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**USE OF A DISEASE SPECIFIC DECISION AID
TO DETERMINE THE MINIMAL CLINICALLY IMPORTANT DIFFERENCE
BETWEEN AUTOLOGOUS BONE MARROW TRANSPLANTATION
VERSUS STANDARD SALVAGE THERAPY FOR PATIENTS
WITH HIGH RISK LOW GRADE NON-HODGKIN'S LYMPHOMA**

By

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Thesis submitted to
the School of Graduate Studies and Research
in partial fulfillment of the requirements for the
M.Sc. degree in Epidemiology

University of Ottawa



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0-612-26304-5

Abstract

Background: Low grade non-Hodgkin's lymphoma accounts for approximately 40% of all non-Hodgkin's lymphomas. Although initially responsive to many therapies these tumors, unless localized at diagnosis, are incurable with a median survival from diagnosis of 8 to 10 years. Therapy after relapse is quite varied and survival is poor with a second median disease-free survival period of 13 months. The introduction of high-dose chemoradiotherapy with autologous peripheral blood stem cell and/or bone marrow transplantation (ABMT) has been used to treat patients with low grade non-Hodgkin's lymphoma who fail to achieve a complete response to standard therapies or who progress after achieving a remission, in an attempt to improve disease-free and overall survival. Phase II studies suggest this approach may result in prolongation of disease-free and possibly overall survival in these high-risk patients. It is unknown whether this will result in patients being cured, but at present, this is felt to be unlikely.

The introduction of ABMT for the treatment of high-risk low grade non-Hodgkin's lymphoma has introduced an interesting clinical question for patients and physicians. Patients must decide whether the up-front increased morbidity and risk of treatment related mortality (TRM) with an ABMT is worth accepting for an as yet undefined potential benefit over standard salvage therapies (SST). Nonetheless, ABMT is chosen by an increasing number of these patients.

The decision these patients face is clearly difficult. As there is no correct choice, patients must make value judgments and balance preferences regarding the risks and benefits of potential therapies. One method of examining the choice between therapeutic options is to determine the minimal clinically important difference (MCID) the

patient would require to choose one therapy over its alternate. The MCID may be viewed as the amount of therapeutic benefit needed to outweigh the negative aspects of a particular therapy compared to its alternates. Physicians have an obligation to try to communicate these treatment trade-offs in an effective fashion so patients can make informed choices. To achieve this, many groups have introduced decision aids (DAs) to assist patients in making choices. Decision aids are different from traditional patient education materials because they are focused on the patient making a decision, the information supplied to the patient is specific to their situation and the possible treatment outcomes and their likelihoods are clearly reviewed and communicated.

Objectives: The primary objective of this study was to describe, using a disease specific DA, the MCID required to choose ABMT over SST in a cohort of patients with high risk low grade non-Hodgkin's lymphoma. Secondary objectives were to determine clinical correlates of the MCID and to compare the MCID in previously transplanted patients to patients with low grade non-Hodgkin's lymphoma who have not undergone transplantation and to healthy volunteers. As a sub-study, two methods of numerical presentation of outcome data within the DA were compared with regards to the MCID elicited, patient comprehension and acceptability. The final objective was to evaluate the DA's educational value, clarity, usefulness and efficiency.

Methods: Three study groups underwent a semi-structured interview comparing ABMT and SST for high-risk low grade non-Hodgkin's lymphoma. The patients were randomized to either a graphical-numerical or numerical-alone format for the presentation of outcome probabilities. The primary outcome measures were the patients' MCIDs defined as the 6 month TRM and the 4-year treatment free survival (4-yr TFS) necessary with ABMT to choose it over SST. The DA consisted of a series of booklets and a summary board that summarized both SST and ABMT in terms of

treatment time course, therapeutic procedures, toxicity and outcomes. A second booklet was used for the elicitation of the MCID. To facilitate participation, interviews were conducted in the patient's city of residence, either at their home or in a physician's office.

Results: Forty patients who previously had undergone ABMT for low grade non-Hodgkin's lymphoma and 8 patients who had so far declined that therapy were available to participate in the study. In addition, 10 healthy volunteers completed the study. Post-transplant patients identified a TRM MCID of 23.8%, the no-transplant group 27.5% and healthy controls 27.7%. There were no differences between the groups. These values were high compared to the known risk of ABMT (TRM 10%, 4-yr TFS 50%). The 4-yr TFS MCID was 21.3% for the post-transplantation group, 28.4% for the no-transplantation group and 24.4% for the healthy controls. There was a significant difference between the no-transplant and post-transplant groups with regards to the 4-yr TFS MCID, with patients who had not undergone transplantation requiring a higher chance of being treatment free at 4 years. Again, the results overall identified that patients required only a small increased benefit with ABMT in order to choose it over SST. Several possible explanations were considered but it is felt that this reflects an acceptance of the undefined possible benefit associated with the experimental therapy compared to the clearly defined continuous decline associated with SST.

Two clinical correlates of the 4-yr TFS were identified. Men identified a higher median 4-yr TFS MCID than women did. As well, there was a correlation between the patient-rated period of recovery post-transplantation and the 4-yr TFS MCID.

All 40 subjects in the post-transplant group were randomized between the graphical-numerical or numerical-alone presentation of probabilities within the DA. There were no differences in the treatment-related mortality MCID or the 4-yr TFS MCID

using either presentation format during the MCID elicitation although the power to determine a true difference was lower than the a priori estimates for the study.

The overall evaluation of the DA was very favourable. Completion of the background portion of the DA was significantly longer in patients receiving the graphical-numerical presentation (median 28 mins) compared to the numerical-alone presentation (median 20 mins). Time to complete the MCID elicitation was not affected by the presentation format. Nearly all subjects, however, identified the interview process, including the DA and its evaluation, to be too long.

Conclusion: It is possible to design an effective disease specific DA for patients with relapsed low grade non-Hodgkin's lymphoma and to determine the MCID of ABMT versus SST for this patient population. The ultimate role of DAs in clinical practice will depend on multiple factors including the appropriateness and complexity of the clinical situation, the ability to represent the choice in a meaningful and accessible manner and the demonstration that the use of these aids results in improved health outcomes for individuals.

Acknowledgments

I would like to take this opportunity to express my appreciation to Dr. Annette O'Connor, my thesis supervisor, whose enthusiasm for the Art and Science of Decision Making captured my attention and broadened my view beyond the survival curves that hematologists more traditionally focus upon. Her immediate willingness to be my Thesis Supervisor did not wane as she guided me through this project. I consider myself privileged to have had the opportunity to have been taught by the Master and welcomed into her fold.

My thanks are also extended to the other members of my Thesis Committee. Their patience and availability as well as their willingness to share their expertise, not only during the period of my thesis but during my entire Master's programme defines them as educators. I would like to express a special thank you to Dr. Lothar Huebsch who has been equal part mentor, friend and colleague during the past 10 years. His wisdom, energy, clinical skills and compassion have enabled him to build a highly respected and forward thinking transplantation programme.

I owe an unending debt of gratitude to my spouse Caroline who holds the rest of my world together and gently leads me back when I get too far from what is truly important. As well to my boys who do not understand the reasons for my absences but show unquestioning love and open arms whenever I am home.

I would also like to acknowledge the support of my colleagues and other members of the Division of Hematology, in particular Diane Thauvette whose secretarial and editing skills have been exceeded only by her patience during the past several months. Lastly, I would like to recognize the contribution of Janine Malcolm (Meds

1997, Queen's University) who as a summer student conducted all the patient interviews; dashing off to the Maritimes and Southern Ontario whenever another study subject was found.

I dedicate this thesis to my parents who throughout my life have led by example. Their values, commitment and generous nature have established a standard that I strive to achieve.

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Chapter 1

1.0 Background and Rationale

1.1 *The Burden of Disease*

The non-Hodgkin's lymphomas are a heterogeneous group of lymphoproliferative malignancies that have considerable variation in their clinical behaviour, management, and prognosis. Therapy and prognosis depends on their histological subtype, stage, and bulk of disease.¹ Non-Hodgkin's lymphomas rank in the top 5 causes of cancer deaths in young men and women despite contributing only 5% of new cancer cases. Of these, the low grade non-Hodgkin's lymphomas account for between 35% and 45% of all non-Hodgkin's lymphomas.²

The low grade non-Hodgkin's lymphomas include three subtypes as classified in the Working Formulation: small lymphocytic lymphoma, follicular predominantly small cleaved cell lymphoma and follicular mixed small cleaved and large cell lymphoma.³ Of these, the follicular lymphomas clinically represent spectrums of the same disease, while small lymphocytic lymphoma is considered a separate entity.

Approximately 500 cases of low grade non-Hodgkin's lymphoma are diagnosed each year in Canada. In the majority of patients the disease involves both nodal and extranodal sites, such as the bone marrow, at the time of diagnosis.⁴ The median age of patients presenting with these lymphomas is between 50 and 60 years. Nonetheless, as many patients presenting with low grade non-Hodgkin's lymphoma are in their young adult life, the impact of these illnesses on society and family is disproportionately large for their incidence.

Although responsive to many therapies, these tumors unless localized at diagnosis, are currently incurable. The median overall survival of patients with low grade non-Hodgkin's lymphoma from diagnosis is approximately 8-10 years.²

1.2 Range and Variation of Therapies

The introduction of therapies in the mid 1960's for low grade non-Hodgkin's lymphoma had a significant impact on overall survival of these patients, increasing it from ~5 years to ~10 years.⁵ Unfortunately little further improvement has occurred during the last 25 years. Survival curves for all primary therapies are essentially overlapping. Therefore, until very recently, the standard approach to these illnesses was watchful waiting; treatment was given only when patients became symptomatic from tumor burden or immune complications. When initiated, primary therapy typically consisted of oral chemotherapy with chlorambucil, an alkylating agent, with or without prednisone. More intensive chemotherapy may have been used as primary therapy in high-risk patients to achieve a faster response. More recently, interest in early treatment has increased with the intention of achieving a state of minimal residual disease prior to initiating therapy with biological response modifiers such as interferon alpha 2b.⁶ Although demonstrated in controlled clinical trials to improve disease free survival, it is unclear whether interferon significantly improves overall survival.⁶⁻⁸ As well, interferon therapy is associated with significant side effects and the net effect on patient quality of life with this approach remains to be determined. Although a variety of therapies produce partial or complete responses in a large percentage of patients with advanced stage disease, none have proven curative and invariably the disease relapses.

Treatment after relapse is also varied, reflecting attempts of different groups to improve on the poor results of second line therapy.⁶ Overall, the survival of patients with these lymphomas after first relapse is poor. Median survival is less than 4 years and the

median disease free survival for these patients is 13 months.⁵ Subsets of patients with high risk features have an even worse prognosis.² In response to the poor prognosis of high-risk low grade non-Hodgkin's lymphoma new approaches continue to be explored.

Over the past ten years, advances in medicine have allowed for the development of dose intensive treatments (chemotherapy with or without radiation) that require a portion of the patient's bone marrow to be cryopreserved and given back to them after the dose intensive treatment to allow their blood cells and immune system to reconstitute. More recently, it has been shown that peripheral blood, after stimulation with chemotherapy and/or hematopoietic growth factors contains circulating blood stem cells that can be collected and used in an analogous fashion to bone marrow to reconstitute the bone marrow and the immune system after high dose chemoradiotherapy.^{4,9} Dose escalation of chemotherapy and/or radiotherapy with autologous bone marrow or peripheral blood stem cell transplantation is given to the patient in an attempt to eradicate the malignant clone of cells. This approach offers the potential of prolonging the disease free interval or perhaps curing patients of their disease compared to therapies utilizing lower doses of chemotherapy and/or radiation.⁹⁻¹¹

Another recent development for the treatment of high risk low grade non-Hodgkin's lymphoma has been the development of new chemotherapeutic agents, purine analogues, such as 2 fluoro-deoxyadenosine¹² and 2-chlorodeoxyadenosine¹³. While achieving high response rates with limited acute toxicity, as with other salvage therapy approaches, to date they have not been demonstrated to be curative for these illnesses. The role of the purine analogues in young (<65 years) patients with high-risk low grade non-Hodgkin's lymphoma remains to be defined.

The role of HLA matched sibling allogeneic transplantation for these patients is also unclear.¹⁴ While the focus of research at some transplant centres, this approach

continues to carry with it significant up-front toxicity and treatment related mortality (TRM)(~20%) and is generally restricted to younger patients (≤ 55 years). As well, because of the requirements for an HLA matched sibling, this approach is applicable to only 10 or 15% of the target population.

Presently, the only therapeutic option available for patients with high-risk low grade non-Hodgkin's lymphoma that has been demonstrated to have the potential to significantly improve disease free survival and overall survival is high dose therapy and autologous peripheral blood stem cell and/or bone marrow transplantation (ABMT). High dose chemoradiotherapy with autologous stem cell rescue in the form of bone marrow or stimulated peripheral blood is currently offered to patients <65 years of age with high-risk disease in an attempt to improve on the disappointing results of standard salvage treatments. Although preliminary, the results are promising with low rates of TRM (5-10%) and 4-year disease free survival between 50-65%.^{4 9 10} Longer follow up is required to determine if the current rates of disease free survival are maintained and if so, to determine the optimal timing of high dose therapy. Although felt to improve on survival, it is not clear that this approach is curative. At present, patients are informed that this therapy is not curative.

1.3 Risks and Benefits of ABMT and SST

There are significant differences between SST and ABMT. While both approaches impart the majority of their acute toxicity by killing dividing cells such as bone marrow (causing infection, bruising, bleeding), hair (causing alopecia) or the cells that line the gastrointestinal tract (causing nausea, mucositis, diarrhea), standard salvage treatments generally have less severe side effects than the higher doses of drugs and radiation used in ABMT. Standard salvage therapies, however, require repeated or chronic

administration and visits to the clinic or hospital. Usually the entire treatment course can be administered in the out-patient setting and treatment related deaths are very uncommon with SST (<3% within the first six months). We know, however, that standard salvage therapies are only effective in controlling the disease for a limited period of time (median disease free survival 13 months).⁵

High dose chemoradiotherapy with autologous marrow or peripheral blood stem cell transplantation involves much more intensive therapies, with an initial higher chance of more severe toxicity such as life-threatening bleeding, infections and an increased chance of major organ (liver, kidney, lung, or heart) damage, in addition to the more routine toxicities of fever, nausea, hair loss and fatigue. Delayed toxicities such as hypothyroidism, lung fibrosis or secondary malignancies may also occur in a number of patients.^{15 16} Presently, patients undergoing ABMT generally require admission to the hospital, usually for several weeks over a three month treatment period. With ABMT there is a small but real risk (5-10%) of treatment related death during the three months of therapy.^{10 17 18} An advantage of transplantation is that once treatment is finished (approximately three months) and the patient has had time to recover (approximately 3 to 6 months) no further treatment is required unless the disease recurs.

To summarize, the major differences in the approaches to salvage therapy for high-risk low grade non-Hodgkin's lymphoma are the increased toxicity and TRM and the intense up front time commitment with transplantation versus chronic or repeated therapy with more standard treatments. The ultimate benefit in survival of one over the other is at present unknown but may favor ABMT.^{4 9 10} Again, it is believed that no patients are cured with either approach.

Although the ideal situation would be to perform a randomized clinical trial of standard salvage therapy (SST) versus ABMT in patients with low grade non-Hodgkin's

lymphoma, this is unlikely to yield meaningful results in less than 10 years. Due to small numbers of patients at any one centre, multi-centre, multi-national studies would likely be required. Planning of such studies is at the informal discussion phase. In the interim, patients are faced with the choice of SST versus ABMT. Despite the short-term risks and unclear longer-term advantages, a significant number of patients ultimately choose to undergo ABMT. Moreover, there is increasing interest in extending this therapy to patients over the age of 65. The basis upon which patients reach the decision to undergo (or not) high dose therapy with ABMT is as yet unstudied.

1.4 The Decision

The decision faced by patients is clearly a difficult one. It is, however, a decision in which patients are becoming increasingly involved. The continuing movement towards consumerism in health care has led to an increase in patient participation in decision making. This is particularly so for younger patients and women.¹⁹⁻²¹ Balanced against this is the inherent difficulty of the decision to be made. There is no "correct choice" and patients must make value judgments and balance tradeoffs regarding the risks and benefits of the potential treatment. Specifically, for patients with low grade non-Hodgkin's lymphoma does the potential benefit of ABMT with increased disease free and potentially greater overall survival outweigh the significant side effects, up-front time commitment and increased TRM compared to standard salvage therapies.

Over the past several years, a re-evaluation of the understanding of the decision-making wishes of patients has occurred. Earlier literature supporting paternalism and a belief that patients do not want to participate in decision making has come into question.²²

²³ What was once conceptualized as decision making is now felt by some to include two separate concepts, problem solving and decision making.²⁴ While problem solving, the collection and interpretation of the relevant medical data related to the health question at

issue is arguably the health care experts role, the decision making requires the patient's input as to their values and risk-benefit preferences prior to a choice being made. The misunderstanding of what medical decision making is, has been a stumbling block on the path to informed patient choice and shared decision making.

The process of patient decision making is further hindered by the setting in which it presently occurs. For despite the increasing support from physicians and provincial and national governments²⁵⁻²⁸ for the principle of informed choice, this principle is often difficult to achieve through traditional doctor-patient discussions. These discussions can often result in patient misunderstanding.^{29 30} Patients, in particular cancer patients, have been known to both underestimate the risks as well as overestimate the potential benefits of therapy. It has been shown that they may also have poor recall of what was said during the physician-patient encounter.^{29 30}

Furthermore, the process of decision making becomes more difficult when dealing with potentially risky or dangerous interventions³¹ and cancer treatments.²⁰ As well, when looked at in a formal manner there is significant variation in the style and timing of presentation when physicians use traditional approaches during decision making discussions of value-laden issues with patients.^{29 32 33} Health care workers may have different values of and preferences for health states than patients.^{34 35} Framing of health states or therapy information discussions with patients can influence patient choice^{24 36} and may occur in order to influence patient choice based on the physician's perceived outcome expectations.³² Lastly, the transition from one model of patient-doctor interaction (paternalism) towards the ideal (enhanced patient autonomy) is not likely to be smooth with overshooting by patients (independent choice) and reluctance by some doctors to give up their traditional "power" role.²⁸

In order to achieve informed decision making consistent with personal values and to diminish bias in presenting therapy-related information, many groups have developed decision aids (DAs) to assist patients in their decision making for a variety of clinical situations.³⁷⁻⁴² To date a structured DA for patients with high risk low grade non-Hodgkin's lymphoma does not exist.

1.5 *Decision Aids*

As stated above, a DA is one method of facilitating shared decision making and quantifying the aspects of the decision upon which a choice is made. DAs outline for patients, treatment options and the resultant outcomes for each option, based on tailoring of the outcome possibilities to the patient's specific clinical situation. In addition to containing medical information related to the health choices under consideration, their probabilities and likely consequences, DAs may contain other components such as values clarification exercises or strength of preference scales. These are designed to assist patients in weighing the personal importance of the potential benefits or adverse consequences for themselves. They may also include prompts to list questions for discussion with their doctors or others. Important aspects of DAs that differentiate them from traditional patient educational materials are: 1) they are focused on the patient making a decision between the alternatives outlined; 2) the information supplied to the patient is specific to their particular clinical situation; 3) the possible outcomes and the likelihood of their occurrence are clearly reviewed; and 4) implicit or explicit values clarification occurs. DAs as part of shared decision making should result in more effective decisions being made.⁴³ Preliminary results in other clinical situations show that DAs improve comprehension, create realistic expectations and reduce the uncertainty in

making choices.⁴⁴ It is hoped that this will ultimately translate into improved health outcomes for patients.

The optimal format of a DA has yet to be determined. Decision boards,^{21 40 45} group workshops,⁴⁶ treatment trade off index cards,⁴⁷ videodisks,^{39 42} audio booklets,⁴⁴ and automated computer interviews⁴¹ have all been used by different groups. Mixed results have been seen regarding the effect of information presentation format within the DA. Some⁴⁸⁻⁵² but not all^{33 53 54} studies have indicated that patient preferences may be strongly influenced by how information is presented. While research addressing the best method of presentation is clearly needed, at present the choice of medium or format remains arbitrary, based on budget, resources and local expertise available for the design and implementation of the DA.

Similar choices exist for data presentation (graphical, numerical, both), framing of outcomes (positive or negative), order of presentation (risks or benefits first), and the methods to describe potential benefits (percentages, number needed to treat). Little is known about the influence of numerical versus graphical presentation of information on preferences for treatment in the patient population. Different groups have used either numerical^{46 47} or graphical formats^{21 39 44} effectively in DAs. Hadourn et al⁵⁵ have suggested that the use of pictorial information may increase patient comprehension of health states. As the decision faced by patients is a difficult one, and the information needed to arrive at the decision is often detailed and technical, the optimum method of presentation of this data is essential in facilitating the decision making process. An evaluation of graphical plus numerical versus a numerical-alone presentation of outcome data is a necessary part of the development and improvement of patient DAs.

Do we need a decision aid for high-risk low grade lymphoma if ABMT offers a 30% improvement in 4-yr TFS over SST with only a 7% increase in TRM? If these differences

are confirmed in as yet unplanned randomized controlled trials, than on a survival basis it would seem not. There are and will likely continue to be, however, marked differences with regards to morbidity and quality of life with the two approaches. A balanced decision aid that helps patients clarify the relevance of these trade-offs to them personally will likely remain a valuable tool as the best choice at a population level may not necessarily be the same as for a particular patient.

1.6 The Minimal Clinically Important Difference

One way of examining the decision between therapeutic options faced by patients is to attempt to determine the minimal clinically important difference (MCID) that patients would need to choose treatment 1 (ABMT), over treatment 2 (SST).

The MCID may be viewed as the amount of therapeutic benefit (disease-free and overall survival) needed to outweigh the negative aspects (increased side-effects and treatment related mortality) of therapy.⁵⁶ The concept of a patient determined MCID is of great significance in the assessment of treatment options as it allows for a quantitative measure to be applied to patient decision making, a commodity previously considered only qualitatively.

Determining an MCID for a population of patients in a particular clinical scenario can help guide several aspects of clinical care and clinical therapeutics research. At a patient level, determining the MCID contributes to the values clarification that is an integral component of informed choice. By grappling with the specifics of the trade-offs between treatment options, the patient and physician are more aware of the relative importance the patient attaches to the risks and benefits of the alternatives under consideration.

In clinical situations where risk-benefit information for one or both therapeutic options is not well defined, an individual's MCID for risks and benefits can be compared to

the range of possibilities known for the treatment alternatives. If the patient's MCID for risks and benefits fall within the range of possibilities for the treatment options, both the patient and physician can be more confident that the correct choice is being made. It is possible, that this may result in improved adherence to a chosen therapeutic plan.⁴³ Alternately, if the patient's MCID falls outside what is felt to be the range of probabilities, alternate treatments may be considered, more information pursued prior to making a choice or the patient may proceed aware of the uncertainty of their situation.

Lastly, MCIDs may help in clinical trials design and interpretation.⁵⁷ In terms of trial design, knowing before initiating a trial what the patient determined MCID is, will aid in planning a sample size with adequate power to identify such a benefit (or risk) if it exists. In terms of interpreting clinical trial results, judgements about their relevance is often attributed to what is perceived as the MCID. In the past, attempts to determine the relevance of results have relied heavily on physicians' judgments of treatment outcomes or patients' judgments of situations with which they have little or no clinical experience.^{53 56 58} There has been less research investigating the MCID or preferences of patients with a particular disease, who have undergone a period of treatment for that illness.^{53 59 60} It is likely that these patients would have the most accurate perception of what it is that makes them choose and stay committed to one experienced treatment over another. As with other aspects of patient preference, there has been some variability in the results of studies addressing preference elicitation in relation to the timing of therapy and the clinical scenario at issue.^{53 61 62} What has been most consistent is the overall choice of quantity of life over short-term quality of life.^{53 59}

Whether society is willing to accept patient determined MCIDs for these expensive therapies and to make resource allocation decisions based on these values is a separate issue. At present, a decision as to the appropriateness of therapy choices for a particular

patient rests with the patient and his physician or health care team. While economic considerations may lead to health care resource rationing in the future, at present, a philosophy of universal access with limited external restrictions on choices remains within the Canadian health care system. Until such time as this principle changes, patients should be the ones determining what the acceptable risk-benefit relationships are for potential therapies in their particular clinical setting.

1.7 Summary

Patients with high-risk low grade non-Hodgkin's lymphoma face a difficult choice between SST and high dose therapy with autologous stem cell rescue. Little is known about the decision making process or the decision making needs of this patient population. Research in other areas suggests that the development of DAs can facilitate decision making for patients and their significant others, although the best methods of data presentation are still being debated. Use of DAs to determine the MCID between two treatment options will help clarify what patients view as necessary to choose and follow through on a treatment option. Researchers will also benefit, as the MCID will be able to guide the design and interpretation of future clinical trials. As a result, DAs and MCIDs may benefit future patients by improving informed decision making.

1.8 Objectives

1.8.1 Primary objective

The primary objective of the study was:

- i. To describe, using a disease specific DA, the MCID necessary to choose ABMT over SST in a cohort of patients who have experienced both standard chemotherapy and who have undergone ABMT for low grade non-Hodgkin's lymphoma.

1.8.2 Secondary objectives

The secondary objectives were:

- i. To determine clinical correlates of the MCID based on patient demographics, disease characteristics, prior therapy, time since treatment, subjective impression of patients regarding their prior therapy experiences and patient cited reasons for undergoing ABMT.
- ii. To compare two methods of numeric presentation of data within the DA with regards to the MCID elicited, patient comprehension and acceptability of the DA.
- iii. To evaluate the DA's educational value, clarity, usefulness and efficiency.
- iv. To compare the MCID in the previously transplanted patient group to two other cohorts; low grade non-Hodgkin's lymphoma patients who have not undergone ABMT and healthy volunteers.

Chapter 2

2.0 Methods

2.1 *Study Population*

Three groups of subjects were utilized in the study: patients with low grade non-Hodgkin's lymphoma who have previously undergone bone marrow transplantation, a population of low grade non-Hodgkin's lymphoma patients who have not undergone ABMT and a control population of healthy volunteers.

2.1.1 Group 1: Low grade non-Hodgkin's lymphoma patients who have previously undergone autologous transplantation

Group 1 patients (n = 40) were the principal group of patients in the study. This group was drawn from the low grade lymphoma patients in the Ottawa General Hospital Bone Marrow Transplant Programme (OGH BMTP). These patients have previously faced the decision of choosing between treatment options for high-risk low grade non-Hodgkin's lymphoma and had undergone ABMT. Patients in this group met the following inclusion criteria.

1. Patients must have / have had relapsed or primary refractory low grade non-Hodgkin's lymphoma.
2. The patient must have had to choose between standard salvage chemoradiotherapy and high dose therapy with stem cell support for their relapsed lymphoma.
3. The patient must have undergone high-dose therapy and ABMT.

4. The patient must have been deemed well enough by their treating physician to participate in the study.

5. The patient's age must have been greater than 18 years.

6. The patient must have given informed consent. (Appendix A)

7. The patient must have been able to speak and write in English.

2.1.2 Group 2: Patients with low grade non-Hodgkin's lymphoma who had not undergone autologous transplantation

This group (n = 8) consisted of patients referred to the OGH BMTP who: were in the process of being assessed regarding their suitability for ABMT, had not yet decided whether to undergo an ABMT, had declined an ABMT after consulting with the OGH BMT programme members or who had been deemed ineligible for an ABMT by the OGH BMT programme members.

Group 2 patients recruited for this study met the following inclusion criteria.

1. The patient must have / have had relapsed or primarily refractory low grade non-Hodgkin's lymphoma.

2. The patient must have been referred for therapy that included the consideration of ABMT.

3. The patient must have been deemed well enough by their treating physician to participate in the study.

4. The patient must not have undergone an ABMT for their low grade non-Hodgkin's lymphoma.

5. The patient's age must have been greater than 18 years.

6. The patient must have given informed consent. (Appendix A)

7. The patient must have been able to speak and write in English.

2.1.3 Group 3: Control population

The control population consisted of a convenience sample of volunteers (n = 10). They included hospital employees, family members of the research assistant conducting the interviews and other hematology patients seen in the Outpatient Clinic who did not have low grade non-Hodgkin's lymphoma or any other malignancy. None of the volunteers had received chemotherapy in the past. The gender balance in the convenience sample was chosen to approximate that seen in the transplanted population. Strict age matching was not conducted although the spectrum of ages was similar to the age range of the transplanted population.

2.2 Subject Recruitment Procedures

2.2.1 Group 1

All patients in the OGH BMTP database who met the criteria outlined above for group 1 patients were contacted via mail by the Head of OGH BMTP. (Appendix B) Two weeks after the letters were mailed, follow-up phone calls were made by members of the research team to determine the subject's interest in participating in the study. A verbal consent was obtained over the phone and a mutually convenient time to conduct the interview was arranged with the subjects. Written consent was obtained at the time of their interview. The OGH ethics board approved the patient selection and recruitment process. (Appendix C) Two patients, when contacted by phone, declined to participate.

2.2.2 Group 2

The group 2 patients also met the eligibility criteria as outlined above. Patients were identified from the OGH BMTP database. As well, new patients who had been referred to the OGH BMTP with low grade non-Hodgkin's lymphoma for assessment

regarding ABMT were eligible to participate. As these patients were identified, a study member would approach the consulting physician to determine the eligibility in keeping with the criteria outlined above. If they fit these criteria, the patient was contacted by their physician to determine their interest in participating in the study. If interested, a verbal consent was obtained and again, a mutually convenient time to conduct the interview was arranged with the patient. Written consent was obtained at the time of their interview. All identified patients participated in the study.

2.2.3 Group 3

Group 3 subjects were a convenience group of volunteers most of whom were known to the study team. They were contacted on an individual basis by a member of the study team and if interested in participating, a convenient time was arranged to conduct the interview.

Written consent was obtained from all study subjects at the time of their interview.

2.3 Interview Design

Information was gathered in order to address the primary and secondary objectives outlined above. To achieve this goal the interview was given in several steps (Figure 1). First, a pre-interview questionnaire was administered to determine the patient's baseline knowledge about the risks (TRM) and benefits (4-yr TFS) of SST and ABMT. This was followed by completion of part 1 of the DA. This was composed of the educational information that summarized the two treatments that were to form the basis of the MCID elicitation. Following this, screening for comprehension of the MCID elicitation technique was undertaken. The subject's comprehension of the treatment scenarios was assessed by asking the subject to make a choice between SST and ABMT from a scenario where transplantation was clearly of no benefit. If the subject chose ABMT, it

was assumed that the information was not understood and further explanation was undertaken. This was followed by a repeat of the comprehension testing. Continued difficulties resulted in exclusion of the patient from the MCID estimation. Following successful completion of the comprehension screen, the subject's MCID was elicited regarding TRM and 4-yr TFS for ABMT versus SST. At the completion of the MCID elicitation, a post-interview questionnaire that assessed the patient's knowledge regarding risks (TRM) and benefits (4-year TFS) of the two approaches was administered again. Once all aspects of the DA were finished, a questionnaire evaluating the DA, the MCID elicitation exercise and the interview process was completed by the study subject. No subjects were excluded because of comprehension problems.

2.4 Allocation to Data Presentation Method

In order to address the effect of alternative methods of data presentation, study subjects were randomized to one of two groups by a witnessed coin toss. Group 1 subjects were presented information in the DA regarding risks and benefits of the two treatment options and their probabilities using a combined graphical and numerical format. Graphical-numerical presentation of the probabilities of risks and benefits was done using the numerical percent (e.g. 3%) plus face icons to represent hypothetical patients. One hundred hypothetical patients were depicted for risks (TRM) or benefits (4-year TFS). The probability of each occurring was indicated by shading in the appropriate number of patient icons (faces). For example, if the chance of dying from standard salvage chemotherapy was 3%, 100 patients were represented by 100 faces with 3 faces shaded in black to indicate they had died. In an analogous fashion the icon for patients well with no active disease was a smiling face while the icon for patients with relapsed/progressive disease was a frowning face shaded blue.

Group 2 subjects were presented the same quantitative information using a numerical-alone format. The probabilities were presented simply as a percent. If a patient's chance of dying from SST was 3% and from ABMT 20%, then a page with a heading "Chance of Dying from Treatment" with these numbers in a large font under the correct treatment sub-heading was shown to the subject (Appendix H). The scripted narrative portion of the DA and MCID interview was the same in both groups except where in Group A the meaning of the icons and the graphical representation was given.

2.5 Interview Location

Interviews were conducted in a number of venues. For patients residing in New Brunswick, the interviews were carried out in a patient examination room in the office of the patient's primary hematologist or oncologist. Patients in southern Ontario were seen either at their primary hematologist/oncologists office or in the patient's home. The remaining patients were seen at the Ottawa General Hospital in either a conference room or a clinic room outside of clinic hours. In each situation, a quiet, undisturbed setting was possible in which to conduct the interview.

2.6 Decision Aid

2.6.1 Format

The DA consisted of a series of booklets and a summary board. The primary booklet summarized the two treatment options. Within this booklet there were descriptions of both SST and ABMT in terms of the treatment time course, therapeutic procedures described monthly for six months, expected common and uncommon but serious side effects, TRM, and probable outcomes 6 months, 18 months, 3 years and 4 years post-treatment. These reference time points were chosen for several reasons. Six months was

selected because this was the time necessary to complete SST. The 4-year time point was chosen as it was the maximum period with reasonable follow-up data from ABMT studies. The middle two time points, 18 months and 3 years were arbitrarily chosen as one year from each of the outer time points. This number of reference points would give patients a reasonable amount of information on outcome without utilizing survival curves, which have previously been identified as being confusing for patients.⁶³ A second booklet contained the probability trade-off for use in the MCID elicitation for TRM and 4-year TFS. A summary board highlighted the major differences between the two treatments in terms of time course, side effects and outcome to 4-years post transplantation. As outlined above, all booklets and the summary board were constructed in graphical-numerical and numerical-alone versions.

2.6.2 Design Process

The content of the DA and interview was determined after discussion with patients, family members of patients, transplant physicians, other members of the transplant team including nurse specialists, general duty nurses and pharmacists. A thorough literature search using Medline was conducted for the years 1981 to present to identify relevant articles from which to extract the most appropriate values for baseline TRM, probabilities of disease progression and death out to 4-years following both SST and ABMT. Hand searches of hematological journals and meeting reports from 1995 forward were also conducted. Colleagues were asked for other appropriate references that they were aware of regarding low grade non-Hodgkin's lymphoma. Two important papers were available during this time which summarized the current knowledge in this area.^{5 10} Reports published after the completion of the interviews continue to be in keeping with the values used in the DA. Although only limited numbers of randomized controlled trials exist in this area, the experience with standard therapies has been consistent during the past 20

years.⁵ For ABMT, no randomized trials were available. Realistic but conservative estimates for the risk and benefit of ABMT based on the available Phase 2 trials in the literature were used for the baseline values in the DA.

Once the content of the DA was finalized, the format of the DA was developed using an iterative loop approach where drafts of the booklets and board were shown to various members of the transplant team and patients, followed by revision based on their feedback. Several approaches to the layout of the DA were considered prior to deciding upon the final format. The DA was further refined after pre-testing a beta version on medical students and members of the OGH BMT team. The graphical-numerical and numerical-alone versions of Part 1 of the DA as used in the study are included in Appendices D and E respectively. The interview script to help standardize the interview is included in Appendix F. Also, as an example, the format of the graphical-numerical version of the summary board available to patients as a reference during the MCID elicitation is included in Appendix G. Full size, the summary board occupied a full sheet of bristol board (22" x 28").

2.7 Measurement

The **MCID** was the primary outcome and was defined as the percent chance of TRM and 4-year TFS that made ABMT preferable to SST from a patient's perspective. The MCID elicitation was determined by holding constant the outcome probabilities of TRM and 4-yr TFS for SST and systematically altering the probabilities of treatment outcome for ABMT. The outcomes for SST were held constant as they are well defined in the literature and we were interested in determining what the TRM and 4-yr TFS would have to be with ABMT to choose it over SST. Two separate MCIDs were elicited, one for percent TRM and one for percent 4-year TFS. Sample pages from the graphical-

numerical version of the MCID elicitation booklet for 4-year TFS are included in Appendix H.

Llewellyn-Thomas has previously described the standardized approach to eliciting an MCID.⁴⁷ The patient was presented with two options, in this case ABMT and SST and the known or suspected toxicity and efficacy of the options (i.e. % TRM, % 4-year TFS). Patients were asked to choose between these two options. If Option A was chosen (i.e. ABMT), the efficacy of this option was systematically reduced until the patient switched preference to Option B (i.e. SST). If SST was chosen, the efficacy of ABMT was systematically increased until ABMT was chosen. The probability at which the patient just switched preferences was defined as the MCID.

In this study an MCID was determined for TRM by fixing the 4-year TFS benefit with ABMT (50%) and having the patient determine what TRM they were willing to accept for this amount of benefit when the TRM of SST was 3% and there was a 20% chance of having a 4-year TFS with SST. Similarly, the 4-year TFS MCID was determined by fixing the TRM of ABMT at a standard level (10%) and having the patient determine what chance of 4-year TFS they required to accept this risk, given the same fixed outcomes of SST. In both scenarios, the comparator group was the best estimate of the benefits of SST which have remained unchanged for approximately 20 years with a TRM of 3% and a 4-year TFS of 20%.⁵

Knowledge regarding the expected risks and benefits was elicited before and after completion of the DA by asking patients their estimate in percent of the TRM and 4-year TFS of SST and ABMT for patients with high risk low grade non-Hodgkin's lymphoma. The pre-interview and post-interview questionnaires for the patient's estimate of TRM and 4-year TFS are included in Appendices I and J.

Acceptability of the DA was elicited using a number of measurements. The amount of time taken to complete both the background portion and the MCID portion of the DA was measured. As well, patients were asked to subjectively rate whether they felt the time necessary to complete the DA was too short, reasonable or too long. The comprehensibility of the DA was evaluated on a 1 (not at all) to 5 (very much) scale looking at specific subsections of the DA including the risks and benefits of both SST and ABMT. The same scale was used to measure the helpfulness of the DA in making a decision. The overall amount and detail of information in the DA was rated using the classifications of “too little”, “just right” or “too much”. Similarly, the balance of the presentation of the risks and benefits was rated using classifications “too much emphasis on risks”, “just right”, “too much emphasis on benefits” for both SST and ABMT. The questionnaire to evaluate the DA and interview process is included as Appendix K. Factors taken into consideration when deciding whether to undergo ABMT were collected at the end of the evaluating questionnaire. (Appendix L).

Demographic (age, marital status, education, employment) and **clinical information** (diagnosis, treatments, transplant date, outcome, current status) was collected from the patient at the time of completion of the DA as well as from the OGH BMTP database and patient chart (Appendix L).

Classifying a **patient's disease status** following transplantation can be done at many levels. Within the OGH BMTP, patients are divided into two groups: those who achieve clinical stability and are referred to as “free from clinical progression” and those who develop progressive disease. Patients free from clinical progression may have complete absence of evidence of disease at a clinical and radiological level or they may have residual lymph node masses that do not change over a period of several months while being observed. Clinically they have no other evidence of active disease. Patients

with progressive disease may experience disease progression during or shortly after completion of the transplant or following some period of disease stability post-transplantation. It is felt that these definitions, although, not as objective as with pathological restaging, are a better indication of clinical disease activity and reflect what the patient experiences. It is also the process by which clinical decisions are made.

We felt that the **patient's subjective experience of the severity of their transplant** might be associated with MCID values. We used as a comparator the summary description of an ABMT in the DA. Patients rated their experience as 1 (much worse than the transplant outlined in the DA) through 4 (their transplant was similar to what was described) to 7 (their experience was much better than the transplant in the DA). One of the potential difficulties with having the patient rate their transplant experience is separating the patient's subjective experience from what the transplant team viewed as the medical difficulty of the transplant course. Correlation with the MCID may be with one versus the other. For this reason, the transplant coordinator and the Head of the transplant programme who were responsible for the majority of these patients' care, were asked to rate how they viewed the patient's transplant experience at a medical level (i.e. was it a medically complicated or uncomplicated transplant compared to the average). They retrospectively rated by consensus the patients' transplant experiences compared to the average transplant on the same 7 point scale as the patients. Ratings were carried out, blinded to the patients' ratings. Each patient was assigned a value after a short discussion between the two raters of the patient's ABMT course. As well, they were asked to indicate which patients would rate their transplant experience as more difficult than the average even though medically it was less complicated than the average.

2.8 Statistics

2.8.1. Sample Size

The number of available subjects for the primary study group (transplanted low grade non-Hodgkin's lymphoma patients) was limited to between 40 and 50. This was based on the number of English speaking patients who had been transplanted for this diagnosis in the OGH BMTP. Although low grade lymphoma is a relatively common hematological malignancy, ABMT for this illness remains experimental and often only considered for selected, younger patients by referring physicians. As a referral centre for low grade non-Hodgkin's lymphoma transplants within the province of Ontario and the Maritimes, we had the largest available population in Canada in whom to undertake this study. This group of patients was felt to be large enough to determine the MCIDs and possible clinical or demographic correlates. In addition, based on the arguments below, we felt that this sample size was adequate to allow us to detect a clinically significant difference in MCID based on presentation format, if one existed.

For sample size calculations to detect differences in presentation format, the TRM MCID was used because we have better estimates of it and it is the value more commonly discussed with patients who are making the choice between SST and ABMT. We used the mean TRM available with ABMT as the estimate of the true MCID in the sample size calculations. Although arbitrary, we had no other reasonable value to use and this TRM is the value discussed with patients when deciding whether to undergo ABMT. Whether the true MCID would be similar to the known TRM was unknown, as in practice, patients are not asked what risk they would accept but are asked whether they would accept the estimated known TRM. As some patients accept and others decline ABMT based on this value (TRM 10%) it seemed a reasonable value to use in the sample size calculation.

If the TRM MCID was ~10%, we believed that an absolute difference of 5 % based on a different presentation format would be clinically important as an MCID for TRM of 5% would not have been within deliverable care. In this situation, the presentation format giving more conservative MCIDs would then need to be used with prospective patients. Most patients who we see for this consideration choose to undergo a transplant, thus it was felt that the group was fairly homogeneous and that this would be reflected in a small standard deviation of between 5% and 8%. If these conditions were correct, then we would have precise enough estimates of the MCID to be meaningful, even if the total sample size was split into two groups as part of the format presentation sub-study. The possibilities for the range on the bound of the error of estimation are summarized in Table 1a.

As shown in Table 1b, with this sample size we would be able to detect a clinically significant absolute difference of 4% to 7.3% between the presentation formats, if one existed. This difference was felt to be clinically important because of the possibility that it would move the estimate outside of deliverable care as stated above. This difference, also, if detectable, would represent a moderate to large effect size as described by Cohen, where effect size is expressed as the difference between the mean values over the standard deviation $[(\text{mean value group 1} - \text{mean value group 2}) / \text{standard deviation}]$.⁶⁴ A small effect size is equal to ~0.3, a moderate ~0.5 and a large ~0.8.⁶⁴

For all calculations, the power of the study was set at 80% and the alpha error set at 0.05. The range of deltas that we would be able to detect based on our estimated available sample size is summarized in Table 1b.

If after completing the study, we are unable to detect a difference between the presentation formats, then we would be able to combine the two groups to obtain a more

precise estimate of the MCID. Summarized in Table 1c are the possibilities for the range of the bound on the error of estimation for the TRM MCID if study group 1 is used in total.

2.8.2 Analysis

Data were collected and entered in Microsoft Excel and analyses were conducted using the GraphPad Prism statistical software package (GraphPad Software Inc., San Diego, California). Descriptive statistics (median, minimum, maximum, means with standard deviation (SD) were determined for all variables. The primary outcome measure of the MCID for post-transplant patients was tested for normality using the Kolmogorov-Smirnov test. For comparison of sub-groups within the post-transplant group and for comparison with the no-transplant group, data was not assumed to be Gaussian. Parametric (t-test) or non-parametric (Mann-Whitney rank some test) tests were utilized as appropriate. Paired data was analyzed with the Wilcoxon Signed Rank test. Comparisons of proportions amongst groups were done with Fisher's exact test. All statistical tests were two-tailed and P values <0.05 were considered as statistically significant. Survival curves were generated using the methods of Kaplan and Meier.⁶⁵

2.9 Ethics' Approval

Our study was submitted to the Ethics Review Board of the Ottawa General Hospital. Approval was received in July 1995 (Appendix M).

Chapter 3

3.0 Results

3.1 Group 1: Patients Who Have Received an Autologous Transplant (Post-transplant Group)

Forty patients were identified who met the eligibility criteria for Group 1 and who consented to participate in the study. Two other patients declined, one from New Brunswick and one from Ontario. Nine patients lived in New Brunswick, four in the province of Quebec, 27 in Ontario. The New Brunswick patients and nine patients in the Southern Ontario region were interviewed in their city of residence. The remaining 22 patients from other parts of Ontario and the patients from west Quebec were interviewed at the Ottawa General Hospital. All patients were interviewed by the same research assistant.

Demographic data on the Group 1 patients is summarized in Table 2. There were twice as many males as females interviewed which is representative of our ABMT patient population. Although the median age of 49 years is low compared to the median age of all patients with low grade non-Hodgkin's lymphoma, it is as expected for the population receiving an ABMT. Group 1 patients spanned the age spectrum of patients transplanted for this diagnosis. The majority of patients (77%) were married or in a stable relationship, employed and had a high school diploma or some post-secondary education.

The disease related information for patients in Group 1 is summarized in Table 3. The typical patient had follicular small cleaved cell lymphoma, was transplanted in either a

first or second partial remission and was currently free from clinical progression post-transplant.

Table 4 summarizes the transplant experience data. The median length of hospitalization for ABMT was 28 days with a range of 9 to 60 days. This was a typical length of stay for ABMT during the time period these patients were treated. The patient determined median time until full recovery was achieved was 20 weeks. There were, however, outliers at both ends of the spectrum with some patients feeling that they had recovered completely within one month of discharge from their transplant and others requiring several years. One patient stated that they still had not recovered completely even though they were nearing five years post-transplantation. Overall, the patient-rated time to recovery is in keeping with quality of life surveys post-ABMT.⁶⁴ Sixteen patients felt that their transplant was similar to that described in the DA (median rating 4). There were nine patients rating their experience as much worse (1 out of 7) or somewhat worse (2 out of 7) than the description in the DA. Similarly nine patients rated their transplant either somewhat or much better (6 or 7 out of 7) than that described in the DA. Six patients did not rate their transplant experience.

The patient's rating of their experience was not always the same as the transplant team determined medical experience (Table 5). In 8 of the 9 patients, who had rated themselves as having a much worse experience, the transplant team felt that they had a medically significantly better experience than the patient had indicated. The same pattern was seen with patients who rated themselves as having a good transplant experience. The medical team felt that all 7 had had a significantly worse transplant experience than the patient's self report. Of note, the transplant team without knowing the patients' ratings was also able to readily identify which patients rated themselves as having a poor transplant experience despite having a medically uncomplicated transplant. Overall,

however, there was no statistical difference in the ratings between the patients and the transplant team with the patients' mean transplant rating 4.1 (SD 1.8) and the transplant team's mean rating 3.9 (SD 1.3). Overall, patient rating and transplant team rating were in agreement within 1 on the scale of 7, 42% of the time.

3.2 Possible Clinical Correlates of the MCID

Demographic, disease and therapy related items were tested for their association with the MCID. Gender, current disease status, marital status, age, education level, time since BMT, days hospitalized, patient-rated recovery time post-BMT and patient-rated transplant experience were all tested (Table 6). Of these, two statistically significant associations were identified: gender and patient-rated recovery time post-BMT both in relation to the 4-year TFS MCID. Men identified a statistically higher median 4-year TFS MCID (21.5%) versus females (18%) ($p = 0.04$). There was a moderate degree of correlation between the patient-rated recovery time post-BMT and the 4-year TFS MCID ($r = 0.44$, $p = 0.005$). Those taking a longer time to recovery had higher MCIDs.

Several other items were found to have a strong trend towards statistical significance despite the overall small sample size. Patients whose disease had progressed since their transplant had a non-statistically significant higher 4-yr TFS MCID compared to patients still free of clinical progression ($p = 0.06$). Similarly, married ($p = 0.09$), and older ($r = 0.29$, $p = 0.06$) patients identified non-statistically significant higher 4-yr TFS MCIDs.

3.3 MCID for Treatment Related Mortality

Table 7 describes the MCID for TRM using the standardized scenario in the DA of 3% TRM for SST resulting in a 20% 4-year TFS versus the 50% TFS expected with

ABMT. The mean MCID was 23.8% (95% CI: 20.0%, 27.5%) meaning that patients would switch from choosing SST to ABMT if the TRM of ABMT was less than 23.8%. The distribution was symmetric, with few outliers, resulting in a median similar to the mean. As outlined in Figure 2, only one patient out of forty identified an MCID for TRM with ABMT that was less than what is currently accepted as the expected risk in 1997 (i.e. less than 5%). Four patients identified an MCID for TRM between 6% and 10%. Although below the conservative 10% used in the DA, ABMT currently has a TRM of ~5%. At the other extreme, three patients were willing to accept an extremely large TRM of between 46% and 50% to have a 50% chance of being treatment free four years later. Those three patients had the lowest 4-year TFS MCID at 10%. The distribution of the TRM MCID and 4-year TFS MCID are also depicted in Figure 3.

3.4 4-Year Treatment Free Survival MCID

Table 7 summarizes the MCID for 4-year TFS as determined in the 40 patients using the scenario as described in the DA. In this scenario, patients again were given the SST TRM of 3%, 4-year TFS of 20% and a fixed accepted TRM with ABMT of 10%. The patient, by working through the MCID elicitation exercise was to determine what percent chance of 4-year TFS with ABMT they would accept given these risks. The mean 4-year TFS MCID was 21.3% (95% CI: 18.9%, 23.7%). This mean value was very similar to the 20% with SST.

It should be noted that 13 out of 40 patients identified an MCID for the 4-year TFS less than the 20% 4-year TFS available with SST despite an increased up-front TRM with ABMT (Figure 4). Eight patients identified a 4-year TFS MCID of 15% or less. In fact six identified an MCID for 4-year TFS of 10%.

3.5 Disease and Therapy Related Knowledge Before and After Completion of the Decision Aid

The results of the pre and post DA knowledge test with regard to TRM and 4-year TFS of both SST and ABMT are summarized in Tables 8 and 9 respectively for the post-transplant group. With regards to SST, patients' estimates of the TRM and 4-year TFS were high prior to completion of the DA. The amount of over estimation was markedly higher with regards to the 4-year TFS following SST. This can also be seen in the number of patients who gave what was rated as reasonable estimates before versus after the DA. In nearly all cases a statistically significant improvement in patient knowledge was measured by the proportion of patients giving reasonable versus unreasonable (high and low) estimates for the TRM and 4-year TFS after completion of the DA.

The same pattern can be seen with the ABMT scenario (Table 9). Initially, TRM was correctly estimated by just over half of respondents, while after completing the DA all but 2 were able to give a reasonable estimate. As with SST, a statistically significant improvement in knowledge of transplantation related risks and benefits was measured after completion of the DA.

3.6 Methodological Sub-Study: Graphical-Numerical vs. Numerical-Alone Format of the Decision Aid

All 40 participating patients in group 1 were randomized to either graphical-numerical or numerical-alone representation of the probabilities contained within the DA. These results are summarized in Table 7. There was no statistically significant difference in the mean estimate of TRM or 4-year TFS using either approach to the MCID elicitation.

The overall evaluation of the DA was equally positive whether it contained the graphical-numerical or numerical-alone representation of probabilities. This can be seen in Table 10 where both groups indicated that they understood the risks and benefits much better after completion of the DA. Similarly, both groups felt that the DA would help others in making their decision, and there were no differences between the groups.

3.7 Evaluation of the Decision Aid

The feedback from the subjects completing the DA and MCID elicitation is summarized in Tables 10-14. The length of time to complete the DA background section took on average 6.4 minutes longer in the graphical-numerical group compared to the numerical-alone group (Table 13). The time to complete the MCID section of the DA was not different between the two presentation format groups. Common to both groups, however, was a feeling that the completion of the entire process was too long. (Table 13)

In contrast, nearly all subjects in the healthy control and the no-transplant group felt that the completion time for the DA was just right. Interestingly, this despite a significantly longer median completion time for the background portion in the no-transplant (32.5 mins) versus the post-transplant group (25.0 mins).

The overall content of the DA was rated to be “just right” by the majority of respondents in all groups (Table 11). However, approximately ~15% - 20% of subjects in the post-transplant and the healthy control groups felt that more information and more detail were required in the DA. There were no differences based on the presentation format in the post-transplant group.

3.7.1. Decision Aid Evaluation: Standard Salvage Therapy

Both the graphical-numerical and numerical-alone groups rated the information about the risks of SST as very understandable (Table 12). Similarly, patients found this

information to be helpful. Overall, subjects rated highly the understandability and helpfulness of the information in the DA regarding the benefits of SST. The vast majority of subjects felt that the information in the SST section of the DA was well balanced (Table 14). Overall, few respondents rated the DA below the neutral rating in any category.

3.7.2. Decision Aid Evaluation: Autologous Bone Marrow Transplantation

Ratings of the information regarding risks and benefits in the DA for the bone marrow transplantation scenario are summarized in Table 12. Subjects thought that the information on risks was both understandable and helpful. Similarly, information about the benefits of ABMT contained in the DA received uniformly high ratings for both comprehensibility and helpfulness. Again, the presentation of the DA was felt to be balanced by nearly all respondents. (Table 14)

3.8 Reasons for Undergoing Autologous Transplantation

The reasons given by patients for having undergone ABMT are summarized in Figure 5. Ninety percent of the patients indicated they underwent transplantation because of recommendations by their physician or because of the possibility of long-term survival. Similarly, just over 2/3 of patients cited unspecified personal "long-term goals" as a reason to have undergone ABMT. The remainder of the items were listed as contributing to the choice in less than 1/2 of the patients. Only 1/4 of the patients indicated that "time off treatment" and 1/5 "treatment time commitment" contributed to their choice of ABMT. No differences in the TRM or 4-year TFS MCIDs were found in relation to the reasons listed for consideration by patients prior to undergoing ABMT.

There was some evidence of consistency between stated reasons for undergoing ABMT and the MCIDs. Only 7 out of 40 cited "short-term mortality" as being important in their decision making. This is in keeping with the mean TRM MCID of 23.8% in the overall

group, a value much higher than the anticipated result of clinical therapy (< 10%). The low number of subjects citing "short-term goals" as a consideration is also in keeping with this high TRM MCID. Overall, > 80% of patients stated they would undergo an ABMT again.

3.9 Group 2: Patients Who Have Not Undergone an Autologous Transplant (No-Transplant Group)

Eight patients with low grade non-Hodgkin's lymphoma who had not yet undergone an autologous bone marrow transplant were available to be interviewed. The group consisted of 5 patients who had declined ABMT, 1 patient under assessment regarding suitability of ABMT, 1 patient who had yet to decide whether to undergo ABMT and 1 patient who had been deemed ineligible for ABMT. Their relevant demographics and disease related information is available in Tables 2 and 3 along with the other patient groups. The mean age of this group was 45 years and most patients had follicular small cleaved cell lymphoma. A higher proportion of patients in the no-transplant group were female. The no-transplant group also had a lower proportion with post-secondary school education (Table 2.). The TRM and 4-year TFS MCIDs for the no-transplant patients are plotted in Figures 2 and 4 and summarized in Table 7. Overall, the no-transplant patients had a significantly higher 4-year TFS MCID (median 25.5%) than the transplanted group (median 21.0%) ($p=0.015$). Due to the small number of patients available in the no-transplant group, we were unable to balance or adjust for the differences in demographic characteristics between the no-transplant and post-transplant groups. The TRM MCID was not different between the two groups.

The time to complete the background section of the DA in the no-transplant group was significantly longer than in the patients who had previously been transplanted (Table 13). The time to complete the MCID elicitation, however, was not different between the

no-transplant and post-transplant groups. As noted above, in contrast to the post-transplant group who felt the DA took too long to complete, the no-transplant group felt the time necessary to complete the DA was “just right”.

The baseline or pre-completion of the DA estimates as well as the post-completion estimates of the TRM and 4-year TFS associated with SST and ABMT are summarized in Tables 15 and 16. Despite the small number of available patients in the no-transplant group, after completion of the DA, the proportion giving what were felt to be reasonable estimates of the percent chance of TRM and 4-year TFS with SST improved significantly (Table 15) as did their estimate of the percent chance of 4-year TFS with BMT (Table 16).

Ratings of the DA by the no-transplant group were uniformly positive regarding the understandability, helpfulness and balance of the DA (Tables 12 and 14).

3.10 Group 3: Control Patients

The control patients had a median age similar to the other groups (Table 2). Their TRM and 4-year TFS MCIDs are shown in Figures 2 and 4 and summarized in Table 7. Their MCIDs were not statistically different from the no-transplant or post-transplant groups. This comparison is limited statistically, particularly between the controls and the no-transplant groups because of the small sample sizes. However, when looked at graphically (Figures 2 and 4), there is no suggestion of a difference between this group and the others.

There was a statistically significant improvement in the subjects' estimates of the TRM with SST after completion of the DA (Table 17). Due to the small sample sizes, before and after differences could not be calculated in all comparisons.

Chapter 4

4.0 Discussion

4.1 *Interpretation of the MCID Results*

The risks and benefits that patients with high-risk low grade non-Hodgkin's lymphoma are willing to accept when considering ABMT as salvage therapy has not previously been described. Using a disease specific DA to measure the MCID, we determined that patients with high-risk low grade non-Hodgkin's lymphoma were willing to accept on average, a 6 month TRM of 24% for a 50% probability of requiring no further therapy for 4 years. If the 6 month TRM of ABMT was set at 10%, patients would accept this therapy for a 21% chance of being treatment free for the next 4 years. Overall, these results are internally consistent; patients required an increased benefit for an increased risk. What was somewhat unexpected is the degree of risk patients were willing to take and the limited chance of benefit needed by some patients to accept a moderate mortality risk. This has, however, been found in some other studies of patients' willingness to undergo therapy for cancer.^{40 59}

There are several implications of these results. First, the risk-benefit ratio far exceeds what some practicing clinicians think patients are willing to accept with this diagnosis. As a result, some physicians do not offer this therapy option to patients, believing the risk is too high. Second, the MCIDs are within the limits of deliverable care. The risk-benefit ratio identified by patients is far greater than the published risk-benefit ratios of ABMT for high-risk low grade non-Hodgkin's lymphoma.^{10 17 18} Finally, a significant amount of resources and research activity has centered around minimizing toxicity,

emphasizing that TRM is now 3% or 5% vs. 10%, expecting that this will alter the therapy choice of patients. While decreasing toxicity and TRM is an effort worthy goal, on its own it may not be where the primary focus of activity needs to be placed. This is particularly true if attempts to minimize toxicity and TRM result in reduced efficacy of therapy as measured by relapse free or overall survival.

While overall the results appear consistent and plausible, further attention to the upper and lower quartiles of the TRM and 4-year TFS MCIDs reveals results that are not so obviously logical. This is particularly so for the 4-year TFS MCID. As noted in the results section, the median 4-year TFS MCID was only marginally higher than the SST arm despite a higher up-front risk with ABMT. Furthermore, a significant proportion of patients identified a 4-year TFS MCID less than the 20% available with SST. At first glance it is difficult to reconcile the responses of these 13 subjects with regards to their 4-year TFS MCID. What explanations are there for people apparently choosing lower benefit and higher risk than standard therapy by undergoing an ABMT? The simplest explanation would be that the patients did not understand the MCID elicitation procedure or the content of the DA. All these patients, however, gave answers on the post-DA questionnaire regarding SST and ABMT TRM and 4-year TFS close to the baseline values in the DA. Only one patient continued to overestimate the post-SST TRM at 20% compared to the 3% outlined in the DA and the post-transplant 4-year TFS at 75% versus the 50% contained in the DA. This patient also overestimated post-SST 4-year TFS. Overall, the post-transplant patients' estimates of the TRM and 4-yr TFS with the two treatment options does not indicate that lack of comprehension of the information in the DA was the explanation.

The second possible explanation for the seemingly inappropriately low 4-year TFS MCIDs would be that the trade-off question being asked in the MCID elicitation is too

complex. Although when tested on individual portions of the overall question patients were able to respond appropriately, perhaps they were unable in the MCID elicitation procedure to keep track of all aspects of the question and therefore responded inappropriately. It is also possible that because of the complexity, patients lost sight of the trade-off versus SST and responded with the minimum benefit necessary with ABMT to accept it.

A third possible reason would be that the DA is flawed either in its treatment option summary or method of MCID elicitation, resulting in confusion in the patient. This possibility however does not seem to be the explanation based on the evaluation of the DA, as it received uniformly high ratings on all aspects of its clarity, content and design.

A fourth series of possibilities relates to the rationalizations and psychological make up of patients with a fatal disease. Of concern is the fact that the primary study group for determining the MCIDs were patients who had already been transplanted and who may be biased in favour of ABMT. This population of survivors, facing an eventually fatal illness may see themselves outside the laws of probability having already survived the transplant experience.⁶⁶ Therefore they may have ignored the higher TRM of ABMT. Another rationalization may be the patients' unspoken, perhaps subconscious hope for cure associated with a new therapy, in contrast to the nihilism associated with the clear continuous demise of patients with SST.⁵ We did not specifically elicit patients' beliefs about the possibility of cure because we did not want to imply there was one. In future studies, this belief should be elicited.

The other observation of the results in the 4-year TFS MCID is that the highest quartile of patients all fall within both the best estimates from the medical literature^{10 17 18} and the OGH BMTP 4-yr TFS experience for ABMT in high-risk low grade non-Hodgkin's lymphoma patients.

Interpretation of the results of the TRM MCID are less complicated. All patients, save one, identified TRM MCIDs consistent with results obtained in most ABMT programmes. Remarkably, however, the highest quartile of patients included three who were willing to accept a TRM approaching 50%. These three patients had preferences that were internally consistent as they also identified the lowest 4-year TFS MCID and as such represent one end of the spectrum of risk acceptance by patients.^{59 67 68} It is possible that this again reflects an underlying hope at a chance for cure with ABMT and that they were willing to accept a significant initial risk for this chance. Inside these extremes, were the majority of patients who were willing to accept a moderate but still higher than necessary risk with transplantation for less benefit than is felt to be available with this treatment. Lastly, the less complicated TRM MCID results may reflect the relative ease of comprehension of TRM compared to 4-year TFS by the lay person.

4.2 Clinical Correlates of the MCID

Patients who have undergone an ABMT and survived are expected to be biased to some degree by their prior choice. However, many transplant related factors as well as demographic or disease characteristics may potentially influence their strength of preference for transplantation. In attempting to identify these clinical correlates, despite the relatively small sample size, 2 factors (gender, patient-rated recovery period) were found to be statistically associated with 4-year TFS. None were found to be associated with TRM. Several other factors had a trend towards association with either the TRM MCID or the 4-year TFS MCID. Due to the small sample size, our study may have lacked adequate power to determine their true significance.

4.2.1 Gender

Men identified a higher 4-year TFS MCID than women but there was no difference between gender with respect to TRM MCID. When trying to determine if this gender difference was a reflection of some other clinical or demographic difference between men and women, none could be identified based on the collected data. Little is known regarding gender based preference differences.⁶⁹ Flynn reported gender differences in the perceptions of environmental health risks but, in contrast to our results, women were identified as being more conservative than men in his study.⁷⁰ It is possible that the lower 4-yr TFS MCID identified in women is the result of an unidentified confounder or reflects a chance finding as a manifestation of the large number of comparisons that were conducted in this hypothesis generating analysis. The possibility that women with high-risk low grade lymphoma are more risk taking remains a possibility and should be studied further in future preference studies of transplantation patients.

4.2.2 Patient Rated Time to Recovery

The association between the 4-year TFS MCID and patient rated recovery time post-ABMT indicated that those patients experiencing prolonged recovery desired a greater return for their efforts. It should be noted that "recovery time post-ABMT" was determined from the patients' perspectives. In many cases the time to recovery as determined by the transplant team was very different. If the MCIDs in the upper quartile of patients ranked by "patient rated time to recovery post-ABMT" was clinically significantly different than the MCID in the lower quartile of patients, then it would be prudent to use the conservative estimate of the MCIDs when discussing the results with patients pre-transplantation. In our study, the MCIDs in the upper and lower quartiles were not felt to be clinically significantly different, as both fell within results currently available with ABMT.

The TRM MCID was not associated with "patient rated time to recovery post-ABMT". This may reflect the fact that the respondents had already survived the short-term risk and were therefore less influenced by it in relation to their overall recovery. This would be in keeping with preference variations that have been demonstrated in relation to the timing of a transient medical situation.⁶¹ Alternatively, the lack of association may reflect the fact that most patients identified a recovery period of between 6 and 30 months with few outliers. This clustering of patients' responses along with the sample size limited our ability to discriminate between subjects.

4.2.3 Disease Status at the Time of Completing the MCID Exercise

The trend towards an association between 4-year TFS MCID and disease status at the time of completing the DA is interesting, again reflecting the influence of patient experience on the MCID. It is possible that those patients with disease progression post-transplant are identifying a hope for more time prior to requiring further therapy. Although there was a trend towards a statistical difference in the 4-year TFS between patients who had clinically progressed and those who had not, the difference was small (~6%) and clinically unimportant. Furthermore, as the ultimate use of DAs is prior to therapy, this factor would not come into consideration.

4.2.4 Hospital Stay During Transplant

The trend towards a higher 4-year TFS MCID in those patients having a longer hospital stay is analogous to the relationship identified with patient rated recovery period. Those patients who had longer hospital stays and who were therefore presumably sicker immediately post-transplant, seemed to want a greater benefit for their investment. These patients were not necessarily the same patients as those with a long self-rated recovery

post-transplantation, as there was no correlation between hospital stay and overall patient rated recovery period post-transplant.

4.2.5 Age

There was a trend towards a higher MCID for 4-year TFS as age increased. The difference in the MCID between the youngest and oldest quartiles, however, was not clinically significant as both results fell within the range of outcomes available with ABMT. While age has been shown to be of importance in a patient's desire to be involved in decision making,^{19 20 33} risk attitude in relation to perceived gains or losses has not been shown to be age dependent.^{33 67} In general, studies have demonstrated that people of diverse ages are not willing to trade quantity of life for improved quality of life^{40 53 67}

4.2.6 Marital Status

Patients who were married or living common-law did not identify a statistically higher 4-year TFS MCID than the group of patients who were single, separated or divorced. While social factors have previously been shown to influence hypothetical treatment decisions in cancer patients, marriage was not found to be one of the factors associated with therapy choices.⁶⁹ This strict separation of marriage from other correlates such as patient determined social and family well being, however, is problematic as they are interdependent facets of a person's psychosocial being. Furthermore, our understanding of these factors in transplantation has been identified as primitive.⁷¹ Future studies of decision making in transplantation needs to include consideration of sociodemographic features as to date so little is known.

4.3 Factors Considered by Patients Prior to Undergoing Autologous Transplantation

The premise that some subjects' MCIDs may reflect a belief or hope for chance of cure is supported in part by the fact that 90% of patients cited "long-term survival" as a factor contributing to their choice to undergo an autologous transplant. Similarly, 25 of 40 patients cited "long-term goals" as a factor behind their choice of ABMT. Only "long-term survival" and "physician recommendation" were listed more frequently than "long-term goals". Unfortunately, a definition of "long-term survival" was not included, so this may have meant different things to different patients. Based on my own clinical experience and discussions with other patients and members of the OGH BMTP, I feel that "long-term survival" is usually interpreted to mean "near normal life-span".

It is not surprising that >90% of patients listed "physician recommendation" as one of the factors in their decision to undergo an autologous transplant. Most patients we see in the OGH BMTP come for a consultation with a baseline preference, for or against transplantation, but still seeking an opinion. No patients gave "physician recommendation" as the only factor considered when deciding on ABMT. These results are in keeping with a shared decision making model, in which patients consider the physician's opinion along with the objective data and their own personal values in reaching a decision regarding therapy.^{22 24}

The low percentage of patients citing "time off treatment" as a reason to undergo transplantation was surprising. During the design of the DA, the developers considered "time off treatment" as one of the most important differences between SST and ABMT. This same factor is an integral part of discussions we have with patients considering ABMT versus standard chemotherapy for metastatic breast cancer. It may be that this is

another example of physicians projecting their value system on patients and failing to relate the information that is relevant to the patient.

How important the individual factors are in the decision process needs to be determined in future studies. This could be done by having patients rate the relative importance on a scale or possibly rank order them. This could be followed by a post-decision interview that explicitly explores the personal factors considered and the weighting of personal factors versus the objective evidence and physician recommendation.

4.4 Comparison of MCIDs Measured in No-Transplant Vs. Post-Transplant Subjects

The 4-year TFS MCID of those patients who had not yet undergone an ABMT was higher than the patients who had already been transplanted. The difference was statistically significant but this may only reflect the effect of the two high outliers in the no-transplant group. The possibility that patients who had declined a transplant required a higher degree of benefit is plausible as some of these patients may have declined or deferred a transplant, because of too much risk or not enough benefit. Most patients, however, still identified a 4-year TFS MCID less than the expected efficacy with ABMT. Perhaps this is because patients considered other factors in addition to TRM and 4-yr TFS in making their decision.

The generalizability of the results must be viewed with caution given the small number and heterogeneity of respondents in the no-transplant group. One patient was not a candidate for transplantation, most patients had “declined for now” and one patient had likely declined forever.

The choice between the known and unknown introduces another possible difference between the patients who had previously undergone an ABMT and non-transplanted patients; their risk profile. It has been shown that risk attitude can change in relation to the severity of the situation one faces.⁶⁷ Under situations that have a reasonably good long-term outcome with the status quo (the future is close to their aspirations in terms of quantity) people are risk averse. If, however, the future is not so certain (decreased life expectancy potential compared to their aspirations) people become risk seeking to try and achieve their long-term aspirations. Perhaps the patients who declined or “declined for now” still felt that their chances of achieving their long-term aspirations were high enough without undergoing a transplant. Again, there was no difference in the desire for long-term survival between the no-transplant and the post-transplant patients, just a difference of opinion on how they felt they could best get there. The post-transplant group, based on their MCIDs and the fact that they chose a transplant indicate a preference for future years over short-term mortality.⁶⁷ Such preferences are displayed in other patients with serious illnesses who choose therapy that offers a chance of improved survival but with up-front risk of TRM.^{40 59 67} Of note, since completion of the study 6 of the 8 patients who originally declined ABMT have undergone ABMT for progressive disease. Patients facing these types of therapeutic choices need to be studied to resolve methodological issues of how to measure preferences that reflect actual choice and to better understand what these preferences are based on.

4.5 Comparison of MCIDs Measured in Controls vs. Post-Transplant Subjects

The control population's MCIDs did not differ statistically or clinically from the post-therapy patients. It is intriguing that these chemotherapy naive patients, with little prior

knowledge of low grade non-Hodgkin's lymphoma, identified the same qualitative and quantitative valuations of risk-benefit as post-transplant patients. While this comparison has not previously been reported in lymphoma patients, it is known that healthy control populations tend to devalue the quality of life of patients with chronic illnesses such as dialysis dependent renal failure.³⁵ They also generally respond differently to trade-off exercises than patients with disease.^{34 38 59} One possible explanation for the lack of difference between the healthy controls and the post-transplant group is that the clarity and representativeness of the DA were such that a convenience sample of healthy individuals were able to have a meaningful internalization of the scenario and arrive at the same conclusions as patients.³³ This possibility is supported by the positive ratings post-transplant patients gave to the DA in terms of realism, clarity and comprehensibility. When decision aids accurately reflect reality, they are considered "salient" and are better able to negate framing effects.³³ It remains possible, however, that differences were missed due to the small sample size.

4.6 Implications of the Observed Clinical Correlates and Comparator Groups

The influence of patient experience on MCIDs measured post-therapy is important to note. In future studies it may be that patients prior to therapy should be the preferred group studied to determine the MCID. If, however, as in our study there does not appear to be clinically significant differences between the MCID measured in patients declining or pre-therapy versus post-therapy, this may not be a concern. In our study even if the differences were statistically significant, they were not clinically important as all groups values fell within current ABMT results.

The lack of difference between no-transplant and post-transplant patients is also relevant for other rare diseases where it may not be feasible to determine the MCID on incident cases alone. The MCID measured post-therapy may be used as a proxy if one takes into consideration the effect of demographic and clinical characteristics until the MCID can be validated through the prospective entry of de novo patients.

Future studies of MCIDs should collect relevant demographic and clinical data elements to try and clarify their influence on the MCID. As the similarity of the MCID in the control population is counter to what is expected based on prior reports and because the number of subjects studied was small, this result should be viewed cautiously. It is unlikely that salience of a DA can replace real patient experience and insight. The use of healthy volunteers to measure MCIDs for complex health states and therapies can not be recommended based on the limited observations in this study. Future preference studies should include larger numbers of healthy subjects to try to address this issue.

4.7 Clinical Significance

Although we were able to identify the potential importance of determining MCIDs before therapy and potential correlates of the MCID, clinically important differences between the sub-groups have not been identified. In all situations examined, including comparisons between no-transplant versus post-transplant groups, the observed differences are small compared to expected outcomes of current transplantation practices for this population. The average TRM MCID for all sub-groups was very high in comparison to clinical transplantation results. Similarly, the benefit required by patients is much lower than what is achievable with current clinical practice. Presently, ABMT is safer and more efficacious than patients required to accept this therapy choice.

4.8 Graphical-Numerical vs. Numerical-Alone Format

Developers of decision aids have come to realize that the manner in which the information is presented is just as important as the content. This has been demonstrated for the framing of outcomes in several though not all studies.^{32 48 49 50 53} Mazur et al also has demonstrated that the interpretation of survival curves was beyond the comprehension of many patients and therefore not helpful in a DA.⁶³ One approach to probabilities presentation within a DA developed by O'Connor has been the use of a graphical-numerical format, combining face icons to represent people, with percentages to try and give individuals visual representation of the probabilities of the possible outcomes.^{44 41} This may be a more meaningful depiction than percentages alone, particularly when the educational background of the target population is likely to be quite varied. When compared in a randomized fashion, no difference was detected for MCIDs elicited using graphical-numerical versus numerical-alone formats in our study. Again, this may be due to the clarity of the DA, which was well received in both presentation formats. Alternatively, our concern over percentages may have been unfounded as they occur so commonly in daily life that most people are comfortable with their meaning. As well, in our study, nearly all subjects were educated beyond the level where these concepts are taught. Lastly, it may be that by avoiding more difficult concepts such as survival curves⁶³ and focusing instead on discrete time points, the information contained in the DA was easier to comprehend.

While both methods of presentation were rated favourably with regards to helping patients understand the choice before them, the combination of the graphical-numerical format took longer to complete. The increased time was likely due to the extra explanations about the meaning of the graphical representations. It is unlikely that the

time difference was due to subject confusion, as responses (MCIDs) and ratings were not different for the two presentation formats.

4.9 Sample Size and Study Power to Detect Differences

In our a priori estimates of the sample size (Table 1), we underestimated both the means and variances of the groups. As a result, we were unable to detect a difference between the presentation formats (t-test $p=0.36$). In our post hoc determination of the power to detect differences between the presentation formats, we found that the sample size of 20 per group had approximately 30% power ($\alpha = 0.05$, pooled SD = 11.739).

With our baseline assumptions (α 0.05, power 80%) and the pooled standard deviation from the study we would have required a sample size of approximately 100 per group to detect a difference of approximately 5% if present. As we evaluate ~20 patients regarding ABMT for this diagnosis each year, it would not be feasible to conduct such a study.

4.10 Evaluation of the Decision Aid

In order to measure the MCIDs, we first needed to develop a disease specific DA. As outlined earlier, DAs not only contain educational components, they are also specifically designed to facilitate decision making and to clarify personal values regarding benefits and risks. A well designed DA should achieve these goals with a clear and balanced presentation. We evaluated our DA on all of these aspects in order to be able to interpret the results of the MCID elicitation and to determine if this approach would be useful in other settings. As summarized earlier, the DA was rated favourably on all measures. Of particular note, patient estimates of the outcome measures (TRM and 4-year TFS) were greatly improved after completing the DA. This is somewhat surprising as

the primary group of patients had previously chosen ABMT but in approximately half of the cases had poor baseline estimates of the risk-benefit ratio for SST or ABMT. Could the poor estimates be due to biased presentations of information to patients by physicians? It is impossible to know. Physicians in other settings have been reported to frame information in discussions with patients to influence patient choice, even in life threatening situations.³² The baseline risks stated by the post-transplant group may in fact reflect both what they were told and the evidence at the time of their original transplant discussions. The higher estimate of TRM is in keeping with what was the standard in the medical literature until recently. Another plausible explanation is the common observation in cancer medicine, that patients overestimate the benefits of therapy even when given clear information.^{29 30}

Whereas there was some concern with the baseline estimates of the TRM and 4-yr TFS, these estimates were significantly improved after using the DA. Of the subjects who continued to give incorrect responses, they persisted in their tendency to overestimate benefits.

If measured on its ability to improve patient knowledge base, the DA was very successful. Moreover, patients found that the DA helped them to understand the risk-benefit ratio of the choices and felt that it would be helpful to others facing the same situation. With only 3 patients giving a negative evaluation of the helpfulness of the DA, no characteristics could be identified that separated them from the others.

While the DA was effective, it was considered excessively long by most respondents. Other DAs have been reported to take similar or greater periods of time to complete.³⁹ Several factors contributed to the completion time including the complexity of the choice and treatment options, the elicitation of two MCIDs, the interview process and the post-DA evaluation questionnaire. Changing to a self-complete audio-booklet or flip-

chart would likely shorten the completion time. A novel, simpler approach, such as the use of linear analogue scales⁷² or a “risk thermometer” to define the MCID could potentially be developed and validated against the MCID elicitation exercise of Llewellyn-Thomas. Breaking the exercise into two stages, a self-study background section and a MCID elicitation interview would be a compromise measure that retains some of the traditional approaches. Condensing the DA may be difficult if one is to include even more detail as requested by ~15 - 20% of the subjects in this study. However, the removal of the research procedures for a clinical practice version would likely increase efficiency and acceptability.

In our study, a SST arm was used to represent all non-curative chemotherapy approaches available at the time. More recently, less toxic but still non-curative single agent chemotherapeutic agents have become available^{12 13} as has a minimally toxic experimental therapy using a monoclonal antibody⁷³ against a surface antigen on the lymphoma cells. The re-introduction of allogeneic bone marrow transplantation for this indication by some centres as a potentially curative but higher risk approach further complicates the choice.¹⁴ Incorporating 3, 4 or 5 choices into this type of DA is unrealistic. As well, decision making in the face of multiple alternatives has been shown in theoretical studies to result in a preference for the status quo.⁷⁴ Whether this would occur with a real therapy decision is unknown. It may be possible to define MCIDs on pairs of choices but patient numbers are small so that validating this approach would be difficult. As well, patients may define different MCIDs for one therapy depending on its comparator, a type of “framing bias”.

If a DA is to be used in such a complex and rapidly changing setting, the approach may be to first define patient goals and risk taking profile. This could be accomplished by asking them generically, without therapy details what TRM, 4-year TFS or other endpoint

of relevance they are willing to accept and then guide them to therapies in keeping with their profile. With this approach, the rapidly changing therapy options can be included or excluded from the DA as their value is proven or refuted in the medical literature.

Despite the changes, there is a sufficient amount of uncertainty about the outcomes of one treatment alternative compared to another to require the additional input of patient preference. Therefore, for the time being, treatments can be defined as “options” to consider as opposed to “guidelines” to follow.⁷⁵ If with further research and clinical developments, the medical community is able to define the therapy with the best clinical outcome, treatment “options” could be replaced with treatment “guidelines”. These still would require the input of patient preferences. The results of this study demonstrate that although a patient’s MCID may fall within deliverable care, this does not necessarily mean they will chose that therapy option. Choosing between non-curative options for a fatal illness remains a complex issue. A DA would seem to be a useful adjunct to this process.

Assuming that a useful approach to developing a DA for a complex and dynamic problem with rapidly evolving therapies is possible, the question remains, will people in these settings use them. Consumerism in health care, a growing politic in the mainstream population, is generally limited to non-life-threatening decisions, usually with limited complexity involved in the choice. Although of variable quality and open to reinterpretation^{22 24} the literature supports that at least some patients with serious illness still wish the decision making role along with the problem solving role to rest primarily with the physician.^{19 20} This can be seen in our study, where nearly all patients who had undergone a transplant indicated that their doctor’s recommendation was a factor in their choice. Ultimately, a balance of information, personal values clarification and medical guidance offers the greatest potential for patients to receive optimal therapy.

4.11 Conclusions

It was possible to design an effective disease specific DA for patients with high-risk low grade non-Hodgkin's lymphoma and to determine the MCID of ABMT versus SST for this patient population. The measured MCIDs generated important insights into patients' attitudes toward risks and benefits in this life threatening setting. Several demographic and clinical factors that may influence the MCID were identified and are worthy of further study. In this setting, however, these factors did not result in clinically important different values for the MCID. The format of presentation within this DA did not affect the elicited MCIDs. This is primarily due to the limited sample size and greater patient variability than expected. Whether this is also influenced by the clarity of the DA, the use of discreet time-points and percentages instead of survival curves, or an underlying truism that will hold in other settings needs to be explored in future studies. The ultimate role of DAs in clinical practice will depend on multiple factors including the appropriateness and complexity of the clinical situation, the ability to represent the choice in a meaningful and accessible manner and the demonstration that the use of these tools results in improved health outcomes for individuals.

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Table 1: Sample Size Considerations

Table 1a: Range of the bound on the error of estimation for original sample size assumptions

N	$T_{(n-1)}$	bound on the error of estimation of 95% CI*	
		SD 5%	SD 8%
20	2.093	2.34%	3.74%
25	2.064	2.06%	3.30%

* Bound on the error of estimation is defined: $\frac{1}{2}$ the width of the 95% confidence interval. Abbreviations: CI = confidence interval; n = number of subjects per group; $t_{(n-1)}$ = critical value of the probability distribution of T, for n subjects; SD = standard deviation

Table 1b: Range of possible deltas detectable based on original sample size assumptions

SD	N	Delta
5%	20	4.5%
5%	25	4.0%
8%	20	7.3%
8%	25	6.5%

Abbreviations: SD = standard deviation; n = number of subjects in group; delta = difference detectable between two groups by Student's t test.

Table 1c: Range of the bound on the error of estimation based on Group 1 sample size.

	$T_{(n-1)}$	Bound of the error of estimation of 95% CI*	
		SD 5%	SD 8%
40	2.022	2.26%	3.61%
50	2.009	2.01%	3.21%

Bound on the error is defined: $\frac{1}{2}$ the width of the 95% confidence interval. Abbreviations: CI = confidence interval; n = number of subjects per group; $t_{(n-1)}$ = critical value of the probability distribution of T, for n subjects; SD = standard deviation

Table 2: Respondent Demographics

		Controls	No-Transplant Group	Post-Transplant Group
		n = 10	n = 8	n = 40
		Number (%)	Number (%)	Number (%)
Gender				
	Male	5 (50.0)	3 (37.5)	26 (65.0)
	Female	5 (50.0)	5 (62.5)	14 (35.0)
Marital Status				
	Married	3 (30.0)	4 (50.0)	31 (77.5)
	Single	7 (70.0)	3 (37.5)	4 (10.0)
	Divorced	0	1 (12.5)	4 (10.0)
	Widowed	0	0	1 (2.5)
Employment Status				
	Employed	6 (60.0)	5 (62.5)	26 (65.0)
	Unemployed	4 (40.0)	3 (37.5)	14 (35.0)
Education Level				
	< High school diploma	0	3 (37.5)	5 (12.5)
	High school diploma	1 (10.0)	4 (50.0)	11 (27.5)
	Some post-secondary	0	0	9 (22.5)
	College/university degree	9 (90.0)	1 (12.5)	15 (37.5)
		Years	Years	Years
Age				
	Median	42	45	49
	Minimum, Maximum	23, 63	31, 60	23, 61
	Mean	42	45	46.5

Table 3: Disease and Therapy Related Information

		No-Transplant Group	Post-Transplant Group
		n = 8 (%)	n = 40 (%)
		Number	Number
Diagnosis			
	Follicular Small Cleaved Cell	6 (75)	32 (80)
	Follicular Mixed Small & Large Cell	2 (25)	8 (20)
Number of Relapses Prior to Transplant			
	0	5 (62.5)	6 (15)
	1	1 (12.5)	22 (55)
	2	0 (0)	6 (15)
	3	2 (25.0)	6 (15)
Disease Status at BMT			
	Clinical Complete Remission (1st,2nd)	NA	7 (17.5)
	Partial Remission (1st,2nd)	NA	23 (57.5)
	Untreated Relapse	NA	10 (25.0)
Present Disease Status			
	Free From Clinical Progression	NA	29 (72.5)
	Progressive Disease	NA	11 (27.5)
	Primary Refractory Disease	1 (12.5)	NA
	Complete Clinical Remission	1 (12.5)	NA
	Partial Remission	4 (50.0)	NA
	First Relapse	2 (25.0)	NA
Time Since ABMT			years
	median	-	2.35
	(minimum, maximum)	-	(0.40, 5.50)

Table 4: Post-Transplant Group: Autologous Transplant Experience

		Post-Transplant Group
		n = 40
Days Hospitalized		
	median (minimum, maximum)	28 (9, 60)
	mean (std dev)	26.9 (11.2)
Recovery Time (weeks)		
	median (minimum, maximum)	20 (1, 260)
	mean (std dev)	31.6 (46.6)
Patient-Rated Transplant Experience Compared to Decision Aid Description ^a		
	median (minimum, maximum)	4 (1, 7)
	mean (std dev)	4.4 (5.6)
Would Choose Transplant Again		n (%)
	Yes	33 (82.5)
	No	4 (10.0)
	Unsure	3 (7.5)

^a Scores ranged from 1 (personal experience much worse than decision aid) to 4 (personal experience same as decision aid) to 7 (personal experience much better than decision aid).

Table 5: Post-Transplant Group:
Transplant Team Vs. Patient Rating of Transplant Experience ^a

n = 34

		Clinician Rating^{b,c}		
Patient Rating		1 or 2	3 to 5	6 or 7
	1 or 2	1	6	2
	3 to 5	2	12	4
	6 or 7	0	7	0

^a Scores ranged from 1 (personal experience much worse than decision aid) to 4 (personal experience same as decision aid) to 7 (personal experience much better than decision aid).

^b Clinician Rating within 1 of patient rating 14/34 (42%).

^c Clinician Rating within 2 of patient rating 22/34 (65%).

Table 6: Post-Transplant Group: Possible Clinical Correlates of the MCID

	Post-Transplant Group n = 40				Test Statistic / Measurement of Association
	median TRM ^a %	p value	median 4-yr TFS ^b %	p value	
Gender					
Male/Female	24.0 / 22.5	0.90	21.5 / 18.0	0.04	Mann Whitney
Current Disease Status					
Remission / Progressed	23.0 / 25.0	0.66	21.0 / 25.0	0.06	Mann Whitney
Marital Status					
Married / Other	21.0 / 27.0	0.10	21.0 / 19.0	0.09	Mann Whitney
Age	r-value / p-value		r-value / p-value		Pearson
	0.19 / 0.23		0.29 / 0.06		
Education Level	-0.04 / 0.81		0.05 / 0.77		Pearson
Time Since BMT	-0.12 / 0.48		0.01 / 0.94		Pearson
Days Hospitalized	0.80 / 0.63		-0.27 / 0.10		Pearson
Patient-Rated Recovery Time Post-BMT	-0.06 / 0.72		0.44 / 0.005		Pearson
Patient-Rated Transplant Experience	0.22 / 0.18		-0.22 / 0.18		Pearson

^a TRM = Treatment Related Mortality

^b 4-yr TFS = 4- Year Treatment Free Survival

Table 7: Treatment Related Mortality and 4-Year Treatment Free Survival MCIDs

		TRM ^a	4-yr TFS ^b
	N	Mean (95% CI)	Mean (95% CI)
Healthy Controls	10	27.7 (17.8, 37.6)	24.4 (21.0, 27.8)
No-Transplantation Group	8	27.5 (14.3, 40.7)	28.4 * (22.0, 34.8)
Post-Transplantation Group			
Overall	40	23.8 (20.0, 27.5)	21.3 * (18.9, 23.7)
Graphical-Numerical Format	22	25.3 [†] (20.3, 30.3)	21.9 [‡] (15.79, 28.0)
Numerical-Alone Format	18	20.9 [†] (17.2, 24.7)	21.7 [‡] (18.7, 24.8)

^a TRM = Treatment Related Mortality

^b 4-yr TFS = 4-Year Treatment Free Survival

* Difference in 4-yr TFS between No-Transplantation Group and Post-Transplantation Group statistically significant, Mann Whitney: p = 0.015

[†] No difference in TRM between Graphical-Numerical Format and Numerical-Alone Format, Mann Whitney: p=0.32

[‡] No difference in 4-yr TFS between Graphical-Numerical Format and Numerical-Alone Format, Mann Whitney: p=0.61

Table 8: Post-Transplant Group: Patient Estimate of Treatment Related Mortality and 4-Year Treatment Free Survival With Standard Salvage Therapy Before and After Completion of the Decision Aid

Standard Salvage Therapy									
Patient Estimate of Treatment Related Mortality					Patient Estimate of 4-Year Treatment Free Survival				
Before Decision Aid	n = 40	After Decision Aid	n = 40	Wilcoxon signed rank test	Before Decision Aid	n = 40	After Decision Aid	n = 40	Wilcoxon signed rank test
Median	10%	3%			Median	50%	20%		
Mean	15.4%	6.7%		<0.0001	Mean	50.2%	23.7%		<0.0001
Standard Deviation	19.6%	8.9%			Standard Deviation	25.1%	11.7%		
Rating of Patient Estimate ^a					Rating of Patient Estimate ^b				
Reasonable	n	n	n	p value	Reasonable	N	n	n	p value
High	18	34			(10%-40% TFS)	22	35		
Low	11	5		0.0003*	(>40% TFS)	18	4		<0.026*
	11	1			(<10% TFS)	0	1		

^a TRM = Treatment Related Mortality
^b TFS = 4-year Treatment Free Survival
 * Reasonable vs. others by Fisher's Exact Test

Table 9: Post-Transplant Group: Estimate of Treatment Related Mortality and 4-Year Treatment Free Survival With Autologous Transplantation Before and After Completion of the Decision Aid

Autologous Bone Marrow Transplantation						Autologous Bone Marrow Transplantation					
Patient Estimate of Treatment Related Mortality						Patient Estimate of 4-Year Treatment Free Survival					
Before Decision Aid	n	After Decision Aid	n	Wilcoxon signed rank test		Before Decision Aid	n	After Decision Aid	n	Wilcoxon signed Rank test	
Median	10%	10%	10%			Median	70%	50%	50%		
Mean	18.9%	11%	11%	<0.0001		Mean	68.3%	50.1%	50.1%		<0.0001
Standard Deviation	19.6%	5.6%	5.6%			Standard Deviation	20.7%	12.1%	12.1%		
Rating of Patient Estimate ^a						Rating of Patient Estimate ^b					
Reasonable	n	n	n	X ²	p value	Reasonable	n	n	n	X ²	p value
High	22	38	1			High	12	33	4		
Low	11	1	1	0.003 [*]		Low	24	4	3		<0.0001 [*]
	7						4				

^a TRM = Treatment Related Mortality
^b TFS = 4-year Treatment Free Survival
^{*} Reasonable vs. others by Fisher's Exact Test

Table 10: Decision Aid Evaluation: Decision Aid’s Ability to Improve Understanding of the Therapeutic Choice and Its Potential Usefulness in Helping Others Choose Between Standard Salvage Therapy and Autologous Transplantation

	Post-Transplant Group			No-Transplant Group	Healthy Controls
	Graphical-Numerical		Numerical-Alone		
	All n = 40	n = 22	n = 18		
Criterion	1 (not at all) through 5 (very much)	1 (not at all) through 5 (very much)	1 (not at all) through 5 (very much)	1 (not at all) through 5 (very much)	1 (not at all) through 5 (very much)
				n = 8	n = 10
Understanding of Risks & Benefits Better After Completing the Decision Aid					
median (minimum, maximum)	5 (1, 5)	5 (1, 5)	4.5 (2, 5)	4 (3, 5)	5 (4, 5)
mean (std dev)	4.2 (1.0)	4.3 (1.1)	4.2 (1.0)	3.75 (0.7)	4.5 (0.5)
Would Decision Aid Help Others					
median (minimum, maximum)	5 (1, 5)	4 (1, 4)	5 (2, 5)	4 (3, 5)	4 (3, 5)
mean (std dev)	4.2 (1.1)	4 (1.3)	4.4 (1.0)	4.1 (0.7)	4.4 (0.5)

Table 11: Decision Aid Evaluation: Rating of the Overall Amount and Detail of Information in the Decision Aid

	Group I		Group II		Group III	
	Post-Transplant		No-Transplant		Healthy Controls	
	Overall	Graphical-Numerical	Numerical-Alone	Chi Square		
Overall Content	n = 40	n = 22	n = 18	p-value	n = 8	n = 10
Amount of Information	not enough	4	4		0	2
	just right	17	13	0.93	8	8
	too much	1	1		0	0
Detail of Information	too little	5	4		0	2
	just right	16	14	0.65	8	8
	too much	1	0		0	0

Table 12: Decision Aid Evaluation: Rating of Understandability and Helpfulness of Information Concerning Risks and Benefits of Standard Salvage Therapy and Autologous Transplantation

		Healthy Controls	No-Transplant Subjects	Post-Transplant Subjects		
STANDARD SALVAGE THERAPY						
	1 (not at all) through 5 (very)	n = 10	n = 8	Overall n = 40	Graphical-Numerical n = 22	Numerical -Alone n = 28
<i>Information About Risks</i>						
Understandable	> = 3	10	8	40	22	18
	< = 2	0	0	0	0	0
Helpful	> = 3	9	8	38	21	17
	< = 2	1	0	2	1	1
<i>Information About Benefits</i>						
Understandable	> = 3	10	8	39	22	17
	< = 2	0	0	1	0	1
Helpful	> = 3	10	8	38	21	17
	< = 2	0	0	2	1	1

				Overall	Graphical-Numerical	Numerical - Alone
BONE MARROW TRANSPLANTATION						
	1 (not at all) through 5 (very)					
<i>Information About Risks</i>						
Understandable	> = 3	10	8	39	21	18
	< = 2	0	0	1	1	0
Helpful	> = 3	10	8	38	20	18
	< = 2	0	0	2	2	0
<i>Information About Benefits</i>						
Understandable	> = 3	9	8	39	22	17
	< = 2	1	0	1	0	1
Helpful	> = 3	10	8	38	21	17
	< = 2	0	0	2	1	1

Table 13: Evaluation of Decision Aid: Time To Complete Decision Aid and Patient Rating of Completion Time

	Healthy Controls	No-Transplant Subjects		Post-Transplant Subjects		
		(minutes)	(minutes)	Overall n = 40	Graphical- Numerical n = 22	Numerical- Alone n = 18
Length of Time				(minutes)	(minutes)	(minutes)
To complete background	mean (std dev)	25.2 (6.9)	35.8 (13.2)	24.5 (9.4)	27.4 (9.5)*	21 (8.1)*
	median (range)	22 (20-40)	32.5 (25-60) **	25 (5-50) **	28 (10-50)	20 (5-35)
To elicit MCID	mean (std dev)	11.7 (5.6)	17.5 (6.9)	19.4 (9.0)	20 (8.0)	18.5 (10.3)
	median (range)	10 (5-20)	15 (15-30)	20 (6-40)	20 (6-35)	15 (6-40)
Patient's Rating of Completion Time ***						
	n	n	n	n	n	n
too short	1	0	2	2	2	0
just right	8	8	2	2	0	2
too long	1	0	36	36	20	16

* t test $p = 0.027$ for Graphical-Numerical vs. Numerical-Alone format

** Mann Whitney $p = 0.015$ for no-transplant group vs. post-transplant group

*** Chi Square $p < 0.0001$ for healthy controls group vs post-transplant group rating of completion time

Chi Square $p < 0.0001$ for no-transplant group vs post-transplant group rating of completion time

Chi Square $p = 0.13$ for graphical-numerical group versus numerical-alone group rating of completion time

Table 14: Evaluation of Decision Aid: Rating of the Balance of Presentation of Information in the Decision Aid

	Healthy Controls	No-Transplant Subjects	Post-Transplant Subjects		
			Overall n = 40	Graphical- Numerical n = 22	Numerical- Alone n = 18
STANDARD SALVAGE THERAPY					
<i>Balance of Information</i>	n = 10	n = 8			
too much emphasis on risks	0	1	0	0	0
just right	10	7	39	22	17
too much emphasis on benefits	0	0	1	0	1
BONE MARROW TRANSPLANTATION					
<i>Balance of Information</i>					
too much emphasis on risks	0	1	2	0	2
just right	10	7	37	22	15
too much emphasis on benefits	0	0	1	0	1

Table 15: No-Transplant Group: Estimate of Treatment Related Mortality and 4-Year Treatment Free Survival With Standard Salvage Therapy Before and After Completion of the Decision Aid

Standard Salvage Therapy				Standard Salvage Therapy			
Patient Estimate of Treatment Related Mortality				Patient Estimate of 4-Year Treatment Free Survival			
Before Decision Aid	After Decision Aid	Wilcoxon signed rank test		Before Decision Aid	After Decision Aid	Wilcoxon signed rank test	
n = 8 %	n = 8 %			N = 8 %	n = 8 %		
Median	2.5	4	0.58	Median	40	20	0.15
Range	0-30	3-5		Range	0-90	20-35	
Rating of Patient Estimate ^a				Rating of Patient Estimate ^b			
Reasonable	n	n	X ²	Reasonable	n	n	X ²
(2%-15% TRM)	2	8		(10%-40% TFS)	2	8	
High	2	0	0.007 *	High	4	0	0.007 *
Low	4	0		Low	2	0	
(<2% TRM)				(<10% TFS)			

a TRM = Treatment Related Mortality

b TFS = 4-year Treatment Free Survival

* Fisher's Exact Test for Reasonable vs. Others

Table 16: No-Transplant Group: Estimate of Treatment Related Mortality and 4-Year Treatment Free Survival With Autologous Transplantation Before and After Completion of the Decision Aid

Autologous Bone Marrow Transplantation					Autologous Bone Marrow Transplantation				
Patient Estimate of Treatment Related Mortality					Patient Estimate of 4-Year Treatment Free Survival				
Rating of Patient Estimate ^a Reasonable High Low	Before Decision Aid	After Decision Aid	Wilcoxon signed rank test	n = 8 %	n = 8 %	n = 8 %	n = 8 %	X ²	p value
	Median		Median		Median		X ²		
	Range		Range		Range		p value		
	n = 8		n = 8		n = 8		X ²		
	%		%		%		p value		
	5-40		10		67.5		X ²		
	5-10		5-10		20-90		p value		
	0.11		0.11		0.11		X ²		
	X ²		X ²		X ²		p value		
	p value		p value		p value		p value		
	0.2 *		0.2 *		0.03 *		0.03 *		

^a TRM = Treatment Related Mortality
^b TFS = 4-year Treatment Free Survival
 * Fisher's Exact Test for Reasonable vs. Others

Table 17: Healthy Control Group: Estimate of Treatment Related Mortality and 4-Year Treatment Free Survival With Standard Salvage Therapy Before and After Completion of the Decision Aid

Standard Salvage Therapy									
Patient Estimate of Treatment Related Mortality					Patient Estimate of 4-Year Treatment Free Survival				
Before Decision Aid		After Decision Aid		Wilcoxon signed rank test	Before Decision Aid		After Decision Aid		Wilcoxon signed rank test
n	%	n	%		n	%	n	%	
10	15%	10	5%	0.002	10	40%	10	20%	NA *
Median	5%-50%	3%-10%			Median	20%-50%	20%-20%		
Range					Range				
Rating of Patient Estimate ^a					Rating of Patient Estimate ^b				
Reasonable	n	n	n	X ² p value	Reasonable	N	N	N	X ² p value
High	6	10			(10%-40% TFS)	9	10		
Low	4	0		0.09**	High (>40% TFS)	1	0		1.0 **
	0	0			Low (<10% TFS)	0	0		

^a TRM = Treatment Related Mortality

^b TFS = 4-year Treatment Free Survival

* NA = Analysis not possible because the two samples have the same standard error.

** Fisher's Exact Test for Reasonable vs. Other's

Table 18: Healthy Controls: Estimate of Treatment Related Mortality and 4-Year Treatment Free Survival With Autologous Transplantation Before and After Completion of the Decision Aid

Autologous Bone Marrow Transplantation				Autologous Bone Marrow Transplantation			
Patient Estimate of Treatment Related Mortality				Patient Estimate of 4-Year Treatment Free Survival			
Before Decision Aid	After Decision Aid	Wilcoxon signed rank test		Before Decision Aid	After Decision Aid	Wilcoxon signed rank test	
n = 10	n = 10			n = 10	n = 10		
Median Range	15% 5%-50%	10% 10%-10%	NA *	Median Range	60% 40%-90%	50% 50%-50%	NA *
Rating of Patient Estimate ^a				Rating of Patient Estimate ^b			
Reasonable	n	n	X ² p value	Reasonable	n	N	X ² p value
High	7	10		High	8	10	
Low	3	0	0.21 **	Low	2	0	0.47 **
	0	0			0	0	

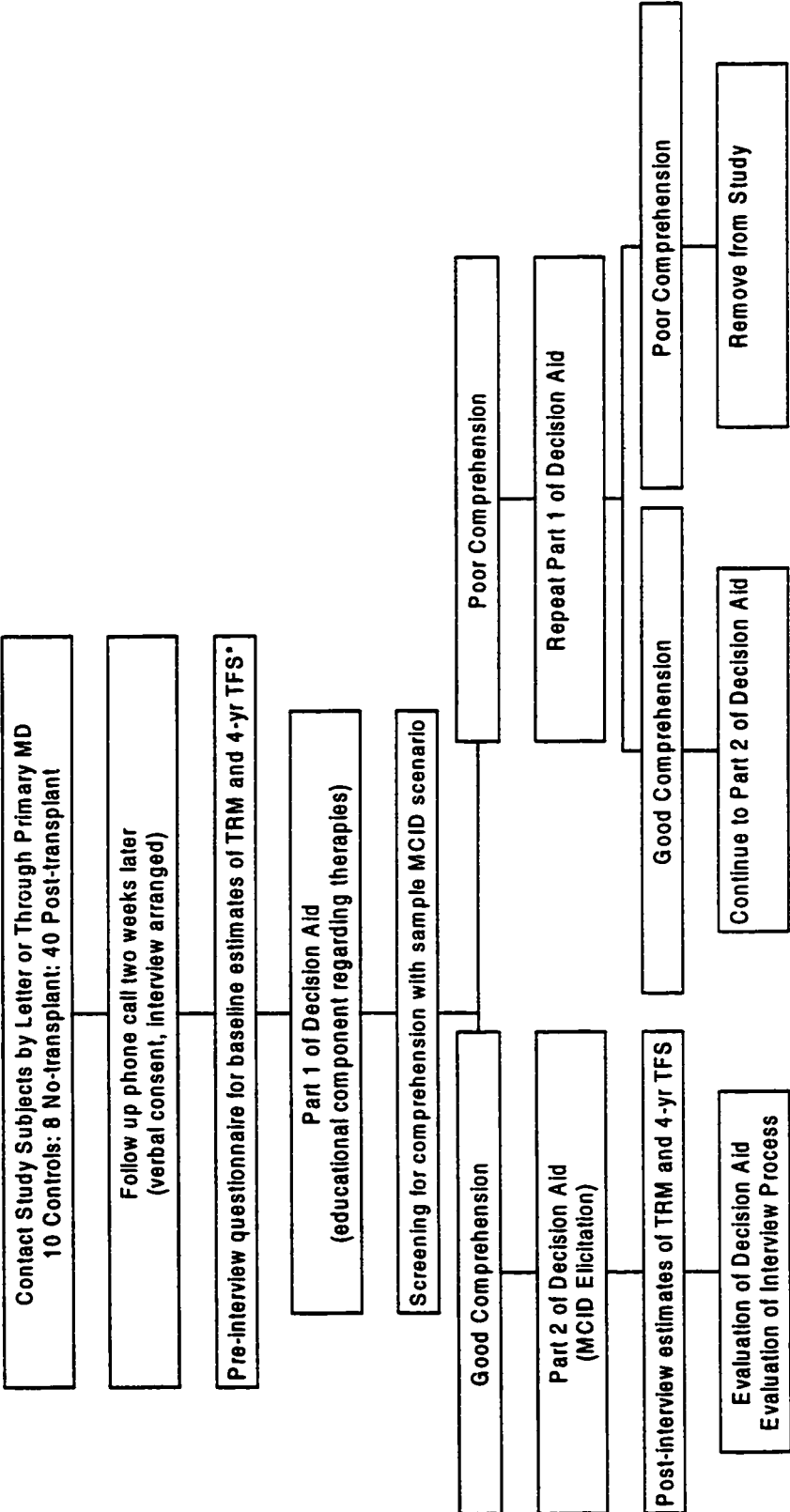
^a TRM = Treatment Related Mortality

^b TFS = 4-year Treatment Free Survival

* NA = Analysis not possible because the samples have the same standard error

** Fisher's Exact Test for Reasonable vs. Others

Figure 1: Study Process



* TRM = Treatment Related Mortality
4-yr TFS = 4-year Treatment Free Survival

Figure 2: Distribution of Treatment Related Mortality MCID

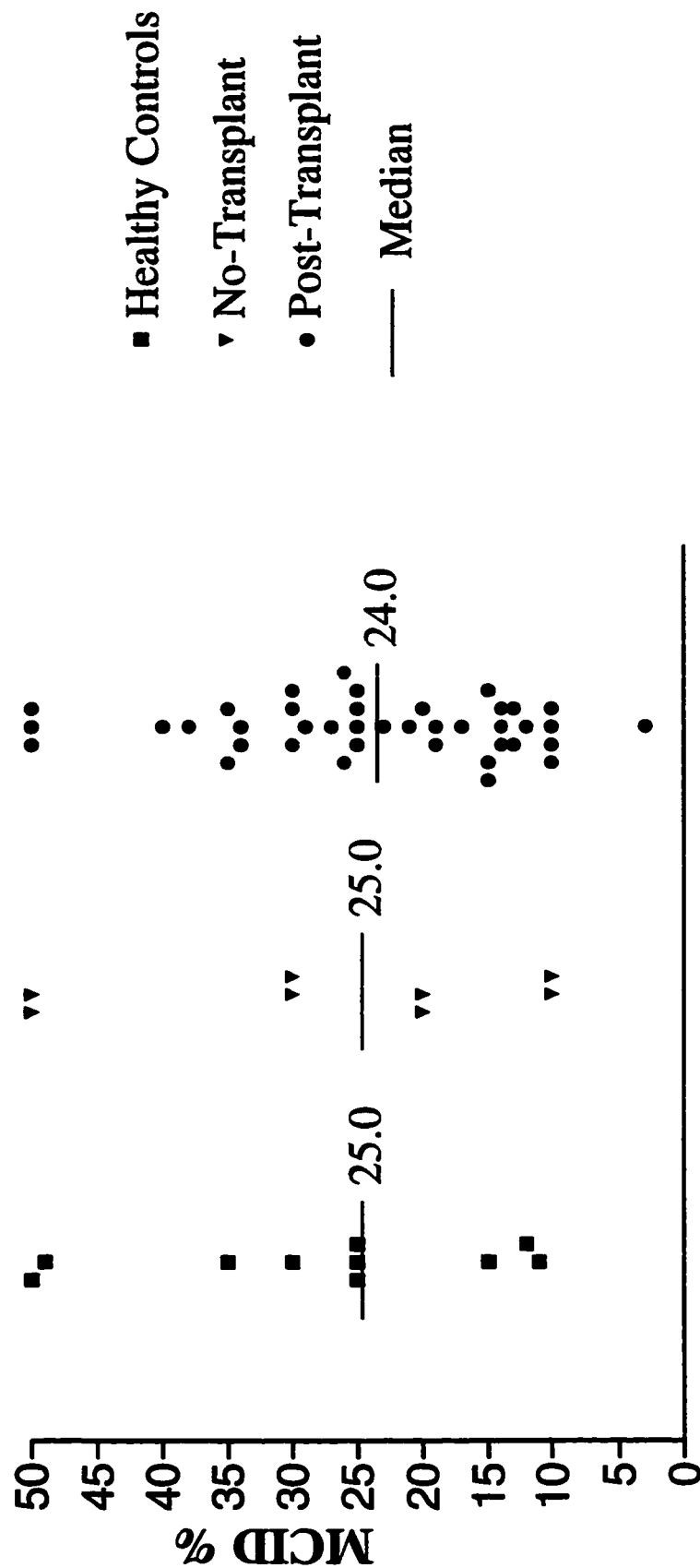


Figure 3: Distribution of MCIDs for Post-Transplant Patients

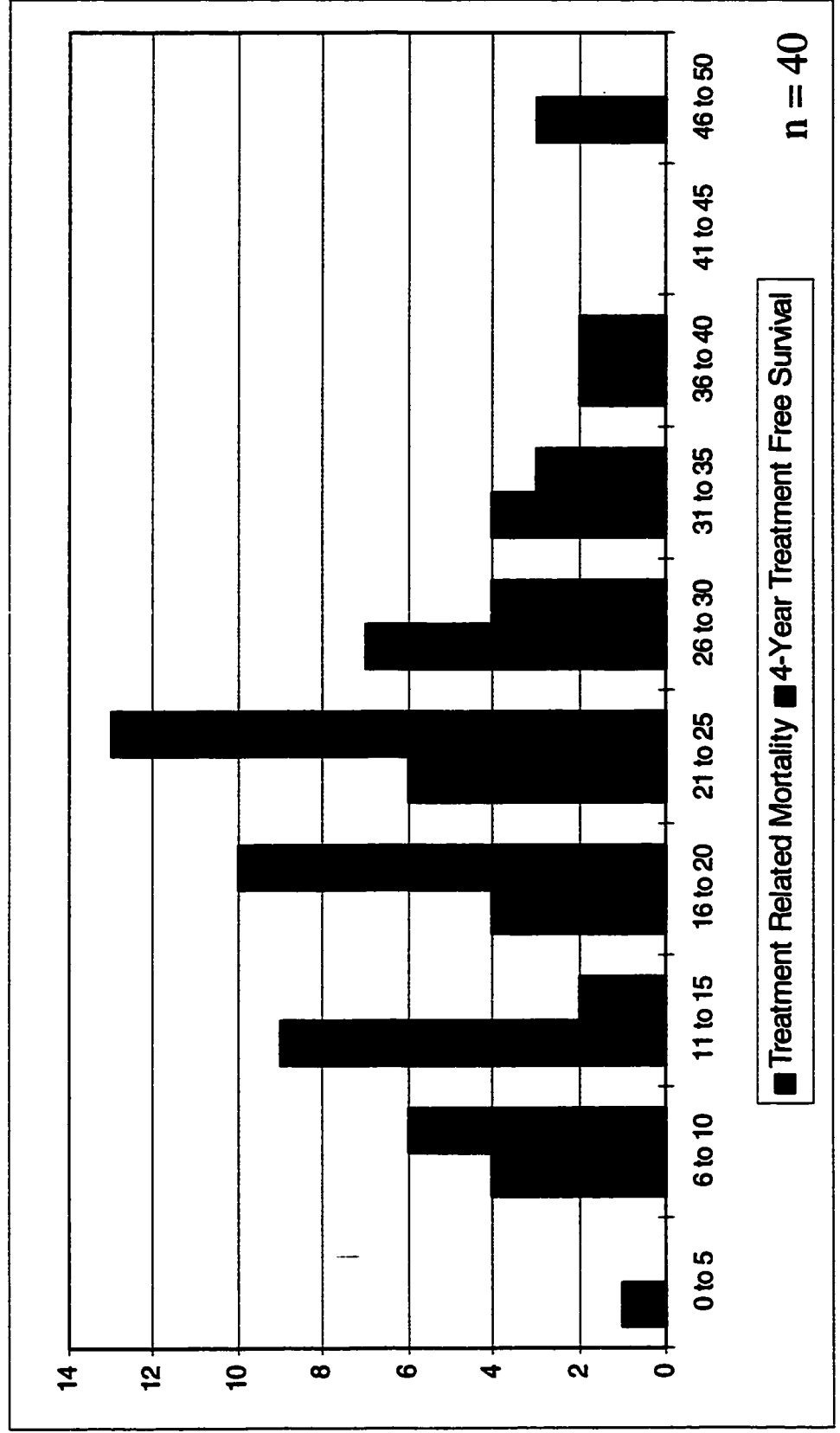
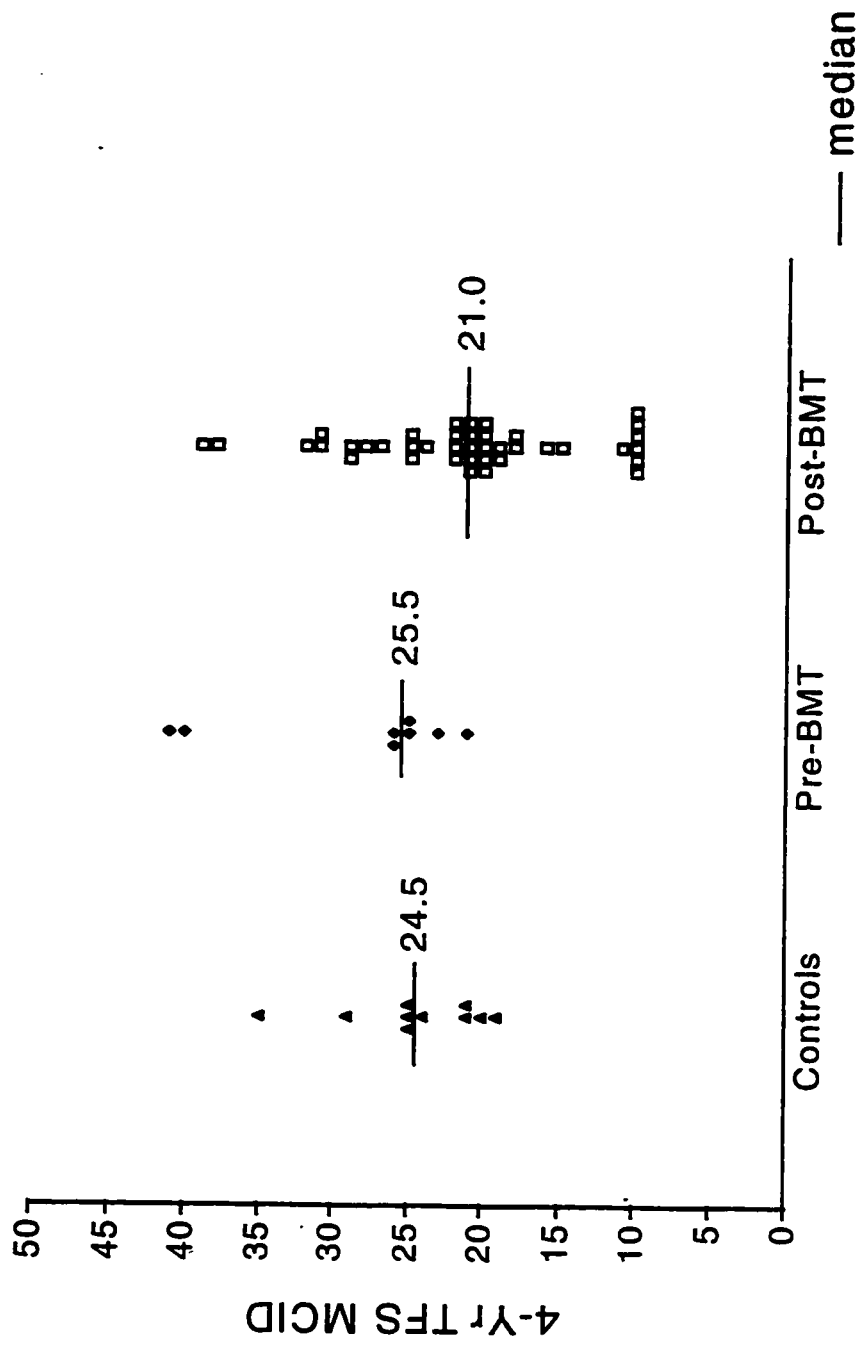
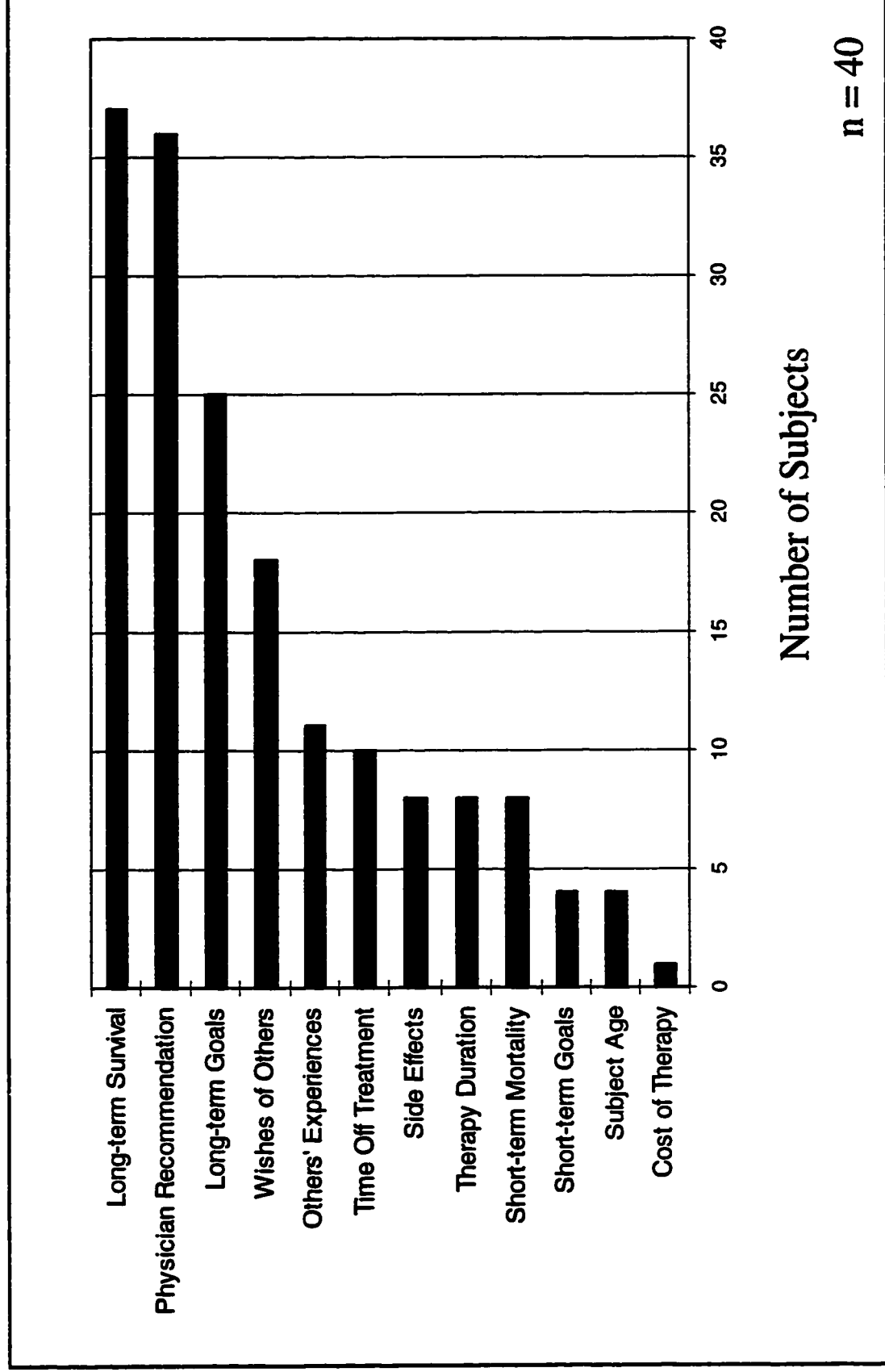


Figure 4: Distribution of 4-Year Treatment Free Survival MCID: All Groups



Mann Whitney: pre vs. post $p = 0.015$

Figure 5: Factors Considered by Patients Prior to Undergoing Autologous Transplantation





HÔPITAL GÉNÉRAL D'OTTAWA OTTAWA GENERAL HOSPITAL

PATIENT INFORMATION AND CONSENT FORM

Determining the Minimal Clinically Important Difference between Autologous Bone Marrow and/or Peripheral Blood Stem Cell Transplantation Vs Standard Care for Patients with Low Grade non-Hodgkin's Lymphoma

The minimal clinically important difference represents the smallest difference in the benefit of a treatment that would result in a change in a patient's treatment. In other words, when choosing between treatment A and treatment B, it is the smallest difference between the benefits and the risks of treatment A that would result in a choice of treatment A over treatment B.

The physicians conducting this study are attempting to estimate the minimal clinically important difference between autologous bone marrow +/- peripheral blood stem cell transplantation and standard salvage chemotherapy for patients with low grade non-Hodgkin's lymphoma. This information would be helpful to both patients and physicians in assessing whether a treatment is of benefit to a patient.

As you know, you have been diagnosed with low grade non-Hodgkin's lymphoma. Lymphoma is a disease that may be treated in a number of different ways. After the initial treatment and relapse of the disease occurs, there are two treatment options. These are 1) standard salvage chemotherapy and 2) autologous bone marrow +/- peripheral blood stem cell transplantation. The choice between the two treatment options is a difficult one and since you have experienced both types of treatment and have had to make a choice between them, the physicians conducting this study would like to talk to you about how you made your choice. Although undergoing this exercise may not directly help you, it is hoped that the information received from talking with you will help future patients in their decision making process.

If you decide to participate in the study, your involvement would consist of a two step process and would require approximately one hour of your time. You will be asked to work through a decision aid describing the two treatment options with a research assistant. Following this, the research assistant will conduct a 20 to 30 minute interview. There are no right or wrong answers to the choices and your answers will be kept completely confidential. You may refuse to answer any question at any time for any reason.

There is no obligation to participate in this study. There are no foreseeable risks or benefits from your participation in the study. Choosing to participate or not to participate will in no way affect the care that you are currently receiving. If you choose to participate, your anonymity will be guaranteed. That is, your name will not be known to anyone reading the final results of the study. As well, any information learned about you in the study will be kept confidential.

The protocol for this study has been approved by the Research Ethics Board of the Ottawa General Hospital. This board considers the ethical aspects of all hospital research projects using human studies. If you wish, you may talk to the chairman of the research ethics board (Dr. Glen Goss) at 737-7777.

For further information concerning this study, please contact Dr. C. Bredeson at 737-8152.

If you would like to receive a copy of the study results please check here.

☐

Patient Signature

Date

Witness Signature

Date

Appendix B: Letter of Contact to Prospective Study Subjects (English)

John Doe Patient

123 Street

City, Province

K2K K2K

Date:

Dear Patient Name,

Dr. Christopher Bredeson, a Hematologist within the Division of Hematology, and Janine Malcolm, a medical student, are conducting a research project to investigate how patients with low grade lymphoma make decisions between their treatment options. As these decisions are difficult ones, it is hoped that this study will identify factors that patients consider important in making decisions so that future patients will be better informed about their treatment options. This information may benefit future patients by improving and facilitating the decision making process.

Since you have been treated for low grade lymphoma and have had to make a choice between receiving regular (standard) chemotherapy or receiving high-dose therapy and an autologous bone marrow and/or peripheral blood stem cell transplant, we would like to talk to you about what factors you considered important in making that choice. Janine Malcolm will be calling you within the next week to 10 days about your possible participation in the study.

If you decide to participate in the study, your involvement will consist of a two step process and will require approximately one hour of your time. You will be asked to meet with the research assistant, Janine Malcolm, to work through a decision aid outlining the two treatment options. Following this you will be asked to participate in a 20 to 30 minute interview, conducted by Janine Malcolm, about the choices you have made. The meeting will take place at a mutually convenient time either at the Ottawa General Hospital, or at your home depending on your

Appendix B: Letter of Contact to Prospective Study Subjects (English)

preference. If the interview takes place at the Ottawa General Hospital, your parking expenses will be paid by the Division of Hematology.

You are under no obligation to participate, and you may refuse to answer any specific questions at any time for any reason. There are no right or wrong answers to the choices and your answers will be kept completely confidential. There are no foreseeable risks or benefits to you, from your participation in the study. Choosing to participate or not to participate will in no way affect the care that you are currently receiving. If you choose to participate, your anonymity will be guaranteed. That is, any information learned about you in the study will be kept confidential.

If you have any questions concerning this study, please feel free to contact myself or Dr. Christopher Bredeson at 613-737-8152.

Sincerely,

Dr. LB Huebsch
Head, Bone Marrow Transplantation Programme
Ottawa General Hospital

HÔPITAL GÉNÉRAL D'OTTAWA

OTTAWA GENERAL HOSPITAL

Thursday, 13 July 1995

Dr. C. Bredeson
Department of Medicine
Ottawa General Hospital

Dear Dr. Bredeson:

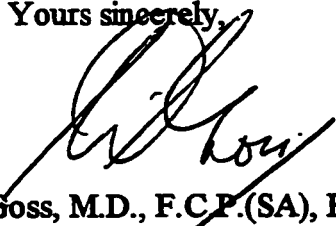
RE: OGH-95-055 Determining the Minimal Clinically Important Difference (MCID) of Autologous Blood and Marrow Transplantation vs Standard Salvage Chemotherapy in Patients with Low Grade Non-Hodgkin's Lymphoma.

The Research Ethics Board has reviewed your response to a letter of concerns that you submitted on the above protocol.

I am pleased to inform you that the REB finds these revision to be acceptable with respect to the ethics of research with human subjects and has therefore approved this protocol from July 1995 to July 1996.

The new guidelines of the Medical Research Council require a greater involvement of the REB in studies over the course of their execution. You must maintain, as part of your records, copies of the signed consent form. As well, you must inform the REB of adverse events encountered during the study, here or elsewhere, or of significant new information which becomes available after the REB review, either of which may impinge on the ethics of continuing the study. The REB will review the new information to determine if the protocol would be modified, discontinued, or should continue as originally approved.

Yours sincerely,



G.D. Goss, M.D., F.C.P.(SA), F.R.C.P.C.
Chairman
Research Ethics Board

GG/tam (SUBMITTED TO REB FOR SIGNATURE JULY 13/95)

????????????

*Choosing Between
Standard Salvage Chemotherapy
And
Autologus Bone Marrow Transplantation*

????????????

Standard Salvage Chemotherapy



Treatment Time Course:

Month 1						
IV chemo + pills	pills	pills	pills	pills		
clinic visit						

Month 2						
IV chemo + pills	pills	pills	pills	pills		
clinic visit						

Month 3						
IV chemo + pills	pills	pills	pills	pills		
clinic visit						

Month 4						
IV chemo + pills	pills	pills	pills	pills		
clinic visit						

Month 5						
IV chemo + pills	pills	pills	pills	pills		
clinic visit						

Month 6						
IV chemo + pills	pills	pills	pills	pills		
clinic visit						

Standard Salvage Chemotherapy



Treatment time course:

- Every month for 6 Months



Treatment:

Day 1: Intravenous drugs (given through a needle in your arm) + pills

Days 1 to 5: Pills taken

Day 28: Monthly clinic visits between treatments

Standard Salvage Chemotherapy

Side effects from standard salvage chemotherapy:

- **Nausea:**

You may get a mild upset stomach while on drugs and for a couple of days after. This happens to more than half of the patients treated. Drugs are given to decrease this.

- **Hair Loss:**

You will lose some or all of your hair during the treatment period. Your hair usually grows back a few months after the treatments have stopped.

- **Limited Activities:**

You will be unable to work for part or all of the time while you are undergoing treatment. Usually patients feel able to return to their normal activities by the last two weeks of the month.

Standard Salvage Chemotherapy

Side effects from standard salvage chemotherapy:

- **Fatigue:**

You likely will be more tired than normal during the treatment period.

- **Risk of Infection or bleeding:**

One of the side effects of the chemotherapy can be the suppression of your bone marrow. This can cause you to be at risk for infections or bleeding. 10% to 20% of patients having this treatment have to be hospitalized for infection or less commonly bleeding.

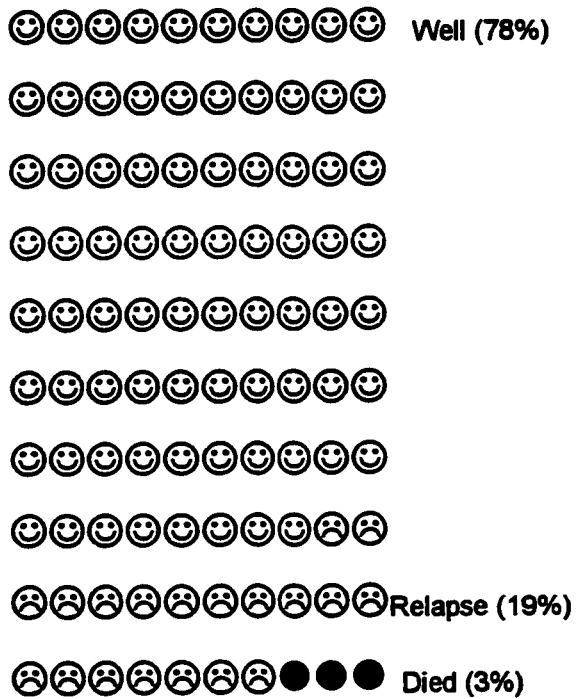
- **Risk of Blood Transfusion:**

You may have to receive a blood or platelet transfusion.

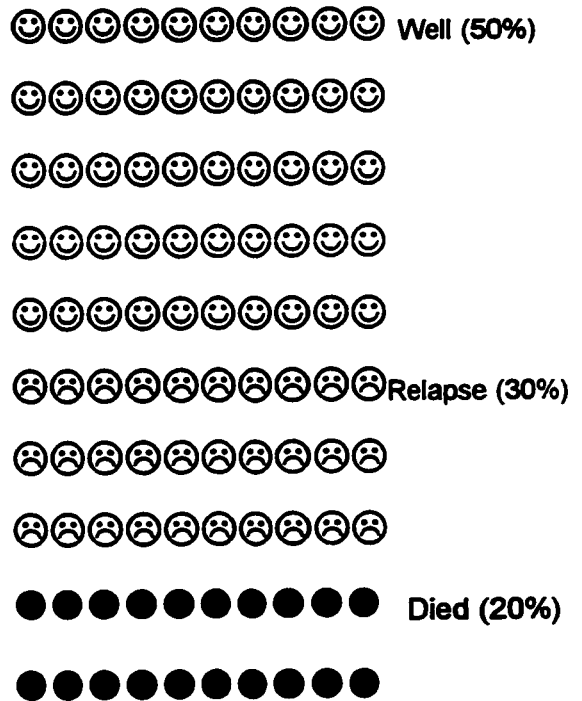
Standard Salvage Chemotherapy

Treatment outcome:

6 Months:



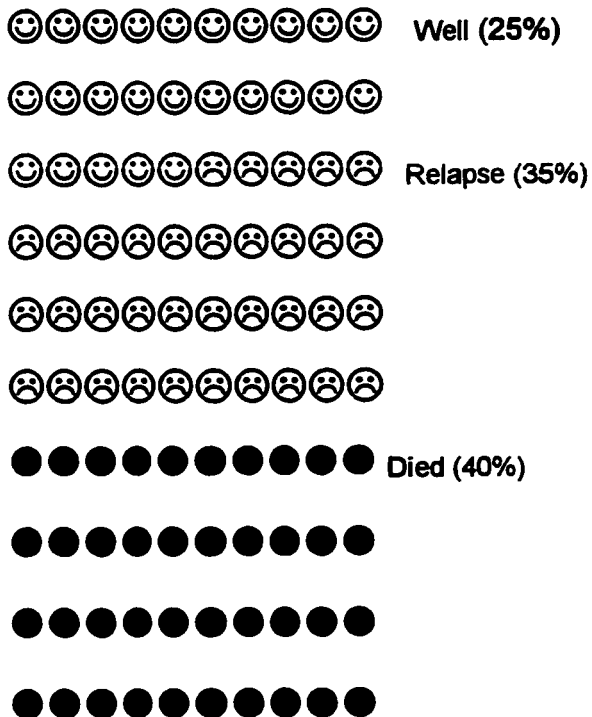
18 Months:



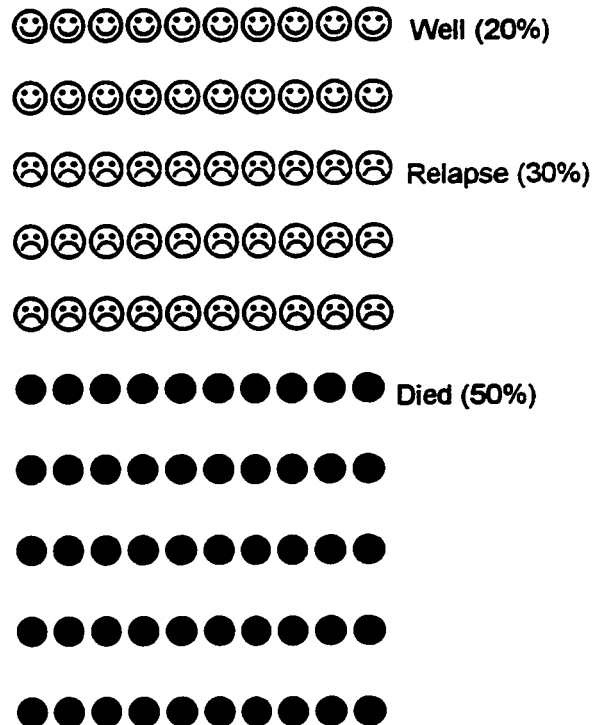
Standard Salvage Chemotherapy

Treatment outcome:

3 Years:



4 Years:



Autologous Bone Marrow Transplant



Treatment Time Course:

Month 1						
Hickman	IV chemo	IV hemo	pills	pills		
clinic visit						

Month 2						
IV chemo	IV hemo	pills	pills			
			PBSC	PBSC		
clinic visit						

Month 3						
Harvest	IV chemo	IV chemo		Radiation		Cells Back

Month 4						
clinic visit						
clinic visit						
clinic visit						
clinic visit						

Month 5						
clinic visit						
clinic visit						

Month 6						
clinic visit						
clinic visit						

Autologous Bone Marrow Transplant



Treatment time course:

- 6 Months, Intensive therapy for months 1-3
Recovery during months 4-6

Month 1:

😊Treatment:

<u>Day 1:</u>	<u>Hickman line insertion:</u>	A special intravenous catheter, put in by a surgeon in the OR, that allows for blood tests and transfusions without needle sticks. This catheter stays in for the entire treatment (~ 4 to 6 months).
<u>Days 2&3:</u>	<u>Chemotherapy 1:</u>	Intravenous drugs given in hospital to fight and kill the lymphoma.
<u>Days 4&5:</u>	<u>Chemotherapy 1:</u>	Pills given by mouth to fight and kill the lymphoma.

Autologous Bone Marrow Transplant

☹ Side effects in Month 1:

Related to the Hickman line (Day 1) :

- A small risk of local bleeding or infection
- A slight local discomfort for a few days after it is put in. This is controlled with Tylenol.

Autologous Bone Marrow Transplant

☹ Side effects in Month 1:

Related to Chemotherapy 1 (Days 2-6). These are:

- Similar to side effects with standard salvage therapy, but they may be more severe or prolonged. These are:
 - Nausea:
 - Hair Loss:
 - Limited Activities:
 - Fatigue:
 - Risk of Infection or bleeding:

About half (50%) of patients having this treatment have to be hospitalized for infection or less commonly bleeding.
- Risk of Blood Transfusion:

You probably will have to have a blood transfusion.

Autologous Bone Marrow Transplant

Month 2:

😊 Treatment

<u>Days 1&2:</u>	<u>Chemotherapy 2:</u>	Intravenous drugs in the hospital to fight and kill the lymphoma.
<u>Days 3&4:</u>	<u>Chemotherapy 2:</u>	Pills given by mouth to fight and kill the lymphoma
<u>Days 4-12:</u>	<u>Growth factor:</u>	(bone marrow stimulant) injections given under the skin.
<u>Days 11-12</u>	<u>Peripheral Blood Stem Cell (PBSC) collection:</u>	These are circulating cells that regrow the bone marrow. They are collected from the circulating blood by putting a needle in both your arms or by using the Hickman catheter and hooking you up to a special machine that extracts the peripheral blood stem cells from your blood.

Autologous Bone Marrow Transplant

Side effects in Month 2:

Related to Chemotherapy 2 (Days 1 to 4)

This chemotherapy is like the chemotherapy that was given in month 1.
The possible side effects are also the same.

- **Nausea:**
- **Hair Loss:**
- **Limited Activities:**
- **Fatigue:**
- **Risk of Infection or bleeding:**
- **Risk of Blood Transfusion:**

Autologous Bone Marrow Transplant

☹ Side effects in Month 2:

Caused by Peripheral Blood Stem Cell Collection (Days 5-13):

- **Bone Pain:**

You may have some mild bone pain from the growth factor. Tylenol is given to reduce this.

Autologous Bone Marrow Transplant

Month 3:

Treatment:

<u>Day 1:</u>	<u>Bone Marrow Harvest:</u>	A collection of bone marrow cells with large needles from your pelvis bones done by the transplant doctors in the Operating Room under general anaesthesia. These cells will regrow your bone marrow. The procedure takes about 1 hour, but it may not need to be done.
<u>Days 2 & 3:</u>	<u>Pre-transplant chemotherapy</u>	Very strong intravenous drugs to kill/fight the lymphoma. This chemotherapy is much stronger than the chemotherapy that was given previously.
<u>Day 5:</u>	<u>Radiation:</u>	This is radiation for your whole body. This radiation is to fight and kill the lymphoma.
<u>Day 7:</u>	<u>Reinfusion:</u>	Stored stem cells and/or bone marrow are reinfused (given back to you) through the Hickman Catheter.

Autologous Bone Marrow Transplant

Side effects in Month 3:

Caused by the Bone Marrow Harvest (Day 1):

- **Risk of General Anaesthetic:**

In general there is less than a 1/1000 risk of serious side effects from general anaesthesia.

- **Sore pelvis bones/Bruising:**

You may have sore hips and a bad bruise for about a week after the harvest was done. This pain is relieved with Tylenol #3.

- **Risk of Infection:**

There is a small risk of having a local infection (an infection where the needles were put in) after the harvest.

- **Risk of Blood Transfusion:**

You may have to have a packed red blood cell and/or platelet transfusion after the harvest.

Autologous Bone Marrow Transplant

Caused by Pretransplant chemotherapy and Reinfusion:

Generally, the side effects are similar to those experienced in the last 2 months but may be more severe. These are:

- **Nausea**
- **Hair Loss**
- **Limited Activities**
- **Fatigue**
- **Risk of Infection or bleeding**
- **Risk of Blood Transfusion:**

There are some other possible side effects. These are:

- **Mouth Ulcers:**

You may have painful ulcers in the throat and mouth. This is controlled with pain medication.

- **Diarrhea:**

You may have diarrhea. It occurs in many patients. The diarrhea normally stops within a few days to a week.

- **Decreased Appetite:**

You may have a decreased appetite.

Autologous Bone Marrow Transplant

Month 4 :

Recovery from Transplant. You should be feeling generally better and be off antibiotics by 3 weeks after the transplant.

<u>Weekly:</u>	<u>Clinic Visit:</u>	a visit to the Bone Marrow Transplant Clinic at the hospital to see your doctor and for blood tests.
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Month 5 and 6:

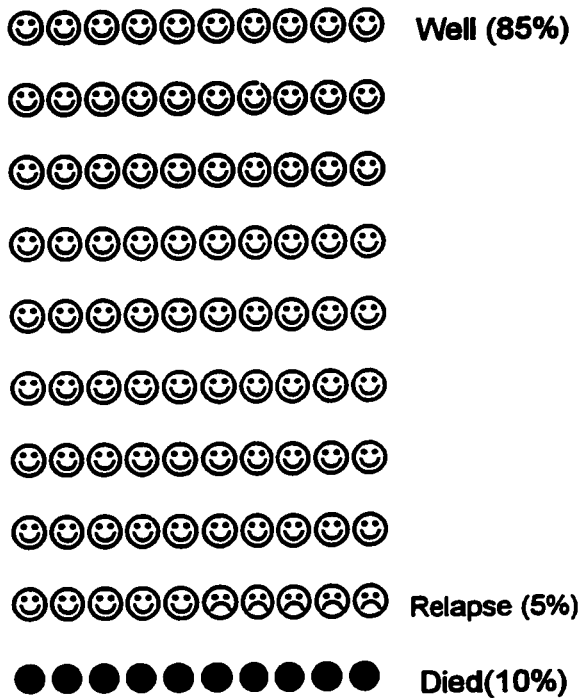
<u>Every other week:</u>	<u>Clinic Visit:</u>	a visit to the Bone Marrow Transplant Clinic at the hospital to see your doctor and for blood tests.
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Recovery from transplant and return to normal activities.

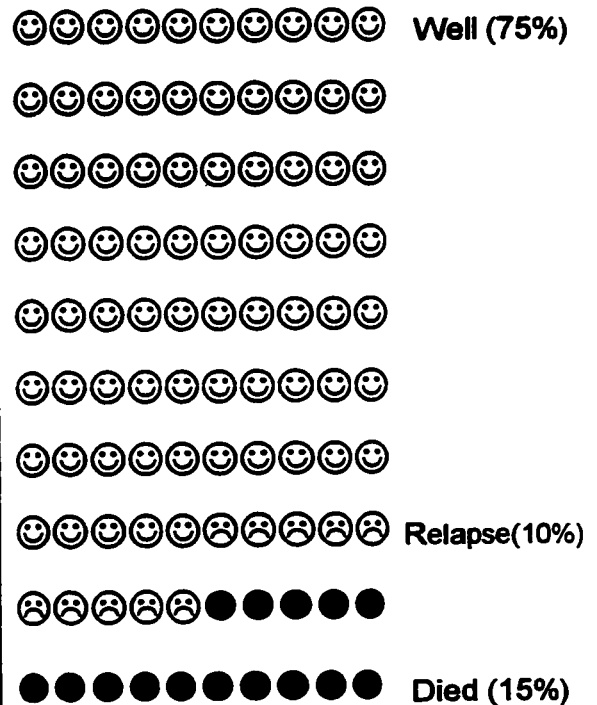
Autologous Bone Marrow Transplant

Treatment outcome:

6 Months:

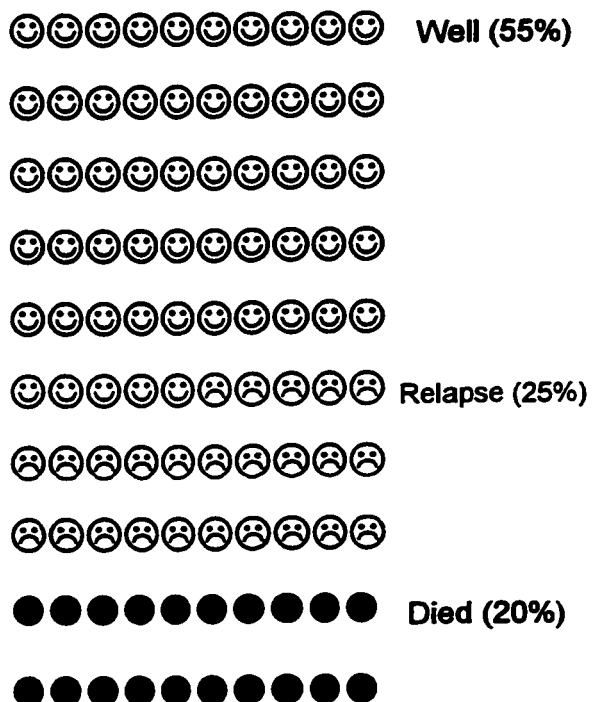


18 Months:

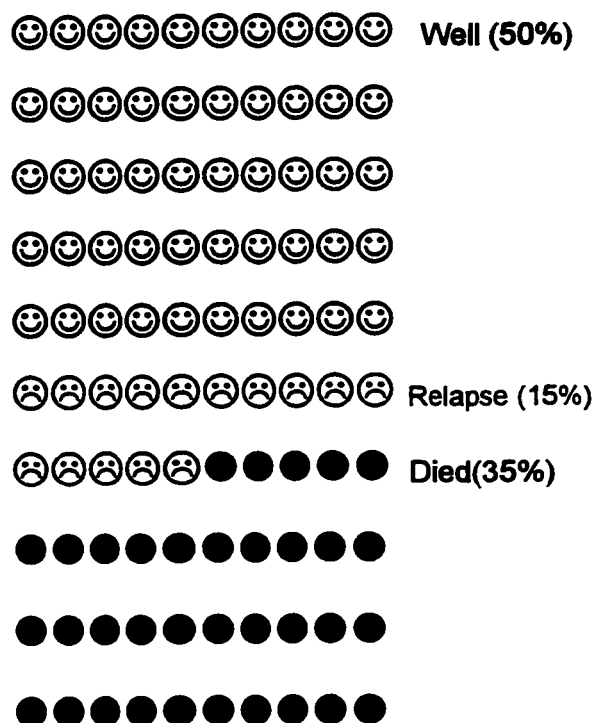


Autologous Bone Marrow Transplant

3 Years:



4 Years:



????????????

*Choosing Between
Standard Salvage Chemotherapy
And
Autologus Bone Marrow Transplantation*

????????????

Standard Salvage Chemotherapy



Treatment Time Course:

Month 1						
IV chemo + pills	pills	pills	pills	pills		
clinic visit						

Month 2						
IV chemo + pills	pills	pills	pills	pills		
clinic visit						

Month 3						
IV chemo + pills	pills	pills	pills	pills		
clinic visit						

Month 4						
IV chemo + pills	pills	pills	pills	pills		
clinic visit						

Month 5						
IV chemo + pills	pills	pills	pills	pills		
clinic visit						

Month 6						
IV chemo + pills	pills	pills	pills	pills		
clinic visit						

Standard Salvage Chemotherapy



Treatment time course:

- Every month for 6 Months



Treatment:

Day 1: Intravenous drugs (given through a needle in your arm) + pills

Days 1 to 5: Pills taken

Day 28: Monthly clinic visits between treatments

Standard Salvage Chemotherapy

Side effects from standard salvage chemotherapy:

- **Nausea:**

You may get a mild upset stomach while on drugs and for a couple of days after. This happens to more than half of the patients treated. Drugs are given to decrease this.

- **Hair Loss:**

You will lose some or all of your hair during the treatment period. Your hair usually grows back a few months after the treatments have stopped.

- **Limited Activities:**

You will be unable to work for part or all of the time while you are undergoing treatment. Usually patients feel able to return to their normal activities by the last two weeks of the month.

Standard Salvage Chemotherapy

Side effects from standard salvage chemotherapy:

- **Fatigue:**

You likely will be more tired than normal during the treatment period.

- **Risk of Infection or bleeding:**

One of the side effects of the chemotherapy can be the suppression of your bone marrow. This can cause you to be at risk for infections or bleeding. 10% to 20% of patients having this treatment have to be hospitalized for infection or less commonly bleeding.

- **Risk of Blood Transfusion:**

You may have to receive a blood or platelet transfusion.

Standard Salvage Chemotherapy

Treatment outcome:

6 Months:

Well	78%
Relapse	19%
Died	3%

18 Months:

Well	50%
Relapse	30%
Died	20%

Standard Salvage Chemotherapy

Treatment outcome:

3 Years:

Well	25%
Relapse	35%
Died	40%

4 Years:

Well	20%
Relapse	30%
Died	50%

Autologous Bone Marrow Transplant



Treatment Time Course:

Month 1						
Hickman	IV chemo	IV chemo	pills	pills		
clinic visit						

Month 2						
IV chemo	IV chemo	pills	pills			
			PBSC	PBSC		
clinic visit						

Month 3						
Harvest	IV chemo	IV chemo		Radiation		Cells Back

Month 4						
clinic visit						
clinic visit						
clinic visit						
clinic visit						

Month 5						
clinic visit						
clinic visit						

Month 6						
clinic visit						
clinic visit						

Autologous Bone Marrow Transplant



Treatment time course:

- **6 Months**, Intensive therapy for months 1-3
Recovery during months 4-6

Month 1:

😊Treatment:

<u>Day 1:</u>	<u>Hickman line insertion:</u>	A special intravenous catheter, put in by a surgeon in the OR, that allows for blood tests and transfusions without needle sticks. This catheter stays in for the entire treatment (~ 4 to 6 months).
<u>Days 2&3:</u>	<u>Chemotherapy 1:</u>	Intravenous drugs given in hospital to fight and kill the lymphoma.
<u>Days 4&5:</u>	<u>Chemotherapy 1:</u>	Pills given by mouth to fight and kill the lymphoma.

Autologous Bone Marrow Transplant

☹ Side effects in Month 1:

Related to the Hickman line (Day 1) :

- A small risk of local bleeding or infection
- A slight local discomfort for a few days after it is put in. This is controlled with Tylenol.

Autologous Bone Marrow Transplant

☹ Side effects in Month 1:

Related to Chemotherapy 1 (Days 2-6). These are:

- **Similar to side effects with standard salvage therapy, but they may be more severe or prolonged. These are:**
 - **Nausea:**
 - **Hair Loss:**
 - **Limited Activities:**
 - **Fatigue:**
 - **Risk of Infection or bleeding:**

About half (50%) of patients having this treatment have to be hospitalized for infection or less commonly bleeding.
- **Risk of Blood Transfusion:**

You probably will have to have a blood transfusion.

Autologous Bone Marrow Transplant

Month 2:

😊 Treatment

Days 1&2: **Chemotherapy 2:** Intravenous drugs in the hospital to fight and kill the lymphoma.

Days 3&4: **Chemotherapy 2:** Pills given by mouth to fight and kill the lymphoma

Days 4-12: **Growth factor:** (bone marrow stimulant) injections given under the skin.

Days 11-12 **Peripheral Blood Stem Cell (PBSC) collection:** These are circulating cells that regrow the bone marrow. They are collected from the circulating blood by putting a needle in both your arms or by using the Hickman catheter and hooking you up to a special machine that extracts the peripheral blood stem cells from your blood.

Autologous Bone Marrow Transplant

Side effects in Month 2:

Related to Chemotherapy 2 (Days 1 to 4)

This chemotherapy is like the chemotherapy that was given in month 1.
The possible side effects are also the same.

- **Nausea:**
- **Hair Loss:**
- **Limited Activities:**
- **Fatigue:**
- **Risk of Infection or bleeding:**
- **Risk of Blood Transfusion:**

Autologous Bone Marrow Transplant

Side effects in Month 2:

Caused by Peripheral Blood Stem Cell Collection (Days 5-13):

- **Bone Pain:**

You may have some mild bone pain from the growth factor. Tylenol is given to reduce this.

Autologous Bone Marrow Transplant

Month 3:



Treatment:

Day 1:

Bone Marrow Harvest:

A collection of bone marrow cells with large needles from your pelvis bones done by the transplant doctors in the Operating Room under general anaesthesia. These cells will regrow your bone marrow. The procedure takes about 1 hour, but it may not need to be done.

Days 2 & 3:

Pre-transplant chemotherapy

Very strong intravenous drugs to kill/fight the lymphoma. This chemotherapy is much stronger than the chemotherapy that was given previously.

Day 5:

Radiation:

This is radiation for your whole body. This radiation is to fight and kill the lymphoma.

Day 7:

Reinfusion:

Stored stem cells and/or bone marrow are reinfused (given back to you) through the Hickman Catheter.

Autologous Bone Marrow Transplant

Side effects in Month 3:

Caused by the Bone Marrow Harvest (Day 1):

- **Risk of General Anaesthetic:**

In general there is less than a 1/1000 risk of serious side effects from general anaesthesia.

- **Sore pelvis bones/Bruising:**

You may have sore hips and a bad bruise for about a week after the harvest was done. This pain is relieved with Tylenol #3.

- **Risk of Infection:**

There is a small risk of having a local infection (an infection where the needles were put in) after the harvest.

- **Risk of Blood Transfusion:**

You may have to have a packed red blood cell and/or platelet transfusion after the harvest.

Autologous Bone Marrow Transplant

Caused by Pretransplant chemotherapy and Reinfusion:

Generally, the side effects are similar to those experienced in the last 2 months but may be more severe. These are:

- **Nausea**
- **Hair Loss**
- **Limited Activities**
- **Fatigue**
- **Risk of Infection or bleeding**
- **Risk of Blood Transfusion:**

There are some other possible side effects. These are:

- **Mouth Ulcers:**

You may have painful ulcers in the throat and mouth. This is controlled with pain medication.

- **Diarrhea:**

You may have diarrhea. It occurs in many patients. The diarrhea normally stops within a few days to a week.

- **Decreased Appetite:**

You may have a decreased appetite.

Autologous Bone Marrow Transplant

Month 4 :

Recovery from Transplant. You should be feeling generally better and be off antibiotics by 3 weeks after the transplant.

<u>Weekly:</u>	<u>Clinic Visit:</u>	a visit to the Bone Marrow Transplant Clinic at the hospital to see your doctor and for blood tests.
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Month 5 and 6:

<u>Every other week:</u>	<u>Clinic Visit:</u>	a visit to the Bone Marrow Transplant Clinic at the hospital to see your doctor and for blood tests.
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Recovery from transplant and return to normal activities.

Autologous Bone Marrow Transplant

Treatment outcome:

6 Months:

Well 85%

Relapse 5%

Died 10%

18 Months:

Well 75%

Relapse 10%

Died 15%

Autologous Bone Marrow Transplant

3 Years:

Well	55%
Relapse	25%
Died	20%

4 Years:

Well	50%
Relapse	15%
Died	35%

**Determining The Minimal Clinically Important Difference
In Patients With Low Grade Lymphoma**

**Draft Of Interview Script For Use With The Decision Aid
Graphical-Numerical Format**

PERSONAL INTRODUCTION

THANK-YOU

- **EXPLAIN PROJECT:**
- **PHONE CALL AND LETTER**
- **TALK WITH YOU ABOUT YOUR OPINIONS ABOUT THE DECISION TO HAVE A BONE MARROW TRANSPLANT**

- **INTERVIEW = 1 HOUR**
- **TALKING WITH 50 PATIENTS**
- **STRUCTURED**
- **TWO PARTS**
- **EXERCISE**
- **HYPOTHETICAL CHOICES**
- **QUESTIONNAIRES**
-

Introduction:

Hello, my name is Janine Malcolm and I am a second year medical student from Queen's University. I am the research assistant who is working with Dr. Bredeson on this project and I will be speaking with you for the next 30 - 60 minutes. I would like to thank-you again for taking the time to help us with this project. As you will recall, we would like to discuss your opinions about decision to have a bone marrow transplant. This decision is a difficult one and we hope that the information that we gain from speaking with you and with others in similar situations we will help us make decision making easier for future patients and help the transplant team to better inform potential transplant patients.

This interview should take approximately one hour to complete. We are going to be speaking with approximately 50 patients like yourself and hope to be able to find out the average patient's opinions. For this reason, the interview is quite structured. This is so that we will be able to get similar information from all of the patients that we talk to. We should, however, have some time at the end of the interview to speak about your personal experiences with the transplant process.

To start, we are going to work through a structured exercise where we will present both treatment options, standard chemotherapy and bone marrow transplant, and ask you to make hypothetical choices based on the information that we present. During the course of the interview we are also going to ask you to fill out three questionnaires. Two of them will be about the information that we are presenting to you. The other questionnaire will be an opportunity for you to evaluate this interview and make suggestions for improvements.

Do you have any questions before we begin?

As you know, in the past you were diagnosed with low grade lymphoma, a type of chronic blood cancer. Lymphoma is a disease that may be treated in a number of different ways. After the lymphoma has been treated for the first time and the disease comes back (relapses) and requires future treatment, there are two treatment options. These are standard salvage chemotherapy and autologous bone marrow transplantation and/or peripheral blood stem cell transplantation.

The choice between the two treatment options, chemotherapy or bone marrow transplantation, is a difficult one and since you have experienced one or both of these treatments, we would like to talk to you about how you made your choice.

To help you review the two treatment options, we are going to spend the next 10 to 15 minutes describing the two treatment options. To help present this information to you, we have what we call a decision aid. This decision aid consists a booklet (*point to booklet*) and a decision board (*point to decision board*). The booklet contains the information about the treatment options in detail and we will be working through this booklet for this first part of the interview. The decision board summarizes the key information for you. If you are unclear about any of the information, you can refer back to the booklet or the decision board at any time.

We will be providing you with a lot of information in one sitting, so you should feel free to take as much time as you need. Please ask questions if anything is unclear to you.

Lets start by reviewing the Standard Salvage Chemotherapy Treatment (*Point to the appropriate section on the decision aid*)

Please turn to page 1 of your booklet.

Standard Salvage Chemotherapy

As you can see from the diagram on page 1, the standard salvage chemotherapy treatment takes 6 months to complete. It involves intravenous drugs (drugs that are given by a needle in your arm) on the first day of each month. As well, pills have to be taken for the second to the fifth day of each month. You will also have to visit the doctor for a clinic visit once a month while you are on this treatment. The clinic visit takes approximately one hour of your time and involves a blood test and an appointment with your doctor. *(point to treatment schedule for standard salvage chemotherapy in booklet which indicates the different aspects of the treatment)*

There are a number of side effects that maybe caused by standard salvage chemotherapy. These are summarized for you on the decision board and in your booklet starting on page 3. *(point to side effects section)*. Lets go through these side effects together.

Nausea

- You may get a mild upset stomach while on drugs the first week of each month.

This happens to more than half of the patients treated. Drugs are given to decrease this. Vomiting is uncommon.

Hair Loss:

- You will lose some or all of your hair during the treatment period. Your hair usually grows back a few months after the treatments have stopped.

Limited Activities

- It is likely that you will be unable to work for part or all of the time while you are undergoing treatment. Usually patients feel able to return to their normal activities by the last two weeks of the month.

Fatigue:

- You likely will be more tired than normal during the treatment period.

Risk of Infection or bleeding:

- One of the side effects of the chemotherapy can be the suppression of your bone marrow. This can cause you to be at risk for infections or bleeding. Approximately 1 to 2 out of 10 patients having this treatment have to be hospitalized for this problem.

Risk of Blood Transfusion:

- You may have to receive a red blood cell transfusion for anemia or a platelet transfusion if your platelet count is low to try to prevent bleeding.

Do you have any questions about the information presented so far?

May we go on?

Now let's look at what may happen if you choose to have the standard salvage therapy option. We will look at your chance of being well (which means feeling well and having no evidence of lymphoma), relapsing (which means your lymphoma has come back and you may feel well or unwell) and dying. We will look at these situations at 4 different times: 6 months, 18 months, 3 years, and 4 years after the start of the treatment.

The white happy faces (☺) represent the number of people out of 100 (percent) that are well (*point to the happy faces*)

The blue sad faces (☹) represent the number of people out of 100 (percent) that have relapsed which means that their disease has come back. (*point to sad faces*) These people may or may not feel well.

The black dots (●) represent the number of people out of 100 (percent) that have died. *(point to the black dots)* They may have died from either their disease or the treatment.

As you will recall, the treatment takes six months to complete. Let's look at what happens once this is over. *(point to 6 months diagram in the booklet)*

After 6 months of therapy

Out of 100 people treated with standard salvage therapy:

80 will be well

17 will have relapsed

and 3 will have died from the treatment.

Another way of saying this is:

80% chance of being well *(point to happy faces)*

17% chance of relapsing *(point to sad faces)*

and a 3% chance of dying from the treatment or the disease *(point to black dots)*

Do you have any questions so far?

May we go on?

Lets look at 18 months after therapy.

After 18 months of standard salvage therapy

Out of 100 people treated with standard salvage therapy:

50 will be well

30 will have relapsed

and 20 will have died.

Another way of saying this is:

50% chance of being well (*point to happy faces*)
30% chance of relapsing (*point to sad faces*)
and a 20 % chance of dying from the treatment or the disease (*point to black dots*)

Is this information clear so far? May we go on?

Lets look at 3 Years after standard salvage therapy.

After 3 years of standard salvage therapy

Out of 100 people treated with standard salvage therapy:
25 will be well
35 will have relapsed
and 40 will have died.

Another way of saying this is:

25% chance of being well (*point to happy faces*)
35 % chance of relapsing (*point to sad faces*)
and a 40 % chance of dying from the treatment or the disease (*point to black dots*)

Any questions?

Lets look at 4 years after standard salvage therapy.

After 4 years of standard salvage therapy:

Out of 100 people treated with standard salvage therapy:
20 will be well
30 will have relapsed
and 50 will have died.

Another way of saying this is:

20% chance of being well (*point to happy faces*)
30 % chance of relapsing (*point to sad faces*)
and a 50 % chance of dying from the treatment or the disease (*point to black dots*)

So you can see, that over 4 years, your chance of being well drops from 80% right after treatment to 20% at 4 years.

This completes the description of Standard Salvage Therapy.

Do you have any questions about the information presented so far? We can go back to anything that is unclear.

Now let's review the Autologous Bone Marrow Transplant treatment option.
Please turn to page 7 in your booklet

Autologous Bone Marrow Transplant

Autologous bone marrow transplantation has many steps that starts with intensive treatment for 3 months and is followed by approximately 3 months of recovery. The steps are outlined for you on page 7 of your booklet (*point to the treatment schedule for the autologous transplant in the booklet*).

Although not all treatments are identical, the one described here is typically what is done and should be fairly close to what you had.

Lets go through each step of treatment. Remember to ask questions anytime something is unclear.

During the first month (*point to month 1*), the first step in the treatment is the insertion of a central venous line, also called a Hickman line. The Hickman line is a small tube that allows for blood tests, medications, and transfusions to be given to you without needle sticks in your arm. The tube is put in by a surgeon in the operating room with local anaesthetic. This tube stays in for the entire treatment period (~ 4 to 6 months).

After the Hickman line insertion , you have the first course of salvage chemotherapy to fight and kill the lymphoma. This is given as intravenous drugs (through a needle) for the first 2 days and as pills taken by the mouth for 2 more days.

There are a few common side effects within the first month of treatment. Let's go through them now. (*point to corresponding side effects section on the decision aid*). These are outlined for you on pages 8 and 9 of your booklet.

There are two main side effects related to the Hickman line which is the first day of treatment. These are :

- A small risk of bleeding or infection where the tube comes out of the skin.
and
- A slight discomfort where the tube was put in for a few days after it is put in.
This is controlled with Tylenol.

There are a number of possible side effects from the salvage chemotherapy. In general, these are similar to the side effects of standard salvage chemotherapy, but may be more severe or last longer because the dosage of drugs is higher:

These are :

Nausea:

Hair Loss

Limited Activities:

Fatigue

Risk of infection or bleeding: This is higher - you may have a 50 out of 100 chance or 1 out of having to be hospitalized for this problem.

Risk of Blood Transfusion:

Is the information that we have presented clear so far? Do you have any questions?

The second month (*point to month 2*) involves a second course of salvage chemotherapy for four days. This is like the first course of chemotherapy. It is given as intravenous drugs (through a needle) for the first 2 days and as pills taken by the mouth for 2 more days.

The only thing that is different in this month is the collection of your peripheral blood stem cells. You will have a series of injections for 9 days of another drug, called a growth factor, that makes these cells go into your circulation. After these injections your cells will be collected by a special machine in the hospital for 4-6 hours each day for 2 days.

Side effects related to Chemotherapy 2:

These side effects are like the ones that you had in month 1.

Nausea:

Hair Loss

Limited Activities:

Fatigue

Risk of infection or bleeding:

Risk of Blood Transfusion:

You may also have one more side effect. This is related to the peripheral blood stem cell collection.

Bone Pain:

- You may have some mild bone pain from the growth factor. Tylenol is given to reduce this.

Do you have any questions so far?

May we go on?

The third month of the treatment is the third stage of treatment. *(point to month 3)*.

On the first day of the third month, you may need a special procedure to obtain bone marrow. The procedure, known as a bone marrow harvest, is a collection of cells from your pelvis bones that will regrow your bone marrow after the pre-transplant chemotherapy. It is collected by the transplant doctors in the Operating Room under general anaesthesia. Large needles are used to remove the bone marrow from the pelvis bones (this is like a bone marrow test a fifty times over). The entire procedure takes about an hour.

Following the bone marrow harvest, you will have the pretransplant chemotherapy. This is very strong intravenous drugs to fight and kill the lymphoma. This chemotherapy course takes 6 days.

After the pretransplant chemotherapy course is finished, you are given back the stored bone marrow and/or peripheral blood stem cells. These cells are given through the Hickman catheter.

There are a number of side effects associated with the third month of treatment. Lets go through them now.

These are the side effects related to the Bone Marrow Harvest

Risk of General Anaesthetic:

- **In general, there is a less than a 1/1000 risk of serious side effects such as heart or breathing problems from general anaesthesia.**

Sore pelvis bones/bruising:

- You will probably have sore pelvis bones and will feel tender for about a week after the harvest is done. This pain is relieved with Tylenol #3.

Risk of infection:

- There is a small risk of a local infection (where the needles were put in) after the harvest.

Risk of Blood Transfusion:

- You may have to have a red blood cell transfusion after the harvest.

The side effects of the Pre-transplant chemotherapy are similar to the ones experienced in the first two months of therapy, but they may be more severe or last longer. This is because the dose of drugs is higher.

Nausea

Hair Loss

Limited Activities

Fatigue

Risk of infection or bleeding:

Risk of Blood Transfusion:

- You almost certainly will have to receive a blood transfusion.

You may also have some other side effects. These are:

Mouth Ulcers:

- You may have painful ulcers in the throat and mouth. This is controlled with pain medication. These ulcers normally last for about 2 weeks. The ulcers get better once the blood counts recover.

Diarrhea:

- You may have diarrhea. It occurs in many patients. The diarrhea normally stops within a few days to a week.

Decreased Appetite:

- You may have a decreased appetite which may last up to 1 month.

Hospital Stay:

Overall there is a greater than 75% chance (75 out of 100) chance of having to stay in hospital for some time during this treatment.

Do you have any questions? May we go on?

Month four is the start of the recovery phase. (point to months 4 to 6).

Generally, you should be feeling reasonably well (for example you are at home or are going home from the hospital) and be off antibiotics by 3 weeks after the transplant.

During month 4, you will have to make weekly clinic visits to see the transplant doctors. A clinic visit normally takes about an hour to an hour and a half at the hospital and it involves having a blood test and seeing your doctor.

During months 5 and 6, you continue your recovery and return to your normal activities. During this time, you only have to have clinic visits every other week for blood tests and to see your transplant doctor.

Do you have any questions about the information given so far?

May we continue?

Let's now look at what the outcomes might be if you choose the autologous transplant treatment option.

As with the standard chemotherapy, we will look at your chance of being well (which means feeling well and having no evidence of lymphoma), relapsing (which means your lymphoma has come back and you may feel well or unwell) and dying. We will look at these situations at 4 different times: 6 months, 18 months, 3 years, and 4 years after the start of the treatment.

The white happy faces (☺) represent the number of people out of 100 (percent) that are well (*point to the happy faces*)

The blue sad faces (☹) represent the number of people out of 100 (percent) that have relapsed which means that their disease has come back. (*point to sad faces*) These people may or may not feel well.

The black dots (●) represent the number of people out of 100 (percent) that have died. (*point to the black dots*) They may have died from either their disease or the treatment.

Let's start at 6 Months after the treatment has started. (*point to 6 months diagram on the decision board*)

6 months after the transplant process has started:

Out of 100 people, 85 will be well

5 will have relapsed

and 10 will have died from the treatment. Another way of saying this is you have a

85% chance of being well (*point to happy faces*)

5% chance of relapsing
and a 10% chance of dying (*point to black dots*) from the transplant.
Do you have any questions? May we go on?

18 Months after the transplant process has started:

Out of 100 people, 75 will be well

10 will have relapsed

and 15 will have died from the treatment. Another way of saying this is
you have a

75% chance of being well (*point to happy faces*)

10% chance of relapsing

and a 15% chance of dying (*point to black dots*) from the transplant.

Do you have any questions? May we go on?

3 years after the transplant process has started:

Out of 100 people, 55 will be well

25 will have relapsed

and 20 will have died from the treatment. Another way of saying
this is you have a

55% chance of being well (*point to happy faces*)

25% chance of relapsing

and a 20% chance of dying (*point to black dots*) from the transplant.

Do you have any questions? May we go on?

4 years after the transplant process has started:

Out of 100 people, 50 will be well

15 will have relapsed

and 35 will have died from the treatment. Another way of saying
this is you have a

50% chance of being well (*point to happy faces*)

15% chance of relapsing

and a 35% chance of dying (*point to black dots*) from the transplant.

Do you have any questions? May we go on?

So as you can see, over four years, your chance of being well drops from 85% to 50%.

Do you have any questions about this information?

This completes the information about the autologous transplant process.

We are now going to review the information that we have just gone through by looking at the decision board and looking at the treatment course, the side effects, and the outcome information for both treatment options together to make it easier for you to review your choices.

(Point to the decision board)

This side of the decision board has information about standard salvage chemotherapy (*point to the standard salvage section*)

This side of the decision board has information about the autologous transplant. (*point to the autologous transplant section*)

As you can see on the decision board the treatment schedule for standard salvage therapy is monthly treatments for 6 months (*point to treatment schedule section board*). The treatment schedule for autologous transplant is 3 months of intensive therapy followed by 3 months of recovery (*point to treatment schedule of the decision board*).

The main side effects for standard salvage therapy are:(*point to the board*)

- Nausea
- Hair Loss
- Limited Activities
- Fatigue
- Risk of infection or bleeding
- Risk of blood transfusion

The main side effects for autologous transplant are:(*point to the board*)

In general, these side effects may be more severe or last longer than Standard Salvage Therapy

- More Nausea
- Hair Loss
- More Limitation of Activities
- More Fatigue
- Greater Chance of infection or bleeding
- Greater Risk of blood transfusion
- Diarrhea
- Decreased Appetite
- Mouth Ulcers
- Mild bone pain
- Risk of local infection from Hickman catheter
- Risk of local infection from Harvest
- Sore pelvis bones/bruise from Harvest x 1 week
- Risk of having a general anaesthetic

Remeber , the white happy faces (☺) represent the number of people out of 100 (percent) that are well (*point to the happy faces*)

The blue sad faces (☹) represent the number of people out of 100 (percent) that have relapsed which means that their disease has come back. (*point to sad faces*) These people may or may not feel well.

The black dots (●) represent the number of people out of 100 (percent) that have died. (*point to the black dots*) They may have died from either their disease or the treatment.

.

The outcome information is summarized on the decision board for you here

Now you have the entire picture in front of you. You have gone through a description of both treatments (standard salvage chemotherapy and autologous transplant), their side effects and likely outcomes.

Is there anything that I did not make clear? It is important that you feel comfortable with the information that we just reviewed. I would be happy to go over any of the information that you would like explained further.

Know, based only on the information that was just presented to you, independent from your previous experience , what treatment option, standard salvage therapy or autologous transplantation, would you favor or recommend to a family member of friend.

Remember, there are no right or wrong answers, the choice is entirely yours. This completes this section of the interview. Do you have any questions?

Record the Answer

Administer post interview comprehension testing questionnaire

Go on to the determination of the MCID

Text for MCID elicitation method for Treatment Related Mortality:

This is an example of the elicitation technique for the MCID of treatment-related mortality for autologous transplantation. The technique used is the ping-ponging technique in which the probabilities are varied first at one end of the scale and then the other after starting at the known value.

"Now that you have made your choice, let us try an imaginary situation. You will again be asked to make a choice between autologous bone marrow transplantation and standard salvage chemotherapy. "

" As we discussed before, your chance of dying from standard salvage chemotherapy within the first 6 months is 3 out of 100." *(point to sheet showing the standard salvage risks)*

"Here are 100 people who have had standard salvage therapy, as you can see, 3 of them will die from the salvage chemotherapy."

Place the card on the table that shows 10 out of 100 "autologous transplant risk"

"Let us imagine that if these 100 patients decided to have an autologous bone marrow transplant, ten of them (10) would die from the transplant. Keep in mind that we are only changing the chance of dying from the treatment. The longterm outcome will remain the same"

"Which of these two situations looks better for you, standard salvage chemotherapy or autologous bone marrow transplantation? Please take into account the information that was presented to you earlier in the interview. Refer back to the decision aid if this helps you."

Subject chooses to : have autologous transplant

**go to next
page**

have standard salvage

**further explanation
is necessary**

20 OUT OF 100 CHANCE OF DYING FROM AUTOLOGOUS TRANSPLANT

"Now that you have made that choice, let us try another situation. Again you will be asked to choose between autologous transplantation and standard salvage chemotherapy. As we discussed previously, your chance of dying if you have

standard salvage chemotherapy is 3 out of 100 within the first 6 months. I will show you this again.

Show subject standard salvage chemotherapy risk card and point to icon

"Here are 100 people with lymphoma who have had standard salvage chemotherapy. As you can see, three have died."

Point to card showing 20 out of 100 chance of dying from autologous transplant

"Here are 100 people with lymphoma who have had an autologous transplant. 20 of them will have died within the first 6 months. "

"Which of these situations looks best to you, standard salvage chemotherapy or autologous transplantation? Please take into account the information about both the treatment options that was presented to you earlier in the interview".

In this imaginary situation, would you choose to have an autologous transplant or to have standard salvage therapy?

**Subject chooses: Autologous transplant further explanation may be necessary
or
increase the probability to 30/100 and start from there**

Standard Salvage therapy Go to 1/100

(Repeat the above procedure until the subject switches their choice. Please see the flow sheet of the ping-ponging procedure on the following page).

Ping-Pong Probabilities starting at 20/100 and 0/100

Hypothetical chance of dying from autologous bone marrow transplant in first 6 months	Patient chooses Autologous Transplant based on the probability from column 1	Patient chooses Standard Salvage based on the probability from column
10 out of 100	go to 20/100	go to 1/100
20 out of 100	further explanation may be necessary or increase the probability to 30/100 and start there.	go to 1/100
1 out of 100	go to 19 /100	stop
19 out of 100	stop	go to 2/100
2 out of 100	go to 18/100	stop
18 out of 100	stop	go to 3 out of 100
3 out of 100	go to 17 / 100	stop
17 out of 100	stop	go to 4 out of 100
4 out of 100	go to 16/100	stop
16 out of 100	stop	go to 5 out of 100
5 out of 100	go to 15 / 100	stop
15 out of 100	stop	go to 6 out of 100
6 out of 100	go to 14 /100	stop
14 out of 100	stop	go to 7 out of 100
7 out of 100	go to 13 /100	stop
13 out of 100	stop	go to 8 out of 100
8 out of 100	go to 12/100	stop
12 out of 100	stop	go to 9 out of 100
9 out of 100	go to 11/100	stop
11 out of 100	stop	go to 10 out of 100

10 out of 100	stop	stop
---------------	------	------

Text for MCID elicitation method for disease and treatment free 4 year survival:

This is an example of the elicitation technique for the MCID of disease and treatment free 4 year survival for autologous transplantation. The technique used is the ping-ponging technique in which the probabilities are varied first at one end of the scale and then the other. The same format will be used for the MCID of overall survival.

"Now that you have made your choice, let us try an imaginary situation. You will again be asked to make a choice between autologous bone marrow transplantation and standard salvage chemotherapy. "

" As we discussed before, your chance of being alive with no disease and requiring no treatment 4 years after treatment is 20 out of 100." (point to sheet showing the standard salvage risks)

"Here are 100 people who have had standard salvage therapy, as you can see, 20 of them will be alive and have no disease and require no treatment in 4 years after standard salvage chemotherapy."

Place the card on the table that shows 50 out of 100 "autologous transplant risk"

"Let us imagine that if these 100 patients decided to have an autologous bone marrow transplant, fifty of them (50) would be alive with no disease and require no treatment 4 years after the transplant

"Which of these two situations looks better for you, standard salvage chemotherapy or autologous bone marrow transplantation? Please take into account the information that was presented to you earlier in the interview. Refer back to the decision aid if this helps you."

Subject chooses to : have autologous transplant

**go to next
page**

have standard salvage

**further explanation
is necessary**

**10 OUT OF 100 CHANCE OF BEING ALIVE AND OFF TREATMENT 4 YEARS
AFTER AUTOLOGOUS TRANSPLANT**

"Now that you have made that choice, let us try another situation. Again you will be asked to choose between autologous transplantation and standard salvage chemotherapy. As we discussed previously, your chance of being alive and requiring no treatment 4 years after standard salvage chemotherapy is 20 out of 100.

Show subject standard salvage chemotherapy risk card and point to icon

"Here are 100 people with lymphoma who have had standard salvage chemotherapy. As you can see, after 4 years 20 have no disease and require no treatment."

Point to card showing 10 out of 100 chance of being disease and treatment-free 4 years after the autologous transplant

"Here are 100 people with lymphoma who have had an autologous transplant. 10 of them will have no disease and will not need treatment. "

"Which of these situations looks best to you, standard salvage chemotherapy or autologous transplantation? Please take into account the information about both the treatment options that was presented to you earlier in the interview".

In this imaginary situation, would you choose to have an autologous transplant or to have standard salvage therapy?

Subject chooses: Autologous transplant further explanation may be necessary

Standard Salvage therapy Go to 90/100

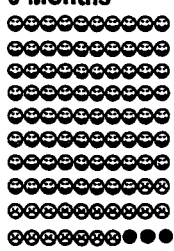
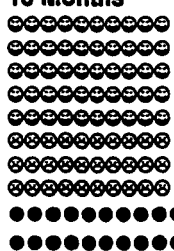
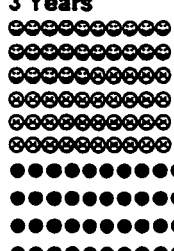
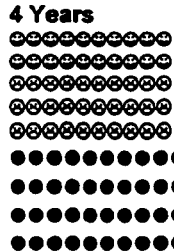
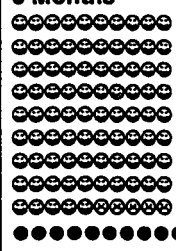
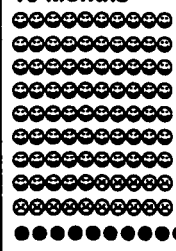
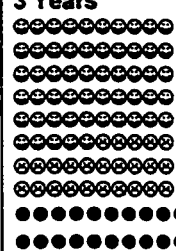
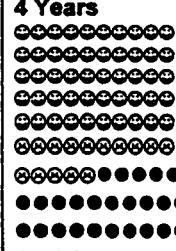
(Repeat the above procedure until the subject switches their choice. Please see the flow sheet of the ping-ponging procedure on the following page).

Ping-Ponging Probabilities starting at 20/100 and 0/100

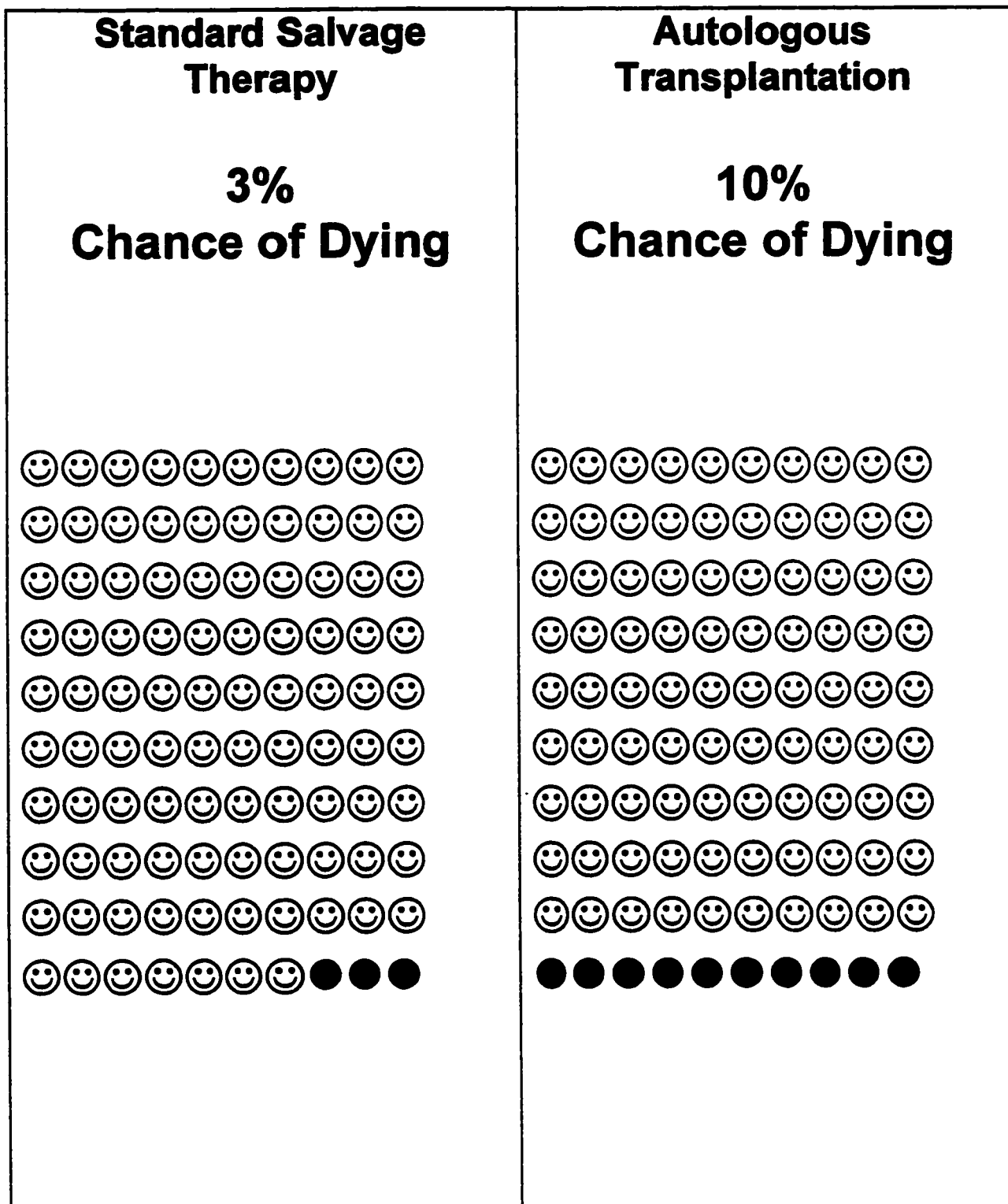
Hypothetical chance of disease and treatment free survival 4 years after bone marrow transplant	Patient chooses Autologous Transplant based on the probability from column 1	Patient chooses Standard Salvage based on the probability from column 1
50 out of 100	go to 10/100	go to 90/100
90 out of 100	go to 10/100	further explanation may be necessary
10 out of 100	stop	go to 89/100
89 out of 100	go to 11/100	stop
11 out of 100	stop	go to 88/100
88/100	go to 12/100	stop
12 out of 100	stop	go to 87/100
87 out of 100	go to 13/100	stop
13 out of 100	stop	go to 86/100
86 out of 100	go to 14/100	stop
14 out of 100	stop	go to 85/100
85 out of 100	go to 15/100	stop
15 out of 100	stop	go to 84 out of 100
84 out of 100	go to 16/100	stop
16 out of 100	stop	go to 83 out of 100
83 out of 100	go to 17/100	stop
17 out of 100	stop	go to 82 out of 100
82 out of 100	go to 18 out of 100	stop
18 out of 100	stop	go to 81 out of 100
81 out of 100	go to 19 out of 100	stop
19 out of 100	stop	go to 80 out of 100

[illegible]

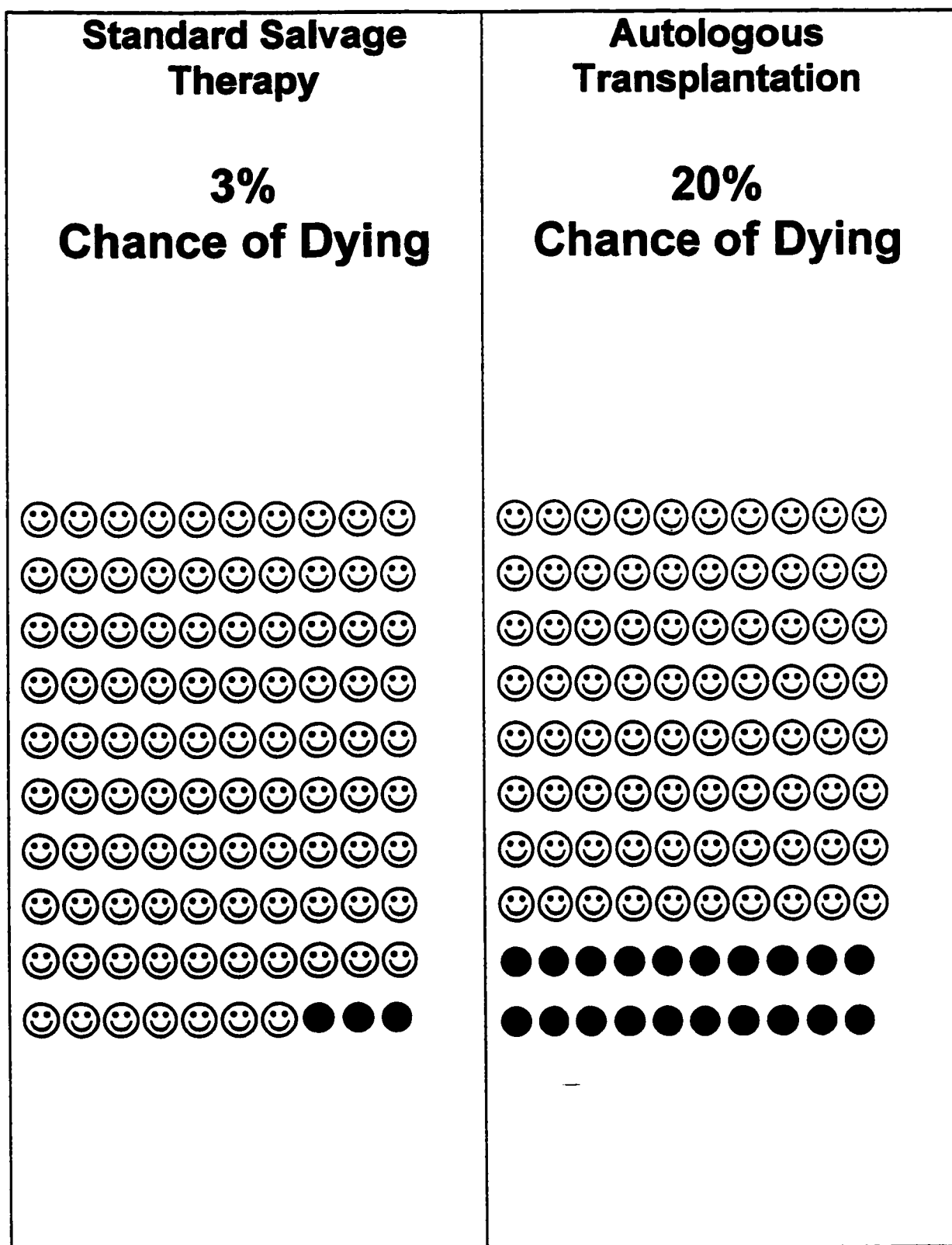
Appendix G:
Summary Decision Board Used in Graphical-Numerical Decision Aid (Photo Reduced)

Standard Salvage Chemotherapy	Autologous Transplantation
Treatment Schedule over 6 Months: - Monthly treatment X 6 - Monthly clinic visits between treatments	Treatment Schedule over 6 Months - Intensive Treatment x 3 months - Recovery x 3 months
Side effects: - Nausea - Hair Loss - Limited Activities - Fatigue - Risk of infection or bleeding - Risk of blood transfusion	Side effects: - More Nausea - Hair Loss - More Limitation of Activities - More Fatigue - Greater Chance of infection or bleeding - Greater Risk of blood transfusion - Diarrhea - Decreased Appetite - Mouth Ulcers - Mild bone pain - Risk of local infection from Hickman catheter - Risk of local infection from Harvest - Sore pelvis bones/bruise from Harvest x 1 week - Risk of having a general anaesthetic
Outcome: 6 Months  Well (78%) Relapse (19%) Dead (3%) 18 Months  Well (50%) Relapse (30%) Dead (20%) 3 Years  Well (25%) Relapse (35%) Dead (40%) 4 Years  Well (20%) Relapse (30%) Dead (50%)	Outcome: 6 Months  Well (85%) Relapse (5%) Dead (10%) 18 Months  Well (75%) Relapse (15%) Dead (10%) 3 Years  Well (55%) Relapse (25%) Dead (20%) 4 Years  Well (50%) Relapse (15%) Dead (35%)

Chance of Dying from Treatment:



Chance of Dying From Treatment:



Chance of Dying from Treatment:

Standard Salvage Therapy	Autologous Transplantation
3%	10%
Chance of Dying	Chance of Dying

Chance of Dying from Treatment:

Standard Salvage Therapy	Autologous Transplantation
3%	20%
Chance of Dying	Chance of Dying

Pre-Interview Questionnaire

Subject Initials

--	--	--

Subject No.

--	--	--

Date of visit

mm	dd	yy

Please fill in the following questionnaire remembering that 0 out of 100 means no chance, 50 out of 100 means an equal chance that it will/ will not happen, like a toss of a coin, and 100 out of 100 means it will happen for sure.

- 100 people with low-grade lymphoma have had standard salvage chemotherapy. Out of those 100 people, how many do you feel will be alive with no lymphoma and require no treatment 4 years after receiving standard salvage chemotherapy?

No chance											toss of a coin											for sure
0	10	20	30	40	50	60	70	80	90	100												

- 100 people with low-grade lymphoma have had standard salvage chemotherapy. Out of those 100 people, how many do you feel will have died within the first six months of receiving standard salvage chemotherapy?

No chance											toss of a coin											for sure
0	10	20	30	40	50	60	70	80	90	100												

3. 100 people with low-grade lymphoma have had a bone marrow transplant. Out of those 100 people, how many do you feel will be alive with no lymphoma and require no treatment 4 years after having a bone marrow transplant?

4. 100 people with low-grade lymphoma have had a bone marrow transplant. Out of those 100 people, how many do you feel will have died within the first six months of receiving a bone marrow transplant?

No chance

toss of a coin

for sure

0 10 20 30 40 50 60 70 80 90 100

Post-Interview Questionnaire

Subject Initials

--	--	--

Subject No.

--	--	--

Date of visit

mm	dd	yy

Please fill in the following questionnaire remembering that 0 out of 100 means no chance, 50 out of 100 means an equal chance that it will/ will not happen, like a toss of a coin, and 100 out of 100 means it will happen for sure.

1. 100 people with low-grade lymphoma have had standard salvage chemotherapy. Out of those 100 people, how many do you feel will be alive with no lymphoma and require no treatment 4 years after receiving standard salvage chemotherapy?

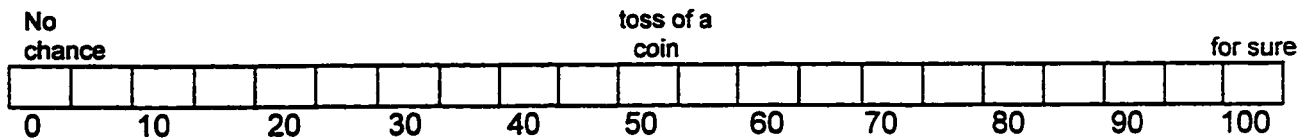
No chance	toss of a coin	for sure																				
<table style="width: 100%; border-collapse: collapse;"> <tr> <td style="width: 33px; height: 20px;"></td> <td style="width: 33px; height: 20px;"></td> <td style="width: 33px; height: 20px;"></td> <td style="width: 33px; height: 20px;"></td> <td style="width: 33px; height: 20px;"></td> <td style="width: 33px; height: 20px;"></td> <td style="width: 33px; height: 20px;"></td> <td style="width: 33px; height: 20px;"></td> <td style="width: 33px; height: 20px;"></td> <td style="width: 33px; height: 20px;"></td> <td style="width: 33px; height: 20px;"></td> <td style="width: 33px; height: 20px;"></td> <td style="width: 33px; height: 20px;"></td> <td style="width: 33px; height: 20px;"></td> <td style="width: 33px; height: 20px;"></td> <td style="width: 33px; height: 20px;"></td> <td style="width: 33px; height: 20px;"></td> <td style="width: 33px; height: 20px;"></td> <td style="width: 33px; height: 20px;"></td> <td style="width: 33px; height: 20px;"></td> </tr> </table>																						
0	10	20	30	40	50	60	70	80	90	100												

2. 100 people with low-grade lymphoma have had standard salvage chemotherapy. Out of those 100 people, how many do you feel will have died within the first six months of receiving standard salvage chemotherapy?

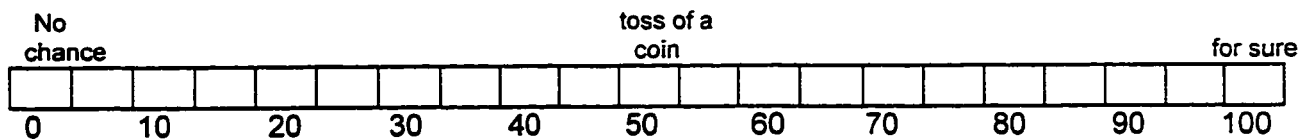
No chance	toss of a coin	for sure																				
<table style="width: 100%; border-collapse: collapse;"> <tr> <td style="width: 33px; height: 20px;"></td> <td style="width: 33px; height: 20px;"></td> <td style="width: 33px; height: 20px;"></td> <td style="width: 33px; height: 20px;"></td> <td style="width: 33px; height: 20px;"></td> <td style="width: 33px; height: 20px;"></td> <td style="width: 33px; height: 20px;"></td> <td style="width: 33px; height: 20px;"></td> <td style="width: 33px; height: 20px;"></td> <td style="width: 33px; height: 20px;"></td> <td style="width: 33px; height: 20px;"></td> <td style="width: 33px; height: 20px;"></td> <td style="width: 33px; height: 20px;"></td> <td style="width: 33px; height: 20px;"></td> <td style="width: 33px; height: 20px;"></td> <td style="width: 33px; height: 20px;"></td> <td style="width: 33px; height: 20px;"></td> <td style="width: 33px; height: 20px;"></td> <td style="width: 33px; height: 20px;"></td> <td style="width: 33px; height: 20px;"></td> </tr> </table>																						
0	10	20	30	40	50	60	70	80	90	100												

Appendix J: Post-Interview Questionnaire Measuring Subjects' Estimate of Treatment Related Mortality and 4-Year Treatment Free Survival with Standard Salvage Therapy and Autologous Transplantation

3. 100 people with low-grade lymphoma have had a bone marrow transplant. Out of those 100 people, how many do you feel will be alive with no lymphoma and require no treatment 4 years after having a bone marrow transplant?



4. 100 people with low-grade lymphoma have had a bone marrow transplant. Out of those 100 people, how many do you feel will have died within the first six months of receiving a bone marrow transplant?



Bone Marrow Transplant Programme

Ottawa General Hospital

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Page 1

Subject Initials

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Subject No.

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Date of Visit

/	/
m	d y

Please fill out the following questionnaire like the following examples.

1. Summer Hollidays are:

☒ too short ☐ just right ☐ too long

2. I like ice cream

not at all

1	2	3	4	5
---	---	---	---	---

 a lot

QUESTIONNAIRE FOR ASSESSMENT OF PROTOTYPE DECISION AID	Score					
1. The amount of information in the decision aid was? ☐ not enough ☐ just right ☐ too much	—					
2. Was the information about the possible <u>risks</u> of a <u>bone marrow transplant</u> contained in the decision aid <u>easy to understand</u>? not at all <table border="1"><tr><td>1</td><td>2</td><td>3</td><td>4</td><td>5</td></tr></table> very easy	1	2	3	4	5	—
1	2	3	4	5		

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Subject Initials

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Subject No.

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Date of Visit

/	/
m	d
	y

3. Was the information about the possible risks of a bone marrow transplant contained in the decision aid helpful?

not at all

1	2	3	4	5
---	---	---	---	---

 very helpful

—

4. Was the information about the possible benefits of a bone marrow transplant contained in the decision aid easy to understand?

not at all

1	2	3	4	5
---	---	---	---	---

 very easy

—

5. Was the information about the possible benefits of a bone marrow transplant contained in the decision aid helpful?

not at all

1	2	3	4	5
---	---	---	---	---

 very helpful

—

6. Was the information about the possible risks of standard salvage therapy contained in the decision aid easy to understand?

not at all

1	2	3	4	5
---	---	---	---	---

 very easy

—

7. Was the information about the possible risks of standard salvage therapy contained in the decision aid helpful?

not at all

1	2	3	4	5
---	---	---	---	---

 very helpful

—

8. Was the information about the possible benefits of standard salvage therapy contained in the decision aid easy to understand?

not at all

1	2	3	4	5
---	---	---	---	---

 very easy

—

9. Was the information about the possible benefits of standard salvage therapy contained in the decision aid helpful?

not at all

1	2	3	4	5
---	---	---	---	---

 very helpful

—

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Subject Initials

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Subject No.

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Date of Visit

 / /
m d y

10. Was the presentation of the possible risks and benefits of a bone marrow transplant in the decision aid balanced?

- ☐ too much emphasis on risks ☐ just right ☐ too much emphasis on benefits

11. Was the presentation in the decision aid on the possible risks and benefits of standard salvage therapy balanced:

- ☐ too much emphasis on risks ☐ just right ☐ too much emphasis on benefits

12. The amount of detail in the decision aid was?

- ☐ too little ☐ just right ☐ too much

13. Do you feel you understand the possible risks and benefits of the treatment choices better after completing the decision aid?

not at all

1	2	3	4	5
---	---	---	---	---

 very much

14. Do you think the decision aid would be helpful to other patients in choosing which treatment to receive for their lymphoma?

not at all

1	2	3	4	5
---	---	---	---	---

 very helpful

15. The time it took to complete the decision aid was?

- ☐ too short ☐ just right ☐ too long

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Page 4

Subject Initials

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Subject No.

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Date of Visit

	/		/	
m		d		y

16.	Which of the following factors did you consider in deciding to have a bone marrow transplantation? (please check all that apply)	
☐	Chance of long term survival from the treatment	☐ Cost of Treatment
☐	Chance of dying within the first few months from the treatment	☐ Your age
☐	Time commitment for treatment	☐ Short term goals
☐	Side effects of treatment	☐ Experience of others with BMT
☐	Time off treatment	☐ Long term goals
☐	Recommendations of physician	☐ Wishes of significant others/family

17. Any other comments or ways to improve the decision aid or the interview process?

Bone Marrow Transplant Programme

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Subject Initials

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Subject No.

--	--	--	--

Date of Visit

	/		/	
m		d		y

18. How long were you in the hospital for your transplant? _____ days

19. How long did it take you to get back to your regular activities after the transplant?

_____ weeks

21. How does your transplant experience compare to what was described here?

Worse			The same			Better
1	2	3	4	5	6	7

22. Would you choose to have a transplant again? ____Y ____ N

Please explain:

Appendix K: Questionnaire to Evaluate the Decision Aid Interview Process and to Identify Factors Considered by Subjects While Deciding Between Treatment Options

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Subject Initials

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Subject No.

--	--	--	--

Date of Visit

	/		/	
m		d		y

Appendix L: Demographic and Disease Related Information Data Sheet
Decision Aid Study

Demographic Information

Patient #	Date:
Subject Name:	
Highest Education Level: Grade school or less ☐ Some high school ☐ High school diploma ☐ Some post secondary ☐ College Diploma ☐ University Degree ☐	Occupation: Currently employed: Y ☐ N ☐ Part time ☐ Full time ☐ Seasonal ☐
Marital Status: Single ☐ Married/Common Law ☐ Divorced ☐ Widowed ☐	

Appendix L: Demographic and Disease Related Information Data Sheet

Disease-Related Information

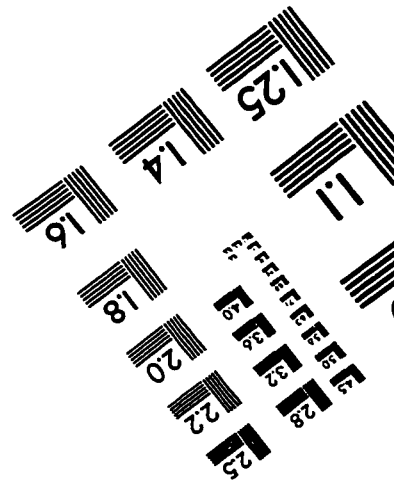
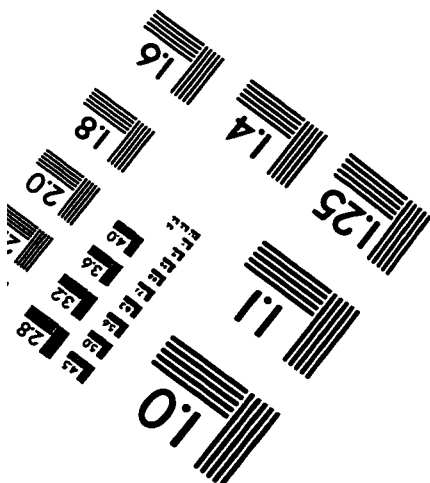
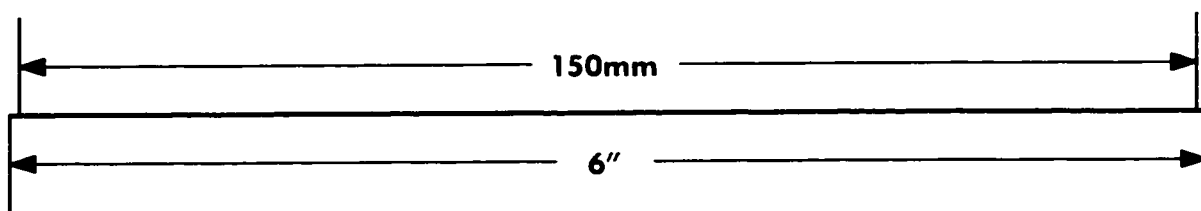
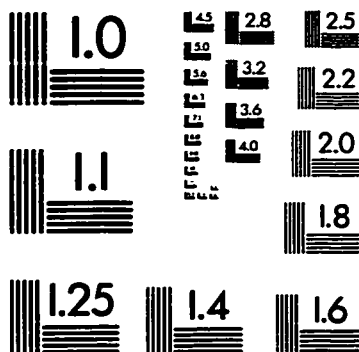
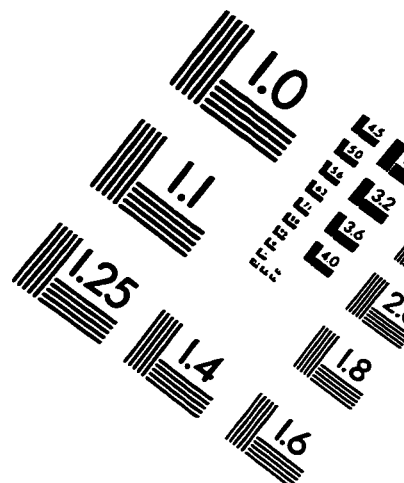
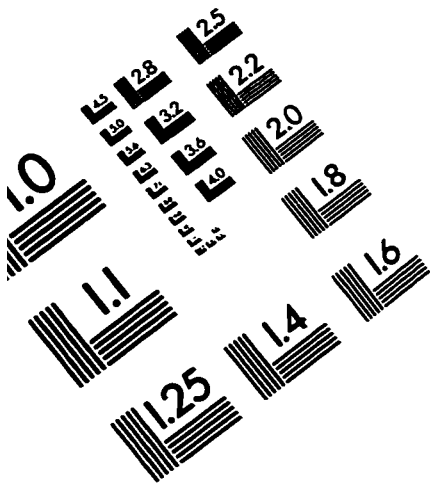
Patient #
Subject Name:

Diagnosis:	Date of Diagnosis: / / DD MM YY
# of Relapses:	Status at BMT:
Date of BMT: / / DD MM YY	Current Status:

MCID Elicitation and Decision Aid Review:

MCID: Treatment Related Survival %	MCID: 4 Year Treatment Free Survival: %
Impression of patient understanding: No understanding (did not understand any of information presented) : ☐ Some understanding (understood at least 50% of information presented): ☐ Good understanding (understood most of information presented): ☐ Excellent understanding (understood all of information presented): ☐	
Length of time to present background: mins	
information	
Length of time to elicit MCID: mins	

IMAGE EVALUATION TEST TARGET (QA-3)



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