Economic Evaluation of Strategies to Prevent and Treat Febrile Neutropenia in Lymphoma Patients

by

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A thesis submitted in conformity with the requirements for the degree of Doctor of Philosophy
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Abstract

This thesis employed methods used in health care decision making to evaluate strategies for prevention and treatment of febrile neutropenia (FN) in non-Hodgkin lymphoma (NHL) patients. The objectives of this thesis were to quantify the cost-effectiveness of filgrastim and pegfilgrastim as primary prophylaxis against FN in NHL patients, to develop an algorithm for converting health-related quality of life data collected in non-Hodgkin lymphoma patients into preference-based health utility values, and to evaluate NHL patients’ preferences for outpatient treatment of FN. The cost-effectiveness analysis demonstrated that neither filgrastim, nor pegfilgrastim are cost-effective, with respective incremental cost-effectiveness ratios [95% confidence interval] of $4,599,000/QALY [$597,045, dominated] and $6,272,000/QALY [$730,692, dominated], well above the normally accepted threshold of $50,000/QALY. The algorithm for deriving health utility values was based on a regression model that used health utility values obtained from the EQ-5D instrument as the outcome variable and the four subscales of the Functional Assessment of Cancer Therapy – General (FACT-G) questionnaire as the predictor variables. The model final model included three of the FACT-G subscales, and had an R-squared value of 0.502 and a mean squared error of 0.013. A discrete choice experiment
was used to examine patients’ preferences for outpatient treatment of FN, and demonstrated that out-of-pocket costs, unpaid caregiver time required daily, and probability of return to hospital are all significant attributes when considering outpatient therapy for FN. Adjusted odds ratios [95% confidence intervals] of accepting outpatient treatment for FN were 0.84 [0.75 to 0.95] for each $10 increase in out-of-pocket cost; 0.82 [0.68 to 0.99] for each 1 hour increase in daily unpaid caregiver time; and 0.53 [0.50 to 0.57] for each 5% increase in probability of return to hospital. These results provide important information for clinicians and health care decision makers involved in implementing programs for NHL patients with FN.
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Chapter 1
Introduction, Literature Review, and Objectives

The purposes of this chapter are:

1) To provide an outline of this dissertation.

2) To present a literature review of the topics and methodologies presented in this dissertation.

3) To explain the rationale and objectives for this dissertation.

1.1 Outline of thesis

Chapter 1 provides a background literature review about the topic, discusses the rationale for conducting the study, and outlines the objectives of the study.

Chapter 2 addresses the first study question. It presents cost-effectiveness analyses of filgrastim and pegfilgrastim, compared to no intervention, when used for primary prophylaxis against febrile neutropenia (FN) in NHL patients. This analysis used a decision analytic model to combine HRQOL and cost data to estimate incremental cost-effectiveness ratios (ICER) for these two technologies. It was carried out from the perspective of the publicly funded health care system in Ontario. A probabilistic sensitivity analysis was done to test the robustness of the results, and to generate cost-effectiveness acceptability curves.

Chapter 3 addresses the second study question. It presents an algorithm for converting non-preference-based health-related quality of life (HRQOL) data obtained from the Functional Assessment of Cancer Therapy – General (FACT-G) instrument into preference-based HRQOL data, otherwise known as health utility values. Cost-effectiveness analyses incorporate HRQOL
through the use of health utility values; however, they are not commonly elicited from patients. Non-preference-based HRQOL is more often elicited, using disease-specific instruments, as they provide more clinically relevant information. These algorithms will enable data collected from the FACT-G instrument to be used in cost-effectiveness analyses.

Chapter 4 addresses the third study question. It presents results from a discrete choice experiment (DCE) done to elicit preferences for attributes describing outpatient treatment of FN in NHL patients. The attributes examined were out-of-pocket costs, daily unpaid caregiver time required, and probability of return to hospital. Data obtained from this study included relative preferences for the attributes and information on how patients traded off between them. Knowledge related to preferences for outpatient FN care could be incorporated into designing and implementing such programs.

Chapter 5 presents a summary of the findings from the three studies presented in this dissertation. It discusses the significance of the findings and their impact on the prevention and treatment of FN in NHL patients within the Canadian health care system. It also outlines future research that could be undertaken using the results of this work.

1.2 Literature review

This section summarizes the published literature on the following topics:

- Epidemiology and treatment principles of NHL
- Pathophysiology and risk factors for development of FN
- Outpatient management of FN
- Cost-effectiveness analyses and health care decision making
- HRQOL and methods used in its measurement
Eliciting patient preferences for processes of care

Cost-effectiveness analyses of filgrastim and pegfilgrastim when used as primary prophylaxis against FN

Conversion of non-preference-based HRQOL data into preference-based HRQOL data

Patient preferences related to outpatient treatment for FN

1.2.1 Epidemiology and treatment principles of NHL

Non-Hodgkin lymphoma is a term used to describe a variety of malignant solid tumours occurring in the lymphoid tissue, that can be derived from either B-cells or T-cells.\textsuperscript{1} It is estimated that there were 7500 new cases of NHL diagnosed in Canada in 2010. Between the late 1970’s and the late 1990’s, the incidence of this condition has increased by about 50% in Canada, although incidence rates have stabilized since then.\textsuperscript{2} Diffuse large B-cell lymphoma (DLBCL) is the most common histologic subtype of NHL, accounting for approximately 30% of all cases.\textsuperscript{3} The studies presented in this dissertation focus on the B-cell subtypes of NHL.

About 70% of those with DLBCL present with advanced stage disease, defined as either stage III or IV. The mainstay of therapy for advanced DLBCL is systemic chemotherapy using a combination of agents, along with the recombinant anti-CD20 antibody, rituximab\textsuperscript{4}. Since the introduction of combination chemotherapy with cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP), disease free survival rates of 35-45% at four years have been achieved\textsuperscript{5}. The addition of rituximab to the CHOP-based regimen (R-CHOP), has increased overall survival in all age groups by about 10%, beginning one year after initiation of therapy, with almost no increase in adverse effects\textsuperscript{6-8}.

Other B-cell lymphomas, such as follicular lymphoma (FL) and marginal zone lymphoma (MZL), are classified as indolent lymphomas, defined as those in which survival of untreated
patients can be measured in years\(^9\). Patients who present with advanced disease (stages III or IV), however, do require treatment. No standard chemotherapy regimens exist for these NHL subtypes, although a recent study indicates that the majority of FL patients are treated with chemotherapy plus rituximab. R-CHOP or the combination of rituximab, cyclophosphamide, vincristine, and prednisone (R-CVP) were the most common regimens\(^{10}\). In one study, FL patients treated with R-CHOP had a two-year overall survival rate of 95\%\(^{11}\); in another study, those treated with R-CVP had a four-year overall survival rate of 83\%\(^{12}\). Patients with MZL are treated similarly to those with FL, however, the long-term prognosis is poor with a five-year overall survival rate of 50\%; at 10 years, the overall survival rate drops to 20\%\(^5\).

1.2.2 Pathophysiology, risk factors for development of FN, and current treatment practices

FN is serious hematologic toxicity of lymphoma chemotherapy. It is defined as a single oral temperature of \(\geq 38.3^\circ C\) or a temperature of \(\geq 38.0^\circ C\) for at least one hour, combined with an absolute neutrophil count (ANC) of \(< 0.5 \times 10^9/L\), or a count of \(< 1.0 \times 10^9/L\) with a predicted decrease to \(< 0.5 \times 10^9/L\) within the next 48 hours\(^{13}\). Up to 50\% of patients who receive R-CHOP chemotherapy will experience a FN episode\(^8\),\(^{14}\).

Cytotoxic chemotherapy inhibits neutrophil production, diminishing the inflammatory response to developing infections, consequently allowing for bacterial invasion and replication\(^{15}\). A literature review done to identify risk factors for the development of chemotherapy-induced neutropenia and its complications found that dose-intense chemotherapy, advanced age, female sex, poor performance status, poor nutritional status, and low baseline and first-cycle nadir blood cell counts all significantly predicted for the development of neutropenia; high lactate dehydrogenase levels and bone marrow involvement in patients with NHL were also significant\(^{16}\). Significant predictors for the development of neutropenia complications, including
FN, prolonged hospitalization, and death were advanced age, hematologic malignancies, advanced-stage disease and uncontrolled cancer, high temperature, hypotension, pneumonia, IV site infection, laboratory abnormalities (e.g., decreased neutrophil and platelet counts, increased blood urea nitrogen level), organ dysfunction and prolonged neutropenia.\textsuperscript{16}

Although FN can lead to potentially life-threatening complications, some patients who develop this condition are at low-risk of experiencing these complications. Several criteria and risk assessment models have been developed to classify patients as at either high- or low-risk for FN complications. The most widely accepted prediction model was developed by Klastersky et al. for the Multinational Association for Supportive Care in Cancer (MASCC)\textsuperscript{17} The authors identified seven patient- and disease-specific characteristics, evaluated at the time of FN presentation, that significantly predicted clinical outcomes. Each factor was assigned an integer score based on a regression model. The total score for a patient is calculated by adding together the scores for each factor. A higher score corresponds to a lower risk for FN complications. A score of $\geq 21$ identifies patients in the low risk category with a sensitivity of 80%, a specificity of 71% and a positive predictive value of 94%. This model was later validated in a prospectively conducted study\textsuperscript{18}.

The Infectious Diseases Society of America has published guidelines on empiric therapy for patients who present with FN. For patients at high risk for complications they recommend hospitalization and one of the following options for single-agent empiric therapy: 1) an antipseudomonal beta-lactam (e.g., cefepime); 2) a carbapenem (e.g., meropenem); or 3) piperacillin-tazobactam. They suggest the addition of other antimicrobial agents to address any complications (e.g., pneumonia) or antimicrobial resistance. For treatment of patients at low risk of complications they recommend administering initial doses of either oral or intravenous
antibiotics in a hospital or clinic setting, followed by a possible transition to outpatient care if certain criteria, such as the safety and appropriateness of the home environment and availability of prompt access to medical care, are met\textsuperscript{13}. The next section details published studies on outpatient treatment of FN.

1.2.3 Outpatient management of FN

While administration of intravenous antibiotics in hospital remains the mainstay of FN therapy at most centres, several studies evaluating outpatient therapy for FN patients at low risk for complications have been published. A comprehensive search of the published literature was carried out on March 18, 2011 to identify studies evaluating outpatient treatment for FN that met the following criteria:

- Original research study conducted in adult oncology patients being treated for FN at home
- Method for stratifying patients in low-risk FN category had to be identified
- Clinical outcomes following outpatient care must have been reported for all patients included in the study

MEDLINE was searched between the years 2000 and 2011 using the subject heading [subheadings] “Neutropenia” [Classification, Complications, Diagnosis, Drug Therapy, Economics, Epidemiology, Mortality, Prevention & Control, Therapy] combined with the subject headings “Outpatients” or "Length of Stay" or “Patient Discharge” or “Treatment Outcome” or the keyword “early discharge”. EMBASE was searched between the years 2000 and 2011 using the subject heading “Febrile neutropenia” combined with the subject headings “Outpatient” or “Outpatient care” or “Hospital discharge” or “Length of stay” or “Home care”. These searches
were updated with biweekly alerts until February 28, 2013. A total of 296 articles were identified. Figure 1.1 outlines how relevant publications were selected for inclusion in this review.

Of the ten studies that reported outcomes of outpatient FN treatment, only one of the studies was a randomized clinical trial (RCT) comparing outpatient therapy with oral antibiotics to inpatient therapy with intravenous antibiotics. The remaining nine studies were observational studies done in low-risk patients being treated in the outpatient setting; eight were conducted prospectively and one was based on a retrospective review of medical charts. The RCT demonstrated no significant difference in the success rates of treatments between the two groups (p=0.55). The nine observational studies reported rates of re-hospitalizations ranging from 4% to 21%. Table 1.1 provides a detailed summary of the relevant publications.

1.2.4 Cost-effectiveness analyses and health care decision making
Health care decision makers in countries with publicly funded health care system are increasingly requiring economic evaluations of new health technologies before deciding whether to fund them. The Canadian Agency for Drugs and Technologies in Health, the Pharmaceutical Benefits Advisory Committee in Australia, and the National Institute for Health and Clinical Excellence (NICE) in the United Kingdom all require pharmaceutical manufacturers to submit cost-effectiveness analyses for new products under consideration for government reimbursement19-21. The preferred method for quantifying and reporting the cost-effectiveness of a particular technology is by generating incremental cost-effectiveness ratios (ICERs). Effects should be measured in quality-adjusted life years (QALYs), to account to for quality-enhancing as well as life-extending benefits. ICERs are used to compare a new health technology with the next best alternative, and are generated using decision-analytic models to combine the costs and
effects associated with both options. The difference in costs between the two options is then
divided by the difference in effects to generate the ICER\textsuperscript{22}. ICERs are a measure of the
efficiency, or the value returned on money spent, of a particular intervention. Technologies with
ICERs of $50,000 per QALY, or less, are generally considered cost-effective.\textsuperscript{23}

ICERs provide a useful summary measure of the efficiency of a particular health intervention,
which could be used by health care decision makers to allocate resources; however, there are
several challenges associated with how they are generated. First, while HRQOL is now
recognized as an important clinical endpoint in many fields of medicine and is often evaluated in
clinical trials, data on health utility, a summary measure of HRQOL, is often not collected.
Health utility values are required to ascertain QALYs associated with a particular health
intervention, but the generic instruments used to assess health utility often provide less clinically
relevant information that disease-specific HRQOL instruments which tend to be employed more
frequently in clinical trials\textsuperscript{24}. Second, although ICERs account for patients’ preferences for
disease states through the use of QALYs as the standard outcome measure, they do not account
for patients’ preferences with respect to processes of care.\textsuperscript{25,26} For example, several disease states
have more than one treatment modality that yields the same health outcome. One such example
is the treatment of low-risk FN patients who can be either hospitalized or treated on an outpatient
basis. \textsuperscript{27} Further information on addressing these two challenges surrounding ICERs would be
helpful to health care decision makers when evaluating health care programs.

1.2.5 HRQOL and methods used in its measurement
HRQOL refers to the physical, psychological, and social domains of health that are affected by a
person’s experiences, beliefs, expectations, and perceptions.\textsuperscript{28} Measuring HRQOL is important
for a number of reasons. First, laboratory and physiologic measures used to assess disease status
may not correlate well with a patient’s functional status or overall wellbeing\textsuperscript{29}. Second, individual patient may experience similar clinical outcomes as a result of a particular therapy but vast differences in resulting HRQOL\textsuperscript{29}. Third, for some diseases no cure is available and improved HRQOL is the main goal of therapy (e.g., lung cancer)\textsuperscript{30}. Finally, patients may experience significant adverse effects from treatment that could lead to physical or functional impairments\textsuperscript{30}. HRQOL becomes an important tool for evaluating patient response to therapy in each of the above situations.

A variety of instruments have been developed to measure HRQOL, and they can be categorized as being either generic or disease specific. Generic instruments allow for assessment of HRQOL across a number of different disease states and patient populations. Disease-specific instruments are designed to measure HRQOL within a disease state or patient population\textsuperscript{28,29}. Generic instruments allow for comparison of HRQOL between different populations, whereas disease-specific instruments have increased sensitivity to capturing the concerns of a specific patient group\textsuperscript{29,30}. Examples of generic instruments include the Medical Outcomes Study 36-Item Short Form (SF-36) and the EuroQol (EQ-5D). The SF-36 evaluates eight separate health dimensions encompassed within categories of physical health and mental health\textsuperscript{30}. The EQ-5D asks patients to rate their health on three levels in five different domains and to give an overall rating of their health on a visual analog scale (VAS) ranging from 0 to 100\textsuperscript{30}. Information obtained from the EQ-5D can be converted into a health utility value, which is a summary measure of HRQOL that is reported along a continuum of 0.0 to 1.0, where 0.0 represents death and 1.0 represents perfect health\textsuperscript{29}. Utilities are a measure of patient preferences for health states and are assigned values based on societal assessments of various health states\textsuperscript{31}. They are used in cost-effectiveness analyses to calculate QALYs, which combine duration and quality of life\textsuperscript{29}. Examples of disease-specific instruments include the Functional Assessment of Cancer Therapy - General
questionnaire (FACT-G) and the European Organization for Research and Treatment of Cancer QLQ-C30 questionnaire. The FACT-G asks cancer patients to rate their health on four sub-scales each containing seven items. The QLQ-C30 is asks cancer patients to rate their health on five functional scales, three symptom scales, one global health status scale and several single-item scales.  

1.2.6 Eliciting patient preferences for processes of care

Eliciting patient preferences for processes of care would enhance benefits to patients and help health care decision makers when deciding how to allocate funds for the design and implementation of new programs. Discrete choice experiments (DCE) have been widely used to elicit consumer preferences in fields such as marketing and economics and are now increasingly being used in health services research to elicit patient preferences. They are based on the assumption that a particular product or service can be described by its attributes and that an individual’s preference for this product or service depends on the levels of these attributes. DCEs provide researchers with a method to quantify patient preferences beyond health outcomes and the QALY framework. They provide information on which attributes are important to patients and how patients trade-off between different attributes. They also allow for the relative ranking of the different attributes being evaluated.

The first step involved in designing a DCE is to determine the attributes and their corresponding levels that will be evaluated. This step usually involves searching the published literature and/or interviewing individual patients. Once the attributes and levels have been established, choice sets that will be presented to patients must be defined. Presenting a complete set of choices, representing all combinations of attributes and levels, is often impractical, as a large number of sets would have to be generated. Recently, several authors have published statistically efficient
designs to help construct choice sets for DCEs\textsuperscript{35,36}. Choice sets are presented to patients in a paired format and they are asked to indicate their preferred option either by using a scale to indicate strength of preference or choosing one alternative over the other\textsuperscript{32}. Regression analysis is used to analyze patient responses; the type of data collected determines the most appropriate regression model to employ for the analysis\textsuperscript{32,34}.

1.2.7 Cost-effectiveness analyses of filgrastim and pegfilgrastim when used as primary prophylaxis against FN

Filgrastim and pegfilgrastim are two granulocyte-colony stimulating factors (G-CSF) that have been established as efficacious in preventing FN\textsuperscript{37}. Several cost-effectiveness analyses evaluating these drugs, when used as primary prophylaxis against chemotherapy-induced FN, have been published. A comprehensive search of the medical literature was done on March 23, 2011 to identify cost-effectiveness evaluations of filgrastim and pegfilgrastim that met the following criteria:

- Adult oncology patient population undergoing chemotherapy
- Filgrastim and/or pegfilgrastim used as primary prophylaxis against FN
- Outcomes reported in QALYs

MEDLINE was searched between the years 2000 and 2011 using the subject heading ‘Neutropenia’ combined with the subject heading ‘Costs and Cost Analysis’. In a separate search the subject heading [subheading] ‘Lymphoma [Economics]’, was combined with the subheadings ‘Neutropenia [Economics]’, and ‘Filgrastim [Economics]’. EMBASE was searched between the years 2000 and 2011 using the subject heading “recombinant granulocyte colony stimulating factor” combined with the subheadings “cost effectiveness analysis” and “febrile
neutropenia”. These searches were updated with biweekly alerts until February 28, 2013. A total of 93 articles were identified. Figure 1.2 outlines how relevant publications were selected for inclusion in this review.

The seven published cost-effectiveness analyses of examining the use of pegfilgrastim as primary prophylaxis against FN all reported ICERs of less than $50,000/QALY when converted into Canadian dollars. Four of the analyses were conducted using data from the United States, one was conducted using Italian data, one used data from the UK, and one used data from the UK and France to generate two separate ICER estimates. All of the analyses assumed an FN-related mortality benefit and some analyses also assumed a long-term mortality benefit associated with G-CSF use, which has not been demonstrated in clinical trials or meta-analyses. One cost-effectiveness analysis meeting the search criteria was identified for filgrastim. This analysis did not assume an FN-related mortality benefit and yielded an ICER estimate much higher that the pegfilgrastim analyses that did. Cleary incorporating this assumption the pegfilgrastim analyses resulted in lower ICERs compared to the filgrastim analysis in which no mortality benefit was assumed. Table 1.2 provides a summary of the eight relevant cost-effectiveness analyses identified.

1.2.8 Algorithms for converting non-preference HRQOL measures into preference-based HRQOL measures

Health-related quality of life (HRQOL) is an important measure of health outcome in patients with non-Hodgkin lymphoma (NHL). Cost-effectiveness analyses incorporate health utility, a preference-based summary measure of HRQOL, through the use of quality-adjusted life years (QALYs). However, health utility scores are elicited using generic HRQOL instruments that are not commonly employed, since cancer specific HRQOL instruments generally provide more clinically relevant information. Mapping is a technique now commonly used to predict health
utility values from non-preference based HRQOL data. A comprehensive search of the medical literature was done on September 20, 2011 to identify studies presenting algorithms for converting non-preference based HRQOL measures into health utility values, that met the following criteria:

- Data collected from one or more non-preference based HRQOL instruments was converted into health utility values based on the generic EQ-5D instrument, and;
- The analysis had to be done in oncology patients.

MEDLINE was searched between the years 2000 and 2011 using the keyword ‘EQ-5D’ combined with the keywords ‘mapping’ or ‘derivation’ or ‘converting’. The search was restricted to studies done in humans and written in English; review articles were also excluded from the search. EMBASE was searched between the years 2000 and 2011 using the same keywords detailed above. The same restrictions, as used in the MEDLINE search were applied to this search. These searches were updated with biweekly alerts until February 28, 2013. A total of 47 articles were identified. Figure 1.3 outlines how relevant publications were selected for inclusion in this review.

All of the publications that presented algorithms for converting non-preference based HRQOL data into health utility values in oncology patients used regression analysis. None of these studies, however, were done in lymphoma patients. Table 1.3 provides a summary of the five relevant mapping analyses that were identified.

1.2.9 Patient preferences related to outpatient treatment of FN

In-hospital treatment is the mainstay of therapy for patients who develop FN. However, as noted in section 1.2.3 above, several studies have indicated that outpatient treatment is a safe and
effective alternative for treatment in low-risk FN patients. A comprehensive search of the medical literature was done on April 2, 2011 to identify publications that evaluated patient preferences for outpatient treatment of FN. MEDLINE was searched between the years 2000 and 2011 using the subject heading ‘Neutropenia’ combined with the subject heading ‘Outpatients’ and subsequently combined with the subject headings ‘Attitude to Health’ or ‘Cost-Benefit Analysis’ or ‘Health Services Needs and Demand’ or ‘Health Expenditures’ or ‘Questionnaires’. EMBASE was searched between the years 2000 and 2011 using the subject heading “febrile neutropenia” combined with the subject headings “outpatient” or “outpatient care” or “outpatient department” and the keyword “preference”. These searches were updated with biweekly alerts until February 28, 2013.

One relevant article was identified by Sung et al42. This study examined preferences for inpatient versus outpatient treatment for FN in the pediatric population. This study was based on interviews with parents and healthcare professionals caring for children with low-risk FN. They were asked whether they would prefer inpatient or outpatient treatment for FN based on four attributes: 1) frequency of clinic visits, 2) probability of admission to hospital, 3) risk of ICU admission, and 4) risk of mortality. They were also asked how seven factors would affect their choice to of inpatient versus outpatient treatment. These factors included 1) fear and/or anxiety; 2) comfort with surroundings at home or hospital; 3) needs of other family members; 4) travel issues; 5) work issues; 6) child does not like taking pills or is afraid of needles; and 7) cost issues. Outpatient management was favoured by 53% of parents and 71% of health care professionals; this difference was not statistically significant (p=0.08). Parents who favoured outpatient treatment anticipated higher quality of life associated with home-based treatment, placed a higher importance on comfort, and expressed less fear and/or anxiety. Health care
professionals who favoured outpatient care tended to rank fear and/or anxiety lower than those who did not.

1.3 Study rationale and objectives

NHL is currently the fifth most common type of cancer in Canada, and its incidence doubled in the 20-year period from the late 1970’s to the late 1990’s. FN is a common side effect of chemotherapy regimens used to treat this malignancy. Currently in Canada there are two hematopoietic growth factors, filgrastim and pegfilgrastim, available for use as prophylaxis against FN. These agents are expensive with a single daily 300mcg dose of filgrastim costing $144; normally this medication is used for 5 to 12 days following each cycle of chemotherapy. Pegfilgrastim is a long-acting agent that is administered as a single dose following each chemotherapy cycle, which costs $2645. Currently, the Ontario government does not cover the cost of either of these medications when used as primary prophylaxis against FN; however, patients with private insurance plans may be eligible for coverage of one or both of these medications. No cost-effectiveness analyses have been done in Canada to estimate the ICERs associated with filgrastim or pegfilgrastim use for primary prophylaxis against FN. Cost-effectiveness analyses for these two medications will help inform decisions on whether they should be publicly funded for all patients or not.

Algorithms for converting non-preference based HRQOL measures, obtained from commonly used disease-specific instruments, into preference-based health utility values will enable these data to be incorporated into cost-effectiveness analyses.

For patients who do develop FN, the mainstay of therapy is hospitalization and treatment with intravenous antibiotics, despite the fact that studies demonstrate outpatient therapy for low-risk patients is a safe and effective alternative. While ICERs incorporate patient preferences for
disease states through the use of QALYs to express outcomes, but they do not account for patient preferences for processes of care. This information would be helpful to health care decision makers when establishing programs for outpatient FN management.

The goals of this thesis were to employ methods used in medical decision making to evaluate the cost-effectiveness of G-CSFs for prevention of FN and to demonstrate how two limitations of cost-effectiveness analyses, the lack of published health utility data available and the fact that the QALY framework does not account for patient preferences regarding processes of care, can be addressed.

The specific objectives of this thesis are

1) To examine the cost-effectiveness of filgrastim and pegfilgrastim, relative to no intervention, as primary prophylaxis against FN in NHL patients from the perspective of a publicly financed health care system;

2) To develop algorithms to convert non-preference-based HRQOL data obtained from the FACT-General instrument in NHL patients into preference-based health utility values derived from the EQ-5D instrument, and;

3) To quantify NHL patients’ preferences for attributes describing outpatient treatment of FN using a discrete choice experiment.
Table 1.1: Summary of studies evaluating outpatient therapy for febrile neutropenia

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<tr>
<td>Sebban et al., 2008(^4^4)</td>
<td>France</td>
<td>Solid tumour, lymphoma, myeloma (90 patients, 96 FN episodes) (2 episodes could not be evaluated)</td>
<td>• MASCC score ≥ 21  • Received chemo in previous month  • 18 years or older  • Oral temp ≥ 38.5 once or ≥ 38 twice in 12h  • ANC &lt; 0.5 or &lt; 1 with predicted decrease  • No symptoms of septic shock  • No contraindications to antibiotics  • Able to take oral medications</td>
<td>MASCC score</td>
<td>Randomization to oral moxifloxacin or IV ceftriaxone with patients being discharged for outpatient care after 1st antibiotic dose if clinically stable</td>
<td>• 34 of 46 episodes (73.9%) in ceftriaxone arm, and 38 of 48 episodes (79.2%) in moxifloxacin arm treated successfully  • 7 episodes not discharged by 48h  • 14 episodes required re-hospitalization (9 in ceft, 5 in moxi)</td>
<td>• No comparison to inpatient treatment  • Sample size insufficient to demonstrate equivalence of oral and IV therapies  • Poor study recruitment</td>
</tr>
<tr>
<td>Elting et al., 2008(^4^5)</td>
<td>US</td>
<td>Solid tumours (712; 1 FN episode only per patient)</td>
<td>• Underlying solid tumour  • Registered on low-risk FN pathway between 1997 and 2003  • Low risk patients</td>
<td>M.D. Anderson low-risk pathway</td>
<td>Retrospective chart review of FN episodes treated as</td>
<td>• 79% of inpatients and 80% of outpatients treated successfully  • 21% of</td>
<td>• Retrospective design  • Many more outpatients than inpatients included in study</td>
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| Klastersky et al., 2006<sup>46</sup> | Belgium | All types of cancer (mostly solid tumours enrolled in study) (178) | • MASCC score ≥ 21  
• Not on antibiotic prophylaxis at fever onset  
• Able to take oral medications | MASCC score | Prospective, observational study of low-risk FN episodes treated with oral amoxicillin-clavulanate and ciprofloxacin and eligible for early discharge | • 79 of 178 patients discharged early (<2 days in hospital; mean LOS 26h)  
• No serious medical complications in patients discharged early, but 3 re-admissions required  
• 99 remained in hospital due to reluctance of physician, family, or patient refusal  
• 9 of 99 hospitalized patients had | • Observational study  
• Single centre |
|-------------|---------|------------------------|--------------------|-------------------------------|-----------------|----------|-------------|
| Cherif et al., 2006<sup>47</sup> | Sweden | Hematologic malignancies (predominantly acute leukemia and NHL) (105) | • Hematologic malignancy  
• Temperature >38 twice in 4 hours or > 38.5 once  
• ANC < \(=\) 0.5  
• MASCC score \(\geq\) 21 | MASCC score | Prospective, observational study of LR patients with FN (initial treatment with IV antibiotics, switch to oral antibiotics in 24h if clinically stable)  
**oral antibiotic regimen tailored to individual patient** | • 105 of 279 (38%) FN episodes were LR  
• 38 LR episodes not eligible for oral antibiotics and thus no early discharge  
• 67 episodes ended with early discharge 24h after defervescence  
• 3 of 67 patients had to be re-admitted to hospital, but no deaths in this group  
• Mean LOS for early discharge group = 3.8d | serious medical complication  
• Observational study  
• Single centre |
|---------------------|-----------|------------------------|-------------------------------------------------------------------------------------|--------------------------------|-----------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------|----------------------------------------|
| Innes et al., 2008  | England   | Solid tumours and lymphomas | • MASCC score ≥ 21  
• Temperature >38 twice or > 38.5 once  
• ANC < =0.5 or < = 1 with predicted decrease  
• Able to take oral antibiotics  
• Not on oral antibiotics at fever onset | MASCC score                        | Prospective, observational study of LR FN episodes eligible for early hospital discharge 24h after admission if clinically stable | • 90 of 100 episodes LR  
• 75 of 90 LR episodes eligible for oral antibiotics and early discharge  
• 87 of 90 LR episodes had no serious medical complications  
• 3 re-admissions of 75 early discharges  
• No deaths in LR group  
• Median LOS for early discharge group 2d | • Single centre                      |
| Innes et al., 2003  | England   | Solid tumours and lymphomas (126) | • Temperature >38 twice in 4 hours or > 38.5 once  
• ANC<0.5 or <1 with predicted decrease  
• Hemodynamically stable | Defined by authors (modification of Talcott criteria) | Randomized clinical trial of outpt oral antibiotics after being in  
• Successful treatment of 90% of episodes in IV arm and 84.8% of episodes in oral arm (p=0.55) | | • Single centre  
• Mostly solid tumour patients  
• Number of FN episodes screened not reported |
|-------------|---------|------------------------|-------------------|-------------------------------|-----------------|----------|-------------|
| Rolston et al., 2006<sup>50</sup> | US      | Breast cancer and sarcoma (40) | • LR FN episode as defined by study criteria  
• Residence within 30 miles  
• 24-hour telephone access and adult caregiver  
• Permission of primary care physician | Talcott grouping with additional criteria | Prospective, observational study of LR FN patients treated as outpatients with gatifloxacin | • 38 of 40 patients responded to gatifloxacin  
• 3 patients required hospitalization  
• No deaths | • Single centre  
• Small sample size  
• Number of patients screened not reported |
<table>
<thead>
<tr>
<th>Chamilos et al.</th>
<th>Greece</th>
<th>Solid tumours</th>
<th>• MASCC score ≥ 21</th>
<th>MASCC score</th>
<th>Prospective, observational study</th>
<th>• 5 of 55 episodes</th>
<th>• Observational study</th>
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<tr>
<td>al., 200551</td>
<td></td>
<td>and hematologic malignancies (55)</td>
<td>• Not receiving antibiotics within previous 7 days • Lives within 1 hour of hospital</td>
<td>observational study of LR FN outpatients treated with moxifloxacin</td>
<td>required hospitalization • No deaths</td>
<td>• Small sample size • Number of patients screened not reported</td>
<td></td>
</tr>
<tr>
<td>Escalante et al., 200452</td>
<td>US</td>
<td>Solid tumours (257)</td>
<td>• Solid tumour • Expected duration neutropenia, 1 week • Temperature &gt; 38 • ANC &lt; 1 • Lives within 30 miles of hospital • Has a 24h adult caregiver</td>
<td>MD Anderson low-risk pathway</td>
<td>Prospective, observational study of LR FN outpatients treated with oral or IV antibiotics</td>
<td>• 251 episodes treated with oral antibiotics, 6 episodes treated with IV antibiotics • 52 episodes required hospital admission with median LOS of 5d • 198 of 205 episodes treated successfully as outpatients 198 did not require antibiotic modification</td>
<td>• Observational study • Single centre • Number of patients screened not reported</td>
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</table>
| Mizuno et al., 2007<sup>53</sup> | Japan | Breast cancer (30) | • Expected duration of neutropenia < 10 days  
• No serious co-morbidity  
• ECOG performance status 0 or 1  
• Able to take oral medication  
• Controlled cancer  
• No signs, besides fever, of systemic infection | As defined by investigators | Prospective, observational study of LR FN episodes treated with oral antibiotics as outpatients | • 30 of 35 FN episodes LR  
• 27 of 30 LR episodes treated successfully as outpatients  
• Of 3 failures, 2 required change in antibiotics and 1 required G-CSF support | • No deaths or significant morbidity  
• Small sample size  
• Non-standard criteria used to define LR episodes |
Table 1.2: Summary of cost-effectiveness analyses of granulocyte-colony stimulating factors

<table>
<thead>
<tr>
<th>Study, Year</th>
<th>Country</th>
<th>Patient Population</th>
<th>Perspective</th>
<th>Model comparators &amp; assumptions</th>
<th>ICER (in CAD*)</th>
<th>Limitations</th>
</tr>
</thead>
</table>
| Eldar-Lissai et al., 2008<sup>54</sup> | United States | Mixed adult oncology patients with solid tumours | Societal | • Pegfilgrastim compared to 7 to 12-day filgrastim as primary prophylaxis  
• 21 day model time horizon  
• Assumed mortality benefit associated with pegfilgrastim | • Pegfilgrastim dominant compared to filgrastim and no prophylaxis strategies | • Time horizon only one course of chemotherapy  
• No evidence of mortality benefit with pegfilgrastim use even though assumed in model |
| Danova et al., 2009<sup>55</sup> | Italy | Breast cancer | Italian National Health System | • Pegfilgrastim primary compared to 6-day filgrastim as primary prophylaxis  
• Lifetime model time horizon  
• Assumed mortality benefit associated with pegfilgrastim | • €429/QALY ($590) | • No evidence of mortality benefit with pegfilgrastim use even though assumed in model |
| Borget et al., 2009<sup>56</sup> | France and United Kingdom | Breast cancer | French and UK health care payer | • Pegfilgrastim compared to 6-day and 11-day filgrastim as primary prophylaxis  
• Lifetime model time horizon  
• Assumed mortality benefit associated with pegfilgrastim | • Pegfilgrastim dominant compared to 11-day filgrastim in France and UK  
• €10,810/QALY ($14,866) compared to 6-day filgrastim in France  
• £4,161/QALY ($6,491) in UK | • No evidence of mortality benefit with pegfilgrastim use even though assumed in model |
<table>
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<tr>
<th>Study, Year</th>
<th>Country</th>
<th>Patient Population</th>
<th>Perspective</th>
<th>Model comparators &amp; assumptions</th>
<th>ICER (in CAD*)</th>
<th>Limitations</th>
</tr>
</thead>
</table>
| Liu et al., 2009<sup>57</sup> | United Kingdom        | Breast cancer      | UK National Health Service | • Pegfilgrastim compared to 6-day filgrastim as primary prophylaxis  
• Lifetime model time horizon  
• Three scenarios modelled: one assumed no mortality benefit; second assumed FN mortality benefit; third assumed long-term survival benefit | • £4,200/FN episode avoided ($6,552) with no additional mortality benefit assumed  
• £8,526/QALY ($13,300) when FN mortality benefit assumed  
• £4,161/QALY ($6,491) when long-term mortality benefit assumed | • ICER not reported as cost/QALY when no mortality benefit assumed so cannot be used for comparison  
• No evidence of mortality benefit with pegfilgrastim use even though assumed in model |
| Lyman et al., 2009<sup>58</sup> | United States         | Breast cancer      | Health payer          | • Pegfilgrastim compared to 6-day and 11-day filgrastim as primary prophylaxis  
• Lifetime model time horizon  
• Three scenarios modelled: one assumed no mortality benefit; second assumed FN mortality benefit; third assumed long-term survival benefit | • Pegfilgrastim always dominant over 11-day filgrastim  
• $12,904/FN episode avoided ($13,382) with no mortality benefit  
• $31,511/QALY ($32,690) with FN mortality benefit  
• $14,415/QALY ($14,950) with long-term survival benefit | • ICER not reported as cost/QALY when no mortality benefit assumed so cannot be used for comparison  
• No evidence of mortality benefit with pegfilgrastim use even though assumed in model |
<table>
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<tr>
<th>Study, Year</th>
<th>Country</th>
<th>Patient Population</th>
<th>Perspective</th>
<th>Model comparators &amp; assumptions</th>
<th>ICER (in CAD*)</th>
<th>Limitations</th>
</tr>
</thead>
</table>
| Lyman et al., 2009<sup>59</sup> | United States | Non-Hodgkin lymphoma | Health insurer    | • Pegfilgrastim compared to 6-day filgrastim as primary prophylaxis  
• Lifetime model time horizon  
• Three scenarios modelled: one assumed no mortality benefit with pegfilgrastim; second assumed FN mortality benefit; third assumed additional long-term survival benefit | • $5,532/LYG ($5,737) with no additional mortality benefit assumed  
• $6,190/QALY ($6,419) when additional FN mortality benefit assumed  
• $1,677/QALY ($1,739) when long-term mortality benefit assumed | • ICER not reported as cost/QALY when no mortality benefit assumed so cannot be used for comparison  
• No evidence of mortality benefit with pegfilgrastim use even though assumed in model |
| Ramsey et al., 2009<sup>60</sup> | United States | Breast cancer      | Health insurer    | • Pegfilgrastim primary prophylaxis compared to pegfilgrastim secondary prophylaxis  
• Lifetime model time horizon  
• Two scenarios modelled: one assumed no mortality benefit with pegfilgrastim; second assumed mortality benefit | • $48,000US/FN episode avoided ($49,584) with no mortality benefit  
• $116,000US/QALY ($119,828) when mortality benefit assumed | • ICER not reported as cost/QALY when no mortality benefit assumed so cannot be used for comparison  
• No evidence of mortality benefit with pegfilgrastim use |
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<tr>
<th>Study, Year</th>
<th>Country</th>
<th>Patient Population</th>
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<th>ICER (in CAD*)</th>
<th>Limitations</th>
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<tbody>
<tr>
<td>Chan et al., 2012&lt;sup&gt;61&lt;/sup&gt;</td>
<td>Canada</td>
<td>Diffuse large B-cell lymphoma</td>
<td>Health system</td>
<td>• 10 days of filgrastim prophylaxis compared to secondary prophylaxis • No mortality benefit with filgrastim assumed</td>
<td>• $700,500/QALY</td>
<td>• Indirect costs not borne by health system not accounted for • Utility value used for FN health state not obtained from direct measurement in patient; surrogate value obtained from nurses used.</td>
</tr>
</tbody>
</table>
Table 1.3: Summary of algorithms for converting non-preference-based HRQOL measures into health utility values

<table>
<thead>
<tr>
<th>Study, Year</th>
<th>Patient Population and Sample Size (N)</th>
<th>Non-Preference Based HRQOL* Instrument(s) Used</th>
<th>Results</th>
<th>Limitations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jang et al., 201062</td>
<td>Non-small cell lung cancer (N=172)</td>
<td>EORTC QLQ-C30†</td>
<td>QLQ-C30 dimensions of physical functioning, role functioning, emotional functioning, social functioning and pain best predicted health utility score.</td>
<td>Small sample size.</td>
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<tr>
<td></td>
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<td></td>
<td>Adjusted R² for model = 0.58.</td>
<td>No test for external validity.</td>
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<td>High utility scores that may reflect biased sample.</td>
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<tr>
<td>Crott et al., 201063</td>
<td>Locally advanced breast cancer (N=220, with repeated observations)</td>
<td>EORTC QLQ-C30†</td>
<td>Final model included QLQ-C30 dimensions of physical functioning, emotional functioning, social functioning, pain, insomnia, constipation, and diarrhea.</td>
<td>No external dataset to test for validity.</td>
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<td>Some outliers dropped from dataset because could no distinguish whether they were coding errors or not.</td>
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<td>Model overestimation of observed utilities less than 0.5</td>
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<tr>
<td>Kontodimopoulos</td>
<td>Gastric cancer</td>
<td>EORTC QLQ-C30†</td>
<td>QLQ-C30 dimensions of physical</td>
<td>Very small sample size.</td>
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<tr>
<td>Study, Year</td>
<td>Patient Population and Sample Size (N)</td>
<td>Non-Preference Based HRQOL* Instrument(s) Used</td>
<td>Results</td>
<td>Limitations</td>
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<td>et al., 2009&lt;sup&gt;64&lt;/sup&gt;</td>
<td>(N=48)</td>
<td>functioning, emotional functioning, and global health status were significant predictors of EQ-5D health utility.</td>
<td>Adjusted R² for model = 0.611.</td>
<td>No external dataset to test for validity.</td>
</tr>
<tr>
<td>McKenzie, et al., 2009&lt;sup&gt;65&lt;/sup&gt;</td>
<td>Inoperable esophageal cancer (N=199, with repeated observations)</td>
<td>EORTC QLQ-C30&lt;sup&gt;†&lt;/sup&gt;</td>
<td>QLQ-C30 dimensions of global health status, role functioning, emotional functioning, cognitive functioning, pain, and fatigue were significant predictors of EQ-5D values.</td>
<td>Predicted mean EQ-5D value is higher than actual value by mean of 0.014; actual value of 0.76 is just inside 95% confidence interval of predicted values, which ranges from 0.76 to 0.788.</td>
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<tr>
<td>Study, Year</td>
<td>Patient Population and Sample Size (N)</td>
<td>Non-Preference Based HRQOL* Instrument(s) Used</td>
<td>Results</td>
<td>Limitations</td>
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<tr>
<td>Wu et al., 200766</td>
<td>Metastatic hormone-refractory prostate cancer (N=280, with repeated observations)</td>
<td>EORTC QLQ-C30† and FACT-P‡</td>
<td>QLQ-C30 and FACT-P scores combined in various models tested. Best fitting model was that which included QLQ-C30 component scores and FACT-P individual component scores without interactions between HRQOL measures and demographic variables.</td>
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<tr>
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<td>Adjusted R² for model = 0.732.</td>
<td>Lack of racial diversity in study group (98% white subjects).</td>
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<td>Cross-validation R² for model = 0.582.</td>
<td>Study did not address how predicted EQ-5D results compared to observed results.</td>
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<td></td>
<td>Need data from both QLQ-C30 and FACT-P in order to use algorithm</td>
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</tbody>
</table>
Figure 1.1: Flowchart of literature search for publications evaluating outpatient treatment of FN

Number of publications identified with initial search criteria
(N=296)

- Excluded publications: reviews, editorials, practice guidelines, commentaries, or letters to the editor (N=73)
- Excluded publications: pediatric population (N=124)
- Excluded publications: Outpatient FN treatment outcomes not evaluated or reported (N=89)
- Included publications: Outpatient FN treatment outcomes reported (N=10)
Figure 1.2: Flowchart of literature search of cost-effectiveness analyses of filgrastim and pegfilgrastim

Number of publications identified with initial search criteria
(N=93)

Excluded publications: reviews, editorials, practice guidelines, commentaries, or letters to the editor
(N=31)

Excluded publications: Other type of analysis (non-cost-effectiveness analysis)
(N=49)

Excluded publications: Cost-effectiveness analyses not reporting outcomes as QALYs
(N=5)

Included publications: Cost-effectiveness analyses with outcomes reported as QALYs
(N=8)
Figure 1.3: Flowchart of literature search of algorithms for converting HRQOL data into health utility values

Number of publications identified with initial search criteria
(N=47)

Excluded publications:
- Review articles
  (N=2)

Excluded publications: non-oncology patient population
(N=24)

Excluded publications: no mapping algorithm presented
(N=16)

Included publications: mapping algorithm presented in oncology patients
(N=5)
Chapter 2 : Cost-effectiveness analysis of filgrastim and pegfilgrastim as primary prophylaxis against febrile neutropenia in lymphoma patients

Submitted for publication in manuscript form:

2.1 Abstract

**Background:** Febrile neutropenia is a serious toxicity of cancer chemotherapy that is usually treated in hospital. We assessed the cost-effectiveness of filgrastim and pegfilgrastim as primary prophylaxis against febrile neutropenia in diffuse large B-cell lymphoma (DLBCL) patients undergoing chemotherapy.

**Methods:** We used a Markov model that followed patients through induction chemotherapy, to compare the three prophylaxis strategies: 1) no primary prophylaxis against febrile neutropenia; 2) primary prophylaxis with 10 days of filgrastim therapy; and 3) primary prophylaxis with a single dose of pegfilgrastim. The target population was a hypothetical cohort of 64-year-old men and women with DLBCL. Data sources included published literature and current clinical practice. The analysis was conducted from a publicly funded health care system perspective. The main outcome measures included costs, quality-adjusted life years (QALYs), and incremental cost-effectiveness ratios (ICERs).

**Results:** In the base-case analysis costs associated with no primary prophylaxis, primary prophylaxis with 10 days of filgrastim, and primary prophylaxis with pegfilgrastim were $6655, $11918, and $17546, respectively; the QALYs associated with the three strategies were 0.2004, 0.2015, and 0.2024, respectively. The ICER for the filgrastim versus no primary prophylaxis strategy was $4,599,000/QALY; the ICER for the pegfilgrastim versus filgrastim primary prophylaxis strategy was $6,272,000/QALY. All 1-way sensitivity analyses yielded ICERs above $1,000,000/QALY. Cost-effectiveness acceptability curves show that 20% of iterations are cost-effective at a willingness-to-pay threshold of $1,260,000 for the filgrastim strategy, and $1,490,000 for the pegfilgrastim strategy.
**Conclusions:** Primary prophylaxis against febrile neutropenia with either filgrastim or pegfilgrastim is not cost-effective in DLBCL patients.
2.2 Introduction

Non-Hodgkin Lymphoma (NHL) is the seventh most common malignancy in the United States.\textsuperscript{67} The incidence of this disease has increased by about 20\% in the 2 decades since 1987.\textsuperscript{68} Diffuse large B-cell lymphoma (DLBCL) is the most common subtype of NHL, accounting for approximately 25\% of cases.\textsuperscript{3} Initial standard treatment for DLBCL includes combination chemotherapy with cyclophosphamide, doxorubicin, vincristine, prednisone, and rituximab (R-CHOP). This regimen yields 5- and 10-year survival rates of 51\% and 45\%, respectively.\textsuperscript{7,69}

Febrile neutropenia is a serious toxicity that can result from R-CHOP chemotherapy, and is typically treated in hospital with intravenous antibiotics.\textsuperscript{13} Several clinical trials have shown that up to 50\% of patients who are treated with the R-CHOP chemotherapy regimen experience a febrile neutropenia episode.\textsuperscript{8,14}

There are two granulocyte-colony stimulating factors (G-CSFs), filgrastim and pegfilgrastim, currently available that have demonstrated efficacy in preventing febrile neutropenia.\textsuperscript{37} The American Society of Clinical Oncology currently recommends using a G-CSFs with all chemotherapy regimens associated with a 20\% or greater incidence of febrile neutropenia. They also specifically recommend G-CSF support for all NHL patients over the age of 65 who are receiving CHOP-based chemotherapy since the risk of neutropenia increases with age. The authors of these guidelines explicitly state that their recommendations were based on clinical evidence showing that G-CSFs reduce the occurrence of febrile neutropenia, not economic evidence, and note that further research into the cost implications of G-CSF use is needed.\textsuperscript{70}

While several cost-effectiveness analyses evaluating pegfilgrastim have been published recently,\textsuperscript{54-60} all of them assumed a mortality benefit associated with G-CSF use despite the fact that randomized clinical trials in lymphoma patients have not demonstrated a survival benefit
with these therapies.\textsuperscript{38,71,72} One recently published cost-effectiveness analysis did not assume a mortality benefit with G-CSF use, but this analysis examined only the cost-effectiveness of filgrastim.\textsuperscript{61}

The objective of this study was to determine whether primary prophylaxis against febrile neutropenia, using either filgrastim or pegfilgrastim in lymphoma patients undergoing chemotherapy, is cost-effective from the perspective of the publicly funded health care system in Ontario, Canada, given the lack of mortality benefit associated with these interventions. We conducted a cost-effectiveness analysis to estimate the incremental cost-effectiveness ratios (ICERs) of filgrastim and pegfilgratim when used as primary prophylaxis against febrile neutropenia, compared to no primary prophylaxis, in DLBCL patients receiving R-CHOP chemotherapy.

2.3 Methods

We used a decision analytic model to estimate the health benefits and costs of using filgrastim and pegfilgrastim as primary prophylaxis against febrile neutropenia compared to no primary prophylaxis, in patients receiving induction chemotherapy for DLBCL. Recommendations for conducting and reporting cost-effectiveness analyses by Philips et al. were followed.\textsuperscript{73} Research ethics board approval for this study was not required since no patient level data was used.

2.3.1 Model cohort, health states, and costs

We constructed a Markov model that followed a cohort of patients over the course of their initial chemotherapy using the R language and environment for statistical computing (R Foundation for Statistical Computing), version 2.14.1 (http://www.r-project.org/). Patients newly diagnosed with DLBCL receiving induction chemotherapy with R-CHOP were evaluated in this analysis.
The base-case analysis considered a cohort of 64-year-old men and women, reflecting the median age of diagnosis. Equal proportions of patients in all International Prognostic Index categories were included. This index is a tool used to predict long-term survival of DLBCL patients; scores range from zero to five, where lower scores represent a greater chance of survival.

Costs and health utilities associated with the health states of febrile neutropenia secondary to chemotherapy and no febrile neutropenia while receiving chemotherapy were included in the model. No other health states were incorporated into the model for several reasons. First, several studies have demonstrated that relapse-free survival and overall survival rates are no different between lymphoma patients who receive G-CSF with chemotherapy and those who do not. Furthermore, a meta-analysis of 148 studies examining the effects of G-CSF in patients with various types of malignancies showed no difference in all-cause mortality between patients who received G-CSFs and those who did not. Second, no fatalities as a result of filgrastim or pegfilgrastim have occurred. Third, the only reported adverse effect of G-CSF was musculoskeletal pain in less than 10% of patients, which was treated with simple analgesics and did not lead to any patients discontinuing G-CSF therapy. Fourth, there was no difference in chemotherapy-related adverse events between patients who received G-CSF and those who did not. Finally, reduction of chemotherapy doses or delays in administration for cycles following an febrile neutropenia episode as a strategy to prevent future febrile neutropenia episodes in DLBCL patients did lead to significantly lower relative dose intensities, but this difference did not lead to an overall lower complete response rate or worse overall survival. Although including a death state in this model would have allowed us to quantify any uncertainty in overall survival that might be related to G-CSF use, this uncertainty is so small that it is clinically meaningless.
A cycle length of 3 weeks was used which represents the time between chemotherapy cycles.

The time horizon of the model was 18 weeks, which represents the total time over which the six chemotherapy cycles are administered. A lifetime time horizon was not used, as G-CSFs are solely supportive care therapies that have no effects, either beneficial or adverse, once the course of chemotherapy has been completed. Health outcomes are reported in quality-adjusted life days (QALDs) as well as quality-adjusted life years (QALYs) because of the model’s short time horizon.

Costs were considered from the Ontario Ministry of Health and Long-Term Care perspective the government ministry responsible for public funding of health care in Ontario, and are reported in 2010 Canadian dollars. No discounting was applied to costs and health benefits because the model time horizon was less than one year.

2.3.2 Data sources

Estimates of costs, health utility values and probabilities were based on published literature where possible. Table 2.1 outlines parameter values used in the model and their sources.

*Meta-analyses*

We identified three published meta-analyses that examined the effectiveness of G-CSF. The results of these studies, however, were not used in this analysis for several reasons. First, they included studies in patients with both solid tumours and hematologic malignancies. Second, they included studies that examined the effectiveness of not only filgrastim, but also of lenograstim and pegfilgrastim. Finally, one of the studies done in lymphoma patients included in all of these meta-analyses did not report the incidence of febrile neutropenia as an outcome, yet was included in the calculation of the risk of febrile neutropenia.
We conducted a separate meta-analysis to estimate the probability of experiencing a febrile neutropenia episode in lymphoma patients when receiving primary prophylaxis with filgrastim and when receiving no primary prophylaxis. A systematic review of the literature was done using the MEDLINE database. The search included articles published between the years 1990 to 2011 to identify clinical trials examining the efficacy of filgrastim for preventing febrile neutropenia in lymphoma patients. The subject headings ‘lymphoma’ and ‘granulocyte-colony stimulating factor’ were combined in the search process. In order to be included in the meta-analysis, trials had to be conducted in adult NHL patients receiving CHOP or CHOP-like chemotherapy and patients had to be randomly assigned to receive primary prophylaxis against febrile neutropenia with filgrastim or placebo, or had to be assigned to a control group of patients who received no primary prophylaxis for febrile neutropenia. The outcome of interest, incidence of febrile neutropenia in both groups, had to be reported in the results. Studies done in patients receiving high-dose chemotherapy prior to peripheral blood stem cell transplantation or bone marrow transplantation were excluded from the analysis.

Three trials met all of the eligibility criteria and were included in the meta-analysis. The data extracted from the publications and used in the analysis included authors, citation, chemotherapy regimen, dose and duration of filgrastim therapy, number of patients included, study design (i.e., placebo controlled or not), and incidence of febrile neutropenia in both groups. Table 2.2 provides a summary of the three studies.

The intention-to-treat results from each trial were used. Summary odds ratios with 95% confidence intervals (CI) were estimated for developing febrile neutropenia with filgrastim therapy, based on a random effects model. Results from the individual studies and the overall odds ratios are presented in the form of a forest plot. Efficacy of filgrastim against febrile
neutropenia is plotted on a natural logarithm scale. No meta-analysis was done for pegfilgrastim since only one published study has examined its efficacy in lymphoma patients.

### 2.3.4 Febrile neutropenia

We assumed that patients who developed febrile neutropenia did so on day 7 post-chemotherapy, which coincides with the nadir in absolute neutrophil count. Although some evidence suggests that the risk of subsequent febrile neutropenia episodes is increased in patients who have experienced a previous episode, it is inconclusive. For this analysis it was assumed that the risk of experiencing febrile neutropenia remains constant over all six chemotherapy cycles.

Patients in the filgrastim primary prophylaxis arm received 300mcg of filgrastim for seven days following each chemotherapy cycle. Patients in the pegfilgrastim arm received a single 6mg dose of this drug. It was assumed that patients in the no primary prophylaxis arm who experience a febrile neutropenic episode would receive secondary prophylaxis with filgrastim 300mcg once daily for seven days with all subsequent chemotherapy cycles, which reflects current clinical practice.

In the base-case analysis it was assumed that all patients who experience a febrile neutropenic episode would be hospitalized for treatment. However, several studies have demonstrated that lymphoma patients at low risk for febrile neutropenia complications can be safely treated as outpatients after an initial in-hospital observation period. Accordingly, an alternate scenario analysis was done in which we assumed that 50% percent of patients who experience a febrile neutropenia episode were at low risk for complications and, as such were eligible for outpatient treatment after an initial in-hospital observation period of 24 hours. We assumed the cost of the 24-hour in-hospital observation period to be the same as the cost of hospitalization for one day.
2.3.5 Quality of life

Hospitalization for febrile neutropenia has been shown to adversely affect patients’ quality of life and, accordingly, has been incorporated in the model in the form of a decrement in the baseline health utility values of lymphoma patients. We assumed that patients experience the decrement in health utility on the first day they develop febrile neutropenia and return to the baseline value after the febrile neutropenia episode resolves (i.e., after discharge from hospital).

2.3.6 Costs

The costs of filgrastim, pegfilgrastim and hospitalization for febrile neutropenia were included in the analysis. All costs were updated to 2010 Canadian dollars, using the Bank of Canada Inflation Calculator. Costs of G-CSFs were obtained from the Ontario Drug Benefit Formulary, a publicly funded insurance program. The cost of hospitalization for febrile neutropenia was obtained from a Canadian study.

2.3.7 Cost-effectiveness calculations and sensitivity analyses

The main outcomes of interest were the ICERs for filgrastim and pegfilgrastim when used as primary prophylaxis against febrile neutropenia. We generated ICERs for filgrastim versus no primary prophylaxis, pegfilgrastim versus filgrastim primary prophylaxis, and pegfilgrastim versus no primary prophylaxis.

Sensitivity analyses were done to test the robustness of the results. One-way sensitivity analyses were done on all parameters and changes in results were observed over the range of values tested. Ranges used are listed in Table 1. All ranges used were the 95% CIs of the variables in order to assess variability on the population level. The only variables for which the 95% CIs were not used in a one-way sensitivity analysis were the baseline NHL utility value, length of stay in hospital for febrile neutropenia, and duration of filgrastim therapy. The 95% CIs of the
baseline utility value and length of stay were too narrow to conduct meaningful sensitivity analyses, and the duration of filgrastim therapy was assumed, so the range was estimated from the medical literature.

A 3000-iteration probabilistic sensitivity analysis (PSA) was done for each of the three ICERs generated to simultaneously reflect parameter uncertainty. Three distribution types were used in the PSA: beta distributions for probabilities of developing febrile neutropenia and health utilities; gamma distributions for costs and length of stay in hospital; and a uniform distribution for duration of filgrastim therapy because no information was available on the shape of this distribution. Since no fixed ICER threshold defines cost-effectiveness, cost-effectiveness acceptability curves (CEACs) were generated with the iterations from the PSAs to examine the robustness of the results under various willingness-to-pay thresholds. Although, the PSAs reflect parameter uncertainty, and may be a more meaningful estimate of the true ICERs associated with these interventions, they were not used as the base-case analysis since current published guidelines recommend that the probabilistic analysis be presented as a sensitivity analysis.73

2.4 Results

2.4.1 Meta-analysis

Results of the meta-analysis are summarized in a forest plot (Figure 2.1). The odds ratio [95% CI] for developing febrile neutropenia when receiving primary prophylaxis with filgrastim is 0.56 [0.41, 0.77]. The odds ratio for developing febrile neutropenia when receiving no primary prophylaxis is 1.78 [1.30, 2.46].
2.4.2  Base-cases analysis

The total and incremental health outcomes and costs associated with all three strategies are detailed in Table 2.3. The lowest total costs were associated with the no primary prophylaxis (secondary prophylaxis) strategy ($6655). Minimal QALY gains were associated with both primary prophylaxis interventions: 0.0011 QALYs with filgrastim compared to no primary prophylaxis, and 0.0009 with pegfilgrastim compared to filgrastim primary prophylaxis. The ICER for filgrastim compared to no primary prophylaxis is $4,599,000/QALY; for pegfilgrastim compared to filgrastim primary prophylaxis it is $6,272,000/QALY; and for pegfilgrastim compared to no primary prophylaxis it is $5,334,000/QALY.

2.4.3  Scenario analysis

When we assumed that 50% of febrile neutropenia episodes would be eligible for outpatient treatment, the analysis yielded the following ICERs: $4,801,000/QALY for filgrastim vs. no primary prophylaxis, and; $16,776,000//QALY for pefilgrastim vs. filgrastim primary prophylaxis; and $9,598,000/QALY for pegfilgrastim vs. no primary prophylaxis.

2.4.4  One-way sensitivity analyses

All one-way sensitivity analyses yielded ICERs greater than $1M/QALY, well above normal thresholds for cost-effectiveness\(^{44}\). These results indicate that the model was not sensitive to the plausible range of any parameter. Cost-effectiveness acceptability curves for the ICERs of the three strategies evaluated: filgrastim vs. no primary prophylaxis, pegfilgrastim vs. no primary prophylaxis, and pegfilgrastim vs. filgrastim. The x-axis represents various ceiling ratios or thresholds for the ICER. The y-axis represents the probability of the intervention being cost-effective at for the given ICER ceiling ratios.
2.4.5 Probabilistic sensitivity analysis

Iterations from the three PSAs indicate that primary prophylaxis with either filgrastim or pegfilgrastim is always associated with increased incremental costs (Figure 2.2). 63%, 60%, and 73% of iterations from the filgrastim versus no primary prophylaxis (secondary prophylaxis) strategy, the pegfilgrastim versus filgrastim primary prophylaxis strategy, and the pegfilgrastim versus no primary prophylaxis strategy were associated with health gains, respectively. Based on the CEACs (Figure 2.3), 20% of iterations would be cost-effective at a willingness-to-pay threshold of $1,260,000 for the filgrastim versus no primary prophylaxis strategy (secondary prophylaxis), $1,490,000 for the pegfilgrastim versus filgrastim primary prophylaxis strategy, and $2,240,000 for the pegfilgrastim versus no primary prophylaxis strategy.

2.5 Discussion

The ICER for filgrastim compared to no prophylaxis (secondary prophylaxis) is $4,599,000/QALY when used as primary prophylaxis against febrile neutropenia in lymphoma patients. The ICER for pegfilgrastim compared to filgrastim is $6,272,000/QALY.

While there is no exact ICER threshold for cost-effectiveness, tentative guidelines suggest that $20,000 – 100,000/QALY is used as a common reference point. The ICERs estimated in the current analysis are well above this range, suggesting that neither filgrastim nor pegfilgrastim would be considered cost-effective interventions for primary prophylaxis against febrile neutropenia. The PSAs indicate that our results are robust with respect to costs since all of the iterations from each analysis were associated with increased incremental costs. In terms of health benefits, the highest percentage of iterations associated with increased incremental QALYs was 71% from the pegfilgrastim versus filgrastim primary prophylaxis strategy, suggesting limited health gains from these interventions.
Our findings are explained by the high costs of G-CSFs and the small incremental gain in QALYs associated with their use. The primary benefit of G-CSFs is their effectiveness in decreasing the probability of febrile neutropenia after receiving cytotoxic chemotherapy.  

While febrile neutropenia treatment is costly as it commonly involves hospitalization, the cost of universal G-CSF primary prophylaxis is more expensive than the costs of febrile neutropenia treatment for patients who do develop this toxicity. G-CSFs do not improve overall survival or progression free survival, as demonstrated by randomized trials in lymphoma patients, leading to very small QALY gains. While these marginal QALY gains may be justification for a cost-minimization analysis, this type of an analysis restricts the ability to do any sensitivity analysis testing on the effectiveness of G-CSF, and such, was not employed in this case.

Recently published literature on G-CSFs includes cost-effectiveness analyses of pegfilgrastim and discussions of G-CSF usage and its costs. All of the cost-effectiveness analyses of pegfilgrastim assumed a mortality benefit associated with its use, even though such a benefit has not been demonstrated in clinical trials. The ICERs resulting from these analyses range from pegfilgrastim being dominant (more effective and less costly) to $US116,000/QALY. One of these analyses was done in lymphoma patients and yielded ICERs of $6,190/QALY when a febrile neutropenia-related mortality benefit was assumed, and $1,677/QALY and when a long-term mortality benefit was assumed. The much lower ICERs from these analyses, compared to ours, clearly resulted from the inclusion of a mortality benefit in the decision models used to generate the ICER estimates. The one paper that examined the cost-effectiveness of filgrastim did not assume a mortality benefit with its use; however, the authors included a death state in the model, and varied the relative risk of death in their sensitivity analysis despite a short model time horizon of only eight chemotherapy cycles. Overall survival from randomized trials was evaluated over a much longer time period (1.3 to 7.9 years), providing more relevant data on
whether G-CSFs actually improve long-term mortality. This analysis yielded an ICER of $700,000/QALY, leading to the same conclusion as our analysis that filgrastim is not cost-effective. The lower ICER estimated by Chan et al. compared to our estimate is related to the lower health utility value they used for the febrile neutropenia health state, the disutility they assumed with a delay in chemotherapy cycle and the longer in-hospital stay they assumed for treatment of febrile neutropenia.

Two publications have examined G-CSF use and its costs. One study reported that 96% of G-CSF use in lung and colorectal cancer patients was not supported by current evidence-based guidelines. The authors suggest that initiatives designed to decrease inappropriate use of G-CSFs would yield considerable cost savings. The second publication, a commentary on decreasing costs of cancer care in the United States, noted that G-CSF use generates $1.25 billion in sales annually despite fewer clinical benefits than anticipated, most notably no mortality benefit. These authors also suggest that decreasing use of G-CSFs would substantially reduce costs without affecting patient outcomes, and instead recommend using antibiotics or reducing chemotherapy doses to prevent febrile neutropenia.

There were two main limitations to the current study. First, some data used in the analysis was taken from studies conducted in patient populations different than the one considered in this analysis. Specifically, data on costs of treating febrile neutropenia in hospital and health utility values associated with hospitalization for febrile neutropenia were collected in patients with a variety of underlying malignancies and thus may not be truly reflective of lymphoma patients. The probability of developing febrile neutropenia with pegfilgrastim was based on one study that considered lymphoma patients who were experiencing a disease relapse and receiving chemotherapy other than R-CHOP. As such, this value may not be reflective of the risk of
febrile neutropenia in the patient population considered in this analysis. Second, this analysis was carried out from the perspective of a publicly funded health care system and did not account for broader societal or indirect costs that may be associated with treatment of febrile neutropenia. For instance, costs of lost productivity or caregiver burden may have been overlooked.

Future work should evaluate the cost-effectiveness of alternate strategies for preventing febrile neutropenia, such as prophylactically administering antibiotics or selectively reducing chemotherapy doses or delaying its administration. Results of this work will inform clinicians and health care decision makers about the relative efficiency of these interventions compared to use of G-CSFs.

Our results indicate that neither filgrastim nor pegfilgrastim are cost-effective when used as primary prophylaxis against febrile neutropenia in lymphoma patients. They provide further evidence against routine of these interventions for primary prophylaxis against febrile neutropenia, and bolster recent arguments that reducing G-CSF use would result in considerable cost savings without adversely affecting patient outcomes.

2.6 Funding

This work was supported by a Clinical Research Fellowship from the Canadian Institutes of Health Research (CFE-109446) that was awarded to Ms. Lathia and an unrestricted educational grant from Amgen Canada that was awarded to Dr. Mittmann and Ms. Lathia. Neither the Canadian Institutes of Health Research, nor Amgen Canada, had any role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; and preparation, review, or approval of the manuscript.
2.7 Conflict of Interest Disclosure

Ms. Lathia and Dr. Mittmann received an unrestricted education grant from Amgen Canada from Sept 2008 to Dec 2010 that, in part, provided funding for this study. Dr. Mittman and Dr. De Angelis, have received unrestricted educational grants from Amgen Canada for work not related to this study. Dr. Mittmann, Dr. De Angelis, and Dr. Hoch have received honoraria from Amgen Canada in the past three years for work not related to this study. None of the other authors have reported any conflicts of interest.
Table 2.1: Variables and sources

<table>
<thead>
<tr>
<th>Model parameters</th>
<th>Mean estimate (range)</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>Costs (2010 Canadian dollars)</td>
<td></td>
<td></td>
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<tr>
<td>Filgrastim 300mcg dose</td>
<td>144*</td>
<td>Ontario Drug Benefit Formulary(^84)</td>
</tr>
<tr>
<td>Pegfilgrastim 6mg dose</td>
<td>2645*</td>
<td>Ontario Drug Benefit Formulary(^84)</td>
</tr>
<tr>
<td>Hospitalization for febrile neutropenia per day</td>
<td>965 (806-1214)</td>
<td>Lathia et al.(^85)</td>
</tr>
<tr>
<td>Health utility values</td>
<td></td>
<td></td>
</tr>
<tr>
<td>NHL (baseline)</td>
<td>0.74 (IPI(^\dagger) scores 0-1) and 0.44 (IPI scores 2-3) Mean (0.59) of both IPI groups used in model (0.44-0.74)</td>
<td>Doorduijn et al.(^86)</td>
</tr>
<tr>
<td>Hospitalization for febrile neutropenia</td>
<td>0.15 less than value for NHL baseline (0.05-0.25 less than baseline value)</td>
<td>Lathia et al.(^87)</td>
</tr>
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<td>Outpatient treatment for febrile neutropenia</td>
<td>0.1 less than value for NHL baseline (used in scenario analysis)</td>
<td>Assumed</td>
</tr>
<tr>
<td>No febrile neutropenia</td>
<td>Parameters same as baseline NHL values</td>
<td>Not applicable</td>
</tr>
<tr>
<td>Febrile neutropenia</td>
<td></td>
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</tr>
<tr>
<td>Probability of developing febrile neutropenia with no primary prophylaxis</td>
<td>0.64 (0.57-0.71)</td>
<td>Meta-analysis (see Figure 1)</td>
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Table 2.1: Variables and sources (continued)

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<td>Febrile neutropenia (continued)</td>
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<tr>
<td>Probability of developing febrile neutropenia with filgrastim</td>
<td>0.36 (0.29-0.44)</td>
<td>Meta-analysis (see Figure 2)</td>
</tr>
<tr>
<td>Probability of developing febrile neutropenia with pegfilgrastim</td>
<td>0.21 (0.10-0.31)</td>
<td>Vose et al.88</td>
</tr>
<tr>
<td>LOS in hospital for febrile neutropenia</td>
<td>8.2 days (6.2-10.2)</td>
<td>Caggiano et al.89</td>
</tr>
<tr>
<td>Duration of filgrastim therapy</td>
<td>10 days (7-14)</td>
<td>Assumed based on current clinical practice at SHSC</td>
</tr>
<tr>
<td>Day on which febrile neutropenia occurs</td>
<td>Day 7 post-chemotherapy</td>
<td>Cullen M et al.78</td>
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Table 2.2: Summary of trials included in meta-analysis

<table>
<thead>
<tr>
<th>Study</th>
<th>No of patients</th>
<th>Chemotherapy regimen</th>
<th>Filgrastim dose</th>
<th>Duration of therapy (days)</th>
<th>Placebo controlled (Yes or No)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Doorduijn et al. 38</td>
<td>389</td>
<td>CHOP*</td>
<td>300mcg daily</td>
<td>10</td>
<td>No</td>
</tr>
<tr>
<td>Osby et al. † †</td>
<td>408</td>
<td>CHOP and CNOP†</td>
<td>5mcg/kg daily</td>
<td>10-14</td>
<td>No</td>
</tr>
<tr>
<td>Pettengell et al. 72</td>
<td>80</td>
<td>VAPEC-B‡</td>
<td>230mcg/m² daily</td>
<td>9-14</td>
<td>No</td>
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Table 2.3: Results of cost-effectiveness analysis

<table>
<thead>
<tr>
<th>Strategy</th>
<th>Cost ($CA, 2010) [95% CI]</th>
<th>Effectiveness (QALDs(^1)) [95% CI]</th>
<th>Effectiveness (QALYs(^3)) [95% CI]</th>
<th>Incremental Cost ($) [95% CI]</th>
<th>Incremental effectiveness (QALYs) [95% CI]</th>
<th>ICER(^1) ($/QALY) [95% CI]</th>
</tr>
</thead>
<tbody>
<tr>
<td>No primary prophylaxis</td>
<td>6655 [5958, 7363]</td>
<td>73.14 [71.19, 75.05]</td>
<td>0.2004 [0.1950, 0.2056]</td>
<td>___</td>
<td>___</td>
<td>___</td>
</tr>
<tr>
<td>Filgrastim</td>
<td>11918 [1033, 13432]</td>
<td>73.56 [71.64, 75.52]</td>
<td>0.2015 [0.1963, 0.2069]</td>
<td>5263 [3523, 6964]</td>
<td>0.0011 [-0.0003, 0.0024]</td>
<td>4,599,000</td>
</tr>
<tr>
<td>Pegfilgrastim</td>
<td>17546 [17099, 18044]</td>
<td>73.89 [71.97, 75.69]</td>
<td>0.2024 [0.1972, 0.2074]</td>
<td>5629 [4032, 7258]</td>
<td>0.0009 [-0.0141, 0.0161]</td>
<td>6,272,000</td>
</tr>
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</table>
Figure 2.1: Forest plot of the odds ratio (OR) (on a logarithmic scale) of developing febrile neutropenia with filgrastim primary prophylaxis from each study and the summary statistic.

<table>
<thead>
<tr>
<th>Study</th>
<th>Filgrastim Events</th>
<th>Filgrastim Total</th>
<th>Control Events</th>
<th>Control Total</th>
<th>OR</th>
<th>95%-CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pettengell</td>
<td>9</td>
<td>41</td>
<td>17</td>
<td>39</td>
<td>0.36</td>
<td>[0.14; 0.96]</td>
</tr>
<tr>
<td>Doorduijn</td>
<td>72</td>
<td>197</td>
<td>86</td>
<td>192</td>
<td>0.71</td>
<td>[0.47; 1.07]</td>
</tr>
<tr>
<td>Ösby</td>
<td>67</td>
<td>204</td>
<td>102</td>
<td>204</td>
<td>0.49</td>
<td>[0.33; 0.73]</td>
</tr>
<tr>
<td>Random effects model</td>
<td>442</td>
<td>435</td>
<td>0.56</td>
<td>[0.41; 0.77]</td>
<td></td>
<td></td>
</tr>
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Odds Ratio
Figure 2.2: Results of probabilistic sensitivity analyses showing three groups of scatter plots on the cost-effectiveness plane: incremental costs and QALYs of filgrastim vs. no primary prophylaxis, pegfilgrastim vs. no primary prophylaxis, and pegfilgrastim vs. filgrastim.
Figure 2.3: Cost-effectiveness acceptability curves for the ICERs of the three strategies evaluated: filgrastim vs. no primary prophylaxis, pegfilgrastim vs. no primary prophylaxis, and pegfilgrastim vs. filgrastim. The x-axis represents various ceiling ratios or thresholds for the ICER. The y-axis represents the probability of the intervention being cost-effective at for the given ICER ceiling ratios.
Chapter 3: Deriving health utility values from a health-related quality of life instrument in non-Hodgkin lymphoma patients

Submitted for publication in manuscript form:

3.1 Abstract

**Introduction:** Health-related quality of life (HRQOL) is an important measure of health outcome. Cost-effectiveness analyses incorporate health utility, a preference-based summary of HRQOL, using quality-adjusted life years (QALYs). The purpose of this study was to develop an algorithm to convert cancer specific HRQOL data obtained from the Functional Assessment of Cancer Therapy-General (FACT-G) instrument in non-Hodgkin lymphoma (NHL) patients into utility values elicited from the EuroQoL instrument (EQ-5D).

**Methods:** NHL patients undergoing chemotherapy completed the FACT-G and EQ-5D questionnaires on each day they received chemotherapy. An ordinary least squares (OLS) regression model was used to quantify the relationship between EQ-5D utility scores and FACT-G subscale scores. The FACT-G subscale scores were the predictor variables and the utility score was the dependent variable. The final model was established using backward variable elimination with the Akaike Information Criterion (AIC). The predictive ability of the final model was tested using 10-fold cross validation.

**Results:** Seventy-five patients completed FACT-G and EQ-5D questionnaires on 379 occasions. The mean age of patients was 59.8 years and 56% were female. The final model included three FACT-G subscales: physical wellbeing (p<0.0001), emotional wellbeing (p<0.001), and functional wellbeing (p<0.0001). The mean predicted utility score was 0.8375, compared to a mean actual utility score of 0.8376. The mean squared error was 0.0130.
**Conclusions:** OLS regression is a reasonable approach to estimating utility values using data from a HRQOL instrument. External validation of this technique would enable it to be used routinely when estimating health utilities using data from non-preference-based instruments.
3.2 Introduction

Health-related quality of life (HRQOL) is often evaluated in clinical trials of new cancer therapies, as it is considered to be an important endpoint in cancer care. Cost-effectiveness (cost-utility) analyses incorporate HRQOL through the use quality-adjusted life years (QALYs), which are used to report health outcomes. Health utility scores, which are preference-based summary measures of HRQOL, are required to determine the QALYs associated with a particular intervention. They are typically expressed as a single number anchored between 0 (representing death) and 1 (representing full health). Health utility scores are usually elicited using generic HRQOL instruments that are not commonly employed, since cancer-specific HRQOL instruments generally provide more clinically relevant information.

Given the lack of utility data available, statistical models for converting non-preference-based HRQOL data derived from cancer-specific instruments into preference-based data would enable HRQOL measures to be incorporated into cost-effectiveness evaluations. Several such models have been published. The most common methods used to convert HRQOL data into utility values are regression-based approaches and response mapping algorithms. Regression-based approaches involve regressing a utility value obtained from respondents on the summary scores (e.g. subscale- or response-level scores) from an HRQOL based instrument obtained from the same group of respondents to derive a predicted utility score. Response mapping algorithms involve regressing levels from each domain of the utility instrument obtained from respondents onto summary scores from an HRQOL-based instrument obtained from the same group of respondents, and then applying preference-based tariffs to derive utility scores. The objective of this study was to derive a regression-based model for converting HRQOL data obtained from
the Functional Assessment of Cancer Therapy-General (FACT-G), a disease-specific instrument, into utility values obtained from the EuroQol (EQ-5D) instrument.

3.3 Methods

Non-Hodgkin lymphoma (NHL) patients receiving chemotherapy with cyclophosphamide, doxorubicin, vincristine, and prednisone with or without rituximab (CHOP/R-CHOP) or cyclophosphamide, vincristine, and prednisone with or without rituximab (CVP/R-CVP) completed the FACT-G and EQ-5D questionnaires with each of their chemotherapy cycles. Demographic and disease state information was collected from the medical records of each patient who participated in the study. This study took place at the Odette Cancer Centre, a regional cancer centre housed at Sunnybrook Health Sciences Centre in Toronto, Canada. The research ethics board at Sunnybrook Health Sciences Centre approved the research protocol for this study. All patients provided informed consent prior to participating. This study was registered with the FACIT (Functional Assessment of Chronic Illness Therapy) Measurement System, the group that developed and validated the FACT-G questionnaire and that is responsible for its distribution.

The FACT-G questionnaire is a 27-item lymphoma-specific HRQOL instrument consisting of 4 subscales: physical wellbeing, social/family wellbeing, emotional wellbeing, and functional wellbeing. Each of the questions is scored on a scale ranging from 0 (not at all) to 4 (very much), with a maximum possible score of 108, where a higher overall score represents a better quality of life. For all items in the physical wellbeing subscale, and for five of the six items in the emotional wellbeing subscale, a higher score represents a worse quality of life; for the social/family wellbeing and functional wellbeing subscales, and one item in the emotional wellbeing subscale, a higher score represents a better quality of life. To account for this scoring
difference, patient responses to the items where higher scores represent a worse quality of life are subtracted from 4 when calculating scores. The total score is calculated by combining the scores from the five subscales; subscale scores are calculated by totalling the score for the individual items in the subscale, multiplying this value by the number of items in the subscale, and then dividing it by the number of items that the patient answered.91

The EQ-5D is a generic, preference-based HRQOL instrument that asks patients to rate their health in five domains: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression.92 There are three levels in each domain: no problems, some problems, and extreme problems. This instrument represents 243 different health states, each of which is associated with a unique utility value based on societal preferences. Several valuations of the EQ-5D based on the time trade-off method, done in different populations, have been published.31,93-95 We used US valuations for this study.31

A model was developed to estimate utility values based on FACT-G scores. We used ordinary least squares (OLS) regression where utility values obtained from the EQ-5D were the dependent variable, and the four subscales of the FACT-G instrument were the explanatory variables. The Akaike Information Criterion (AIC) was used to perform backward variable elimination, reducing the model to include only those FACT-G subscales which most accurately predict utility values. We calculated regression coefficients for both the full model and the reduced model. We did not explore interactions between variables. To test the robustness of the results from the OLS regression method, we also estimated utility values using the response mapping technique, which was initially proposed by Gray et al as a means of increasing the accuracy of the individual utility predictions.96
To test the internal validity of our model, we performed a 10-fold cross validation. This method involves dividing the sample into 10 equal subsets, and using nine of these subsets to fit the model, while the tenth subset is used to validate the model. This process was repeated ten times, so that each subset was used once to validate the model. We calculated mean squared error to quantify differences between actual and predicted utility scores. We also established 95% confidence intervals (CIs) of the EQ-5D utility and FACT-G scores using a 3000-replicate bootstrap analysis. All analyses were done using the R language for statistical computing, version 2.8.

3.4 Results

Seventy-five patients completed the EQ-5D and FACT-G questionnaires on 379 different occasions. Demographic and disease state characteristics of the study patients are summarized in Table 3.1. Fifty-six per cent (56%) of patients were female, the mean age was 59.8 years, and the most common NHL subtype was diffuse large B-cell lymphoma. Mean scores from the two instruments and their 95% CIs are summarized in Table 3.2.

The coefficients for the full and reduced OLS models are listed in Table 3.3. The reduced model included the physical, emotional, and functional wellbeing subscales of the FACT-G instrument. The physical wellbeing coefficient was the greatest with a value of 0.0128, indicating this subscale was most strongly correlated with utility values. The adjusted R2 values for the full were reduced models are 0.501 and 0.502, respectively.

The mean predicted utility score was 0.8375. The mean squared error was 0.0130 based on results of the 10-fold cross validation. Our model tended to overestimate health utilities for those patients whose true utility values were low (less than 0.5), and underestimate utilities for those patients whose true utility was high (1.0). Fifty percent of the predicted utilities had an absolute
deviation of 0.068 or less from the corresponding actual utilities. A scatter plot of actual versus predicted utility scores is presented in Figure 3.1. The distribution of estimated errors (actual minus predicted utility scores) is presented in Figure 3.2.

The response mapping technique yielded a mean predicted utility score of 0.8323, slightly less accurate than the estimate from the OLS regression. Figure 3.3 displays a plot of the cumulative absolute utility difference for both the OLS regression and response mapping techniques. The curves are basically superimposed upon each other, indicating that the response mapping technique did not predict individual utilities any more accurately than the OLS regression technique. This finding is consistent with the results from Gray et al. and another study by Pinedo-Villanueva et al that predicted utility score from the Oxford Hip Score instrument using response mapping.96,97

3.5 Discussion

We developed a model using OLS regression to estimate utility values based on responses to the FACT-G questionnaire from a group of NHL patients. Our model predicts a mean utility score of 0.8375. The mean squared error was 0.0130. This model provides a reasonable method for converting HRQOL data, obtained from a commonly used disease-specific instrument, into utility values that could be used in cost-effectiveness analyses of new cancer therapies.

The results of this analysis are explained by three main factors: 1) similarities between the components of the FACT-G and EQ-5D instruments; 2) the relatively few patients who had low utility scores, and 3) the inability of EQ-5D instrument to detect small deviations from perfect health. Our final model included the physical, emotional, and functional wellbeing subscales of the FACT-G instrument. These aspects of health are also captured in the EQ-5D within the domains of mobility, anxiety/depression, and usual activities, respectively, likely explaining why
the most closely related FACT-G subscales were the best predictors of utility. The greater differences between predicted and actual utility scores for those patients with low actual scores (less than 0.5) may be because patients reported actual utility scores of less than 0.5 on relatively few occasions (13 of 379), explaining why the model performs poorly when predicting utilities in this range. Patients reported utility scores of 1.0, representing perfect health, on 131 of 379 occasions, despite the fact that they were suffering from NHL. The predicted utility scores for these patients ranged from 0.7721 to 1.0. These lower predicted utility scores are most likely related to the fact that the EQ-5D is a generic instrument that is not sensitive enough to detect small deviations from perfect health, while the FACT-G is a disease-specific instrument that is more sensitive to changes in health states; therefore, when FACT-G subscales are used to predict utility scores they are less likely to predict perfect health.

Several models for predicting utility values from HRQOL data in cancer patients have been published. Algorithms for estimating utilities from responses to the European Organization for Research and Treatment of Cancer Quality of Life-Core 30 questionnaire (EORTC QLQ-C30) instrument are available for patients with non-small cell lung cancer, locally advanced breast cancer, gastric cancer, and inoperable esophageal cancer. The adjusted R2 values from these analyses ranged from 0.58 to 0.80. An algorithm published by Wu et al. in men with metastatic hormone-refractory prostate cancer used a combination of data from the EORTC QLQ-C30 and FACT-Prostate instruments to estimate utilities; the adjusted R2 for this analysis was 0.73.

Estimates of the minimally important difference in EQ-5D utilities in cancer patients have also been published for both US- and UK-based EQ-5D valuations. The minimally important difference is defined as the smallest change that is perceived as meaningful to patients or that
would result in treatment changes. For US utility scores, the estimated minimally important difference is 0.06; for UK scores it is 0.08. Based on our model, 50% of the predicted utility values deviated by 0.068 or less from the actual utility values, indicating that for this proportion of the predictions, the deviation was not likely to be clinically important.

There were several limitations to our study. First, we collected data from a relatively small number of patients, and even though we were able to obtain repeated observations from each patient, the results may be affected by a limited sample size. Second, we were not able to test our model for external validity with a unique data set. Third, our results may have been influenced by selection bias since some patients who were screened for participation in the study chose not to consent (8) or were not able to provide consent because they could not read or write English (4). Finally, we applied US valuations of the EQ-5D in a Canadian setting, and they may not reflect the health preferences of Canadian patients.

Results of our study are pertinent to both clinicians and health economists involved in clinical trials and subsequent economic analyses of new lymphoma therapies. Given the number of expensive new cancer therapies that are being introduced onto the market, health care decision makers are increasingly requiring evidence of not only a new therapy’s clinical effectiveness, but also of its cost-effectiveness. Our analysis provides a method for estimating health utilities, which are required to conduct cost-effectiveness analyses, from an instrument commonly used to collect HRQOL data in clinical trials when utility values are scarce.

Our analysis demonstrates that OLS regression is a reasonable approach to estimating utility values using data collected from a disease-specific HRQOL instrument. External validation of this algorithm and similar ones that have been published, using unique data sets, will further the
validity of this technique for converting non-preference-based HRQOL data into preference-based data.

3.6 Funding

This work was supported by a Clinical Research Fellowship from the Canadian Institutes of Health Research (CFE-109446) that was awarded to Ms. Lathia and an unrestricted educational grant from Amgen Canada that was awarded to Dr. Mittmann and Ms. Lathia. Neither the Canadian Institutes of Health Research, nor Amgen Canada, had any role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; and preparation, review, or approval of the manuscript.

3.7 Conflict of Interest Disclosure

Ms. Lathia and Dr. Mittmann received an unrestricted education grant from Amgen Canada from Sept 2008 to Dec 2010 that, in part, provided funding for this study. Dr. Mittman and Dr. De Angelis, have received unrestricted educational grants from Amgen Canada for work not related to this study. Dr.Mittmann, Dr. De Angelis, and Dr.Hoch have received honoraria from Amgen Canada in the past three years for work not related to this study. None of the other authors have reported any conflicts of interest.
Table 3.1: Summary of patient characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>All patients (n=75)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female sex, n (%)</td>
<td>42 (56)</td>
</tr>
<tr>
<td>Age, mean (range), years</td>
<td>59.8 (28.2 - 87.9)</td>
</tr>
<tr>
<td>NHL subtype, n (%)</td>
<td></td>
</tr>
<tr>
<td>Diffuse large B-cell lymphoma</td>
<td>44 (58.6)</td>
</tr>
<tr>
<td>Follicular lymphoma</td>
<td>12 (16.0)</td>
</tr>
<tr>
<td>Mucosa-associated lymphoid tissue</td>
<td>2 (2.7)</td>
</tr>
<tr>
<td>Marginal zone lymphoma</td>
<td>7 (9.3)</td>
</tr>
<tr>
<td>Low grade B-cell lymphoma</td>
<td>2 (2.7)</td>
</tr>
<tr>
<td>Mantle-cell lymphoma</td>
<td>3 (4.0)</td>
</tr>
<tr>
<td>Primary mediastinal B-cell lymphoma</td>
<td>3 (4.0)</td>
</tr>
<tr>
<td>Waldenstrom’s disease</td>
<td>2 (2.7)</td>
</tr>
<tr>
<td>Disease stage, n (%)</td>
<td></td>
</tr>
<tr>
<td>Stage I</td>
<td>14 (18.7)</td>
</tr>
<tr>
<td>Stage II</td>
<td>13 (17.3)</td>
</tr>
<tr>
<td>Stage III</td>
<td>13 (17.3)</td>
</tr>
<tr>
<td>Stage IV</td>
<td>35 (46.7)</td>
</tr>
</tbody>
</table>
Table 3.2: Mean EQ-5D and FACT-G scores

<table>
<thead>
<tr>
<th></th>
<th>Mean ± SD</th>
<th>95% Bootstrap CI</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>EQ-5D</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Utility score</td>
<td>0.8376 ± 0.1599</td>
<td>0.8217-0.8529</td>
</tr>
<tr>
<td><strong>FACT-G</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total score</td>
<td>81.12 ± 15.78</td>
<td>79.57-82.71</td>
</tr>
<tr>
<td>Physical wellbeing</td>
<td>21.58 ± 5.38</td>
<td>21.04-22.10</td>
</tr>
<tr>
<td>Social/family wellbeing</td>
<td>23.55 ± 5.02</td>
<td>23.00-24.02</td>
</tr>
<tr>
<td>Emotional wellbeing</td>
<td>18.42 ± 4.48</td>
<td>17.98-18.84</td>
</tr>
<tr>
<td>Functional wellbeing</td>
<td>17.58 ± 6.09</td>
<td>16.96-18.17</td>
</tr>
</tbody>
</table>
Table 3.3: Regression coefficients for full and reduced models

<table>
<thead>
<tr>
<th></th>
<th>Full model</th>
<th>Reduced model</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intercept</td>
<td>0.3577*</td>
<td>0.3474*</td>
</tr>
<tr>
<td>Physical wellbeing</td>
<td>0.0128*</td>
<td>0.0128*</td>
</tr>
<tr>
<td>Social/family wellbeing</td>
<td>-0.0007</td>
<td></td>
</tr>
<tr>
<td>Emotional wellbeing</td>
<td>0.0050**</td>
<td>0.0049**</td>
</tr>
<tr>
<td>Functional wellbeing</td>
<td>0.0073*</td>
<td>0.0071*</td>
</tr>
</tbody>
</table>

*p<0.0001, **p<0.01
Figure 3.1: Scatter plot of actual versus predicted utility scores. The vertical distance between each point and the diagonal line represents the difference between actual and predicted utility scores.
Figure 3.2: Distribution of estimated errors (predicted minus actual utility scores)
Figure 3.3: Plot of cumulative absolute utility difference for OLS regression analysis and response mapping.
Chapter 4: Eliciting patients’ preferences for outpatient treatment of febrile neutropenia: a discrete choice experiment

Published in manuscript format:

4.1 Abstract

**Background:** Studies have demonstrated that patients at low risk for febrile neutropenia (FN) complications can be treated safely and effectively at home. Information on patient preferences for outpatient treatment of this condition will help to optimize health care delivery to these patients. The purpose of this study was to elicit non-Hodgkin lymphoma patients’ preferences on attributes related to outpatient treatment of FN.

**Methods:** We used a self-administered discrete choice experiment questionnaire based on the attributes of out-of-pocket costs, unpaid caregiver time required daily, and probability of return to the hospital. Ten paired scenarios in which levels of the attributes were varied were presented to study patients. For each pair, patients indicated the scenario they preferred. Adjusted odds ratios (ORs) of accepting a scenario that described outpatient care for FN were estimated.

**Results:** Eighty-eight patients completed the questionnaire. Adjusted ORs [95 % confidence intervals] of accepting outpatient care for FN were 0.84 [0.75, 0.95] for each $10 increase in out-of-pocket cost; 0.82 [0.68, 0.99] for each 1 h increase in daily unpaid caregiver time; and 0.53 [0.50, 0.57] for each 5 % increase in probability of return to the hospital.

**Conclusions:** Probability of return to the hospital was the most important attribute to patients when considering home-based care for FN. Patients considered out-of-pocket costs and unpaid caregiver time to be less important than probability of return to the hospital. This study identifies factors that could be incorporated into outpatient delivery systems for FN care to ensure adequate patient uptake and satisfaction with such programs.
4.2 Introduction

Febrile neutropenia is a serious hematologic adverse event of cancer chemotherapy that is typically treated in hospital, and as such, is a significant contributor to the costs of cancer care. A 2006 study reported a median cost of $8376 and median length of stay in hospital of 6 days for treatment of a febrile neutropenia episode in the US. A recent Canadian study found that even patients classified as being at low risk for febrile neutropenia complications, based on the Multinational Association for Supportive Care in Cancer (MASCC) risk index, spent a mean of 6.1 days in hospital resulting in a mean cost of $5362 to treat febrile neutropenia. 85

Many studies, however, have demonstrated that the subset of febrile neutropenia patients at low risk for complications may be treated safely and effectively with oral antibiotics on an outpatient basis, with no increased risk of treatment failure or mortality compared to those treated in hospital. Additionally, several publications have shown marked cost savings associated with outpatient therapy for low-risk febrile neutropenia patients, compared to hospitalization.

While evidence exists to support the safety and cost-effectiveness of outpatient febrile neutropenia care, little is known about patient preferences regarding non-hospital based care. Understanding patient preferences towards attributes of outpatient febrile neutropenia treatment will allow health care decision makers and clinicians to design and implement new outpatient febrile neutropenia treatment programs that address relevant patient concerns.

The objective of our study was to elicit patient preferences for attributes describing outpatient treatment of febrile neutropenia using a discrete choice experiment. Discrete choice experiments have been widely used as a method of eliciting consumer preferences in marketing research and
are being increasingly used to assess the delivery of health services.\textsuperscript{32} They have been employed in the healthcare setting to measure patients’ preferences related to asthma management\textsuperscript{104}, human immunodeficiency virus testing\textsuperscript{105}, and diabetes care.\textsuperscript{106} Studies have demonstrated that responses obtained from participants in healthcare-related discrete choice experiments are reliable and internally valid.\textsuperscript{26,107} Discrete choice experiments are based on the assumption that a particular service or product can be described by its attributes and that an individual’s preference for this service or product depends on the levels of these attributes. They provide information on the relative importance of these attributes and on how individuals trade off between them, by having participants choose between pairs of alternatives described by varying levels of the attributes being investigated.\textsuperscript{32}

### 4.3 Methods

#### 4.3.1 Study design

This study was carried out in 2 parts: first, we conducted a pilot study to identify relevant attributes of outpatient febrile neutropenia care and levels of these attributes that would be appropriate to include in our discrete choice experiment; second, the attributes and levels ascertained were used to develop a discrete choice experiment questionnaire that was administered to patients as part of the main study. The setting for this study was the Odette Cancer Centre, one of 13 regional cancer centres in Ontario, Canada, which is housed at Sunnybrook Health Sciences Centre. This cancer centre is the sixth largest such facility in North America and provides almost 24,000 chemotherapy treatments for patients each year. The research ethics board at Sunnybrook Health Sciences Centre approved the research protocols for both parts of this study. All participants in both parts of the study provided informed consent prior to participating.
4.3.2  Pilot study

We conducted a two-phase pilot study to establish which attributes would be important to patients when considering outpatient treatment for febrile neutropenia, and the levels of these attributes that would be appropriate to incorporate in our discrete choice experiment.

In the first phase, we conducted a literature search, interviewed five health care professionals involved in the care of febrile neutropenia patients (three oncologists, one pharmacist and one nurse), and interviewed five non-Hodgkin lymphoma (NHL) patients who had experienced a previous febrile neutropenia episode. Our literature search yielded one article that examined preferences for inpatient versus outpatient treatment for febrile neutropenia in the pediatric population.39 In this study, preferences of parents and healthcare professionals caring for children with low-risk febrile neutropenia were compared based on four attributes: 1) frequency of clinic visits, 2) probability of admission to hospital, 3) risk of intensive care unit admission, and 4) risk of mortality.

Interviews with the health care professionals indicated that out-of-pocket costs, caregiver burden, and probability of return to hospital in the event of clinical deterioration would be important factors. When asked specifically about clinic visits, all health care professionals thought that they would not be necessary at our centre as long as patients lived with another adult capable of providing some care for them, were given detailed written instructions on circumstances that would require them to return to hospital and a logbook in which to record their temperatures every six hours, and daily telephone contact with an oncology nurse for the duration of their febrile neutropenia episode. The feasibility of clinic visits was also mentioned by two of the oncologists as a possible limiting factor in outpatient care since many of the patients live a considerable distance from the centre (> 100 km).
In interviews with NHL patients, we began by asking what factors would be important to them when considering outpatient care for febrile neutropenia. The overriding concern expressed by participants was that they received the most suitable medical care to ensure they had the best chance of recovering from their febrile neutropenia episode. Participants were then asked specifically about the attributes of out-of-pocket costs, caregiver burden and probability of return to hospital in the event of clinical deterioration. All participants felt the attributes identified were appropriate, and they did not identify any additional attributes.

Based on our literature search and interviews we hypothesized that 3 factors would be important to patients when considering outpatient febrile neutropenia treatment: out-of-pocket costs, unpaid caregiver time required daily, and probability of return to hospital. We excluded risk of intensive care unit admission and risk of mortality that were examined in the paper by Sung et al., because studies have demonstrated that there is no difference in risk of these two attributes between low-risk febrile neutropenia patients treated in hospital and those treated as outpatients.45,49,52 We also excluded frequency of clinic visits based on feasibility issues at our centre described above. Furthermore, several studies of outpatient febrile neutropenia treatment did not require patients to attend mandatory clinic visits while being treated at home for febrile neutropenia and these studies did not report any increase in adverse outcomes compared to studies where patients were required to attend follow-up clinic visits.48,49,53

In the second phase of the pilot study we asked 12 NHL patients to complete a discrete choice experiment based on the following attributes and levels: out-of-pocket costs (levels: $50, $250, $500, $1000); unpaid caregiver time required daily (levels: 1 hour, 2 hours, 4 hours, 8 hours); and probability of return to hospital (levels: 5%, 10%, 20%, 50%). We performed an analysis of these 12 results and found that all of the participants consistently chose the scenario with the
lowest out-of-pocket costs. This finding indicated that we would have to alter the levels of this attribute for the main study in order to ensure that participants were trading off between the different attributes.

4.3.3 Main study

Patient population

Patients over the age of 18 years with a diagnosis of non-Hodgkin lymphoma (NHL) who were undergoing chemotherapy with cyclophosphamide, doxorubicin, vincristine and prednisone with or without rituximab (CHOP/R-CHOP) or cyclophosphamide, vincristine and prednisone with or without rituximab (CVP/R-CVP), or who had received chemotherapy with one of these regimens in the past year at the Odette Cancer Centre, formed the eligible patient population screened for this study. Additional inclusion criteria included the ability to read, write, and speak English as well as willingness to provide informed consent.

Designing the discrete choice questionnaire

Based on information gathered from our pilot study, we designed a self-administered discrete choice experiment questionnaire. The attributes included were the same as those in the pilot study. Levels for the attributes of unpaid caregiver time required daily and probability of return to hospital were the same as those used in the pilot study; however, we lowered the costs levels to $10, $25, $50, and $100, as most patients eligible for outpatient febrile neutropenia treatment would be unlikely to encounter out-of-pocket costs of greater than $100 in the context of the Canadian health care system. Out-of-pocket costs would typically be limited to prescriptions for oral antibiotics such as ciprofloxacin and amoxicillin/clavulanate and non-prescription items such as anti-pyretics and thermometers. Levels were chosen to establish thresholds at which patients would trade-off between the attributes.
We generated sets of paired scenarios in which levels of the three attributes were independently varied based on an orthogonal main effects plan. For the final questionnaire, we selected the set with the highest efficiency including one paired scenario to test for internal consistency. Specifically, this test included one scenario where the level of each attribute was more favorable compared to the alternative in order to test if patients understood. A total of ten paired scenarios were included in the final questionnaire; all patients received the same questionnaire. For each pair, we asked participants to select the scenario they preferred, to assess how they traded off between attributes. An outline of the conditions and assumptions under which participants were to select their preferred choice from each pair was presented at the outset of the questionnaire. Table 4.1 provides an example of one of the paired choices included in the questionnaire.

Data collection

We began recruitment of study participants and data collection on March 2010 and ended in February 2011. We approached NHL patients undergoing chemotherapy treatments or attending outpatient follow-up appointments at the Sunnybrook Health Sciences Centre to participate in the study. Those who provided informed consent were asked to complete the discrete choice experiment questionnaire as well as a questionnaire on income level and employment status. Demographic and disease state information was collected from each study participant’s medical chart. Disease state data collected included information on underlying malignancy and chemotherapy regimen.

Statistical analyses

We summarized demographic and disease state data using descriptive statistics and used multilevel logistic regression models, with data grouped by individual patient, to analyze responses obtained from the discrete choice experiment questionnaire. A series of models were
fit and the goodness of fit of each model was assessed using the Akaike information criterion (AIC). The dependent variable was the patient’s choice of scenario (yes or no) from each pair presented in the questionnaire, and the predictor variables were the levels of the three scenario attributes. We began by fitting a series of univariate models that treated the predictor variables as continuous as well as categorical data. Based on the AIC, the categorical models fit slightly better than the continuous ones; however, from a face validity standpoint the continuous models were more appropriate since some of the results from the categorical models were inconsistent with the expected preferences of patients. For example the categorical model evaluating cost predicted that patients would be more likely to accept a scenario where the out-of pocket cost was $50 compared to a scenario where out-of-pocket cost was $25. Table 4.2 details the probabilities of accepting an outpatient scenario for febrile neutropenia treatment based on the univariate categorical and continuous analysis of each attribute. Given the paradoxical results from the categorical models, all predictor variables investigated were treated as continuous data for the multivariate regression analyses. The final model allowed the out-of-pocket cost and caregiver time coefficients to vary at the individual patient level. The coefficient for the probability of return to hospital attribute did not vary at the individual patient level. Interactions between the attributes were investigated, but none were included in the final model. Results of the regression analysis were expressed as the adjusted odds ratios of accepting a scenario describing outpatient care for febrile neutropenia. Probability curves for accepting outpatient care scenarios were generated for each of the attributes evaluated in the study. We also used the parameters from our model to estimate how patients traded off between the three attributes.

Although this study was not designed as a comparison between groups, we performed four exploratory sub-analyses to determine whether the following patient characteristics affected their
choice of outpatient care scenario: 1) type of underlying malignancy and chemotherapy received, 2) age, 3) sex, and 4) income.

All analyses were performed using the R language and environment for statistical computing (versions 2.10.1 and 2.11.1, R Foundation for Statistical Computing).

4.4 Results

88 patients completed the discrete choice experiment questionnaire. 830 paired scenarios, representing data from 83 study patients, were included in the final analysis. Five patients (5.7%) were excluded for failing the test of internal consistency involving of a scenario with favorable levels for each attribute. It was assumed that patients who chose the non-dominant scenario misunderstood the task since their choice is illogical. Compared to the 83 patients analyzed, the excluded patients tended to be older (data not shown). The other demographic variables were similar between the included and excluded patients.

Table 4.3 summarizes the disease state and sociodemographic characteristics of patients included in the analysis. The patients had a mean age of 58.8 years, and 26 (31%) were retired. Eleven (13%) were previously hospitalized for febrile neutropenia. The majority of patients were receiving CHOP-based chemotherapy for the treatment of aggressive-histology diffuse large B-cell lymphoma.

The fixed effects estimates of the multilevel logistic regression model are presented in Table 4.4. All three attribute variables were statistically significant predictors in the final model, indicating that all attributes evaluated were important to patients. The attribute variables were rescaled so that a unit change in the attributes for the regression coefficients represented a $10 increase in
out-of-pocket cost, a 1 hour daily increase in unpaid caregiver time, and a 5% increase in probability of return to hospital.

An additional 5% risk of return to hospital appeared to have been the most important attribute to participants. Adjusted odds ratios [95% confidence intervals] of accepting a scenario describing outpatient treatment for febrile neutropenia were 0.84 [0.75 to 0.95] for each $10 increase in out-of-pocket cost; 0.82 [0.68 to 0.99] for each 1 hour increase in daily unpaid caregiver time; and 0.53 [0.50 to 0.57] for each 5% increase in probability of return to hospital.

Based on our model, we predicted that patients were willing to pay $11.97 per hour of unpaid caregiver time. In comparison, the willingness to pay to avoid a 1% increase in risk of return to hospital was $7.45, or $37.23 for avoiding a 5% increase in risk. A one-hour increase in daily unpaid caregiver time was weighted equal to a 0.62% increase in probability of return to hospital. Figure 4.1 represents plots of the fitted multilevel logistic regression model showing the probability of accepting a scenario based on the attributes. The models are shown as a function of the out-of-pocket cost (figure 1A), unpaid caregiver time (figure 1B), and probability of return to hospital (figure 1C). Figures 1A and 1C assume 2 hours of unpaid caregiver time, and figure 1B assumes out-of-pocket costs of $50.

Results of our exploratory sub-analyses show that risk of return to hospital was the most consistent variable across the subgroups, with patients 60 years or older, as well female patients placing the greatest weight on the risk of returning to hospital with odds ratios of 0.51 and 0.51 per 5% increase in probability of return, respectively. The subgroup of patients with an annual income of less than $60,000 per year was more sensitive to the out-of-pocket cost attribute than those with a higher income. Sensitivity to the unpaid caregiver time attribute was variable across
the subgroups of patients tested. Compared to the primary analysis of all patients, female patients weighted unpaid caregiver time heavily with an odds ratio of 0.63.

4.5 Discussion

We conducted a discrete choice experiment to evaluate attributes related to outpatient care for febrile neutropenia and found that probability of returning to hospital was the most important attribute to participants. This finding was consistent across all subgroups of participants examined. Participants were willing to pay $37.23 to avoid a 5% risk of return to hospital and forgo 1 hour of daily unpaid caregiver time to avoid a 0.62% increased risk of return to hospital.

The strengths of this study include a substantial number of participants from a uniform population of patients at high risk for developing febrile neutropenia, a vast majority of respondents (94.3%) who understood the task they were asked to complete and whose responses were included in the final analysis, and exploratory sub-analyses to investigate whether certain patient characteristics affected preferences for the attributes considered. An additional strength of this study was the use of the discrete choice experiment method, which allowed us to develop a statistical model to predict preferences based various levels of each of the attributes evaluated.

There were 4 main limitations, however, to this study. First, it was conducted at a single institution and participants’ preferences may have been influenced by the specific care they received at this institution. Second, 22 patients who were screened for participation in the study either chose not to consent (6) or were unable to consent because they could not read or write English (16). These patients may have had different underlying characteristics from those who participated, potentially limiting the generalizability of results. Third, we asked participants about only three attributes related to outpatient febrile neutropenia treatment. There may be other attributes which patients consider important in evaluating this treatment option that were
not explored. Finally, we quantified preferences for an overall sample of participants and these may differ from the preferences of individual patients, which need to be accounted for when clinical decisions are made.

The one common attribute examined in our study and the study by Sung et al., which measured preferences related to outpatient treatment of pediatric febrile neutropenia, was probability of return to hospital. Sung et al. found that healthcare professionals were willing to accept a greater probability of return to hospital than parents. They did not provide an overall ranking of the relative importance of the attributes that were evaluated in their study.

In relation to studies evaluating outpatient febrile neutropenia treatment, our findings on patient preferences related to the attributes of probability of return to hospital and informal caregiver time are in line with what patients who received home-based care for febrile neutropenia in these studies actually experienced. While our study found that participants demonstrated an unwillingness to accept increased risk of returning to hospital, our model demonstrates that a large majority of participants were willing to accept home-based care involving rates of return consistent with those found in studies examining outpatient febrile neutropenia treatment. These studies reported rates of re-hospitalization ranging from 4% to 20%. Our model predicts that 95% of participants would be willing to accept outpatient care if they faced a 10% probability of returning to hospital, along with $50 of out-of-pocket costs and 2 hours of unpaid caregiver time daily; increasing the probability of return to 20%, the predicted willingness to accept decreases to 85%. Unpaid caregiver time required each day was an important attribute among participants in our study, but not nearly to the same degree as probability of return to hospital, indicating that caregiver burden is not a major concern to patients when considering outpatient febrile neutropenia treatment. Our results are consistent with a recent study showing
that about half of informal caregivers for both inpatients and outpatients with febrile neutropenia reported no time spent providing care or lost from work. In the other half of caregivers who did report time spent caring for someone with febrile neutropenia, the total time averaged between 8 and 16 hours per febrile neutropenia episode, regardless of whether the patient being cared for was in hospital or at home.\textsuperscript{103}

With respect to out-of-pocket costs, our study indicates that costs of up to $100 were not as concerning for participants as the risk of returning to hospital, although, higher costs may still be important as demonstrated from the results of our pilot study. These results suggest that beyond a certain threshold, costs may be a limiting factor for patients who are otherwise eligible for outpatient treatment of febrile neutropenia. Studies have consistently shown that the length of stay in hospital drives the cost of hospitalization for febrile neutropenia\textsuperscript{85,101,108-110}, and, as such outpatient treatment strategies yield substantial cost-savings\textsuperscript{45,102,103}; however, there has been almost no investigation of out-of-pocket costs related to outpatient febrile neutropenia treatment. One American study did briefly report that out-of-pocket costs for febrile neutropenia inpatients and their caregivers, such as those related to mileage and parking, were significantly greater than for outpatients.\textsuperscript{103} These costs only included non-medical costs related to febrile neutropenia care and did not account for direct medical costs such as those related to oral antibiotics or non-prescription items that may be required during outpatient febrile neutropenia treatment.

Our results can be explained in terms of both patient-centred factors, as well as those related to the publicly funded Canadian health care system. Patients’ preference for decreased probability of having to return to hospital most likely reflects fear or anxiety related to febrile neutropenia treatment failure, since this circumstance would be the primary reason for hospital admission. This concern was evident in our pilot study interviews in which all participants indicated that
their highest priority when considering outpatient febrile neutropenia treatment was receiving the best medical care to ensure recovery from febrile neutropenia. Our finding of a potential cost threshold, above which patients may not consider outpatient febrile neutropenia treatment, could reflect the universal coverage of all in-hospital costs provided by the Canadian health care system. In models of outpatient febrile neutropenia treatment some direct medical costs would invariably be shifted on to patients who are not accustomed to paying out of pocket for medical expenses and may be resistant to incurring these costs. The lesser importance participants placed on caregiver burden may be related to the older average age of study participants (58.8 years), many of whom likely have a retired spouse who would not be excessively burdened with caring for a low-risk febrile neutropenia patient at home. Also, febrile neutropenia is a condition that affects those suffering from an underlying malignancy and some caregivers may already be devoting considerable time to caring for a family member with cancer. The added care required when such a patient develops a low-risk febrile neutropenia episode may be minimal in many cases, adding little to the burden of the caregiver. 111

Both clinicians and policymakers could employ our results when implementing and designing new programs for outpatient delivery of febrile neutropenia treatment. For example, clinicians could use the information on unwillingness to accept increased risk of return to hospital to ensure that when establishing clinical criteria to determine eligibility for outpatient febrile neutropenia treatment, due consideration is given to factors that may increase the risk of patients having to return to hospital. Preferences of individual patients who may be particularly averse to the risk of returning to hospital should also be considered in light of these results. With respect to a possible threshold in out-of-pocket costs willing to be assumed by participants, publicly funded health systems and private insurers could implement policies to cover costs related to outpatient febrile neutropenia treatment (e.g., costs of prescription oral antibiotics, over-the-counter
medications and supplies, in-home nursing care) and still realize cost savings compared to funding hospitalization. Finally, for those patients eligible for outpatient febrile neutropenia care but limited by a lack of available informal caregiver time, publicly funded health systems and private insurers could again avoid the substantially greater costs that would be associated with hospitalizing this group of patients by employing strategies to provide in-home personal support resources for them.

The results of our discrete choice experiment provide initial estimates of the relative importance of attributes related to outpatient therapy for febrile neutropenia, which could be employed when designing and implementing new programs for outpatient delivery of febrile neutropenia treatment. Future studies examining how certain patient-specific factors may influence preferences related to febrile neutropenia outpatient care, as was suggested by our exploratory analysis, will help to identify ways in which home-based febrile neutropenia care could be made feasible for these patients. Additionally, evaluating patient satisfaction with various aspects of established febrile neutropenia outpatient care programs would lead to further support for the use of discrete choice experiments to accurately capture patients’ preferences.

4.6 Funding

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4.7 Conflict of Interest Disclosure

Ms. Lathia and Dr. Mittmann received an unrestricted education grant from Amgen Canada from Sept 2008 to Dec 2010 that, in part, provided funding for this study. Dr. Mittman and Dr. De Angelis, have received unrestricted educational grants from Amgen Canada for work not related to this study. Dr. Mittmann, Dr. De Angelis, and Dr. Hoch have received honoraria from Amgen Canada in the past three years for work not related to this study. None of the other authors have reported any conflicts of interest.
Table 4.1: Example of paired scenarios presented in the discrete choice experiment questionnaire

<table>
<thead>
<tr>
<th>Scenarios</th>
<th>Out-of-Pocket Cost</th>
<th>Unpaid Caregiver Time Required Each Day</th>
<th>Probability of Return to Hospital</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>$10</td>
<td>1 hour</td>
<td>10% (1 in 10 chance)</td>
</tr>
<tr>
<td>2</td>
<td>$100</td>
<td>4 hours</td>
<td>5% (1 in 20 chance)</td>
</tr>
</tbody>
</table>
Table 4.2: Probabilities of willingness to accept a scenario describing outpatient care for febrile neutropenia based on univariate continuous and categorical regression analyses of each attribute

<table>
<thead>
<tr>
<th></th>
<th>Continuous model</th>
<th>Categorical model</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cost attribute</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$10.00</td>
<td>0.57</td>
<td>0.60</td>
</tr>
<tr>
<td>$25.00</td>
<td>0.55</td>
<td>0.21</td>
</tr>
<tr>
<td>$50.00</td>
<td>0.51</td>
<td>0.57</td>
</tr>
<tr>
<td>$100.00</td>
<td>0.45</td>
<td>0.44</td>
</tr>
<tr>
<td><strong>Unpaid caregiver time required daily attribute</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 hour</td>
<td>0.61</td>
<td>0.67</td>
</tr>
<tr>
<td>2 hours</td>
<td>0.51</td>
<td>0.39</td>
</tr>
<tr>
<td>4 hours</td>
<td>0.46</td>
<td>0.37</td>
</tr>
<tr>
<td>8 hours</td>
<td>0.43</td>
<td>0.53</td>
</tr>
<tr>
<td><strong>Probability of return to hospital attribute</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5%</td>
<td>0.83</td>
<td>0.85</td>
</tr>
<tr>
<td>10%</td>
<td>0.78</td>
<td>0.50</td>
</tr>
<tr>
<td>20%</td>
<td>0.64</td>
<td>0.81</td>
</tr>
<tr>
<td>50%</td>
<td>0.19</td>
<td>0.17</td>
</tr>
</tbody>
</table>
Table 4.3: Disease state and sociodemographic characteristics of participants (n=83)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>All patients (n = 83)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sex</strong></td>
<td></td>
</tr>
<tr>
<td>Female, No. (%)</td>
<td>34 (41)</td>
</tr>
<tr>
<td>Male, No. (%)</td>
<td>49 (59)</td>
</tr>
<tr>
<td><strong>Age, mean (range), years</strong></td>
<td>58.8 (31.7-87.6)</td>
</tr>
<tr>
<td><strong>Underlying malignancy and chemotherapy regimen</strong></td>
<td></td>
</tr>
<tr>
<td>Diffuse large B-cell lymphoma treated with CHOP-based regimen, No. (%)</td>
<td>56 (67)</td>
</tr>
<tr>
<td>Other NHL subtype treated with CVP-based regimen, No. (%)</td>
<td>27 (33)</td>
</tr>
<tr>
<td><strong>Previously hospitalized for febrile neutropenia treatment, No. (%)</strong></td>
<td>11 (13)</td>
</tr>
<tr>
<td><strong>Education level</strong></td>
<td></td>
</tr>
<tr>
<td>No degree, certificate, or diploma, No. (%)</td>
<td>8 (10)</td>
</tr>
<tr>
<td>High school diploma, No. (%)</td>
<td>23 (28)</td>
</tr>
<tr>
<td>Trades certificate or college diploma, No. (%)</td>
<td>19 (23)</td>
</tr>
<tr>
<td>Bachelor's degree, No. (%)</td>
<td>14 (17)</td>
</tr>
<tr>
<td>Professional or post-graduate degree, No. (%)</td>
<td>19 (23)</td>
</tr>
<tr>
<td><strong>Employment status prior to NHL diagnosis</strong></td>
<td></td>
</tr>
<tr>
<td>Working fulltime, No. (%)</td>
<td>48 (58)</td>
</tr>
<tr>
<td>Working part-time, No. (%)</td>
<td>2 (2)</td>
</tr>
<tr>
<td>On disability leave from employment, No. (%)</td>
<td>2 (2)</td>
</tr>
<tr>
<td>Unemployed, No. (%)</td>
<td>2 (2)</td>
</tr>
<tr>
<td>Homemaker, No. (%)</td>
<td>2 (2)</td>
</tr>
<tr>
<td>Retired, No. (%)</td>
<td>26 (31)</td>
</tr>
<tr>
<td>Student, No. (%)</td>
<td>1 (1)</td>
</tr>
<tr>
<td><strong>Income level</strong></td>
<td></td>
</tr>
<tr>
<td>Less than $60,000 per year, No. (%)</td>
<td>39 (47)</td>
</tr>
<tr>
<td>More than $60,000 per year, No. (%)</td>
<td>27 (33)</td>
</tr>
<tr>
<td>Did not wish to disclose income, No. (%)</td>
<td>17 (20)</td>
</tr>
</tbody>
</table>
Table 4.4: Regression coefficients

<table>
<thead>
<tr>
<th>Attribute</th>
<th>Coefficient</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intercept</td>
<td>5.51</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Out-of-pocket costs (per $10)</td>
<td>-0.17</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Unpaid caregiver time required daily (per 1 hour)</td>
<td>-0.20</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Probability of return to hospital (per 5%)</td>
<td>-0.63</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>
Figure 4.1: Probability of accepting a scenario for outpatient febrile neutropenia care based on attributes evaluated. Figures 1A and 1C assume 2 hours unpaid caregiver time and Figure 1B assumes $50 in out-of-pocket costs.
Chapter 5 : Summary and Conclusions

The objectives of this chapter are to:

1. Summarize the findings of the three studies that form this thesis
2. Discuss implications of the findings from this thesis on the health care system
3. Discuss the limitations of this thesis
4. Outline directions for future research

5.1 Introduction

The goals of this thesis were to use research methods focused on medical decision making to evaluate the cost–effectiveness of interventions for preventing FN in lymphoma patients, and to demonstrate how two limitations of cost-effectiveness analyses could be overcome. These goals were achieved by conducting a cost-effectiveness analysis of filgrastim pegfilgrastim when used as primary prophylaxis against FN in non-Hodgkin lymphoma patients, deriving an algorithm for converting health-related quality of life data into health utility values that could be employed in cost-effectiveness analyses, and eliciting patients’ preferences for outpatient treatment of febrile neutropenia using a discrete choice experiment. The remainder of this chapter summarizes these three studies, discusses how their findings affect the current health care system, examines their limitations, and finally, outlines directions for future research.

5.2 Summary of studies

5.2.1 Cost-effectiveness of filgrastim and pegfilgrastim (Chapter 2)

This study examined the cost-effectiveness of filgrastim and pegfilgrastim as primary prophylaxis against FN in NHL patients undergoing R-CHOP chemotherapy. Our analysis
estimated that the ICER for filgrastim compared to no primary prophylaxis was $4,599,000/QALY and the ICER for pegfilgrastim compared to filgrastim primary prophylaxis was $6,272,000/QALY. All 1-way sensitivity analyses resulted in ICERs greater than $1,000,000/QALY. CEACs demonstrated that 20% of iterations would be cost-effective at a willingness-to-pay threshold of $1,260,000 for the filgrastim versus no primary prophylaxis strategy, and $1,490,000 for the pegfilgrastim versus filgrastim primary prophylaxis strategy. All of these values are well above normally accepted thresholds for cost-effectiveness, indicating that primary prophylaxis against FN using G-CSFs is not a cost-effective health care intervention. There were two primary limitations to this study: 1) some data used in the analysis was extracted from patient populations that were different from the NHL population considered in this analysis; and 2) the analysis was conducted from the perspective of the publicly funded health care system and, as such, did not account for broader societal or indirect costs that may be associated with treating FN. This analysis suggests that reducing G-CSF use, where appropriate, would yield considerable health care savings without adversely affecting patient outcomes.

5.2.2 Deriving health utility values from an HRQOL instrument (Chapter 3)

This study presented an algorithm for deriving EQ-5D-based health utility values from an HRQOL instrument in NHL patients undergoing chemotherapy. Seventy-five patients completed the FACT-G and EQ-5D questionnaires on 379 occasions. Our analysis demonstrated that when OLS regression was used to derive health utility values from the cancer-specific FACT-G HRQOL instrument, the physical wellbeing, emotional wellbeing, and functional wellbeing subscales of this instrument were significant predictors of health utility. The mean health utility value based on the EQ-5D instrument was 0.8376, while the mean predicted utility based on our model was 0.8375. The mean squared error was 0.0130. This analysis suggests that OLS
regression is a reasonable means for deriving health utility values from disease-specific HRQOL instruments. External validation of such algorithms, using unique datasets, would further arguments that this technique is a valid method for estimating health utilities from HRQOL instruments.

5.2.3 Eliciting patient preferences for outpatient treatment of FN (Chapter 4)

This study examined NHL patients’ preferences for attributes describing outpatient treatment of febrile neutropenia using a discrete choice experiment. The attributes examined were out-of-pocket costs, unpaid caregiver time required daily, and probability of return to hospital. Eighty-eight patients completed the discrete choice questionnaire, which required patients to select a scenario from each of the ten paired scenarios that were presented; each scenario was described by varying levels of the three attributes. Adjusted ORs [95 % confidence intervals] of accepting outpatient care for FN were 0.84 [0.75, 0.95] for each $10 increase in out-of-pocket cost; 0.82 [0.68, 0.99] for each 1 h increase in daily unpaid caregiver time; and 0.53 [0.50, 0.57] for each 5 % increase in probability of return to the hospital. Results of the study indicated that all three attributes were significant predictors of willingness to accept outpatient care for febrile neutropenia, although probability of return to hospital was identified as the attribute that was most important to patients. This study identified factors that should be incorporated into outpatient delivery systems for FN care to ensure adequate patient uptake and success of such programs.

5.3 Implications for the health care system

The findings from this thesis have the potential to influence the delivery of health care services to NHL patients. NHL is the fifth most common malignancy in Canada with about 7500 new
cases diagnosed in 2010. FN is a common side effect of NHL chemotherapy, and, as such, delivery of high quality, cost-effective care to NHL patients who are at risk for FN or who develop this toxicity should be a priority for the health care system. Implementing recommendations from this thesis will help to achieve this goal.

The cost-effectiveness analysis of filgrastim and pegfilgrastim that was presented in Chapter 2 demonstrates that neither of these two interventions is cost-effective for primary prophylaxis against FN in NHL patients. These findings have important implications for both clinicians and health care decision makers. Our results provide definitive evidence for clinicians that use of G-CSFs yield only marginal clinical benefits, while being some of the most expensive cancer therapies available. This work strongly suggests that reducing use of G-CSFs will result in considerable cost savings without adversely affecting patient outcomes.

Our findings also present essential information for health care decision makers. The ICER threshold that normally defines cost-effectiveness is $50,000/QALY. The ICERs estimated for filgrastim and pegfilgrastim based on this analysis are $4,599,000/QALY and $6,272,000/QALY, well above even the highest proposed value of $200,000. These high ICER estimates indicate that filgrastim and pegfilgrastim do not represent value for money compared to other health care interventions. As such, decision makers should focus on funding more cost-effective interventions for the primary prevention of FN, such as the use of prophylactic antibiotics.

The algorithm for converting HRQOL data obtained from the FACT-G instrument in NHL patients into health utility values, presented in Chapter 3, provides a means to convert non-preference based HRQOL data into a preference-based summary measure of HRQOL that can be incorporated into cost-effectiveness analyses. As health care decision makers increasingly
require information on the cost-effectiveness as well as the clinical effectiveness of new health

technologies, the ability to perform cost-effectiveness analyses is essential. Quality of life is

considered an important endpoint in cancer therapies, and, as such, many clinical trials collect

HRQOL data using disease-specific instruments; however, they do not routinely collect health

utility data as non-disease-specific utility instruments generally provide less clinically relevant

information. Our algorithm is valuable to clinicians involved in conducting clinical trials of new

NHL therapies because it allows HRQOL data collected from these trials to be employed in

evaluating the cost-effectiveness of new therapies. Health care decision makers would also find

it valuable as it allows non-preference based HRQOL data to be converted into preference-based

data, thus preventing the need for additional time and resources that would be required to collect

utility data from patients so that the cost-effectiveness of new NHL therapies could be evaluated

in a timely fashion allowing funding decisions to be made in short order.

The evaluation of patient preferences for outpatient treatment of FN that is presented in Chapter

4 provides information for clinicians involved in treating FN and health care decision makers

involved in designing programs for outpatient FN treatment. Our analysis demonstrates that

cost, unpaid caregiver time required daily, and probability of return to hospital were all

significant predictors of patients’ willingness to accept outpatient care. Probability of return was

the attribute most important to patients when considering outpatient care for FN, which likely

reflects fear of treatment failure. Although we found that cost, when varied between $10 and

$100, was not as important to patients as probability of return to hospital, results of our pilot

study in which we varied cost levels up to $1000 demonstrate that there is a cost threshold, above

which patients will not consider outpatient treatment of FN. These results indicate that clinicians

should be conservative in making medical decisions about which patients should be treated at

home for FN to ensure that the probability of return to hospital is minimized. For patients in
whom cost or unpaid caregiver time is a limiting factor for outpatient FN treatment, health care systems or private insurers could provide medications and in-home support free of charges and still realize cost savings, given that the cost of hospitalization for febrile neutropenia is driven by length of stay in hospital.85

5.4 Limitations
The limitations of each study that comprise this thesis are detailed in the respective chapters. There are, however, general limitations to findings in this thesis that warrant discussion. All of the studies were specific to NHL patients. Although the results of the studies may be applicable to other cancer populations, caution must be exercised when generalizing results. For example, our cost-effectiveness analysis concludes that neither filgrastim nor pegfilgrastim are cost-effective as primary prophylaxis against FN in NHL patients, with results being driven by a lack of mortality benefit, which has also been demonstrated in clinical trials of these two agents in other types of cancer. It is likely that G-CSFs are not cost-effective as primary prophylaxis in patients with other types of cancer, but results of our work cannot be generalized to draw such conclusions. Results of our algorithm for converting HRQOL data into health utilities merits similar caution, despite the fact that both instruments used in the analysis could be used to evaluate HRQOL and health utility in patients with other types of cancers. In this case, we cannot make any predictions about how such an algorithm would perform in patients other than those with NHL, and investigators should refrain from applying our findings to populations other than NHL patients. Finally, results of our discrete choice experiment may be appear to be applicable to other cancer populations besides NHL since we asked patients to evaluate three fairly general attributes: out-of-pocket costs, daily unpaid caregiver time required, and probability of return to hospital. However, there may be different underlying characteristics in
patients with other types of malignancies that may affect their preferences when considering outpatient treatment of FN, and caution must be used when extrapolating results of this study.

5.5 Directions for future research

There are a number of important findings detailed in this thesis; however, results of this work also point to a number of areas in which future research would be valuable. Results of our cost-effectiveness analysis have demonstrated that G-CSFs are not cost-effective for the primary prevention of FN in NHL patients. However, FN remains a common and serious adverse effect of R-CHOP chemotherapy\textsuperscript{8,13} As such, the cost-effectiveness of alternate strategies for preventing FN, such as use of prophylactic antibiotics,\textsuperscript{78} employing selective dose reductions and delays, and finally, reducing the cost of G-CSFs to a level where they become cost-effective should be evaluated.

Our algorithm for deriving health utility values from a disease-specific HRQOL instrument was not externally validated with a unique dataset. Future work should focus on external validation of this algorithm and other similar ones that have been published to enhance the validity of this technique as a means of deriving health utility values, which are required to incorporate quality of life into cost-effectiveness analyses.

Our discrete choice experiment determined that out-of-pocket costs, unpaid caregiver time required daily, and probability of return to hospital are significant predictors of NHL patients’ willingness to accept outpatient treatment of FN. Future studies should evaluate whether there are other factors that affect patients’ preferences for outpatient FN treatment. Also, studies evaluating patients’ concerns in established programs for outpatient treatment of FN should be done to evaluate whether discrete choice experiments accurately capture patient preferences.
5.6 Conclusions

This thesis examined methods used in health care decision making to evaluate strategies for the prevention and treatment of FN in NHL patients. Results of this work have the potential to influence health care decision making related to the treatment of FN. We have demonstrated that G-CSFs are not a cost-effective means of primary prophylaxis against FN in NHL patients, and our analysis provides evidence that reducing use of these agents will lead to considerable cost savings without adversely affecting patient outcomes. We have also presented an algorithm for deriving health utility values from a disease-specific HRQOL instrument, which could be employed by investigators evaluating new treatments for NHL. Finally we quantified patients’ preferences for outpatient treatment of FN, which will inform clinicians and decision makers of factors important to patients when establishing such programs. As the incidence of NHL continues to rise, along with costs of treating cancer, results of our work provide health care decision makers with information required to make decisions related to the treatment of FN, a common adverse effect of NHL chemotherapy, that represent a cost-effective use of limited health care resources.
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