which women were transplanted ranged from 19 – 64 years with a mean of 42.5 years (SD 10.8 years). Table 3 summarises the demographic information of the study participants.
Table 3: Demographic and clinical characteristics of participants

<table>
<thead>
<tr>
<th></th>
<th>W99 n = 9</th>
<th>W04 n = 16</th>
<th>M99 n = 24</th>
<th>M04 n = 23</th>
<th>Total</th>
<th>% of Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at time of consent (mean, std dev)</td>
<td>48, 10.4</td>
<td>46, 10.7</td>
<td>51, 11.2</td>
<td>47, 11.2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age at transplant (mean, std dev)</td>
<td>38, 10.6</td>
<td>43, 10.4</td>
<td>42, 11.0</td>
<td>45, 11.1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Disease being transplanted</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AML</td>
<td>3</td>
<td>5</td>
<td>7</td>
<td>7</td>
<td>22</td>
<td>30.6</td>
</tr>
<tr>
<td>ALL</td>
<td>0</td>
<td>2</td>
<td>4</td>
<td>2</td>
<td>8</td>
<td>11.1</td>
</tr>
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<td>CML</td>
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<td>2</td>
<td>6</td>
<td>0</td>
<td>11</td>
<td>15.3</td>
</tr>
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<td>1</td>
<td>1</td>
<td>1.4</td>
</tr>
<tr>
<td>Myelodysplasia</td>
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<td>0</td>
<td>1</td>
<td>1</td>
<td>3</td>
<td>4.2</td>
</tr>
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<td>Aplastic anaemia</td>
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<td>0</td>
<td>0</td>
<td>2</td>
<td>3</td>
<td>4.2</td>
</tr>
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<td>Non Hodgkins Lymphoma</td>
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<td>0</td>
<td>6</td>
<td>8</td>
<td>11.1</td>
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<td>1</td>
<td>0</td>
<td>2</td>
<td>2.8</td>
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<tr>
<td>Hodgkins Lymphoma</td>
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<td>0</td>
<td>1</td>
<td>1</td>
<td>2</td>
<td>2.8</td>
</tr>
<tr>
<td>Other or not specified</td>
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<td>5</td>
<td>4</td>
<td>3</td>
<td>12</td>
<td>16.7</td>
</tr>
<tr>
<td>Menopause status</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Menopausal pre transplant</td>
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<td>4</td>
<td>8</td>
<td>7</td>
<td>22</td>
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<td>50</td>
</tr>
<tr>
<td>Going through menopause</td>
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<td>6</td>
<td>2</td>
<td>2</td>
<td>11</td>
<td>15.3</td>
</tr>
<tr>
<td>Unknown/not answered</td>
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<td>0</td>
<td>1</td>
<td>1</td>
<td>3</td>
<td>4.2</td>
</tr>
<tr>
<td>Donor</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Brother</td>
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<td>1</td>
<td>6</td>
<td>6</td>
<td>14</td>
<td>19.4</td>
</tr>
<tr>
<td>Sister</td>
<td>4</td>
<td>6</td>
<td>9</td>
<td>8</td>
<td>27</td>
<td>37.5</td>
</tr>
<tr>
<td>Mother</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Father</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>2</td>
<td>2.8</td>
</tr>
<tr>
<td>Unrelated</td>
<td>3</td>
<td>9</td>
<td>8</td>
<td>9</td>
<td>29</td>
<td>40.3</td>
</tr>
<tr>
<td>Stem Cell Source</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bone Marrow</td>
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<td>6</td>
<td>16</td>
<td>12</td>
<td>43</td>
<td>59.7</td>
</tr>
<tr>
<td>Peripheral Blood Stem Cells</td>
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<td>5</td>
<td>6</td>
<td>19</td>
<td>26.4</td>
</tr>
<tr>
<td>Cord</td>
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<td>0</td>
<td>1</td>
<td>1</td>
<td>1.4</td>
</tr>
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<td>2</td>
<td>3</td>
<td>4</td>
<td>9</td>
<td>12.5</td>
</tr>
<tr>
<td>GVHD present</td>
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<tr>
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<td>2</td>
<td>5</td>
<td>2</td>
<td>12</td>
<td>16.7</td>
</tr>
<tr>
<td>Skin</td>
<td>5</td>
<td>5</td>
<td>11</td>
<td>9</td>
<td>30</td>
<td>41.7</td>
</tr>
<tr>
<td>Liver</td>
<td>1</td>
<td>7</td>
<td>5</td>
<td>3</td>
<td>16</td>
<td>22.2</td>
</tr>
<tr>
<td>Gut</td>
<td>2</td>
<td>2</td>
<td>5</td>
<td>9</td>
<td>18</td>
<td>25</td>
</tr>
<tr>
<td>Mouth</td>
<td>2</td>
<td>11</td>
<td>14</td>
<td>13</td>
<td>40</td>
<td>55.6</td>
</tr>
<tr>
<td>Eyes</td>
<td>2</td>
<td>8</td>
<td>7</td>
<td>4</td>
<td>21</td>
<td>29.2</td>
</tr>
<tr>
<td>Vagina</td>
<td>2</td>
<td>6</td>
<td>10</td>
<td>10</td>
<td>28</td>
<td>38.9</td>
</tr>
<tr>
<td>Other</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>1</td>
<td>4</td>
<td>5.6</td>
</tr>
</tbody>
</table>
Response Rate

One hundred and fifteen questionnaires were mailed out. Of these, 72 women consented to the study and completed the questionnaire, for an overall return rate of 63%. There were potential participants in the study who were either lost to follow-up with the HSCT centre or for whom the centre did not have current contact details for. One woman in the M04 cohort had unfortunately died after the questionnaire had been mailed out. Table 4 has a summary of the response characteristics and response rate for each cohort.

<table>
<thead>
<tr>
<th>Table 4: Response rate per cohort</th>
<th>W99</th>
<th>W04</th>
<th>M99</th>
<th>M04</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total Eligible</td>
<td>11</td>
<td>17</td>
<td>54</td>
<td>57</td>
<td>139</td>
</tr>
<tr>
<td>Lost to Follow-up/Address Unknown</td>
<td>1</td>
<td>0</td>
<td>7</td>
<td>4</td>
<td>12</td>
</tr>
<tr>
<td>Deceased</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Returned Questionnaire Blank</td>
<td>1</td>
<td>0</td>
<td>5</td>
<td>5</td>
<td>11</td>
</tr>
<tr>
<td>Remaining Participant Pool</td>
<td>9</td>
<td>17</td>
<td>42</td>
<td>47</td>
<td>115</td>
</tr>
<tr>
<td>No Response</td>
<td>0</td>
<td>1</td>
<td>18</td>
<td>24</td>
<td>43</td>
</tr>
<tr>
<td>Consented</td>
<td>9</td>
<td>16</td>
<td>24</td>
<td>23</td>
<td>72</td>
</tr>
<tr>
<td>% In Each Cohort Consented</td>
<td>100</td>
<td>94</td>
<td>57</td>
<td>48.9</td>
<td></td>
</tr>
</tbody>
</table>

Gynaecology Services

There were some important differences in gynaecology referral practices between the Wellington and Melbourne cohorts. The W99 cohort was never exposed to a formal HSCT associated gynaecology service and this was reflected in the fact that 88.9% of participants in this cohort did not see a gynaecologist immediately prior to HSCT and 77.8% of them did not see a gynaecologist post HSCT.

The W04 cohort was exposed to a newly instigated HSCT associated gynaecology service. Fifty-six percent of participants in this cohort saw a gynaecologist pre HSCT and 81% saw a gynaecologist post HSCT.
The routine practice in Melbourne is for women to be referred to a gynaecologist post HSCT (Y. Panek-Hudson, personal communication, July 13, 2004) and this is confirmed by only 30 – 37% of the participants in both the M99 and M04 cohorts being reviewed pre HSCT. Post HSCT however, a gynaecologist reviewed 100% of participants in both Melbourne cohorts.

Across all cohorts 68 – 93% of participants felt that gynaecology involvement pre HSCT was either important or very important. The Wellington cohorts appeared to place more emphasis on this than their Melbourne counterparts (see Figure 3) but there was not a statistically significant difference between the groups \( P = 0.107 \).

Across all cohorts 87.5 – 100% participants agreed that post HSCT gynaecology involvement was either an important or very important part of their care. Nobody thought it was “not important” but 4.2 – 12.5% did not have an opinion about post HSCT gynaecology involvement (see Figure 4).
Women who were seen by a gynaecologist in the post HSCT period had a number of differing visit frequencies. The regularity of visits to the gynaecologist was significantly related to cohort ($P < 0.0005$) with the Melbourne cohorts routinely having regular gynaecology review (see Figure 5).

Despite the Melbourne cohorts having more regular post HSCT gynaecology review, the data shows that the regularity of gynaecology visits is not related to the success of treatment for genital symptoms ($P = 0.663$). The numbers are very small however, so it is difficult to draw any firm conclusions from this.
The gynaecologist was able to detect the presence of genital GVHD prior to study participants’ knowledge of it in approximately 35% of cases (see Figure 6). The study did not ask the question if the gynaecologist detected genital GVHD prior to the participant’s haematologist noticing it. There were six participants who declined to answer this question.

![Figure 6: Participants, response to whether the gynaecologist was able to detect genital GVHD prior to the women themselves noticing it](image)

**Genital GVHD**

Only three of the four cohorts received pre HSCT information about genital GVHD. As expected, due to the lack of an HSCT related gynaecology service, no members of the W99 cohort received any information. Forty-four percent of the W04 cohort received information, as did 58.3% of the M99 and 78.3% of the M04 cohorts.

The BMT coordinators in Melbourne and Wellington were the people who most often spoke with participants about genital GVHD in the pre HSCT period. One hundred percent of participants from the M99 and 94.4% from the M04 cohorts had information provided by the BMT coordinator compared with 57% from the W04 cohort. This was a statistically significant difference between these three cohorts. ($P = 0.008$). Haematologists and gynaecologists also provided information to participants but not as frequently as BMT coordinators (26 – 29% versus 89.5%). The Haematology Registrar discussed genital GVHD with
participants from the W04 cohort but this was not seen in either of the Melbourne cohorts (see Figure 7).

![Figure 7: Health professionals who had discussed genital GVHD with participants](image)

Participants generally felt that the information provided to them had been helpful with 82% either agreeing or strongly agreeing that it was beneficial. For the three cohorts who had received information (W04, M99 and M04), the opinions expressed about the information they had received were not statistically significant between the groups ($P = 0.164$) (See Figure 8). There was universal agreement across all the cohorts that a combination of written and verbal information about genital GVHD should be given to women.

![Figure 8: Responses to the statement “I was given enough information about vaginal GVHD”](image)
One third of women who had received written information about genital GVHD went back to read that information after their HSCT. They reread this information for a variety of reasons:

- They thought they might have genital GVHD and wanted to make sure.
- To remind them of symptoms to look out for.
- For reassurance.
- They were rereading all their HSCT information and came across this section.

Eighty-one percent of all respondents had some kind of genital symptoms in the post HSCT period with the most common being a dry vagina and pain or discomfort during sexual activity (see Figure 9). Most genital symptoms started three to six months post HSCT (39%). It is difficult however to draw any conclusions from this as 21% of respondents couldn’t remember when their symptoms started. There wasn’t a statistically significant difference between the cohorts in the type of symptoms experienced, however 100% of the W99 cohort indicated that they experienced at least one genital symptom that could be attributed to genital GVHD compared to 74 – 83% of women in the other cohorts.

![Figure 9: Genital symptoms experienced by study participants](image-url)
Other symptoms that women experienced were:

- Bleeding with sexual activity
- Bleeding when having a cervical smear test
- Itchiness of the internal and external genitalia.

For women whose genital symptoms had resolved, symptoms had been present for one to thirty six months (mean 12.6 months). Of the women who indicated that they had one or more genital symptoms at some point post HSCT, 53% said that they had ongoing symptoms at the time of completing the questionnaire. When the cohorts were analysed individually, there was a statistically significant difference between them ($P = 0.006$) with all the women in the W99 cohort having ongoing problems with their vagina or with having sex at the time of answering the questionnaire (see Figure 10).

![Figure 10: Percent of participants in each cohort experiencing ongoing genital symptoms](image)

The gynaecologist was the main person with whom women spoke to about genital symptoms (66.7%), with the BMT coordinator and haematologist being the next most common at 19.3%. For those that underwent treatment for their genital symptoms, the women from both Melbourne cohorts and the W04 cohort had better resolution of symptoms than women from the W99 cohort. Though this was not of statistical significance, 50% of the W99 cohort classed the
treatment for their genital symptoms as completely unsuccessful whereas only 7.7–11% of women in the other cohorts felt this way.

Treatment universally across the cohorts consisted of the use of HRT, oestrogen cream and vaginal dilators either singly or in combination. One woman required surgery but did not specify what this involved.

Eighteen percent of women did not speak to anybody at all about their genital symptoms. There was a statistically significant difference ($P < 0.001$) between the cohorts with 78% percent of these women belonging to the W99 cohort (see Figure 11). These women were not exposed to a gynaecology service nor did they receive any information about genital GVHD pre HSCT. The reasons for not speaking to anyone were:

- “I was too embarrassed” – 33%
- “I didn’t think it was important” – 44.5%
- “There were too many other problems at the time” – 44.5%
- “I was just pleased to be alive” – 68%

![Figure 11: Percent of participants who notified someone about their genital symptoms](image)

When the questionnaire was redesigned after pre-testing was completed, an error was made in the genital GVHD section. This meant that a set of new questions, asking about any information that women received post HSCT about genital GVHD, could not be answered. This has not impacted on the main
focus of the study but has meant that I have been unable to ascertain the type of genital GVHD information and education women received in the post HSCT period.

**Sexuality**

Issues around sexuality were poorly addressed in all cohorts with only 38% of all participants receiving information from the BMT coordinator and 21% from the gynaecologist. The haematologist addressed sexuality issues with only 8.5% of participants. Twenty-eight percent of participants said that issues around sexuality post HSCT had not been discussed by any health professional in the pre HSCT period. There was no difference in rates of discussion between the cohorts.

Information about post HSCT sexuality issues was wanted pre HSCT by 96% of participants. Most wanted a combination of written and verbal information (68%) with 21% wanting only written information and 7% wanting only verbal information. Three participants didn’t want any sexuality information at all. These women all came from the M04 cohort.

Participants were asked whether the information that they had been given about post HSCT sexuality issues had been helpful to them. For those that responded (94%), 16% felt that the information that they had been given was not helpful. Over half (62.5%) of those women came from the W99 cohort with another 19% coming from the W04 cohort. No woman from the W99 cohort felt that they had received a satisfactory level of information (see Figure 12).
Most women (73%) considered that they had sexuality problems in the post HSCT period. There was no statistical difference between the cohorts \((P = 0.159)\) however 100% of women in the W99 cohort experienced one or more sexuality problems compared with 60 - 75% of women in the other three cohorts (see Figure 13). When talking about sexuality issues, participants felt most comfortable speaking with the gynaecologist (59%) and the BMT coordinator (34%) ahead of any other health professional.

Figure 12: Responses to the statement “The information I was given about sexuality was helpful to me after I had my bone marrow transplant”

Figure 13: Percent of participants that experienced post HSCT sexuality problems
For women who did experience post HSCT sexuality problems, there were no statistical differences in symptoms experienced between the four cohorts \( (P = 0.676) \) (see Figure 14). Other issues that were problematic for women were their weight (both being overweight and underweight), fatigue and the way they looked.

![Figure 14: Post HSCT sexuality problems experienced by participants](image)

For women who did consider that they had sexuality problems, most sought help from the gynaecologist (48%). For those that sought help, 73% felt that they got the right help for their problems. Almost half (42%) of the women who experienced problems did not seek any help for their sexuality issues. There was a statistically significant difference \( (P = 0.014) \) between the cohorts with 89% of the W99 cohort with post HSCT sexuality issues not talking with any health professionals (see Figure 15). Interestingly, 44% of women in the M99 cohort who experienced sexuality problems also did not speak with anyone about them despite Melbourne having a comprehensive HSCT gynaecology service in place.
Of those women who had post HSCT sexuality issues, 71% of participants at the time of completing the questionnaire felt that their problems were resolved. This left 29% of the women with ongoing problems that included arousal, orgasmic and body image issues. In the W99 cohort where 100% experienced sexuality problems, 89% have ongoing issues.

Almost half (43%) of the participant population were not given any information about when sexual activity could resume post HSCT. Seven of these women were in the W99 cohort, which equated to 77% of that cohort – a significant difference compared with the other cohorts in the study. Seventeen women (24%) were unable to remember whether they had been given any information about this with ten of the women coming from the M99 cohort. Twenty-four women (33%) had been given some information about the resumption of sex but 21% of these women couldn’t remember what they had been told. There were a variety of answers given about when sex could resume:

- “I was told I could have sex at any time” – 52%
- “I was told I could have sex when my white cell count was normal” – 9%
- “About three months post transplant” – 4%

When asked about condom use in the post HSCT period, 40 women (57%) said that they had not received any information. Sixteen women (23%) couldn’t
remember whether they had received information or not. Fourteen (20%) women did receive information but for some reason nine of these chose not to elaborate on what information they had been given. Most women (27%) said that they had been told to use condoms until their total white cell count had normalised.

**Fertility**

Almost half (48.6%) of the participants had not gone through menopause prior to starting conditioning therapy for their HSCT. Most had been told that they would be menopausal post HSCT but 7% hadn’t been told anything about this at all.

Forty-eight women (68%) already had children prior to their HSCT and of these 90% of these had completed their families. Only women who wanted more children or women who had not yet started a family went on to complete this section of the questionnaire (see Table 5). All women answering this section gave a response to each question.

**Table 5: Description of the participants who completed the fertility section**

<table>
<thead>
<tr>
<th></th>
<th>W99</th>
<th>W04</th>
<th>M99</th>
<th>M04</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Women who completed the fertility section of the questionnaire</td>
<td>3</td>
<td>4</td>
<td>9</td>
<td>8</td>
<td>24</td>
</tr>
<tr>
<td>% of their cohort</td>
<td>33.3</td>
<td>25</td>
<td>37.5</td>
<td>34.8</td>
<td></td>
</tr>
</tbody>
</table>

Seventeen women (71%) received information about fertility issues in the post HSCT period. There was no statistically significant difference between the cohorts ($P = 0.28$) however a higher percentage of members of the W04, M99 and M04 cohorts received information compared with the W99 cohort. Numbers were very small however, so nothing of significance can be read into this (see Figure 16). Information was largely provided by a combination of the BMT coordinator (72%), the haematologist (61%) and the gynaecologist (33%) with 17% of the participants receiving information about fertility from the radiation oncologist if they were getting radiation therapy as part of their conditioning regimen.
When asked whether the information received had been beneficial, there was no statistically significant difference between the cohorts ($P = 0.459$) but overall there was dissatisfaction about the quality of information, particularly from participants in the Wellington cohorts (see Figure 17). When asked whether enough information was given to participants, there was a statistically significant difference between the cohorts ($P = 0.013$) with, in particular, the W99 cohort feeling that not enough information was provided (see Figure 18). Once again, it must be remembered that there are only small numbers answering these questions. All participants wanted a combination of written and verbal information given to them about fertility issues post HSCT.
When participants were asked if they had been told prior to their HSCT that they might never be able to become pregnant post HSCT, 50% of the total cohort was aware that they would not be able to conceive post HSCT with 33% having been told that they might not be able to conceive post HSCT. Only 12.5% of the total cohort felt that that had not been told that they would be infertile post HSCT.
Participants were asked if they had been referred to a fertility specialist prior to their HSCT. Forty six percent of the participants were not referred to a specialist but would have liked to be. Because the numbers answering this section were so small (n = 24), there was no significant difference between the cohorts ($P = 0.520$). However, no participants from either Wellington cohort saw a fertility specialist prior to HSCT and there were a greater proportion of participants from these cohorts who didn’t see a fertility specialist prior to HSCT but would have liked to (see Figure 19).

![Figure 19: Percent of participants who were referred to a fertility specialist prior to HSCT](image)

**Summary**

This chapter has presented the results collated from the questionnaire sent out to study participants. Demographic data was presented at the beginning of the chapter. Following this, data about HSCT related gynaecology services and genital GVHD, sexuality and fertility issues for women undergoing allogeneic HSCT were presented. These results will be discussed in the following chapter.
Discussion

Introduction

The literature reviewed in the Background chapter (see page 1) documented that genital GVHD, sexuality and fertility issues are important quality of life issues for women surviving allogeneic HSCT. For many years these issues have been under appreciated by HSCT teams but as more HSCTs are performed and there are more long-term survivors, then these issues must be discussed with women and good education, information and services provided for them.

My study investigated the impact that the involvement of an HSCT specific gynaecology programme had for women undergoing this procedure. The study hypothesis was that the provision of consultative gynaecological care and the delivery of gynaecological information to women undergoing allogeneic HSCT will mean a better informed and better satisfied female HSCT population. The specific aims of the study were:

1. To determine the type of information women have been given about vaginal GVHD, sexuality and fertility before they had their transplants.
2. To discover the kind of information women would like to receive about these issues before and after HSCT.
3. To assess if a gynaecology service designed especially for women undergoing HSCT is helpful with early detection and treatment of vaginal graft versus host disease.
4. To assess if a gynaecology service designed especially for women undergoing HSCT is beneficial when fertility and sexuality issues arise.
5. To discover whether the gynaecology services being provided meet the emotional, psychosocial and physical needs of the woman undergoing allogeneic stem cell transplantation.

This chapter discusses my study findings, which indicate that the provision of consultative gynaecological care and the delivery of gynaecological information
to women as part of their routine care prior to and after allogeneic HSCT results in better informed and more satisfied patients.

**Information and Education**

The results of my study show that the provision of written and verbal information about genital GVHD, sexuality and fertility was seen as very important across all cohorts. The W99 cohort had a complete lack of information pre HSCT about any of these topics and most had no contact with a gynaecologist. The study results showed that 100% of the women in this cohort had genital problems that may have been attributable to genital GVHD. All women in this cohort also had sexuality problems post HSCT with 89% of them not speaking with anyone about their problems. The literature suggests that if these women had been given some information and education pre HSCT, they would have had an awareness of symptoms, felt more comfortable about talking with a health professional because the topics had previously been discussed and may have sought help earlier, perhaps resulting in better outcomes and better quality of life (Krebbts, 2008; McKee & Schover, 2001; Potter & Johnston, 2011; Stratton, et al., 2007; Yi & Syrjala, 2009; Zantomio, et al., 2006). Women in the W04, M99 and M04 cohorts felt more comfortable talking to health professionals (mainly gynaecologists and bone marrow transplant coordinators) about these issues because the issues had been discussed with them pre HSCT and they knew what to be aware of and what to do.

There is now more written information available to women about sexuality and fertility issues for those undergoing cancer therapy (Cancer Society of New Zealand Inc., 2007; Reproductive Services, 2004). This tends to be generic information published by patient support organisations like the Leukaemia and Blood Foundation and The Cancer Society or by individual treatment centres. While this information is helpful and does bring these issues to the fore, there is a real need for written information specifically for women undergoing allogeneic HSCT, as there are specific issues such as genital GVHD that are unique to this patient population. There is no written patient information in the public arena in Australasia specifically about genital GVHD. The provision of written information about genital GVHD is solely reliant on the HSCT centre...
and may not be provided at all. There is virtually no guidance in the medical literature about what kind of information should be provided to women about genital GVHD and how this should be presented. This is largely because the literature consists of case series (Anguenot, et al., 2002; DeLord, et al., 1999; Gossett, et al., 2002; Hayes & Rock, 2002; Jain & Henry, 2001; Louis-Sylvestre, et al., 2003; Yanai, et al., 1999) with a few retrospective studies (Spinelli, et al., 2003; Spiryda, et al., 2003; Stratton, et al., 2007; Zantomio, et al., 2006). Most talk about the need for early detection and treatment of disease and a few talk about prevention and regular surveillance. Nowhere in the literature is there a description of the education and information that women need in order to facilitate early investigation and treatment into this potentially debilitating problem.

Most participants felt that the provision of written and verbal information about genital GVHD, post HSCT sexuality and fertility would be the ideal. Provision of information using more than one medium is supported in the literature because this means that all learning styles and levels of understanding can be catered for (Katz, 2005; McKee & Schover, 2001; Potter & Johnston, 2011). Nakayama et al (2009) comment that it is not yet known what is the best format for delivery of fertility and menopausal information to women undergoing HSCT but the results of their study indicates that women want this kind of information given to them at multiple time points during their treatment journey. They found that the type of information required changed during that journey (eg. menopause related information was seen as more important post HSCT by study participants) but that women still wanted the opportunity to get all the information available whether they were pre or post HSCT.

For participants in my study that did get written information about either genital GVHD or post HSCT sexuality, a quarter to a third of them went back to that information for further reference after their HSCT. This emphasises the importance of having educational material that women can take home or access at home so that they can refer to it at any time of their choosing. This is reinforced in the literature where it is recommended that resources such as books, pamphlets, internet sites and DVDs should be available to women.
These kinds of resources can be accessed repeatedly before, during and for many years after their HSCT, as needed (McKee & Schover, 2001; Nakayama, et al., 2009).

Genital GVHD Information
Of the three cohorts that received some kind of information or discussion about genital GVHD pre HSCT, 30% felt that they did not get enough information. This result is concerning as it is with education and information that women are able to actively participate in a prevention and treatment programme for genital GVHD (Zantomio, et al., 2006). The provision of information also makes women aware of the symptoms associated with genital GVHD and enables them to feel empowered to seek early treatment. My study result reinforces the need for more and better information being provided about genital GVHD using both written and verbal information as preferred by the study respondents.

Sexuality Information
Post HSCT sexuality issues were poorly addressed across all cohorts with almost one third of participants not receiving any information at all. For those that did receive some education and information, only 57% felt satisfied that they had enough information and that it was useful to them. Approximately 60% of the W99 cohort had no information or education pre HSCT about sexuality issues post HSCT and all of them went on to have problems with a statistically significant 89% of them deciding not to say anything about their problems to their healthcare team. This result confirms what is seen in the literature that if the subject of sexuality is not raised in pre HSCT discussions, women are less likely to discuss problems that occur post HSCT because the lack of discussion and information provided about sexuality sends signals to women that this issue is not important (Krebbs, 2008; McKee & Schover, 2001; Potter & Johnston, 2011).

Fertility Information
Study participants considered that there was a lack in both the quality and quantity of information provided about aspects of fertility in the post HSCT period. The Wellington cohorts in particular felt that the information given was neither helpful nor unhelpful and that there was not enough information received. All participants wanted a combination of written and verbal
information given to them. Nakayama et al’s (2009) study into the informational needs about fertility and menopause in women who had undergone HSCT did not manage to discover the best format for giving this kind of information. At their institution, written information is given to all women who may be about to embark on an HSCT. The results of my study suggest that both written and verbal information is what women want but the study did not drill down into what women thought would be the best delivery format for this. Focus groups, consisting of women who have had an HSCT, may be one way to elicit the information and education women would like and the formats in which it should be provided. Nakayama et al (2009) also found that women wanted information given to them about fertility at a number of time points in their treatment trajectory. This did not come through in my study but it was not a question that was specifically asked.

**Consultative Gynaecological Care**

My study is the first, to my knowledge, to specifically ask women to reflect on the importance of gynaecology input into their allogeneic HSCT care and treatment. My results show that the provision of an HSCT related gynaecology service is seen as very important to women both pre and post HSCT. Pre HSCT gynaecology involvement was considered to be an essential part of their pre HSCT care for 78% of the women participating in the study. For those participants where routine HSCT associated gynaecology care was available, there was a consistent finding that gynaecology review pre HSCT was important. This finding was reflected in the W99 cohort even though they had never been exposed to an HSCT associated gynaecology service and had little pre HSCT understanding of potential gynaecological complications. The literature supports pre HSCT involvement by the gynaecologist in order to take a baseline history, perform a baseline examination and preventative screening and also for counselling regarding pregnancy prevention, fertility preservation options, genital GVHD and post HSCT menopausal changes (Milroy & Jones, 2010; Rizzo, et al., 2006). The conditioning regimens for most HSCTs will render the woman infertile so it is very important that discussion around fertility is done prior to the HSCT before any chance of achieving fertility preservation is lost (Lee, et al., 2006; Nakayama, et al., 2009).
Post HSCT gynaecology involvement was viewed as important or very important across all the cohorts in the study. This point of view is well supported in the literature with regular gynaecological follow-up to assess genital GVHD, vaginal health, hormone replacement, sexuality and bone health being seen as essential care in these women (Milroy & Jones, 2010; Rizzo, et al., 2006; Spinelli, et al., 2003; Stratton, et al., 2007; Yi & Syrjala, 2009; Zantomio, et al., 2006). Women in my study had a number of differing frequencies of follow-up with those in the Melbourne cohorts have more regular visits to the gynaecologist than their Wellington counterparts. The data from my study shows that the regularity of gynaecology visits is not related to the success of treatment for genital symptoms. A caveat to this is that the number of participants in this study was small, so a larger study looking at the impact of the frequency of gynaecology visits might show a different result. However, it is clear that a regular pattern of gynaecological follow-up post HSCT is important in order to facilitate the early detection and treatment of gynaecological complications post HSCT (Milroy & Jones, 2010; Rizzo, et al., 2006; Zantomio, et al., 2006).

Communication of Genital GVHD and Sexuality Issues
Women in my study most commonly spoke to the gynaecologist and the bone marrow transplant coordinator about any problems related to genital GVHD and sexuality. Women also indicated that they felt more comfortable talking about these personal issues with these two health professionals. This may be because they were the people who had most commonly raised these issues in pre HSCT discussions. Pre HSCT education and discussion about these issues serves to emphasise that they are legitimate and important concerns and also flags to the recipient that the healthcare professional is a resource for any queries or problems around sexuality or sexual issues either before or after HSCT (Krebbs, 2008; McKee & Schover, 2001; Potter & Johnston, 2011; Tierney, 2005). Only 7% of participants felt comfortable talking about these issues with a haematologist and this may be because only 25% of haematologists raised these topics in their pre HSCT discussions. These results confirm what is commonly seen in the literature, that many health professionals are reluctant to talk about these issues with their patients (Brandenburg & Bitzer, 2009; Hawkins, et al.,
It is critical that health professionals actively educate and inform women about post HSCT gynaecology issues such as sexuality, fertility and genital GVHD. Complications significantly impact on quality of life and may have far reaching physical and psychosocial consequences if not dealt with both pre and post HSCT (Potter & Johnston, 2011; Schover, 1999).

The W99 cohort was poorly served with very little gynaecological support pre and post HSCT. Without exception, all of these women experienced at least one genital symptom post HSCT and they also all had post HSCT sexuality issues. This begs the question as to whether a HSCT related gynaecology service would have reduced the numbers of women experiencing these issues. In this study there were no statistical differences between the cohorts in either genital symptoms or sexuality issues experienced. There was some difference, though not statistically significant, between the cohorts in regards to resolution of genital symptoms, with those women who had gynaecological input (cohorts W04, M99 and M04) having better resolution of symptoms than the cohort that had no gynaecology input (W99). The numbers participating in the study were small so a statistically significant difference might have been seen in a larger study. Though not significant, there was a trend showing that there was better resolution of symptoms and this adds support to the value of establishing and providing an ongoing HSCT related gynaecology service.

An audit was conducted in Wellington Hospital approximately one year after the HSCT related gynaecology service was launched. The feeling amongst respondents was that this was an essential service and should involve both pre and post HSCT review. Most indicated that they would prefer to have a female gynaecologist as part of the service (Wood, Hawley, & Carter, 2006). It has been difficult to maintain a quality HSCT related gynaecology service in Wellington using female gynaecologists. Our experience reflects that, common to many public hospital services, the resources available to provide women with their choice of a female gynaecologist and to provide a regular visit schedule are often not available. This may well have contributed to the observation that
some of the W04 cohort felt that they didn’t get satisfactory information and education around genital GVHD, sexuality and fertility.

**Genital GVHD**

Genital symptoms that may be attributed to genital GVHD were seen in 81% of the study participants with 100% of women in the W99 cohort experiencing symptoms. This is a higher rate of genital symptomatology than has been seen in the genital GVHD literature (Spinelli, et al., 2003; Zantomio, et al., 2006) but it must be remembered that the data obtained from the study questionnaire was self-reported and not able to be substantiated using participants’ medical records. It may be that the symptoms that women interpreted to be genital GVHD were in fact vaginal symptoms related to premature ovarian failure. It was not the aim of this study, nor was the study designed to determine the actual incidence of genital GVHD in the study population. Whether these women had genital GVHD or not, they had genital symptoms which, in some cases, had a significant impact on their quality of life.

Genital symptoms such as dyspareunia and feeling that the vaginal vault was either blocked or appeared to be smaller than prior to HSCT were commonly experienced in my study participants and are consistent with symptoms described in the genital GVHD literature (Spinelli, et al., 2003; Stratton, et al., 2007; Zantomio, et al., 2006). Participants also experienced symptoms such as a dry vagina and pain during sexual intercourse but these could be attributed to either genital GVHD or to premature ovarian failure (Spinelli, et al., 2003; Spiryda, et al., 2003; Stratton, et al., 2007; Zantomio, et al., 2006). Women in the W99 cohort who were premenopausal prior HSCT may not have had contact with a gynaecologist or endocrinologist to start hormone replacement therapy post HSCT and did not receive any education to allow them to determine what these symptoms were attributable to.

The gynaecologist was able to detect genital GVHD, prior to study participants becoming aware of it, in approximately 34% of cases. There were six women who omitted to answer this question so this is not an entirely accurate estimation. Nevertheless, there were a number of women who had treatment
instigated earlier than would have happened if the gynaecologist had not been involved in their care. Earlier detection and treatment of genital symptoms may lead to better outcomes (Zantomio, et al., 2006) so these women were indeed fortunate that a gynaecologist had reviewed them. This provides some evidence that a gynaecologist is a vital part of the multidisciplinary team caring for these women.

Many women, especially from the W04, M99 and M04 cohorts, said that they got the right help for the genital symptoms they had experienced. This usually involved treatment administered by a gynaecologist. Most in these three cohorts had some kind of gynaecological review post HSCT that provided a forum for women to talk about their genital problems. Approximately 50% of the W99 cohort felt that they didn’t get the right help for their problems and continue to have ongoing symptoms. Many in this cohort who had symptoms didn’t communicate these problems to their treating physicians and had no regular contact with a gynaecologist. The gynaecology visit is very focused on women’s issues and there is usually questioning about potential symptoms and often a physical examination is undertaken. The W99 cohort had none of this contact and was reviewed by a haematology team largely ignorant about genital GVHD, as this was only just appearing in the HSCT literature. As has been previously described, health care professionals aren’t very comfortable raising the topic of sex or sexual health so many of these women weren’t routinely asked about any genital problems that might be occurring. If the healthcare team raises these issues in their pre and post HSCT consultations with patients, it legitimises the fact that these are important issues that need to be discussed and it makes the woman feel more comfortable about highlighting any problems that may occur (Krebbs, 2008; Tierney, 2005).

The results of this study do not show a statistically significant difference between the cohorts as far as the gynaecology service having a positive impact on treatment outcomes for genital GVHD, though it does show a trend for the benefits of such a service. It was not the intent of the study to do this because the participant numbers were too small.
Post HSCT Sexuality

Many women in the study also experienced problems with sexuality post HSCT such as body changes (weight gain or loss, fatigue, skin changes), lack of sexual desire and inability to achieve orgasm. These issues are described in the sexuality literature and are common, especially for women, post HSCT (Hordern, 2008; Southard & Keller, 2009; Tierney, 2008; Wingard, et al., 1992; Yi & Syrjala, 2009). Though these issues are well described, approximately a third of the women who participated in my study and who sought help with these problems felt that they didn’t get the right help. Most women sought help from the gynaecologist for their sexuality problems. The literature suggests that post HSCT sexuality problems are multi-faceted with both physical and psychological factors contributing to sexuality problems and sexual dysfunction (Potter & Johnston, 2011; Yi & Syrjala, 2009). This would suggest that a multidisciplinary approach might need to be taken when women present with sexuality problems. A gynaecologist is certainly an important part of that team but the involvement of other healthcare professionals may assist with other aspects impacting on sexuality. Other team members that might be useful are:

- The pharmacist to assist with any drug interactions that may impact on the ability to be a sexual being.
- The haematologist may help with eliciting other physical causes for sexuality problems and can then get other medical colleagues involved (eg. Involving an endocrinologist if steroids for GVHD therapy are causing diabetes).
- A dietician to help with issues around weight loss or gain.
- A counsellor, psychologist or sexual therapist may help to assist with the psychological aspects of dysfunction. They may also be helpful for the woman’s partner who also may have concerns and fears about re-establishing an intimate and sexual relationship post HSCT (Hawkins, et al., 2009).
- The involvement of support groups such as Look Good, Feel Better® to help with issues around body image (Potter & Johnston, 2011; Yi & Syrjala, 2009).
Fertility

The number of participants that completed the fertility section of the questionnaire was very small so it is difficult to draw any firm conclusions about the results from this section. The involvement of a fertility specialist is an important part of pre and post HSCT care for many women. One third of women participating in my study wanted to either start a family or increase the size of their family post HSCT. The literature shows that despite knowing that they maybe infertile due to prior chemotherapy and will almost certainly be infertile after receiving high dose chemotherapy and radiotherapy as part of conditioning regimens, many women who were childless pre HSCT will want to try for a family of their own after HSCT (Hammond, et al., 2007; Nakayama, et al., 2009) with the ideal child being one that is genetically the couple’s own (Schover, 2005).

Though not of statistical significance, almost half of the women who answered this section would have liked to have been referred to a fertility specialist prior to HSCT but did not have that opportunity. None of the participants from Wellington saw a fertility specialist prior to their HSCT but almost three quarters of them would have liked to have had that opportunity. It may be that, due to chemotherapy induced menopause from prior leukaemia treatment, there were not any fertility options open to these women but the opportunity to discuss fertility preservation options with a specialist may have been enough for them. As has already been discussed, there may not be the time to undergo fertility preservation therapy if urgent treatment is required for a haematological malignancy (Lee, et al., 2006; Loren, et al., 2011; Nakayama, et al., 2009).

Study Limitations

There were some limitations to this study that need to be discussed. There was a total response rate for this study of 63%. This is a good response rate for mail surveys, especially for one that dealt with such sensitive issues (Bowling, 2005; Dillman, 2000). Nonetheless there is still a non-response rate of 37% and it is not known what the characteristics are of the non-responders. It is possible that responders were more concerned about genital GVHD, sexuality, fertility and gynaecological services for HSCT recipients and were therefore more motivated
to respond. Conversely, it may be that non-responders may have had significant problems with fertility, sexuality issues and genital GVHD and that revisiting these topics was too painful and they therefore chose not to participate in the study.

There was no demographic data collected on non-responders so it is difficult to analyse whether their lack of response has had an influence on the results of the study. The original lists of eligible participants consisted of names and addresses only and as ethical approval was not applied for to peruse medical records, demographic data on non-responders will remain unknown.

There was a much higher response rate for the study from participants in the Wellington cohorts compared with the Melbourne cohorts (94 – 100% versus 49 – 57%). There are some potential reasons for this:

- Women from the Wellington cohorts, especially the M04 cohort, will know the principal investigator because of her role as bone marrow transplant coordinator at Wellington Hospital. This may mean that they responded because they didn’t want to disappoint her and they wanted her to know about their experiences. The reverse could have also occurred, in that they didn’t want her to know about some of these sensitive things that may have occurred to them post HSCT, however the response rate would indicate that this does not hold true.

- Women in the W99 cohort had little gynaecological involvement and very little education about the issues being investigated. Many of these women are not now routinely followed up in the hospital clinic setting. The responses from this cohort, both in the questionnaire and in some of the letters written (see “Participant Comments” towards the end of this chapter) show that many of these women had been suffering with symptoms for a long time and finally here was a forum in which they could voice what had been happening with them.
The lower response rate from the Melbourne cohorts could be because:

- This was an international study and they didn’t want their responses about these sensitive subjects going across international borders.
- They did not know the principal investigator.
- They had access to a well resourced and structured gynaecology service for women post HSCT and therefore did not have a burning need to express their opinions about a lack of service and education in this area.

The earliest participants in the study were transplanted in 1999. This is a long time ago and people move cities, states and countries and are lost to follow-up in that time. It is not known how many questionnaires didn’t make it to their intended recipients. If correct addresses were known for all potential participants, the response rate might have been higher.

Recall bias is another potential issue for this study as, has already been mentioned, the first participants were transplanted some years ago and may not remember clearly what information and services were provided. An important part of the study design was to minimise the impact of recall bias by splitting the cohorts along the same time frames.

There may have been errors in reporting from the respondents. It might have been that information was provided about the issues being investigated but the women didn’t hear them perhaps due to information overload or the stress of the situation. This is a recognised phenomenon, especially for patients receiving complex verbal information about serious illness and complex treatment (Dermatis & Lesko, 1991; Stiff et al., 2006). Because ethical approval had not been applied for to look at participants’ medical records, there was no way to verify whether the information about the issues being investigated was given or not given, assuming that this would have been documented. There is also the possibility that participants didn’t answer questions truthfully perhaps due to embarrassment, the sensitive nature of the question or to a lack of motivation.

There was no ethnicity data collected on the study questionnaire and no ability to collect this because, as previously mentioned, access to medical records was
not applied for in the ethics committees’ applications. It is therefore unknown if there were any cultural barriers to answering questions of such a sensitive nature. This cultural safety issue was commented on when consultation was undertaken with Māori as part of ethical approval for the Central Regional Ethics Committee application. There is the possibility that the lower response rate from Melbourne participants may have in part been ethnically based in that some ethnic groups may have felt that the information being asked of them was too sensitive to share. In future research in this area, it would be useful to tease this issue out by collecting ethnicity data.

The study did not ask women whether the intent of the conditioning regimens they were exposed to were myeloablative, reduced intensity or non-myeloablative. The small numbers of potential participants for the study meant that the study was not powered to investigate whether the strength of the conditioning regimens had any impact on the rates of genital GVHD, infertility and post HSCT sexuality problems. It is my view that genital GVHD is likely to remain unchanged as the literature shows that the rates of GVHD are similar whatever the intent of the conditioning regimen (Abinun & Cavet, 2007; Anders & Barton-Burke, 2007; Devergie, 2008). It would however be interesting to see whether the lower toxicity profile of reduced intensity and non-myeloablative HSCT were less detrimental to fertility and sexuality. If outcome data for transplantation for a particular disease showed no difference in long-term survival when using either myeloablative or reduced intensity conditioning regimens, then in order to preserve fertility and sexuality post HSCT, routine use of reduced intensity conditioning could be considered for this patient population.

**Recommendations**

My study has given significant insight into what women think of the services provided around gynaecological care post HSCT and also the provision of education and information in the areas of genital GVHD, sexuality and fertility. My data shows that there needs to be a significant improvement in the information available for both patients and medical professionals about genital GVHD, post HSCT sexuality and HSCT associated fertility issues. In the
following sections I will discuss my recommendations for improvements in these areas in light of the results of my study.

**Gynaecology Services**
Gynaecology referral for women undergoing HSCT needs to be embedded into the multidisciplinary review that all patients go through prior to HSCT. It is routine practice in Wellington and in most HSCT centres for patients to have dental and psychiatric reviews in addition to a number of tests (blood, heart, kidney and lung function testing) prior to embarking on an HSCT (Schmit-Pokorny, 2007). It is important that a gynaecology review prior to HSCT becomes routine practice so that baseline assessments, education and information can be provided.

In addition to baseline assessments, preventative screening in this patient population is an important part of their gynaecological care. There need to be clear guidelines available for what type of screening needs to be undertaken and at what time points these should be done in the HSCT journey. Types of screening that should be considered are:

- Cervical screening at baseline and annually as there is an increased risk of secondary malignancies post HSCT. Screening for other gynaecological malignancies should occur post HSCT.
- Human papillomavirus screening pre and post HSCT.
- Screening for sexually transmitted diseases.
- Annual review of sex hormone levels in post-pubertal women (Milroy & Jones, 2010; Rizzo, et al., 2006).

In the post HSCT period, a battery of the pre HSCT multidisciplinary testing is repeated at 100 days post HSCT (Schmit-Pokorny, 2007). Once again, routine gynaecology review needs to be done at this point in order to detect and treat any post HSCT complications and to provide a forum for ongoing education about genital GVHD, sexuality, menopause and fertility (Zantomio, et al., 2006). Gynaecology review at this time also serves as a platform to launch ongoing and regular gynaecology review in the months and years following. Post HSCT gynaecology review is embedded into the post HSCT schedule for
female patients at the Royal Melbourne Hospital as was seen by 100% of both Melbourne cohorts being regularly reviewed by the HSCT gynaecology service. This is a goal that should be emulated in HSCT centres around the world in order to optimise gynaecological health and well-being for HSCT survivors.

Any HSCT associated gynaecology service needs a multidisciplinary approach to the care of these women. There needs to be involvement from haematology, gynaecology, endocrine and psychological services as well as specialist nursing input to ensure that all areas of female sexuality, fertility and genital care are expertly taken care of (McKee & Schover, 2001; Potter & Johnston, 2011; Stratton, et al., 2007; Yi & Syrjala, 2009; Zantomio, et al., 2006).

The insights that this study provides indicate that in Wellington, some changes need to be made to ensure that women are getting the information and service that should be an integral part of HSCT education and workup. With regards to genital GVHD, only 57% of the women in the W04 cohort were spoken to about this issue by the BMT coordinator compared with 94 – 100% in the Melbourne cohorts. This may have been due to the fact that the service was new and the team were still finding out what was needed in terms of service provision and education. It would have been interesting to see if members of the W04 cohort that were transplanted more recently had better information than those that were transplanted around the time that the service began. The numbers in the study were too small to allow this to happen but this would be an area for a further audit of the service. The W04 cohort was certainly more informed and had better gynaecological input than the W99 cohort which is pleasing to see. Nevertheless, the W04 cohort was still more dissatisfied with the information, education and service provided compared to the Melbourne cohorts.

When looking at potential service improvement for Wellington, the involvement of women who have gone through an allogeneic HSCT may help to directly inform what they feel is needed in the service. Suggested improvements that need to be made are:

- Improve the gynaecological service so that patients are seen in a timely manner and have regular post HSCT visits scheduled.
• Provide good written information about sexuality and genital GVHD and fertility.
• Incorporate better education about sexuality and genital GVHD into the routine pre HSCT education sessions.
• Incorporate routine questioning about sexuality and genital GVHD in the post HSCT follow-up and late effects clinics.

The women from the Melbourne cohorts appeared satisfied on the whole with the service and education provided to them around the issues studied. However, approximately 70% of the Melbourne participants viewed having a pre HSCT gynaecology assessment as either a very important or important part of their care. Melbourne patients aren’t currently routinely referred to gynaecology pre HSCT so this is something that the Melbourne team need to look into further in order that they may provide the best possible service to their patients.

Genital GVHD
The provision of good quality education material for women about genital GVHD is vital as has been seen by the results of my study. Any information for women about genital GVHD needs to begin with some basic information about normal female genital anatomy, as many women are uninformed about this. There also needs to be some information about the impact that an HSCT has on genital function (Krychman, 2008; Schover, 1999). Information material then needs to provide a description of what genital GVHD is before educating about:

• Prevention of genital GVHD including:
  o The use of topical oestrogen creams including why they are used, how they are administered, when to use them, any side effects that they might have and the length of time that they should be used for.
  o The use of HRT including what HRT is, in what situations it is used, how it is administered and any side effects that women should be aware of.
  o The use of vaginal dilators including a description of vaginal dilators, how to use them, the frequency of use, the length of
time that they are inserted for and when dilator use can be stopped.

- The resumption of sex including when sex activity may begin post HSCT, the use of lubrication and the use of condoms.
- Signs and symptoms of genital GVHD and what the woman should do if she suspects that she has symptoms.

**Treatment of genital GVHD**

- A general outline of treatment procedures for genital GVHD however more detailed information about treatment should be given to the woman if she does develop GVHD.

- Details about what women need to do and whom to contact should they suspect that they have developed genital GVHD.

It is important that information and education provided to women about genital GVHD is evidence based and consistent across HSCT centres world wide so that wherever a woman may search for information about this topic, the information provided is the same whatever the source. In order for this to happen there needs to be evidence based guidelines available for the prevention, assessment, diagnosis, grading and treatment of genital GVHD. At the current time, no universally validated and accepted guidelines are in use in the clinical setting. Genital GVHD guidelines will allow for standardised care and treatment of women presenting with genital GVHD and will also allow for better and more consistent research to be undertaken in this under-recognised post HSCT complication. Genital GVHD is a relatively rare presentation in gynaecology practices and there may be gynaecologists in smaller allogeneic HSCT centres treating these women who have not had much experience in this particular area. Some standardised grading and treating guidelines would help to ensure that the woman gets the care and treatment that she deserves.

There are some guidelines about aspects of genital GVHD care published in the genital GVHD literature (Filipovich, et al., 2005; Spinelli, et al., 2003; Stratton, et al., 2007; Zantomio, et al., 2006) but none of these have been prospectively validated as they are largely based on data collected from retrospective studies.
With regards to prevention and surveillance, Zantomio et al (2006) have drawn up a useful schedule for women post HSCT. These are intuitive guidelines that have been used in the patient population in Melbourne but have not been used in a clinical trial scenario. The guidelines include baseline assessments, patient education, self-surveillance by the woman, the use of hormone replacement therapy and regular post HSCT gynaecological review (see genital GVHD section in the Background chapter, page 20).

Diagnosis and grading of genital GVHD has been presented in the genital GVHD section of the Background chapter (pages 11 - 14). In the current literature there are four grading systems described. The NIH grading system (Filipovich, et al., 2005) represents a consensus opinion about the grading of genital GVHD, however it is quite a subjective grading scale that may not be particularly useful in the clinical setting. The other three grading systems (Spinelli, et al., 2003; Stratton, et al., 2007; Zantomio, et al., 2006) are more descriptive but do not go on to suggest what the treatment should be for each grade described. The reality in the clinic is that the gynaecologist needs a clear, step-by-step set of guidelines in order that she may diagnose and then go on to treat her patient effectively. This is especially the case in smaller centres where, as previously mentioned, the gynaecologist may not be exposed to many women with genital GVHD.

There are many treatment programmes for genital GVHD described in the literature with women being treated on a case presentation basis (Anguenot, et al., 2002; Corson, et al., 1982; DeLord, et al., 1999; Jain & Henry, 2001; Norian & Stratton, 2008; Rodolakis, et al., 2007) or as part of a systematic treatment programme (Spiryda, et al., 2003; Stratton, et al., 2007; Zantomio, et al., 2006). There has been no prospective research done into the best treatment for the various grades of genital GVHD and outcomes associated with the prescribed therapy. In order for evidenced based guidelines and algorithms to be developed to treat these women, more research needs to be done, whether it is a specific trial looking into genital GVHD or as part of a large GVHD trial.
Sexuality
The provision of good quality information and education about post HSCT sexuality problems was very important to women in my study. Written information about sexuality for women undergoing HSCT should begin with a description of normal genital anatomy as discussed previously and also a description of the normal sexual response cycle (Schover, 1999). Sexuality should then be described and defined and needs to emphasise that it is not all about the act of sex but includes body image, feelings, femininity, intimacy, touch, communication, self-worth and love (Krebs, 2008; Quinn, 2009; Tierney, et al., 2007). Information should then be given about:

- The impact of HSCT on sexuality and intimate relationships.
- The impact that medications used during or post HSCT may have on sexuality.
- Premature menopause and the use of hormone replacement therapy.
- How to return to being a sexual being post HSCT.
- The resumption of sex including at what point post HSCT sexual activity can resume, the use of lubrication, the use of condoms, and guidelines about oral and anal sex.
- Who to contact should the woman feel that there are ongoing problems with sexuality issues post HSCT that are not improving.

Education and information about post HSCT sexuality issues also needs to be provided to the woman’s partner. Intimacy and sexual intercourse does not occur in isolation and the effects of an HSCT will have an impact on how the partner responds to and with the woman. Education and information will help both the woman and her partner plan for a return to intimacy and sexual intercourse (McKee & Schover, 2001; Tierney, 2005; Yi & Syrjala, 2009).

There are no clear guidelines in the HSCT literature for when women are able to resume sexual activity post HSCT and how they should go about this. There has been little research done into this area and most guidelines are institutional guidelines rather than national or international guidelines based on research. Responses from women in this study showed that many women had not been
given any information about when to resume sex post HSCT and whether their partners should use condoms. For those that had received information, there was no consistency about what they had been told.

Literature suggests that sexual activity should start early post HSCT to try and prevent adhesions and strictures associated with genital GVHD (Spinelli, et al., 2003; Zantomio, et al., 2006) however there needs to be some guidance about when it is safe for the woman to do this. Tierney (2005) has proposed some guidelines for this:

- The woman should have a single partner rather than multiple partners.
- The partner should be well, that is, they should not have cold sores, influenza, a cold or a sexually transmitted disease.
- The woman’s platelet count should be greater than 50 x 10^9/L.
- Condoms should be used for three months post HSCT.
- The woman may receive oral sex but shouldn’t give it for three months post HSCT or if on immunosuppressive therapy.
- Anal intercourse should be avoided while on immunosuppressive therapy or if skin breakdown is present.
- Couples should be advised to use birth control until their fertility status has been assessed and confirmed as being unlikely to be able to conceive.

It is debatable as to whether a condom is required if the relationship is monogamous and good hygiene practices are in place. There is however no research based evidence for guidance about this point or on when sexual activity can recommence post HSCT. It is up to the HSCT centre to make the decision about what they think is appropriate given their medical experience and their patient population.

**Fertility**

The information and education given to women in my study about post HSCT fertility issues was viewed as being of poor quality. Good quality information and education therefore needs to be provided to improve patient satisfaction. It needs to be provided at multiple time points, both pre and post HSCT, as
recommended by Nakayama et al (2009). Written information about fertility should include information about normal female anatomy as previously discussed and also about ovarian function and the menstrual cycle. Information should then be provided about the impact that chemotherapy and radiation therapy has on fertility and should then go on to inform about:

- Fertility preservation options and when they might be able to be used.
- Contraceptive use post HSCT especially in the situations of non-myeloablative HSCT and for young women being transplanted for aplastic anaemia.
- Who to contact if there are fertility related questions.

**Male Sexuality, Fertility and Genital GVHD**

There was never any intention with this study to investigate what men felt about the provision of education and information about sexuality and fertility for them post HSCT. When doing background reading for the study however, it was found that issues related to male sexuality, fertility and genital GVHD post HSCT have also been overlooked by healthcare professionals. Sexual function is largely preserved in males in that the ability to have an erection and have sexual intercourse is maintained. Post HSCT, damage is sustained to the leydig cells that are involved in testosterone secretion but this usually recovers and returns to baseline by approximately three years post HSCT. Men’s issues with sexual function are often related to performance anxiety and stress but changes in body habitus post HSCT, relationship changes, fear, loss of fertility and fatigue all have an impact on how they view themselves as men and as sexual beings (Potter & Johnston, 2011; Tierney, 2005; Yi & Syrjala, 2009).

The sertoli cells, which are involved in spermatogenesis, are sensitive to chemotherapy and radiation therapy and are usually irreversibly damaged by the conditioning regimens, rendering the man infertile. Fertility preservation is more easily dealt with in men in that they are usually able to donate sperm for cryopreservation prior to any treatment. The ability to father children without the intervention of fertility services, however, has a significant psychosocial impact (Tichelli, et al., 2008).
There have been occasional reports of GVHD affecting the male genitalia (Nylander, Britt Wahlin, Lundskog, & Wahlin, 2007)(A. D'Souza, personal communication, August 30, 2011 and J. Carter, personal communication, December 20, 2011). Presentation is with erythema, erosions, lichen sclerotic changes and narrowing of the prepuce of the penis. In the published case report, biopsy was consistent with chronic GVHD. Treatment in the above cases consisted of topical steroid use.

Further work needs to be done in the areas of male sexuality, fertility and genital GVHD in order that education and information resources are available in the same way as for women.

**Future Research**

It is quite clear that there needs to be further work and research done into female genital GVHD. There needs to be collaboration amongst allogeneic HSCT centres to ensure that there are enough participants in studies so that there is enough power to generate statistically significant answers to research questions in this field. There needs to be collaboration to ensure a consensus approach is used to generate scoring systems for genital GVHD that has application both in the clinical and research settings. There needs to be collaboration so that clear evidence based guidelines are drawn up for the prevention of genital GVHD and also for the care and treatment of those who have genital GVHD. There needs to be collaboration so that there is standardised and accessible information about genital GVHD for women who are undergoing allogeneic HSCT.

The research done to date in this area is largely retrospective so prospective clinical research needs to be undertaken to confirm that the current methods for preventing, diagnosing, staging and treating genital GVHD are indeed the correct ones.

There also needs to be research looking into the impact of myeloablative versus reduced intensity conditioning regimens and the impact that these have on long-term outcomes, sexuality and fertility.
There needs to be more written in the medical literature about genital GVHD, sexuality and fertility post HSCT. These issues have a huge impact on quality of life for HSCT survivors and they need to be brought to the attention of both the HSCT and gynaecological communities. Sexuality and fertility articles have been more readily seen in the medical literature in recent years, however genital GVHD is not regularly written about and still largely consists of case reports rather than scientific writing about its diagnosis and treatment.

There is a huge opportunity for further audit/study to be done to determine how and when information about genital GVHD, sexuality and fertility post HSCT is delivered to women. As mentioned earlier in this chapter, there is no written information specifically for women undergoing allogeneic HSCT about these topics. More work needs to be done looking at what the informational needs of this group of women are and what information is essential for these women to have. I have outlined some potential points in this chapter about what information should be given but these are my opinions only. There needs to be specific evidence based guidelines and patient information developed that are consistent across HSCT centres in Australasia and the world.

**Participant Comments**

This research was planned as a quantitative study and executed as such. Despite this, some of the study participants wrote notes or letters that accompanied the returned questionnaires. Most of these were from the W99 cohort who had not received any gynaecology input or education about genital GVHD. The themes of their comments were about the lack of information about genital GVHD; body image and sexuality changes post HSCT and premature menopause. Some of the comments include:

“… I struggled with menopause (premature). My GP didn’t believe my symptoms and the hospital specialist didn’t mention menopause once.” (participant W99/007)

“I had never heard of vaginal GVHD until I received your questionnaire and assumed my problems were post menopausal.” (participant W99/004)

“When I had the transplant 10 years ago, I do not think the counselling was adequate. I was aware that doctors, nurses were
all too rushed and the emphasis was on overall GVHD of the skin, liver etc, the vagina seemed not to exist. In fact, my BMT doctor made it clear he would not discuss it…” (participant M99/010)

“…the [information] session was with my male donor and husband – not conducive to ask questions – most unsatisfactory.” (participant M99/010)

“I had weight gain issues and self image issues…. The whole hormones/sexuality issue needs to have a lot more discussion around it. Ten years down the track and I am still struggling – especially self image and coping with never having kids…” (participant W99/007)

“The medical culture is too ‘blokey’ and I wish more nurses would speak up.” (participant M99/010)

“Gynaecology services to younger women especially, I think is very important and hopefully this has been happening.” (participant W99/004)

These comments clearly indicate a level of dissatisfaction with the information and education provided and the way it was delivered. Some of these women have been living with symptoms for many years post HSCT and have not spoken with anyone about them, or if they have, this has not been responded to in a positive manner. There is a significant impact on a woman’s quality of life as can be seen by the comments from participant W99/007.

**Summary**

This is the first study to be done asking women about the information they had received about genital GVHD and also about their opinions of the worth of an HSCT related gynaecology service. One study has been done previously looking solely at the informational needs of women post HSCT about menopause and fertility (Nakayama, et al., 2009).

The hypothesis of this study was that that the provision of consultative gynaecological care and the delivery of gynaecological information to women undergoing allogeneic HSCT will mean a better informed and better satisfied female HSCT population. This study has confirmed this hypothesis by showing that the W99 cohort who had the least amount of education and gynaecological care were the most dissatisfied. The W04 cohort was more satisfied than the
W99 cohort but was less satisfied than the Melbourne cohorts who had access to a structured and well-resourced gynaecological service and good provision of education and information about these issues.

The results of this study have clearly shown that genital GVHD, post HSCT sexuality problems and infertility are quality of life issues that have long term and far reaching implications for female survivors of allogeneic HSCT and their families. The review of the literature about these issues has shown a paucity of information in the HSCT literature and a lack of research specifically in the allogeneic HSCT population. There are now more women surviving long-term post allogeneic HSCT and HSCT providers have a duty of care to their patients to ensure that they are fully aware of these post HSCT complications and that there are services provided to evaluate, treat and provide support and education.
References


Chatterjee, R., & Kottaridis, P. D. (2002). Treatment of gonadal damage in recipients of allogeneic or autologous transplantation for haematological malignancies. Bone Marrow Transplantation, 30, 629 - 635.


Appendices

Appendix One: Ethics Committee Letter One – Wellington

Central Regional Ethics Committee
Ministry of Health
Level 2, 1-3 The Terrace
PO Box 5013
Wellington
Phone (04) 494 2405
Fax (04) 494 2191

18 July 2007

Catherine Wood
Capital & Coast DHB
9 Bann Street
Island Bay
Wellington

Dear Catherine

CEN/07/07/051
An observational study investigating the objective and subjective impact of a structured gynaecology service for women who have undergone allogeneic haematopoietic stem cell transplant.

Catherine Wood
Capital & Coast DHB

(OSEC REFERS TO OPERATIONAL STANDARD FOR ETHICS COMMITTEES APRIL 2006)

Thank you for the above application which was considered by Central Regional Ethics Committee at its meeting on 10 July 2007.

The study was approved subject to the following conditions.

1. Page 8, B4 Please clarify the address that the questionnaires will be returned to.
   Envelopes should be marked "confidential" so that they will not be opened by anyone other than yourself. (OSEC 2.3, 48)
2. Page 11, D5 data should be stored in a de-identified format. (OSEC 2.3, 49)
3. Page 14, D7 data to be stored for 10 years
4. Questionnaire
   • Add the option to nominate “Your General Practitioner” to the following questions, numbers 1, 15, 23, 30, 34, 41, 52
5. Suggestions/Comments (not a requirement of ethical approval)
   • At the end of the questionnaire you could provide participants with direction to further information on support services ie, appropriate website etc.

Your response will be checked by the Administrator and a letter of approval forwarded if all the above points have been satisfactorily addressed.

If you have any queries, please contact me.

Yours sincerely

Claire Yendall
Central Ethics Committee Administrator

Email: claire_yendall@moh.govt.nz
Appendix Two: Ethics Committee Letter Two - Wellington

Central Regional Ethics Committee
Ministry of Health
Level 2, 1-3 The Terrace
P.O. Box 5013
Wellington
Phone (04) 490 2405
Fax (04) 490 2191

16 August 2007

Catherine Wood
Capital & Coast DHB
9 Bann Street
Island Bay
Wellington

Dear Catherine,

CEN/07/07/051 - An observational study investigating the objective and subjective impact of a structured gynaecology service for women who have undergone allogeneic haematopoietic stem cell transplant
Catherine Wood
Capital & Coast DHB

The above study has been given ethical approval by the Central Regional Ethics Committee.

Approved Documents
Protocol version 2, dated 7 August 2007
Information sheet and consent form version 2, dated 7 August 2007
Questionnaire version 2, dated 6 August 2007

Accreditation
The Committee involved in the approval of this study is accredited by the Health Research Council and is constituted and operates in accordance with the Operational Standard for Ethics Committees, April 2006.

Progress Reports
The study is approved until August 2011. The Committee will review the approved application annually and notify the Principal Investigator if it withdraws approval. It is the Principal Investigator’s responsibility to forward a progress report covering all sites prior to ethical review of the project in August 2008. The report form is available on http://www.newhealth.govt.nz/ethicscommittees. Please note that failure to provide a progress report may result in the withdrawal of ethical approval. A final report is also required at the conclusion of the study.
Amendments
It is also a condition of approval that the Committee is advised of any adverse events, if the study does not commence, or the study is altered in any way, including all documentation eg advertisements, letters to prospective participants.

Please quote the above ethics committee reference number in all correspondence.

It should be noted that Ethics Committee approval does not imply any resource commitment or administrative facilitation by any healthcare provider within whose facility the research is to be carried out. Where applicable, authority for this must be obtained separately from the appropriate manager within the organisation.

Yours sincerely

Claire Yendoll
Central Ethics Committee Administrator

Email: claire_yendoll@moh.govt.nz
Appendix Three: Ethics Committee Letter One - Melbourne

RE: HREC Project 2007.248 - An observational study investigating the objective and subjective impact of a structured gynaecology service for women who have undergone allogeneic haematopoietic stem cell transplant

Protocol No:

Your project was considered by the Human Research Ethics Committee at its meeting on the 14th November 2007. The Committee made the following comments:

1. Protocol – Section 9. Statistical Analysis – You state that you expect a difference of 25 - 60%, however it is not clear what difference you are expecting. Please state a clear hypothesis and endpoints. Also, please provide information regarding the method of analysis of the data.
   - Are there two different groups that you are comparing or actually three as the service at RMH has been from 1999, whereas the Wellington service has only been going since 2003? Also, have you considered the differences in the service that these two groups provide? Are they comparable?
   - Please comment on how you will address the inherent bias that participants and the investigator may have, that “more service is better”?
   - The committee questioned the value of questioning people treated up to eight years ago. How good will their recall be? Please comment.
   - Section 4 – Objectives of the study – Please delete that the purpose of the study is to complete a Masters of Health Science. This is your purpose for conducting the study but it is not an objective of the study itself.
   - Has the questionnaire been validated? In questions 15 and 34 you should consider the gender bias element. Participants may feel more comfortable with any of these practitioners based on their gender. Please amend the questions appropriately.

2. Budget - please liaise with the management accountant research, Ms Katerina Canellopoulos, to obtain approval of the budget for your study. Katerina can be contacted on telephone number 61 3 9342 3149.

3. Module One, question 1.8 – Please provide CVs for Catherine Wood and Ms Yvonne Panek-Hudson and add “Student Researcher” and provide details for Ms Wood.

4. Module One, question 1.17 (b) – Please remove the Wellington Hospital participants as this HREC is not responsible for these patients.

5. Module One, question 1.21(c) – Please explain how the coordinator will determine competency when packs are posted to potential participants.
5. Module One, question 1.30 (e) – Please add to your response a description of how the questionnaires will be labelled. For example, will they be labelled with names or code numbers and if coded how will the key to the code be kept and by whom?

6. Module One, question 1.39 – Please note that Prof. Szer cannot sign this section as he is one of the investigators. Investigators who are also heads of department are not permitted to approve their own research projects. Please obtain the signature of the person to whom Prof. Szer reports.

7. The package is being sent to patients via the Bone Marrow Service who have access to patient names and addresses. Therefore a cover letter form Prof. Szer written on Royal Melbourne Hospital letterhead should be sent to participants with the package. This letter should inform patients that the information has been sent to them on behalf of the research and that their names and addresses have not been revealed to anyone. It should also inform them that the research has been approved by the Melbourne Health Human Research Ethics Committee and provide contact numbers for the Bone Marrow Transplant Coordinator for anyone wishing to opt out of participating in the study. Please provide a copy of this letter for review.

8. Participant Information Sheet – Please consider sending participants two copies of the Participant Information Sheet and Consent Form because, for you to send back a copy of the signed form, they will have to provide you with their name and address, which they may not wish to do.
   - Please amend the heading to state, “Gynaecology Service for Women who have had a Bone Marrow Transplant Research Project.”
   - Please amend the first sentence of the second paragraph to state, “This project is looking into the way.” Then amend the third sentence to state, “The aim of this research is to identify what information and treatment has been given to women regarding graft versus host disease and their gynaecological health, post bone marrow transplant.” Then in the following sentence, delete, “often overlooked.”
   - Please amend the first sentence of the third paragraph to state, “Your involvement in this study is voluntary. You do not have to take part in it to continue to receive any care that you may require.”
   - Under the heading, “What are the aims of the study?” – Please amend the first dot point to state, “To find out the kind of information that is given to patients about vaginal GVHD, sexuality and fertility before bone marrow transplant.”
   - Please amend the heading, “Who is in the study?” to state, “Who is being asked to participate in the study?”
   - Please amend the heading, “Where is the study held?” to state, “Where will my information be stored”. Then after, “Wellington” add “at the University of Otago.”
   - Please amend the heading, “Will it cost” to state, “Will being involved in the study cost me anything?”
   - Delete the heading, “What is the study process?” Then in this paragraph add a brief description of what the questionnaire covers. Then in the first sentence of page 2 amend the spelling of, “completed”. Please note that if you choose to send participants two copies of this form you will need to include a sentence here to explain to them that they should keep one copy for their records.
   - Under the heading, “Confidentiality” – Please add a sentence to indicate that the name and addresses of participants will be kept securely and not with the questionnaires.
   - Under, “Yvonne Panch-Hudson”, please add “Bone Marrow Transplant Coordinator, Royal Melbourne Hospital.”
   - Consent Form – Please delete the section requesting an interpreter as the form is going to be mailed to patients and no provisions for interpreters has been declared in the application.
Alternatively, explain how you intend to use interpreters for patients for this site and provide a signed Statement of Approval from the Royal Melbourne Hospital Interpreter Service.

- Please delete the "Yes", "No" sections as they are superfluous and acknowledgement of each of the points is given by the participant's signature.

Please forward your response to me as soon as possible.

When responding to these queries, please ensure that:

1. All amended documents are accompanied by a clean copy of the original, a "Marked up" copy of the original with the changes clearly identified using strikethrough and underlining as required, and a clean copy of the new version which has a new version number and date clearly noted in a footer.
2. Only complete responses to this letter are forwarded. Where a number of changes, comments and/or additional documents are required, these should be forwarded together in the one package. DO NOT REPLY TO THIS LETTER IN TWO OR MORE SEPARATE STAGES.

Yours sincerely

[Signature]

Dr. Angela Watt
Manager - Human Research Ethics Committee
Appendix Four: Ethics Committee Letter Two - Melbourne

The Human Research Ethics Committee operates in accordance with the NHMRC National Statement on Ethical Conduct in Human Research 2007.

PD Royal Melbourne Hospital
Parkville Victoria 3050
Telephone: 61 3 9342 8530
Facsimile: 61 3 9342 8548
Email: research@hr.org.au
Website: http://research.hr.org.au
ABN 73 802 765 972

OFFICE FOR RESEARCH

MELBOURNE HEALTH

Research Directorate - Human Ethics Committee Approval Form
Telephone: 9342 8530 Facsimile: 9342 8548

This is to certify that

HRHC Project No: 2007.248 Approval date: 02/03/2009 Expiry date: 02/03/2012

Project Title: An observational study investigating the objective and subjective impact of a structured gynaecology service for women who have undergone allogeneic haematopoietic stem cell transplant

Principal Investigator: Miss Catherine Wood
Wellington Blood and Cancer Centre
Wellington Hospital
Private Bag 7902
Wellington 6242
NEW ZEALAND

Sponsored by: N/A


Participant Consent Form: Version 2 dated 11/03/2008
Patient Information Sheet: Version 4 dated 27/02/2009

Investigator Brochure: N/A

Other enclosures: (please describe eg. advertisement etc.) Gynaecology Questionnaire Version 3 dated 5th April 2008, Participant Invitation Letter dated December 2008

Conducted at: Royal Melbourne Hospital has been approved

This proposal meets the requirements of the NHMRC National Statement on Ethical Conduct in Human Research 2007.

It is now your responsibility to ensure that all people conducting this research project are made aware of which documents have been approved.

This approval is subject to ongoing, current and valid insurance coverage throughout the duration of the conduct of the study.

You are required to notify the Secretary of the Human Research Ethics Committee of:
• Any change in the protocol and the reason for that change together with an indication of ethical implications (if any) by submitting an amendment to the study.
• Serious adverse effects on subjects and the action taken to manage them, including amended Plain Language Statement and Consent Form where appropriate.
• Any unforeseen events.
• Your inability to continue as Principal Investigator, or any other change in research personnel involved in the study
• A delay of more than 12 months in the commencement of the project.
• The actual date of commencement of the study.

You are required to submit to the Human Research Ethics Committee:
• An Annual Report every twelve months for the duration of the project.
• A detailed Final Report at the conclusion of the project.

The Human Research Ethics Committee may conduct an audit at any time.

An extension of the project beyond the stated conclusion date should be sought from the Human Research Ethics Committee.

Signed: [Signature]
Dr. Angela Wei
Secretary – Human Research Ethics Committee

Incorporating: The Royal Melbourne Hospital (City Campus and Royal Park Campus), North Western Mental Health, North West Diaylsis Service, Victorian Infectious Diseases Reference Laboratory, NHM Shared Support Service

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29 May 2009

Catherine Wood
Capital & Coast DHB
9 Bann Street
Island Bay
Wellington

"Dear Catherine Wood

CEN/07/07/051
An observational study investigating the objective and subjective impact of a structured gynaecology service for women who have undergone allogeneic haematopoietic stem cell transplant Catherine Wood

Amendment:

Thank you for submitting the above amendment, which was considered by the Central Regional Ethics Committee by the Chairperson under delegated authority and approved.

Please quote the above ethics committee reference number in all correspondence.

Yours sincerely

Sonia Scott
Central Regional Ethics Committee Administrator
Email: sonia_scott@moh.govt.nz

Answer: The document is a letter from the Central Regional Ethics Committee regarding an observational study investigating the impact of a structured gynaecology service for women who have undergone allogeneic haematopoietic stem cell transplant. It includes an amendment to the trial protocol and instructions to quote the ethics committee reference number in all correspondence. The letter is signed by Sonia Scott, the Central Regional Ethics Committee Administrator, and includes an email address for further communication.
Appendix Six: Ethics Committee Letter Three - Melbourne

17 March 2010

Miss C. Wood
Wellington Blood and Cancer Centre
Wellington Hospital
Private Bag 7902
Wellington 6242
NEW ZEALAND

Dear Miss Wood

REF: HREC Project 2007.248 - An observational study investigating the objective and subjective impact of a structured gynaecology service for women who have undergone allogeneic haematopoietic stem cell transplant

Thank you for submitting the following correspondence:

A Request for Approval of Amendment form dated 26th January 2010 enclosing:

- Amendment 1
- Participant Information Form Version 5 dated 17th January 2010
- Third Party Consent Form Version 3 dated 17th January 2010
- Potential Participant Study letter dated January 2010
- Protocol Version 5 dated 17th January 2010
- Gynaecology Questionnaire Version 4 dated 25th January 2010

I am pleased to advise that at its meeting on the 17th March 2010 the Human Research Ethics Committee reviewed and approved the amendment(s) to the above named project.

Yours sincerely,

Dr. Angela Watt
Manager - Human Research Ethics Committee
Appendix Seven: Ethics Committee Letter Four - Wellington

7 April 2010

Catherine Wood
Capital & Coast DHB
9 Bann Street
Island Bay
Wellington

Dear Catherine Wood

CEN/07/07/051
An observational study investigating the objective and subjective impact of a structured gynaecology service for women who have undergone allogeneic haematopoietic stem cell transplant

Documents Approved
• Protocol – version 5, dated 23 March 2010. Change of contact numbers of the Principal Investigator and Co-Investigator in Melbourne
• Patient Information Sheet – Version 3 dated 23 March 2010. Change of contact numbers of the Principal Investigator and Co-investigator in Melbourne
• Patient Consent Form – Version 3, dated 23 March 2010. Change of contact number of the Principal Investigator and the date of that preliminary results are expected.
• Letter of introduction to accompany the study pack – the contact number of the Principal Investigator has changed.

Questionnaire
Version 4, dated 25 January 2010. Changes made to the document cover:
• In the fertility section of the questionnaire, the order of questions has been altered slightly to facilitate the flow of the questionnaire.
• Some questions have been added to the questionnaire as a result of the pre-testing Questions 22 and 25 ask about the date to diagnosis and the duration of symptoms of genital GVHB.

Annual Progress Report
• Annual Progress Report to the Central Regional Ethics Committee

Thank you for submitting the above amendment, which was considered by the Acting Chairperson of the Central Regional Ethics Committee and approved.

Please quote the above ethics committee reference number in all correspondence.

Administered by the Ministry of Health                Approved by the Health Research Council                http://www.ethicscommittees.health.govt.nz
Yours sincerely

Sonia Scott  
Administrator  
Central Regional Ethics Committee  
Email: sonia_scott@moh.govt.nz
Appendix Eight: Protocol

An observational study investigating the objective and subjective impact of a structured gynaecology service for women who have undergone allogeneic haematopoietic stem cell transplant.

Version 5, 23 March 2010
**Principal Investigator:** Catherine Wood  
University of Otago  
C/- Wellington Blood and Cancer Centre  
Wellington Hospital  
Private Bag 7902  
Wellington 6242  
New Zealand  
Tel: + 64 4 806 2091  
Fax: + 64 4 385 5843

**Co-investigator:** Yvonne Panek Hudson  
(Melbourne)  
Allograft Nurse Consultant  
Royal Melbourne Hospital  
Parkville 3050  
Victoria  
Australia

**Supervisors:** Associate Professor John Carter  
University of Otago  
C/- Wellington Blood and Cancer Centre  
Wellington Hospital  
Private Bag 7902  
Wellington 6242  
New Zealand  
Tel: + 64 4 385 5999  
Fax: + 64 4 385 5843

Dr David Ritchie  
Consultant Haematologist  
Head of Transplant Immunology  
Division of Haematology / Medical Oncology  
Peter MacCallum Cancer Centre,  
Locked Bag 1, A'Beckett St.,  
Victoria 8006  
Australia  
Tel: + 61 3 9656 1623  
Fax: + 61 3 9656 1408
# Synopsis

<table>
<thead>
<tr>
<th>Protocol title</th>
<th>An observational study investigating the objective and subjective impact of a structured gynaecology service for women who have undergone allogeneic haematopoietic stem cell transplant.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Short title</td>
<td>Gynaecology Services for Women who have had a Bone Marrow Transplant.</td>
</tr>
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</table>
| Background     | Sexuality and fertility problems are issues seen in men and women post allogeneic haematopoietic stem cell transplant. Surviving a transplant is much more likely today due to better supportive care and better medications and these issues have become increasingly important in the lives of survivors. \(^1\text{-}^4\).  
Female genital graft versus host disease is also an important post transplant adverse event. It affects the female lower genital tract causing inflammation, dryness and eventual fibrosis and stricture of the vagina. \(^5\text{-}^{10}\).  
The inclusion of a peri-transplant gynaecology programme is an essential part of a woman’s care. It needs to include pre-transplant counselling to encourage patient participation, regular review by a named gynaecologist post transplant and commencement of hormone replacement therapy early in the post transplant period. \(^5\text{-}^6,^{10}\). |
| Funding Sources| Self funded as this is a student thesis for Masters of Health Science.                                                                                                                              |
| Objective      | The objective of the study is to investigate the impact that a transplant specific Gynaecology programme has for women undergoing allogeneic stem cell transplantation.                                         |
| Study design   | Observational descriptive study  
Convenience sample of women will be recruited in the following groups:  
- All eligible women from the Wellington region who had an allogeneic stem cell transplant from 1999 to July 2004 prior to the instigation of a Gynaecology service for transplant recipients.  
- All eligible women from the Wellington region who had an allogeneic stem cell transplant after the instigation of a newly developed Gynaecology service for transplant recipients.  
- All eligible women from the Royal Melbourne Hospital, Australia who have had an allogeneic stem cell transplant. |
after January 1999. These women have been involved with a comprehensive and long running Gynaecology programme that has been operating there since 1999. This group will be split into two cohorts following the dates of the Wellington cohorts. The first will be eligible women who were transplanted between 1999 and July 2004 and the second will be eligible women who were transplanted after 1st August 2004.

A pack will be handed out or mailed out to women in the above groups. Each pack contains a letter of introduction, an information sheet, two consent forms, the questionnaire and a stamped addressed envelope. All questionnaires will be posted back to the Principal Investigator.

<table>
<thead>
<tr>
<th>Selection criteria</th>
<th>Inclusion Criteria</th>
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<tbody>
<tr>
<td></td>
<td>Age ≥ 16 years.</td>
</tr>
<tr>
<td></td>
<td>Female.</td>
</tr>
<tr>
<td></td>
<td>Received an allogeneic Haematopoietic Stem Cell Transplant post 1st January 1999 and ≥ six months ago at Wellington Hospital or the Royal Melbourne Hospital.</td>
</tr>
<tr>
<td></td>
<td>Ability to understand and the willingness to sign a written informed consent document.</td>
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</tbody>
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<table>
<thead>
<tr>
<th>Exclusion Criteria</th>
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<tbody>
<tr>
<td>Age &lt; 16 years.</td>
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<tr>
<td>Male.</td>
</tr>
<tr>
<td>Unable to understand and sign written informed consent.</td>
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<tr>
<th>Sample size and Study duration</th>
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</thead>
<tbody>
<tr>
<td>All women who have had a transplant post January 1999 at Wellington Hospital or the Royal Melbourne Hospital and at least 6 months ago. Study duration is approximately three years.</td>
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<tr>
<th>Randomisation</th>
<th>Nil</th>
</tr>
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</table>

<table>
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<tr>
<th>Statistical considerations</th>
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<tbody>
<tr>
<td>Consultation has been undertaken with Mr Gordon Purdie, Statistician at the Wellington School of Medicine.</td>
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<tr>
<th>Feasibility</th>
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<tr>
<td>Patients will be recruited from a patient pool that has had a haematopoietic stem cell transplant at either Wellington Hospital or the Royal Melbourne Hospital. This study would involve a single questionnaire that would be completed by eligible participants.</td>
</tr>
</tbody>
</table>

| Follow-up | Nil |
2 Study Schema

Women who have had an allogeneic stem cell transplant.

Had a transplant at Wellington Hospital post 1st January 1999 and never had any gynaecology input pre or post transplant.

Had a transplant in the Wellington Hospital from July 2004 onwards and had the input of a newly instigated transplant gynaecology service.

Had a transplant at the Royal Melbourne Hospital post 1st January 1999 and participated in the BMT gynaecology service programme.


Transplanted post 1st August 2004.

PI identifies patient. Mail out to potential participant a study pack containing:
- Introductory letter
- Patient information sheet
- Consent form
- Questionnaire
- Prepaid addressed envelope

BMT Coordinator identifies potential participant. She gives out or mails out a pack to the participant which contains:
- Introductory letter
- Patient information sheet
- Consent form
- Questionnaire
- Prepaid addressed envelope
3 Background and introduction

Chronic GVHD is one of the most significant problems faced by allogeneic HSCT recipients and is reported to occur in up to 60% of patients. It commonly affects the liver, skin and mucous membranes. It also affects the female lower genital tract causing inflammation, dryness and eventual fibrosis and stricture of the vagina\textsuperscript{5-10}.

Female genital GVHD was first described in 1982 by doctors at the Fred Hutchinson Cancer Institute in Seattle, USA\textsuperscript{9}. They described five women who had symptoms ranging from vaginal inflammation through to complete sealing of the entrance of the vagina.

Apart from sporadic case reports there has been very little published on genital GVHD since its initial description. The first research into this area was conducted by Spinelli and colleagues in 2003\textsuperscript{5}. They undertook a retrospective study looking at the incidence, severity and change over time of female genital GVHD at their institution. 24.9% or 53 of the 213 patients in the study showed clinical evidence of genital lesions which were considered to be GVHD. Of those 53 women, 66% had minimal, 22% had moderate and 12% had severe genital GVHD. The authors admit that this study had its weaknesses but it is the first attempt to describe and grade the clinical presentations of genital GVHD. It indicates that female genital GVHD may be a more common complication than initially thought.

This is confirmed by Flowers in a study comparing chronic GVHD after allogeneic transplantation using peripheral blood stem cells (PBSC) versus bone marrow. It shows that there has been an increase in the amount of vaginal GVHD with the increasing use of PBSC\textsuperscript{11}.

Zantomio et al conducted a retrospective chart audit of the medical records of all female transplant recipients at a single centre between May 1999 and July 2004. They found that the incidence of genital tract GVHD was 49% at 2 years, with one third of surviving females having severe vaginal stenosing disease. They also concluded that female genital GVHD was an under recognised complication of allogeneic HSCT. Furthermore, they commented that a peri-transplant gynaecology programme was an essential part of a patient’s care. It needed to include pre-transplant counselling to encourage patient participation, regular review by a named gynaecologist post transplant and commencement of hormone replacement therapy early in the post transplant period. This allowed early detection of genital GVHD, early treatment and therefore better outcomes for women\textsuperscript{6}.

Sexuality and fertility issues have become increasingly more important as stem cell transplantation becomes a life extending or curative treatment for increasing numbers of women\textsuperscript{1-3}. Issues such as decreased libido, premature menopause and changes in the vagina may have a huge impact on a woman’s quality of life post transplant\textsuperscript{1}. Infertility may be one of the most devastating effects of allogeneic transplantation for adolescent and young women. Research continues in the area...
of infertility to investigate ways of preserving fertility. Currently the only option available to women is embryonic cryopreservation. This requires a woman to go through ovarian stimulation which may not be in the best interests of the woman as it may delay urgent treatment. A comprehensive approach is required to ensure that sexuality and fertility issues in transplant survivors are assessed and treated proactively.

The provision of high quality education and information plus the involvement of a multidisciplinary team is essential in delivering quality care to these patients. Information and education play an important role in the care of patients. It may provide ways for patients to become actively involved in their own care, help to manage the side effects of transplantation and enhance feelings of control by providing means of managing their illness and coping with symptoms whereas lack of good information and education about the side effects of treatment may cause distress, anxiety and dissatisfaction for patients and their families.

This proposed study will more formally evaluate the provision of a structured gynaecology service for women undergoing HSCT and will examine the outcome of this approach to manage these under recognised and complex problems for female survivors of HSCT. It will also look in detail at the information and education provided for women pre and post transplant about sexuality, fertility and vaginal GVHD.

4 Objectives of the study

The hypothesis for this study is that the provision of consultative gynaecological care and the delivery of gynaecological information to women undergoing allogeneic stem cell transplant will mean a better informed and better satisfied female transplant population.

The Objective of this study is to investigate the impact that the involvement of a transplant specific Gynaecology programme has for women undergoing allogeneic stem cell transplantation. The specific aims of the study are:

- To find out the type of information women have been given about vaginal GVHD, sexuality and fertility before they had their transplants.
- To see if a gynaecology service designed especially for women undergoing BMT is helpful with early detection and treatment of vaginal graft versus host disease.
- To see if a gynaecology service designed especially for women undergoing BMT is beneficial when fertility and sexuality issues arise.
- To discover the kind of information women would like to receive about these issues before and after BMT.
- To discover whether the Gynaecology services being provided meet the emotional, psychosocial and physical needs of the woman undergoing allogeneic stem cell transplantation.

It is not the intent of this study to measure physical improvement in genital GVH care. The study numbers are too small rather it is looking at the information and care provided to women.
5 Trial Design

Study Design: Descriptive observational study

Procedures: Pre testing of the questionnaire on six potential participants from the Melbourne cohort will be carried out once approval for the study has been obtained from both sites. Any changes to the questionnaire arising from the pre-testing will be resubmitted to the Ethics Committees for further approval.

All women who have had a bone marrow transplant at Wellington Hospital post 1st January 1999 and at least six months ago will be asked to participate in the study. These participants will form the basis of two groups:

- Women who have not had any routine Gynaecology input pre or post stem cell transplantation.
- Women who have had the input of a newly instigated Gynaecology service for those undergoing allogeneic stem cell transplantation.

All women from the Royal Melbourne Hospital who have had an allogeneic stem cell transplant post 1st January 1999 and who have had involvement with the transplant specific Gynaecology service that has been operating since 1999 will be asked to participate in the study. These participants will form the basis of two groups:

- Women who were transplanted between 1st January 1999 and the 31st July 2004.
- Women who were transplanted after the 31st July 2004.

Potential participants will be either sent or given a pack which contains:

- A letter of introduction
- An ethics committee approved “Patient Information Sheet”.
- Two ethics committee approved consent forms. Both forms are to be completed then one is enclosed with the questionnaire and is sent to the Principal Investigator. The second consent form is to be kept by the participant for their own records.
- A questionnaire.
- A prepaid addressed envelope in which to return the completed consent form and the completed questionnaire.
6 Patient selection criteria

Inclusion Criteria

- Age ≥ 16 years.
- Female.
- Received an allogeneic Haematopoietic Stem Cell Transplant post 1st January 1999 and at least six months ago at the Wellington Hospital, New Zealand or the Royal Melbourne Hospital, Australia.
- Ability to understand and the willingness to sign a written informed consent document.

Exclusion Criteria

- Age < 16 years.
- Male.
- Inability to understand and sign a written informed consent document.

Withdrawal Criteria

- Patient wishes to withdraw from the study.
- Study is complete.

7 Patient recruitment

In Wellington the study participants will be recruited through the Principal Investigator using the Bone Marrow Transplant database held at the Wellington Blood and Cancer Centre. At the Royal Melbourne Hospital study participants will be recruited through the Allograft Nurse Consultant.

8 Clinical evaluation, laboratory tests and follow-up

There will be no clinical evaluation, laboratory testing or follow-up involved in this study.

9 Statistical considerations

Sample size

All eligible women who have had allogeneic stem cell transplant post 1st January 1999 at Wellington Hospital will be asked to participate in the study. This will be a total of approximately 30 participants.
All eligible women who have had an allogeneic stem cell transplant post 1st January 1999 and been involved in the Gynaecology programme at the Royal Melbourne Hospital will be asked to participate in the study. This will be approximately 80 – 100 participants.

**Analysis**

Consultation has been undertaken with Mr Gordon Purdie, Statistician at The Wellington School of Medicine. He has advised with ways to eliminate recall bias from the study population and these have been included into the study design. In order to address issues around recall bias the Melbourne cohort will be split into two groups. The first group will be those who were transplanted from the years 1999 – July 2004 and the second group will be those who were transplanted from August 2004 onwards. These dates match up with the starting of the Gynaecology service in Wellington and allows examination of whether differences that may be found are a consequence of the change in service delivery or a differential recall because of the time difference of these women. Comparing the women from Melbourne pre (post 1999) and post 2004 will give a measure of the differential recall because of the time difference. If the difference in Wellington was greater than this time effect difference then I could conclude that it is likely to be a consequence of the change in service delivery.

Analysis of the data will be by descriptive statistics and confidence intervals. Changes in the proportions of women giving specific answers will be compared with chi-squared tests, differences in these changes between Wellington and Melbourne will be compared with the Breslow-Day Test for Homogeneity of the Odds Ratios. Changes in Likert scales (rating scales) will be compared with Wilcoxon rank-sum tests, differences in these changes between Wellington and Melbourne will be compared with interaction terms in analysis of variance on ranked data.

**10 Data handling**

The returned questionnaires will be held in a locked filing cabinet which is accessible only by the Principal Investigator. Questionnaires and consent forms will be stored separately. Data collated from the questionnaires are stored in a password protected computer. Computer and files are in a locked office. The raw data collected will be held for ten years before being destroyed.

**11 Ethical considerations**

**Patient Protection**

The Principal Investigator will ensure that this study is conducted in accordance with Good Clinical Research Practise guidelines.
The protocol has been approved by the Wellington Regional Ethics Committee and the Human Research Ethics Committee in Melbourne, Australia

**Subject Identification**

A sequential identification number will be automatically attributed to each participant who signs the consent form. This number will identify the participant and must be included on the questionnaire. No other identifying data will be collected on the questionnaire.

The Wellington participants will receive a code number as follows: W/99/001 as the first questionnaire with subsequent sequential numbering (W/99/002, W/99/003 etc) for those women transplant between the 1st January 1999 and the 31st July 2004 and W/04/001 as the first questionnaire with subsequent number (W/04/002, W/04/003 etc) for those women transplanted on or after the 1st August 2004.

The Melbourne participants will receive a similar code as follows: M/99/001 as the first questionnaire with subsequent sequential numbering (M/99/002, M/99/003 etc) for those women transplanted between 1st January 1999 and the 31st July 2004 and M/04/001 as the first questionnaire with subsequent numbering (M/04/001, M/04/003 etc) for those women transplanted on or after 1st August 2004.

The key to the code for the Wellington cohort will be kept by Catherine Wood and for the Melbourne cohort will be kept by Yvonne Panek-Hudson in password protected computers.

**Informed consent**

All participants will be informed of the aims of the study. They will be informed as to the strict confidentiality of their data. An example of a patient information sheet, consent form and questionnaire is given as an appendix to this protocol.

It will be emphasised that participation in the study is voluntary and that the woman is allowed to refuse participation in the study whenever she wants. This will not prejudice her subsequent care. Documented informed consent must be obtained for all participants before a questionnaire can be administered.

**12 Administrative responsibilities**

**The Principal Investigator**

The Principal Investigator and her supervisors will hold final responsibility for all aspects of the trial.

**Principal Investigator**

Catherine Wood  
University of Otago  
C/- Wellington Blood and Cancer Centre
13 Publication policy

The study results will be written up as a thesis by the Principal Investigator on the basis of the final analysis. This will be submitted to the University of Otago for marking. Publications which will be submitted to peer reviewed medical and nursing journals may arise from this research.

A lay summary of results will be sent to all participants who indicated they would like to receive them.

14 References


Appendix Nine: Letter of Introduction - Wellington

Date

Name and Address

Dear

I am writing to ask your help in a study I am doing for my Masters in Health Sciences which I am doing through the University of Otago. The study is looking at Gynaecology Services for women who have had a bone marrow transplant. The study will investigate information and services provided around any problems associated with fertility, vaginal graft versus host disease and sexuality.

You will find attached to this letter an information sheet about the study, consent forms, the questionnaire and a prepaid addressed envelope. If, after reading the information sheet you are happy to participate in the study, then please read over and sign the two consent forms. Then go on and answer the questionnaire. Once you have completed the questionnaire to your satisfaction, place one of the consent forms and the questionnaire in the envelope provided and put it in the mail. The second consent form and the information sheet are for you to keep for your records.

If for some reason you prefer not to respond, please let me know by returning the blank questionnaire in the enclosed stamped envelope.

I would like to reassure you that your answers are completely confidential and will be released only as summaries in which no individual’s answers can be identified. This research has been approved by the Central Regional Ethics Committee.

Results from the study will be used to complete my thesis but will also be used as evidence to help health professionals become more aware of sexuality, fertility and vaginal GVHD issues and to help improve services in this much overlooked area of transplantation.

If you have any questions or comments about this study, I would be happy to talk with you. You may contact me by telephone on 04 806 2091, by email at Catherine.Wood@ccdhb.org.nz or by writing to me at:

Wellington Blood and Cancer Centre
Wellington Hospital
Private Bag 7902
Wellington 6242

Thank you once again for your help with this study.

Yours sincerely

Catherine Wood
Appendix Ten: Letter of Introduction - Melbourne

The Royal
Melbourne Hospital
City Campus

January 2010

Dear Potential Study Participant

Re: Gynaecology Service for Women who have had a Bone Marrow Transplant Research Project.

I am writing to invite you to participate in a study we are undertaking which is looking at Gynaecology Services for women who have had a bone marrow transplant. The study will investigate information and services provided around any problems associated with fertility, vaginal graft versus host disease and sexuality.

This study pack has been sent to you on behalf of the researcher. Your names and addresses have not and will not be revealed to any members of the research team other than myself and Yvonne Panek-Hudson.

You will find attached to this letter an information sheet about the study, a consent form, the questionnaire and a prepaid addressed envelope. If, after reading the information sheet you are happy to participate in the study, then please read over and sign the two consent forms. Then go on and answer the questionnaire. Once you have completed the questionnaire to your satisfaction, place one of the consent forms and the questionnaire in the envelope provided and put it in the mail. The second consent form and the information sheet are for you to keep for your records.

If for some reason you prefer not to respond, please let the researcher know by returning the blank questionnaire in the enclosed stamped, addressed envelope.

I would like to reassure you that your answers are completely confidential and will be released only as summaries in which no individual’s answers can be identified. This research has been approved by the Melbourne Health Human Research Ethics Committee.

If you have any questions about the study please feel free to contact:

Yvonne Panek-Hudson
Allograft Nurse Consultant
Ph: 03 9656 1118
yvonne.panek-hudson@petermac.org

Thank you for your help.

Yours sincerely

Professor Jeff Szer
Director – BMT Service

Grattan Street
Parkville Vic 3052 Australia
Telephone: 61 3 9347 7000
Fax: 61 3 9342 7802
www.mh.org.au

Postal Address: c/o Post Office
The Royal Melbourne Hospital
Parkville Vic 3052 Australia
Appendix Eleven: Patient Information Sheet - Wellington

Gynaecology Services for Women who have had a Bone Marrow Transplant

This is an information sheet about a research project that I am doing for my Masters in Health Science at the University of Otago. You are invited to participate in this study looking at Gynaecology services provided for women who have had a bone marrow transplant.

It is looking into the way that a transplant specific Gynaecology service for women who have had a bone marrow transplant (BMT) might help with fertility, sexuality and vaginal graft versus host disease. I am asking for women who have had a bone marrow transplant at least six months ago to participate in the study. This research will help me to understand what information and treatment women have been given for these issues. I hope that it will lead to better care of women in this often overlooked area of bone marrow transplantation.

This study is voluntary (your choice). You may withdraw at any time without it affecting your health care now or in the future.

What is vaginal graft versus host disease?
Graft versus Host Disease (GVHD) is a common complication of BMT. It can occur when the donated bone marrow grows and your donor cells (the graft) recognise your body (the host) as foreign. The graft may attack certain organs such as the skin, gut and liver. GVHD may also affect a woman’s vagina which may lead to dryness, ulceration and tightening and shortening of the vagina. This may affect your ability to have sex comfortably.

What are the aims of the study?
The aims of this study are:
- To find out the kind of information you were given about vaginal GVHD, sexuality and fertility before you had your transplant.
- To see if a gynaecology service designed especially for women undergoing BMT is helpful with early detection and treatment of vaginal graft versus host disease.
- To see if a gynaecology service designed especially for women undergoing BMT is beneficial when fertility and sexuality issues arise.
- To discover the kind of information women would like to receive about these issues before and after BMT.

Who is in the study? Women who have had their BMT at Wellington Hospital in New Zealand or the Royal Melbourne Hospital in Australia. There will be sixty women involved in total.

Where is the study held? The questionnaires will be returned to me in Wellington where the data will be collated and analysed.

How long is the study? The study will take approximately three years to complete. A summary of results should be available in 2010.

Will it cost? There is no cost for you.

What does this study involve?
- Your permission to be involved in the study (your consent).
- Completion of a questionnaire.

What is the study process? The study material has been provided to you in an envelope. In this envelope along with this information sheet are two consent forms, a questionnaire and a prepaid envelope. The questionnaire consists of a series of questions that are mostly able to be answered by ticking a box. There are questions about your bone marrow transplant, the type of information you received about vaginal GVHD, sexuality and fertility and whether you experienced any of problems related to these
issues. Once you have read this information sheet, had a look at the questionnaire and have decided that you would like to participate in the study then please sign both of the consent forms. You can then go on and complete the questionnaire. Please note that you do not have to answer all the questions if you do not want to.

When the questionnaire is completed to your satisfaction, please place this along with one of the signed consent forms in the prepaid envelope provided and put it in the mail. The second signed consent form and this information sheet are for you to keep for your records.

If for some reason you prefer not to respond, please let the researcher know by posting back the blank questionnaire in the enclosed stamped, addressed envelope.

Confidentiality: No material that could personally identify you will be used in any reports about this study. The questionnaires will be stored in a locked filing cabinet accessible only by me. Data collated from the questionnaires are stored in a password protected computer. Computer and files are in a locked office.

Results of the study: The overall results of the study (from which you cannot be identified) will be published in medical journals and presented at national and international Haematology conferences.

If you would like a copy of the results of the study, please fill in your address details on the consent form. I will mail a copy out to you when the study is completed. This will probably be in 2010.

If you require further information please ring or email me.

Ethical approval: This study has ethical approval from the Central Regional Ethics Committee in New Zealand and the Human Research Ethics Committee of Melbourne Health.

Thank you for taking the time to share your experiences and opinions about this overlooked area in the care of women post transplant.

If you have any concerns about the study you may contact:

Health Trust Advocate
Health and Disability Commissioner
National Freephone: 0800 11 22 33
Wellington: (04) 494 7900
Website: www.hdc.org.nz

Human Research Ethics Committee, Melbourne Health
Dr Angela Watt
Manager, Human Research Ethics Committee
Phone: + 61 3 9342 7550
You will need to tell Dr Angela Watt the name of one of the researchers.

You may also contact the following people at any time to ask about anything you may not understand:

Principal Investigator
Catherine Wood
Phone: + 64 4 806 2091
Catherine.Wood@ccdhb.org.nz

Co-investigator (Melbourne)
Yvonne Panek-Hudson
Phone: + 61 9656 1118

Supervisors
Associate Professor John Carter
Phone: + 64 4 385 5999
Dr David Ritchie
Phone: + 61 3 9656 1111

This study is voluntary (your choice). You may withdraw at any time without any changes to your health care now or in the future.
Appendix Twelve: Patient Information Sheet - Melbourne

Gynaecology Services for Women who have had a Bone Marrow Transplant Research Project

Information Sheet

You are invited to participate in this study looking at Gynaecology services provided for women who have had a bone marrow transplant. The aim of this research is to identify what information and treatment has been given to women regarding graft versus host disease and their gynaecological health post bone marrow transplant. It is hoped that this study will lead to better care of women in this area of bone marrow transplantation. This research project will contribute to my obtaining a Masters in Health Science Degree at the University of Otago.

This project is looking into the way that a transplant specific Gynaecology service for women who have had a bone marrow transplant (BMT) might help with fertility, sexuality and vaginal graft versus host disease. I am asking for women who have had a bone marrow transplant at least six months ago to participate in the study.

Your involvement in this study is voluntary. You do not have to take part in it to continue to receive any care that you may require.

What are the aims of the study?
The aims of this study are:
- To find out the kind of information that is given to patients about vaginal GVHD, sexuality and fertility before bone marrow transplant.
- To see if a gynaecology service designed especially for women undergoing BMT is helpful with early detection and treatment of vaginal graft versus host disease.
- To see if a gynaecology service designed especially for women undergoing BMT is beneficial when fertility and sexuality issues arise.
- To discover the kind of information women would like to receive about these issues before and after BMT.

Who is being asked to participate in the study? Women who have had their BMT at Wellington Hospital in New Zealand or the Royal Melbourne Hospital in Australia. There will be 100 women involved in total.

Where will my information be stored? The questionnaires will be returned to me in Wellington, at the University of Otago, where the data will be collated and analysed.

How long is the study? The study will take approximately three years to complete. A summary of results should be available in 2010.

Will being involved in the study cost me anything? There is no cost for you.

What does this study involve?
- Your permission to be involved in the study (your consent).
- Completion of a questionnaire.

The study material has been provided to you in an envelope. In this envelope along with this information sheet are two consent forms, a questionnaire and a prepaid envelope. The questionnaire consists of a series of questions that are mostly able to be answered by ticking a box.

Your involvement in this study is voluntary (your choice). You may withdraw at any time without any changes to your health care now or in the future.

What is vaginal graft versus host disease?
Graft versus Host Disease (GVHD) is a common complication of BMT. It can occur when the donated bone marrow grows and your donor cells (the graft) recognise your body (the host) as foreign. The graft may attack certain organs such as the skin, gut and liver. GVHD may also affect a woman’s vagina which may lead to dryness, ulceration and tightening and shortening of the vagina. This may affect your ability to have sex comfortably.
There are questions about your bone marrow transplant, the type of information you received about vaginal GVHD, sexuality and fertility and whether you experienced any of problems related to these issues. Once you have read this information sheet, had a look at the questionnaire and have decided that you would like to participate in the study then please sign both of the consent forms. You can then go on and complete the questionnaire. Please note that you do not have to answer all the questions if you do not want to.

When the questionnaire is completed to your satisfaction, please place this along with one of the signed consent forms in the prepaid envelope provided and put it in the mail. The second signed consent form and this information sheet are for you to keep for your records.

If for some reason you prefer not to respond, please let the researcher know by posting back the blank questionnaire in the enclosed stamped, addressed envelope.

Confidentiality: No material that could personally identify you will be used in any reports about this study. The questionnaires will be stored in a locked filing cabinet accessible only by me. The names and addresses of participants will be kept securely and will not be stored with the questionnaires. Data collated from the questionnaires are stored in a password protected computer. Computer and files are in a locked office.

Results of the study: The overall results of the study (from which you cannot be identified) will be published in medical journals and presented at national and international Haematology conferences. If you would like a copy of the results of the study, please fill in your address details on the consent form. I will mail a copy out to you when the study is completed. This will probably be in 2011.

If you require further information please ring or email me.

Ethical approval: This study has ethical approval from the Central Regional Ethics Committee in New Zealand and the Human Research Ethics Committee of Melbourne Health.

If you have any concerns about the study you may contact:

Human Research Ethics Committee, Melbourne Health
Dr Angela Watt
Manager, Human Research Ethics Committee
Phone: + 61 3 9342 7550
You will need to tell Dr Angela Watt the name of one of the researchers.

You may also contact the following people at any time to ask about anything you may not understand:

Principal Investigator
Catherine Wood
Phone: + 64 4 806 2091
Catherine.Wood@cdhbrg.org.nz

Co-investigator (Melbourne)
Yvonne Panek-Hudson
Allograft Nurse Consultant
Phone: + 61 3 9656 1118

Supervisors
Associate Professor John Carter
Phone: + 64 4 385 5999

Dr David Ritchie
Phone: + 61 3 9656 1111

Thank you for taking the time to share your experiences and opinions about this area in the care of women post bone marrow transplant.

Your involvement in this study is voluntary (your choice). You may withdraw at any time without any changes to your health care now or in the future.
Appendix Thirteen: Consent Form - Wellington

Gynaecology Services for Women who have had a Bone Marrow Transplant
Consent Form

Please circle or tick your response

<table>
<thead>
<tr>
<th>REQUEST FOR INTERPRETER</th>
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<tbody>
<tr>
<td>English</td>
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<td>Cook Island</td>
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<td>Niuean</td>
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</table>

I have read and I understand the information sheet for volunteers taking part in the study entitled *Gynaecology Services for Women who have had a Bone Marrow Transplant.*

I understand that the study involves answering a questionnaire about vaginal graft versus host disease, fertility and sexuality after bone marrow transplant. I am satisfied with the answers I have been given to any questions I might have had.

I understand that taking part in this study is voluntary (my choice) and that I may withdraw from the study at any time and this will in no way affect my future health care.

I understand that my participation in this study is confidential and that no material that could identify me will be used in any reports about this study.

I have had time to consider whether to take part.

I know whom to contact if I have any questions about the study.

All persons who take part in research have a right to a copy of the study findings. Please indicate here if you would like a copy and write your address below. Preliminary results are expected in 2011.

I ____________________________________________________ (full name, please PRINT CLEARLY) hereby consent to take part in this study.

Signature: / /  

Address (optional - to receive a copy of study findings):

Thank you for your participation in this study

For further information please telephone Catherine Wood on 04 806 2091 or email Catherine.Wood@ccdhb.org.nz

One copy of the consent form is given to the participant.  
The second copy is filed in the patient’s medical notes.  
The third copy is retained as part of the raw research documentation.
Appendix Fourteen: Consent Form - Melbourne

Gynaecology Services for Women who have had a Bone Marrow Transplant Research Project

Consent Form

<table>
<thead>
<tr>
<th>I have read and I understand the information sheet for volunteers taking part in the study entitled <em>Gynaecology Services for Women who have had a Bone Marrow Transplant Research Project.</em></th>
</tr>
</thead>
<tbody>
<tr>
<td>I understand that the study involves answering a questionnaire about vaginal graft versus host disease, fertility and sexuality after bone marrow transplant. I am satisfied with the answers I have been given to any questions I might have had.</td>
</tr>
<tr>
<td>I understand that taking part in this study is voluntary (my choice) and that I may withdraw from the study at any time and this will in no way affect my future health care.</td>
</tr>
<tr>
<td>I understand that my participation in this study is confidential and that no material that could identify me will be used in any reports about this study.</td>
</tr>
<tr>
<td>I have had time to consider whether to take part.</td>
</tr>
<tr>
<td>I know whom to contact if I have any questions about the study.</td>
</tr>
<tr>
<td>All persons who take part in research have a right to a copy of the study findings. Please indicate here if you would like a copy. If you would like a copy of the results sent to you please write your address in the space below. Preliminary results are expected in 2011. Yes</td>
</tr>
<tr>
<td>I ________________________________ (full name, please PRINT CLEARLY) hereby consent to take part in this study.</td>
</tr>
<tr>
<td>Signature:</td>
</tr>
<tr>
<td>Date (d/m/y): / /</td>
</tr>
<tr>
<td>Address (optional - to receive a copy of study findings):</td>
</tr>
</tbody>
</table>

Thank you for your participation in this study

For further information please telephone Catherine Wood on + 64 4 806 2091 or email Catherine.Wood@ccdhb.org.nz

One copy of the consent form is given to the participant.
The second copy is filed in the patient’s medical notes.
The third copy is retained as part of the raw research documentation.
Appendix Fifteen: Questionnaire

Gynaecology Services for Women who have had a Bone Marrow Transplant

START HERE:

The following questions are about whether your Gynaecology needs were met before and after your transplant.

1. Did you see a Gynaecologist and undergo a gynaecology examination before your transplant?

   □ No → GO TO 4
   □ Yes

2. What issues were covered in your consultation? (tick all that apply)

   □ I had a general examination and a cervical smear was taken
   □ Vaginal GVHD was discussed and I was told signs and symptoms to look out for
   □ I was given a prescription for oestrogen cream to start using after my transplant
   □ I was given a prescription for hormone replacement therapy to begin after my transplant
   □ I was given vaginal dilators and told how and when to use them
   □ I was given information about when I could resume sexual activity after my transplant
   □ Other (please specify)

3. How often did you see the gynaecologist in the post transplant period?

   □ Every three months
   □ Every six months
   □ Initially every three months and then every six months
   □ Once a year
   □ Only when I felt I needed to see them
   □ No regular pattern
   □ Other (please specify)

4. To what extent do you agree or disagree with this statement: “The visits to the Gynaecologist helped me resume my normal sexual activity after my transplant”?

   □ Strongly agree
   □ Somewhat agree
   □ Somewhat disagree
   □ Strongly disagree

5. Do you feel the Gynaecologist detected vaginal GVHD before you were aware of it?

   □ I did not get any vaginal GVHD
   □ Yes
   □ No

6. Do you feel the involvement of a Gynaecologist in your pre transplant care is important?

   □ Very important
   □ Important
   □ Not important
   □ No opinion

7. Do you feel the involvement of a Gynaecologist in your post transplant care is important?

   □ Very important
   □ Important
   □ Not important
   □ No opinion

Ref: ____________________________
Gynaecology Questionnaire
Version 4, 24 January 2010
The questions in this section are about graft versus host disease (GVHD) of the vagina/vulva.

10. Prior to your bone marrow transplant, did you receive any information about GVHD possibly affecting the vagina?
   □ Yes
   □ No → GO TO 26

11. Did any of the following medical professionals discuss vaginal GVHD with you prior to your transplant? (Tick all that apply)
   □ Your Haematologist
   □ The Bone Marrow Transplant Coordinator or nurse
   □ The Gynaecologist
   □ The Haematology Registrar
   □ Your General Practitioner
   □ Other (please specify)

12. What type of information about vaginal GVHD did you receive?
   The transplant team talked to me about it. ...................... Yes  No
   I was given written information. ...................... Yes  No
   I found information on the internet. ...................... Yes  No
   I was given information by another patient. ...................... Yes  No
   Other (Please write in details)

13. If you received verbal information about vaginal GVHD, was it easy for you to understand?
   □ Very easy to understand
   □ Quite easy to understand
   □ Quite hard to understand
   □ Very hard to understand
   □ I didn’t get any verbal information

14. If you received written information about vaginal GVHD, was it easy for you to understand?
   □ Very easy to understand
   □ Quite easy to understand
   □ Quite hard to understand
   □ Very hard to understand
   □ I didn’t get any written information

15. Who did you feel most comfortable with when talking about vaginal GVHD?
   □ Your Haematologist
   □ The Bone Marrow Transplant Coordinator or nurse
   □ The Gynaecologist
   □ The Haematology Registrar
   □ Your General Practitioner
   □ Any female health professional
   □ Any male health professional
   □ You didn’t feel comfortable with anyone
   □ Other (please specify)

16. What type of information about vaginal GVHD would you have preferred to receive pre transplant?
   □ I wouldn’t have wanted any information
   □ Written information
   □ Verbal information
   □ Combination of written and verbal information

17. To what extent do you agree or disagree with this statement: “The information I was given about vaginal GVHD was helpful to me”?
   □ Strongly agree
   □ Somewhat agree
   □ Somewhat disagree
   □ Strongly disagree
   □ No opinion

18. After your transplant did you ever go back and read the information you were given pre transplant about vaginal GVHD?
   □ Yes
   □ No → GO TO 20
   □ I didn’t receive any written information about vaginal GVHD → GO TO 20
19 Why did you go back and read the information about vaginal GVHD?

☐ I thought I might have vaginal GVHD and wanted to make sure
☐ I read about it just because I was re-reading my transplant information.
☐ I was looking for other information, but found this.
☐ Other (please specify)

---

20 To what extent do you agree or disagree with his statement: “I was given enough information about vaginal GVHD”.

☐ Strongly agree
☐ Somewhat agree
☐ Somewhat disagree
☐ Strongly disagree

---

21 Did the information given to you about vaginal GVHD enable you to recognise the signs of this problem in yourself?

☐ Yes → GO TO 26
☐ No → GO TO 26
☐ I don’t think I’ve ever had vaginal GVHD → GO TO 26

---

22 After your bone marrow transplant, did you receive any information about GVHD possibly affecting the vagina?

☐ No → GO TO 26
☐ Yes

---

23 What type of information about vaginal GVHD did you receive?

The transplant team talked to me about it..................Yes No

I was given written information............................Yes No

I found information on the internet..........................Yes No

I was given information by another patient................Yes No

Other (Please write in details)

---

24 Did you feel that the information given to you about genital GVHD was useful?

☐ Very useful
☐ Useful
☐ Neither useful nor useless
☐ Useless
☐ Very useless
☐ No opinion

---

25 Would you have preferred this information pre transplant?

☐ Yes
☐ No

---

26 Did you have any of the following problems at any time post your transplant? (Tick all that apply)

☐ A dry vagina
☐ A discharge from the vagina
☐ Pain or discomfort in the vagina
☐ Pain or discomfort when having sex
☐ My vagina seemed to be smaller than it used to be
☐ My vagina felt like it was blocked
☐ I had none of these problems → GO TO 34
☐ Other (please specify)

---

27 Did you speak to any of the following people about the problems you were experiencing?

☐ Your Haematologist
☐ The BMT Coordinator or nurse
☐ One of the nurses caring for you
☐ The Haematology Registrar
☐ The Gynaecologist
☐ Your General Practitioner
☐ Other (please specify)

☐ I did not talk to anyone → GO TO 32

---

28 When you spoke to a Doctor or Nurse about these problems, did they organise some help for you?

☐ Yes
☐ No → GO TO 33
☐ I don’t think I’ve ever had vaginal GVHD → GO TO 33
29 What help did you get?
☐ I was referred to a Gynaecologist
☐ I was referred to an Endocrinologist
☐ I was referred to a Gynaecologist and an Endocrinologist
☐ I was given some cream to put up my vagina by my Haematologist without being referred to a Gynaecologist
☐ Other (please specify)

30 What treatment were you given for the problems with your vagina?
☐ I was only given some cream to put in my vagina
☐ I was only given hormone replacement tablets
☐ I was only given vaginal dilators to use
☐ I was given cream to put up my vagina and vaginal dilators to use
☐ I was given cream to put up my vagina and hormone replacement tablets
☐ I was given vaginal dilators and hormone replacement tablets
☐ I was given cream to put up my vagina, hormone replacement tablets and vaginal dilators to use
☐ I needed to have an operation to make things better
☐ I can’t remember
☐ Other (please specify)

☐ I didn’t want any treatment → GO TO 33

31 How would you rate the treatment you were given for your vaginal problems?
☐ Completely successful
☐ Moderately successful
☐ No change from before treatment
☐ Moderately unsuccessful
☐ Completely unsuccessful

GO TO QUESTION 33

32 Why do you think you didn’t talk with anyone about these problems?
☐ I was too embarrassed to mention it
☐ I didn’t think it was important
☐ I thought that this was what usually happened after a transplant
☐ I tried to talk with someone about it but I wasn’t listened to
☐ There were too many other problems at this time so I didn’t mention it
☐ The vaginal problems went away so I didn’t say anything
☐ I was just too pleased to be alive after the transplant so I didn’t say anything
☐ Other (please specify)

33 How long after your transplant did your vaginal problems start?
☐ Less than three months after my BMT
☐ Three to six months after my BMT
☐ Six to twelve months after my BMT
☐ Twelve to twenty four months after my BMT
☐ After 24 months post transplant
☐ I can’t remember

34 Do you still have problems with your vagina and/or with having sex?
☐ Yes → GO TO 36
☐ No

35 How long did these problems last for?

____ months

The questions in this section are about sexuality. Sexuality may be seen as feeling and acting sexy. It also involves the act of having sex. Sexuality may be affected by the treatment you have had as it may alter the way you look and feel.

36 Did any of the following medical professionals discuss sexuality issues with you prior to your transplant? (Tick all that apply)
☐ Your Haematologist
☐ The BMT Coordinator or nurse
☐ One of the nurses caring for you
☐ The Haematology Registrar
☐ The Gynaecologist
☐ Your General Practitioner
☐ Other (please specify)
What type of information about sexuality did you receive?
The transplant team talked to me about it......................Yes   No
I was given written information..........................Yes   No
I found information on the internet.........................Yes   No
I was given information by another patient..............Yes   No
Other (Please write in details)

If you received verbal information about sexuality issues after BMT, was it easy for you to understand?

☐ Very easy to understand  
☐ Quite easy to understand  
☐ Quite hard to understand  
☐ Very hard to understand  
☐ I didn’t get any verbal information

If you received written information about sexuality issues after BMT, was it easy for you to understand?

☐ Very easy to understand  
☐ Quite easy to understand  
☐ Quite hard to understand  
☐ Very hard to understand  
☐ I didn’t get any written information

Who did you feel most comfortable with when talking about your sexuality?

☐ Your Haematologist  
☐ The Bone Marrow Transplant Coordinator or nurse  
☐ The Gynaecologist  
☐ The Haematology Registrar  
☐ Your General Practitioner  
☐ Any female health professional  
☐ Any male health professional  
☐ You didn’t feel comfortable with anyone  
☐ You didn’t talk about it with anyone  
☐ Other (please specify)

What type of information about sexuality would you have preferred to receive pre transplant?

☐ I wouldn’t have wanted any information  
☐ Written information  
☐ Verbal information  
☐ Combination of written and verbal information

To what extent do you agree or disagree with this statement: “The information I was given about sexuality was helpful to me after I had my bone marrow transplant.”

☐ Strongly agree  
☐ Somewhat agree  
☐ Neither agree nor disagree  
☐ Somewhat disagree  
☐ Strongly disagree  
☐ No opinion

After your transplant did you ever go back and read the information you were given pre transplant about sexuality?

☐ Yes  
☐ No  
☐ I didn’t receive any written information about post BMT sexuality issues

To what extent do you agree or disagree with this statement: “I was given enough information about the sexuality issues that I might come across post transplant”.

☐ Strongly agree  
☐ Somewhat agree  
☐ Somewhat disagree  
☐ Strongly disagree

Do you consider that you had sexuality problems after your transplant (eg. Did not feel sexy, did not feel like sex)?

☐ Yes  
☐ No → GO TO 50

What kind of problems did you have?

☐ I wanted to have sex but couldn’t seem to get aroused  
☐ I had no desire to have sex at all even though my partner wanted to  
☐ Sex was painful for me  
☐ I couldn’t reach orgasm  
☐ Other (please specify)
47 Did you speak to any of the following people about the problems you were experiencing?

- Your Haematologist
- The BMT Coordinator or nurse
- One of the nurses caring for you
- The Haematology Registrar
- The Gynaecologist
- Your General Practitioner
- Other (please specify)

☐ I did not talk to anyone → GO TO 49

48 Do you feel that you got the right help for your sexuality problems?

☐ Yes
☐ No

49 Do you still have any problems with sexual functioning?

☐ I don’t have any problems with sex at all
☐ I would like to have sex but don’t seem to get aroused
☐ Sex remains painful for me
☐ I can’t reach orgasm anymore
☐ Other (please specify)

50 Were you given any information about when you could resume sexual activity after your transplant?

☐ Yes
☐ No → GO TO 52
☐ I can’t remember → GO TO 52

51 What were you told about when you could resume sex after your transplant? (tick all that apply)

☐ I was told I could have sex at any time
☐ I was told that I could have sex when my platelets were over 50.
☐ I was told that I could have sex when my white cell count was normal
☐ I was told that I couldn’t have sex until I stopped my Cyclosporin
☐ Other (please specify)

52 Were you given any information about the use of condoms to prevent possible infection?

☐ Yes
☐ No → GO TO 54
☐ I can’t remember → GO TO 54

53 What were you told about your partner having to wear condoms?

☐ I was told that my partner needed to wear a condom until my white cell count was normal
☐ I was told that my partner didn’t have to wear condoms at all
☐ I didn’t have a partner at the time so I wasn’t given any instructions
☐ I am a lesbian and had no need of information about condoms
☐ Other (please specify)

54 Were you told before your transplant that you might go into early menopause after your transplant?

☐ I had already gone through menopause when I had my transplant
☐ I was going through the menopause when I had my transplant
☐ I was not told this prior to my transplant
☐ Yes I was told that I might go into menopause after my transplant
☐ Other (please specify)

The questions in this section are about fertility.

55 Did you have children prior to your BMT?

☐ Yes
☐ No → GO TO 57

56 Did you want to have any more children after your BMT?

☐ Yes
☐ No, I had already completed my family → GO TO 66
57 Were you menopausal prior to your BMT?
   ☐ Yes but I hoped to still have children
   ☐ Yes but I didn’t want any children → GO TO 66
   ☐ No
   ☐ I can’t remember

58 Prior to your bone marrow transplant, did you receive any information about fertility issues in the post transplant period?
   ☐ Yes
   ☐ No → GO TO 64

59 Did any of the following medical professionals discuss fertility issues with you before your transplant? (Tick all that apply)
   ☐ The Haematologist
   ☐ The Bone Marrow Transplant Coordinator or nurse
   ☐ The Gynaecologist
   ☐ The Haematology Registrar
   ☐ Your General Practitioner
   ☐ The Radiation Oncologist
   ☐ Other (please specify)__________________________

60 What type of information about fertility issues did you receive?

The transplant team talked to me about it....................Yes No
I was given written information..........................Yes No
I found information on the internet............................Yes No
I was given information by another patient..................Yes No
Other (Please write in details)__________________________

62 What type of information about fertility would you have preferred to receive pre transplant?
   ☐ I wouldn’t have wanted any information
   ☐ Written information
   ☐ Verbal information
   ☐ Combination of written and verbal information

63 To what extent do you agree or disagree with this statement: “I was given enough information about the effects that transplant would have on my ability to have children”.
   ☐ Strongly agree
   ☐ Somewhat agree
   ☐ Somewhat disagree
   ☐ Strongly disagree

64 Were you told before your transplant that you might never be able to become pregnant?
   ☐ I had been told that I would not be able to have children when I started my leukaemia treatment
   ☐ I was not told this prior to my transplant
   ☐ I was told that I would not be able to have children after my transplant
   ☐ I was told that I might not be able to have children after my transplant
   ☐ Other (please specify)__________________________

65 Were you referred to a fertility specialist before your transplant?
   ☐ Yes
   ☐ No but I would have liked to have been
   ☐ No and I didn’t want to see a fertility specialist

The following questions are about you and your transplant.

66 How old are you?

__________________________ Age

How old were you when you had your transplant?

__________________________ Age
At the time of your transplant had you started going through menopause?

☐ No
☐ I was going through the menopause at the time
☐ I had gone through the menopause already
☐ I can’t remember

What illness did you have that meant you needed to have a bone marrow transplant?

_________________________________________ Illness

Who was your bone marrow donor?

☐ My brother
☐ My sister
☐ An unrelated donor
☐ My father
☐ My mother
☐ Other (please specify)

_________________________________________

What was the source of the stem cells for your transplant?

☐ Bone marrow
☐ Peripheral blood stem cells
☐ Cord blood
☐ I don’t know

Have you had proven GVHD at any time since your transplant?

☐ No
☐ Yes

If yes, where? (tick all that apply)

☐ Skin
☐ Liver
☐ Gut
☐ Mouth
☐ Eyes
☐ Vagina
☐ Other (please specify)

______________________________________

Thank you very much for taking the time to answer this questionnaire.

I will post out a summary of the results to those of you that requested them as soon as they are available. This may take up to three years. If you change address in that time and still wish to receive the results, please notify me of your change of address.

If you have any questions, please feel free to contact me:
Phone: +64 4 806 2091
Email: Catherine.Wood@cdhb.org.nz
Mail: Catherine Wood
Wellington Blood and Cancer Centre
Wellington Hospital
Private Bag 7902
Wellington 6242
New Zealand
Appendix Sixteen: Reminder Postcard

Gynaecology Services for Women who have had a Bone Marrow Transplant.

This postcard is to remind you about the study investigating patients' experiences with gynaecology services following bone marrow transplant.

A study pack was sent to you at the end of April this year. I would really appreciate it if you could take the time to look at the information sheet sent with that study pack and have a think about whether you would like to participate in the study. If you didn't receive a questionnaire or can't find it, then please contact me on: +64 4 806 2091 or Catherine.Wood@ccdlhb.org.nz and I will send you one.

Thank you for taking the time to think about this study.

Kind regards

Catherine Wood
Principal Researcher