A cost-utility analysis of Risk Model-Guided versus Physician's Choice antiemetic prophylaxis in patients receiving chemotherapy for early-stage breast cancer: a net-benefit regression approach

Kednapa Thavorn[1,2,3*], Doug Coyle[2], Jeffrey S. Hoch[4], Lisa Vandermeer[5], Sasha Mazzarello[5], Zhou Wang[6], George Dranitsaris[7], Dean Fergusson[1,2,8,9], Mark Clemons[1,2,5]

1 Ottawa Hospital Research Institute, The Ottawa Hospital, Ottawa, Ontario, Canada;
2 School of Epidemiology, Public Health and Preventive Medicine, University of Ottawa, Ottawa, Ontario, Canada;
3 Institute for Clinical Evaluative Sciences (ICES uOttawa), Ottawa, Ontario, Canada;
4 Department of Public Health Sciences, University of California, Davis, California, USA;
5 Division of Medical Oncology and Department of Medicine, University of Ottawa, Ottawa, Canada
6 Department of Statistics and Actuarial Science, University of Waterloo, Waterloo, Ontario, Canada
7 Statistical Consultant, Toronto, Ontario, Canada
8 Department of Medicine, University of Ottawa, Ottawa, Canada.
9 Department of Surgery, University of Ottawa, Ottawa, Canada.

***Corresponding Author**

Kednapa Thavorn, PhD
The Ottawa Hospital–General Campus,
501 Smyth Road, PO Box 201B,
Ottawa, Ontario, Canada K1H 8L6.
E-mail: kthavorn@ohri.ca
Tel: +1-613-737-8899 ext 72330
Fax: +1-613-739-6939

Authors' contributions: KT, LV, SM, DF and MC contributed to the conception of the study question and design. DC, JH and GD guided the analyses. LV and ZW helped with data management. KT performed the analyses and prepared the first draft of the manuscript. All authors reviewed and approved the manuscript.

Authors have no conflicts of interest to disclose.

This study was conducted without funding.

Abstract (maximum 250, current 250)

Purpose:

We assessed the cost-effectiveness of a Risk Model-Guided (RMG) antiemetic prophylaxis strategy compared with the Physician's Choice (PC) strategy in patients receiving chemotherapy for early-stage breast cancer.

Methods:

We conducted a cost-utility analysis based on a published randomized controlled trial of 324 patients with early stage breast cancer undergoing chemotherapy at two Canadian cancer centers. Patients were randomized to receive their antiemetic treatments according to either predefined risk scores or the treating physician's preference. Effectiveness was measured as quality-adjusted life years (QALYs) gained. Cost and utility data were obtained from the Canadian published literature. We used generalized estimating equations to estimate the incremental cost-effectiveness ratios (ICER) and 95% confidence intervals (CIs) over a range of willingness to pay values. The lower and upper bounds of the 95% CIs were used to characterize the statistical uncertainty for the cost-effectiveness estimates and construct cost-effectiveness acceptability curves.

Results:

From the health care system's perspective, the RMG strategy was associated with greater QALYs gained (0.0016, 95% CI: 0.0009, 0.0022) and higher cost ($49.19, 95% CI: $24.87, $73.08) than the PC strategy, resulting in an ICER of $30,864.28 (95% CI: $14,718.98, $62,789.04). At the commonly used threshold of $50,000/QALY, the probability that RMG prophylaxis is cost-effective was >94%; this probability increased with greater willingness to pay values.

Conclusion:

The risk-guided antiemetic prophylaxis is an economically attractive option for patients receiving chemotherapy for early-stage breast cancer. This information supports the implementation of risk prediction models to guide chemotherapy-induced nausea and vomiting prophylaxis in clinical practices.

Introduction

Nausea and vomiting are among the most feared and distressing side-effects of chemotherapy for cancer patients [1-3]. They contribute to the poorer quality of life and can lead to chemotherapy dose delays, reductions and discontinuation. The risk of chemotherapy-induced nausea and vomiting (CINV) varies according to the type and dose of chemotherapy regimen administered and is associated with factors, including female sex, younger age, history of motion sickness, history of CINV with previous chemotherapy cycles as well as the endpoint chosen to measure CINV [4-8]. Effective prophylaxis for CINV therefore requires full consideration of these patient-centered factors in addition to the emetogenic potential of the chemotherapy agents being used. However, most treatment guidelines recommend the selection of antiemetic agents for patients with early stage breast cancer receiving cyclophosphamide with anthracycline-based chemotherapy based on solely the emetogenicity of the chemotherapy regimens [4].

Despite practice-based guidelines recommending that all patients receive an antiemetic combination containing a neurokinin-1 (NK-1) receptor antagonist, it is evident from international data that adherence to these guidelines is not optimal [9-11] and that clinical practice globally is much more variable than the guidelines would suggest. The reasons for this are likely multifactorial but include the relatively high cost of NK1 inhibitors [12] and the fact that no optimal antiemetic regimen has been identified for patients receiving cyclophosphamide with anthracycline-based chemotherapy [5,13].

Recently, a prediction model for identifying patients at high risk of CINV was developed and validated to guide the selection of antiemetic agents for cancer patients [14,15]. The model uses key chemotherapy and patient-related factors for CINV to estimate numerical scoring systems and predict patients at higher risk for acute (the first 24 hours after chemotherapy) and delayed (between 24 hours and five days after chemotherapy) CINV prior to each cycle of the chemotherapy. This prediction tool has good predictive accuracy, and patients identified by the scoring systems as high-risk were three to four times more likely to develop acute and delayed CINV than those with low-risk [16].

The clinical effectiveness of this prediction tool was assessed in a recent randomized controlled trial (RCT) comparing the efficacy of the Risk-Model Guided (RMG) to the Physician's Choice (PC) antiemetic prophylaxis strategies in patients receiving cyclophosphamide with

anthracycline based chemotherapy for early-stage breast cancer in two cancer care centers in Ottawa, Ontario, Canada [17]. The trial showed that the RMG strategy improved control of CINV significantly in both acute and delayed periods compared to the PC group.

Although the RMG strategy is effective in guiding the choice of antiemetic therapy, it may involve the greater use of NK-1 receptor antagonists (e.g. aprepitant) that are more expensive than older antiemetic agents. Given the limited health care budget, the decision to implement the risk-guided model therapy in clinical practice should be informed by its cost-effectiveness profile. This cost-utility study was therefore conducted to estimate the incremental cost and quality-adjusted life years (QALYs) gained associated with the risk-guided compared with the physician's choice antiemetic prophylaxis strategies from the health care system's and the societal perspectives.

Methods

This cost-utility analysis is based on a published RCT [17] which compared the effect of the RMG antiemetic prophylaxis on complete control of nausea and vomiting after chemotherapy with the PC antiemetic prophylaxis. Patients randomized to the RMG arm had their acute or delayed antiemetic risk scores calculated prior to each cycle of chemotherapy (Appendix 1). Patients predicted to be at low-risk received antiemetic prophylaxis for moderately emetogenic regimens based on provincial guidelines (i.e. ondansetron and dexamethasone). Patients predicted to be at high-risk received an emetogenic regimen containing dexamethasone, ondansetron, and aprepitant. The antiemetic protocol is shown in Appendix 2. Patients in the PC group received antiemetic agents based on the treating physician's choice. For each chemotherapy cycle, the primary outcome of the RCT, i.e. complete control of nausea and vomiting, was measured at the first 24 hours (acute), day 2 and day 5 (delayed) after chemotherapy using a self-reported patient diary, supplementing by a telephone call by a study coordinator.

In this present study, we used QALYs to represent the effectiveness of the RMG and the PC antiemetic prophylaxis strategies. We estimated QALYs over the entire 5-day follow-up period by multiplying the number of days spent in four health states (no nausea or vomiting, nausea without vomiting, vomiting without nausea, or experienced both nausea and vomiting) by their respective utility values. We obtained utility scores for CINV from a published study that used a

visual analog scale to estimate the utility values from 96 adult cancer patients undergoing chemotherapy for either breast or lung cancer in the Cancer and Leukemia Group B (CALGB) member institutions [18]. The median age of participants was 55.1 years, and the majority of these participants were women (78.1%) and patients with breast cancer (65.7%). The mean utility values for each health state are presented in Table 1.

We obtained resource use associated with the RMG and the PC antiemetic prophylaxis strategies from the diaries of patients participating in the RCT. Our base case analysis employed a health care system's perspective and included the following health resource components: antiemetic agents, rescue medications, chemotherapy delivered, hospitalization, and physician visits. We sourced the cost of antiemetic agents and rescue medications from the Ontario Drug Benefit Formulary [19]. Total medication cost included dispensing fee and 8% markup. Chemotherapy cost consisted of drug acquisition and administration cost. The cost of 5-fluorouracil, doxorubicin, and cyclophosphamide (FAC) was obtained from the economic analysis of docetaxel in combination with doxorubicin and cyclophosphamide (AC) compared with FAC for women with operable, axillary lymph node-positive breast cancer in Canada [20]. The cost of 5-flurouracil, epirubicin and cyclophosphamide (FEC) was gathered from a Canadian cost-utility analysis of FEC-D versus FEC 100 [21]. The cost of doxorubicin and cyclophosphamide was based on a Canadian published study that assessed the cost-utility of adjuvant chemotherapy using docetaxel and cyclophosphamide compared with AC in breast cancer patients [22]. Hospitalization related to CINV was measured in the RCT [17]. If a participant experienced either acute or delayed nausea/vomiting after receiving chemotherapy, the severity of CINV was assessed by a research coordinator. If the CINV led to any hospitalizations, the severity of the CINV was coded as Grade 3 hospitalization in a case report form. We mapped this hospital admission data to average hospital cost per visit of $3,226 (length of stay=2.7 days) for nausea and $3,602 (length of stay=2.9 days) for vomiting sought from the Ontario Case Costing Initiative [23]. Initial and follow-up fees for a medical oncologist visit were based on the Ontario Schedule of Benefits for Physician Services [24]. We inflated all cost to 2015 Canadian dollars using Consumer Price Index (Healthcare Component) [25].

We performed a cost-utility analysis using the net benefit regression framework [26]. We first converted QALYs into a monetary benefit by multiplying QALYs with a range of willingness to

pay (WTP) values. The WTP represents the amount that a decision maker is willing to pay for an additional unit of QALY. The net benefit is equal to the monetary value of the outcome gain (QALYs*WTP) and the cost difference between antiemetic prophylaxis strategies. Given that the appropriate value of WTP is unknown, we assumed a series of WTP values ranging from $0 to $120,000 per QALY. We used the generalized estimating equations (GEEs) [27] to calculate the incremental net benefit (INB) while controlling for unbalanced confounding factors and repeated nature of cost and outcome data. Patients and cycles of the chemotherapy were the units of analysis in this study. Guided by previous studies [14,15,17], we included the following factors in the net benefit regression: age, type of the chemotherapy received, history of motion or morning sickness, the number of the chemotherapy cycle, alcohol intake per day, and the presence of comorbidity. The INB was denoted by the coefficient of the intervention indicator. The intervention is cost-effective if the INB is greater than zero. An incremental cost per QALY gained is equal to the value at which INB is equal to zero [28].

We characterized the statistical uncertainty by estimating 95% confidence intervals (CIs) using a non-parametric bootstrapping method. Based on 5,000 iterations, we created cost-effectiveness acceptability curves (CEACs), which link the probability of an intervention being cost-effective over a range of threshold values that the decision makers may be willing to pay for an additional unit of QALY. The uncertainty of the INB was also displayed visually by plotting the INB and its 95% CIs over the range of WTP values.

As a secondary analysis, we conducted a cost-utility analysis from a societal perspective and included productivity loss. We approximated the productivity loss associated with CINV by multiplying time lost from paid employment due to CINV with average hourly wages reported by Statistics Canada [29]. A prospective, multicenter, observational study estimated the effect of CINV on functional status and cost in 128 patients receiving cancer care from five Canadian centers and found that patients with CINV lost, on average, 2.8 hours from their paid employment [30]. All resources and unit cost included in our study are shown in Table 1.

We did not discount both cost and QALYs because the time horizon of the analysis was five days following the chemotherapy.

All analyses were performed using STATA version 14.1 (StataCorp, College Station, TX). The study protocol has been approved by local institutional review boards.

Results

The trial enrolled 324 patients (154 patients in the RMG group and 170 in the PC control group). Characteristics of patients enrolled in the trial were described elsewhere [17]. In brief, patients in both groups were well-balanced in terms of age, the stage of breast cancer, the number of chemotherapy cycles, coexisting medical conditions, and risk factors for CINV. However, health resource use varied considerably across arms. In the RMG group, medical oncologists prescribed three antiemetic prophylaxis regimens, including dexamethasone (day 1 or day 1-3), ondansetron (day 1), and aprepitant (day 1-3). The percentage of patients who received aprepitant increased from 83.9% at cycle 1 following the chemotherapy to 94.6% at cycle 4. For patients in the PC group, 17 to 29 antiemetic prophylaxis regimens were used. The three most commonly prescribed regimens included a combination of dexamethasone (day 1-3) and ondansetron (day 1-3) followed by a combination of dexamethasone (day 1-3) and ondansetron (day 1) as well as dexamethasone (day 1-3) and ondansetron (day 1-2), respectively. Patients in both groups had comparable numbers of physician visits (2.2 for RMG vs. 2.2 for PC, p=0.631) during the follow-up period. Patients in the RMG group experienced fewer numbers of hospital admissions (one admission for RMG vs. three admissions for PC, p=0.387) and fewer hours lost due to CINV than the PC group (2.67 vs. 3.68, p-value <0.001).

Table 2 shows the cost, QALYs and incremental cost-effectiveness ratios estimated from this study. For both groups, the cost of medication was the main cost driver (84% for RMG vs. 79% for PC), followed by physician cost (7.3% for RMG vs. 7.4% for PC) and hospital cost (0.7% for RMG vs. 2.1% for PC), respectively. From a perspective of the publicly funded health care system, the RMG strategy led to an additional cost of $49.19 (95% CI: $24.87, $73.08) but also improved 0.0016 units of health outcome (95% CI: 0.0009, 0.0022), yielding an incremental cost-effectiveness ratio of $30,864.28 per QALY gained (95% CI: $14,718.98, $62,789.04).

The net-benefit regressions revealed positive INB when WTP values were greater than $30,000 per QALY gained [Figure 1a], suggesting that the use of the RMG antiemetic prophylaxis is cost-effective if the health care system is willing to pay at least $30,000 to improve one unit of QALY. The INB was also found to increase with the greater value of WTP, ranging from -$46.52 to $143.53. We did not observe any significant interactions between the treatment indicator and other confounding factors.

Uncertainty analysis

The 95% CIs around the INB estimates were wider with the greater value of WTP, indicating higher uncertainty with higher willingness to pay [Figure 1a].

The cost-effectiveness plane [Figure 2a] reveals that the RMG antiemetic prophylaxis incurred higher cost but improved QALYs compared to the PC prophylaxis strategy in 100% of the 5,000 bootstrapping iterations. The CEAC (Figure 3) indicates that the probability that the RMG strategy is cost-effective increased with greater WTP values. At a commonly used threshold of $50,000 per QALY gained, there was 94% that the RMG antiemetic prophylaxis is cost-effective compared with the PC prophylaxis strategy.

Secondary analysis

From the societal perspective, the RMG antiemetic prophylaxis was also associated with higher cost ($20.58, 95% CI: -$4.52, $47.07) and better health outcome (0.0016 QALYs, 95% CI: 0.0009, 0.0022) than the PC prophylaxis strategy, leading to an incremental cost-effectiveness ratio of 12,914.65 per QALY gained (95% CI: -$2,570.40, $41,042.95). Holding other factors constant, the INB values were found to be positive after the WTP value was greater than $10,000 per QALY gained [Figure 1b]. This means that the RMG would be considered as a cost-effective option if the society is willing to pay greater than $10,000 per one additional QALY gained. Similar to our base case analysis, the uncertainty around INB and the probability that the RMG is cost-effective increased with higher WTP values. However, the probability that the RMG strategy is cost-effective compared to the PC strategy was 99.4% at the commonly used WTP of $50,000 per QALY [Figure 2b and 3].

Discussion

Our trial-based cost-utility analysis suggests that the risk-guided antiemetic prophylaxis strategy was cost-effective from the perspective of the publicly funded health care system. This favorable cost-effective finding may be due to fewer hospital admissions and greater QALYs gained as a result of better CINV control in the RMG group. These health benefits could offset the higher cost of a novel antiemetic agent used.

The RMG antiemetic prophylaxis was more economically attractive from the societal perspective whereby productivity loss attributed to CINV was taken into account. Our finding was plausible given that indirect cost of CINV is substantial. In 1993, O'Brien et al. [30] estimated the cost of CINV in five Canadian Centers before the advent of the serotonin (5-HT3) or NK-1 receptor antagonists and found that CINV led to an average loss of 2.8 hours of paid employments or an additional productivity loss of $118.70 per patient. This indirect cost accounted for two-third of total CINV cost. More recently, Lachaine et al. [31] reported that patients with CINV lost an average of 12.9 hours from their paid employment, corresponding to $233 per patient or 83% of total cost of CINV in 2005.

To date, no study has compared the cost-effectiveness of the risk-guided model to the physician's choice CINV prophylaxis. Existing studies assessed the cost-effectiveness of various antiemetic regimens and suggested that compared to non-aprepitant regimens, aprepitant-based regimens were associated with improved QALYs at a higher cost and found to be cost-effective in Belgium [32], Germany [33] and Hong Kong [34] but not in the US [35]. The unfavorable cost-effectiveness findings in the US was deemed to be a result of the omission of hospital cost and the higher cost of aprepitant compared to other countries. Unlike other studies, Moore et al. [35] did not include hospital cost in the cost of care estimation. In their sensitivity analysis, the authors suggested that the use of aprepitant became cost-effective after the total cost of aprepitant was lower than US$32 per dose. In Canada, aprepitant would be cost-effective at a threshold of C$20,000 per QALY from the health system's perspective if its cost was reduced to C$9.53 per dose (in 2015 Canadian dollar) [36]. Our sensitivity analysis was in line with this Canadian study and showed that the ICER of the RMG strategy would be lower than $20,000 per QALY gained if the cost of aprepitant was decreased to 25% of its current price, i.e. from C$34.39 to C$8.60 (data not shown). Although it is difficult to compare our findings to existing studies due to different comparators used in the analysis, their findings could partially explain why patients in the risk-guided model group incurred higher total costs than the PC group. In our study, aprepitant was prescribed more often for patients in the RMG group than the PC group (92.1% vs. 19.2%), and the average cost of aprepitant was C$34.39 per dose.

This economic evaluation was based on an RCT that allows prospective collection of health resource use and effectiveness measures. The use of the net-benefit regression framework

eliminates the ambiguous situation when an incremental cost-effective ratio (ICER) is negative because the cost and QALY measures are combined and shown as a single value called an INB. With a negative ICER estimate, an intervention could be interpreted as a cost-savings (less expensive but improved QALYs) or a non-economically attractive option (more expensive with fewer QALYs) strategy. With the net-benefit regression, the negative INB solely reflects that the intervention is not cost-effective. The net-benefit regression framework also allows us to apply a standard regression technique, i.e. a GEE regression, to estimate the value of money of the antiemetic prevention strategies while adjusting for repeated nature of cost and outcome data and remaining confounding factors.

Our study has some limitations that merit discussion. First, as shown in the results of the sensitivity analyses (Figures 2a and 2b), there was a great level of uncertainty around QALY estimates. The high level of uncertainty may be due to QALY values that were estimated by mapping the number of days spent in different nausea/vomiting states measured in the RCT [17] to their respective utility scores reported in the published study [31]. There is some concern whether QALYs adequately capture all of the benefits in situations with acute, severe health states, like CINV. Although the generic rating scales instrument was able to rank utility values by degrees of nausea and vomiting, it may be insensitive to capture functioning changes expected in patients with CINV. This potential measurement error may under- or over-estimate the cost-effectiveness ratios and the probabilities that the RMG strategy was cost-effective. Although it would have been ideal to estimate utilities from the clinical trial population, a health utility questionnaire was not included in the original trial.

Second, as our study was based on a single RCT, health resource use by trial participants may not represent the actual use in clinical practices. Moreover, hospital cost used in our study may not reflect actual demand for hospital care in this population because the original trial did not collect hospital length of stays. To assess the effect of hospitalization on the cost-effectiveness results, we performed a scenario analysis by excluding hospitalization cost from the analysis. As expected, the estimated incremental cost-effectiveness ratios increased from $30,864 to $39,736 per QALY gained from the perspective of the healthcare system and $12,915 to $22,111 per QALY gained from the societal perspective (Appendix 3).

Another limitation is that the current study compared the RMG to the PC antiemetic prophylaxis strategy, whereby the PC group could choose whatever antiemetic combination they felt was appropriate. Multiple studies have shown that CINV prophylaxis according to guidelines is significantly more effective than CINV prophylaxis at the physician's choice [37]. However, as stated in the introduction, antiemetic prescribing in real-world practice is significantly different from that recommended in guidelines. An important contribution of our analysis is that the Physician's Choice group reflects real-world practice as the oncologist could prescribe whatever antiemetic regimen they wish [17]. While this economic evaluation was conducted from the Canadian perspective, our study provides an example and a framework for others who are interested in evaluating the value for money of real-world antiemetic prophylaxis strategies.

Finally, we obtained productivity loss data from the Canadian study conducted in 1993; these data might be overestimated because the advent of a new class of antiemetic drugs, such as aprepitant, might reduce the incidence, severity and the impact of nausea and emesis on the loss of productivity for patients and their caregivers. Despite these limitations, we characterized the statistical uncertainty in the data using the 95% CIs and presented the results on a cost-effectiveness plane. Our uncertainty analysis suggested that the probability that the RMG is cost-effective was above 94% from the health care system's and 99% from the societal perspectives at the commonly used threshold of $50,000 per QALY.

Despite these limitations, our study highlights that the RMG for prevention of CINV offers a good value for money from both publicly funded health care system's and societal perspectives. The results of this economic evaluation can be used to support the decision to implement the risk prediction model to guide CINV prophylaxis in clinical practices.

References

1. 1. Coates A, Abraham S, Kaye SB, Sowerbutts T, Frewin C, Fox RM, Tattersall MH (1983) On the receiving end--patient perception of the side-effects of cancer chemotherapy. Eur J Cancer 19 (2):203-208
2. Roscoe JA, Morrow GR, Hickok JT, Stern RM (2000) Nausea and vomiting remain a significant clinical problem: trends over time in controlling chemotherapy-induced nausea and vomiting in 1413 patients treated in community clinical practices. J Pain Symptom Manage 20 (2):113-121
3. Kuchuk I, Bouganim N, Beusterien K, Grinspan J, Vandermeer L, Gertler S, Dent SF, Song X, Segal R, Mazzarello S, Crawley F, Dranitsaris G, Clemons M (2013) Preference weights for chemotherapy side effects from the perspective of women with breast cancer. Breast Cancer Res Treat 142 (1):101-107. doi:10.1007/s10549-013-2727-3
4. Jordan K, Sippel C, Schmoll HJ (2007) Guidelines for antiemetic treatment of chemotherapy-induced nausea and vomiting: past, present, and future recommendations. Oncologist 12 (9):1143-1150. doi:10.1634/theoncologist.12-9-1143
5. Ng T, Mazzarello S, Wang Z, Hutton B, Dranitsaris G, Vandermeer L, Smith S, Clemons M (2016) Choice of study endpoint significantly impacts the results of breast cancer trials evaluating chemotherapy-induced nausea and vomiting. Breast Cancer Res Treat 155 (2):337-344. doi:10.1007/s10549-015-3669-8
6. Dranitsaris G, Mazzarello S, Smith S, Vandermeer L, Bouganim N, Clemons M (2016) Measuring the impact of guideline-based antiemetic therapy on nausea and vomiting control in breast cancer patients with multiple risk factors. Support Care Cancer 24 (4):1563-1569. doi:10.1007/s00520-015-2944-x
7. Hernandez Torres C, Mazzarello S, Ng T, Dranitsaris G, Hutton B, Smith S, Munro A, Jacobs C, Clemons M (2015) Defining optimal control of chemotherapy-induced nausea and vomiting-based on patients' experience. Support Care Cancer 23 (11):3341-3359. doi:10.1007/s00520-015-2801-y
8. Dranitsaris G, Clemons M (2014) Risk prediction models for chemotherapy-induced nausea and vomiting: almost ready for prime time? Support Care Cancer (4):863-864. doi:10.1007/s00520-014-2134-2
9. Lee MA, Cho EK, Oh SY, Ahn JB, Lee JY, Thomas B, Jung H, Kim JG (2016) Clinical Practices and Outcomes on Chemotherapy-Induced Nausea and Vomiting Management in South Korea: Comparison with Asia-Pacific Data of the Pan Australasian Chemotherapy Induced Emesis Burden of Illness Study. Cancer Res Treat 48 (4):1420-1428. doi:10.4143/crt.2015.309
10. Zong X, Zhang J, Ji X, Gao J, Ji J (2016) Patterns of antiemetic prophylaxis for chemotherapy-induced nausea and vomiting in China. Chin J Cancer Res 28 (2):168-179. doi:10.21147/j.issn.1000-9604.2016.02.04
11. Caracuel F, Munoz N, Banos U, Ramirez G (2015) Adherence to antiemetic guidelines and control of chemotherapy-induced nausea and vomiting (CINV) in a large hospital. J Oncol Pharm Pract 21 (3):163-169. doi:10.1177/1078155214524809
12. Van Laar ES, Desai JM, Jatoi A (2015) Professional educational needs for chemotherapy-induced nausea and vomiting (CINV): multinational survey results from 2388 health care providers. Support Care Cancer 23 (1):151-157. doi:10.1007/s00520-014-2325-x
13. Hutton B, Clemons M, Mazzarello S, Kuchuk I, Skidmore B, Ng T (2015) Identifying an optimal antiemetic regimen for patients receiving anthracycline and cyclophosphamide-based chemotherapy for breast cancer--an inspection of the evidence base informing clinical decision-making. Cancer Treat Rev 41 (10):951-959. doi:10.1016/j.ctrv.2015.09.007
14. Dranitsaris G, Joy A, Young S, Clemons M, Callaghan W, Petrella T (2009) Identifying patients at high risk for nausea and vomiting after chemotherapy: the development of a practical prediction tool I. J Support Oncol 7:W1–8

15. Petrella T, Clemons M, Joy A, Young S, Callaghan W, Dranitsaris G (2009) Identifying patients at high risk for nausea and vomiting after chemotherapy: the development of a practical prediction tool II. J Support Oncol 7:W9–16
16. Bouganim N, Dranitsaris G, Hopkins S, Vandermeer L, Godbout L, Dent S, Wheatley-Price P, Milano C, Clemons M (2012) Prospective validation of risk prediction indexes for acute and delayed chemotherapy-induced nausea and vomiting. Curr Oncol 19 (6):e414-421. doi:10.3747/co.19.1074
17. Clemons M, Bouganim N, Smith S, Mazzarello S, Vandermeer L, Segal R, Dent S, Gertler S, Song X, Wheatley-Price P, Dranitsaris G (2016) Risk Model-Guided Antiemetic Prophylaxis vs Physician's Choice in Patients Receiving Chemotherapy for Early-Stage Breast Cancer: A Randomized Clinical Trial. JAMA Oncol 2 (2):225-231. doi:10.1001/jamaoncol.2015.3730
18. Grunberg S, WEeks J, Mgnan WF, Herndon J, Naughton M, Blackwell KL, Wood ME, Christian DL, Perry MC, Dees C, Reed E, Marshall E, for the Cancer and Leukemia Group B (2009) Determination of Utilities for Control of Chemotherapy-Induced Nausea or Vomiting–CALGB 309801. J Support Oncol 7:W17–W22
19. Ontario Ministry of Health and Long-term Care (2016) Ontario Drug Benefit Formulary/Comparative Drug Index. https://www.formulary.health.gov.on.ca/formulary/. Accessed May 2 2016
20. Mittmann N, Verma S, Koo M, Alloul K, Trudeau M (2010) Cost effectiveness of TAC versus FAC in adjuvant treatment of node-positive breast cancer. Curr Oncol 17 (1):7-16
21. Younis T, Rayson D, Sellon M, Skedgel C (2008) Adjuvant chemotherapy for breast cancer: a cost-utility analysis of FEC-D vs. FEC 100. Breast Cancer Res Treat 111 (2):261-267. doi:10.1007/s10549-007-9770-x
22. Younis T, Rayson D, Skedgel C (2011) The cost-utility of adjuvant chemotherapy using docetaxel and cyclophosphamide compared with doxorubicin and cyclophosphamide in breast cancer. Curr Oncol 18 (6):e288-296
23. Ontario Case Costing Initiative (2012) OCCI costing analysis tool. http://www.occp.com/mainPage.htm. Accessed February 14 2015
24. Ontario Ministry of Health and Long-term Care (2016) Schedule of Benefits for Physician Services under the Health Insurance Act. http://www.health.gov.on.ca/english/providers/program/ohip/sob/physserv/sob_master20160406.pdf. Accessed May 2 2016
25. Statistics Canada (2016) Table 326-0021 - Consumer Price Index, annual (2002=100 unless otherwise noted), CANSIM (database). http://www5.statcan.gc.ca/cansim/a26?lang=eng&retrLang=eng&id=3260021&&pattern=&stByVal=1&p1=1&p2=37&tabMode=dataTable&csid=. Accessed May 31 2016
26. Hoch JS, Briggs AH, Willan AR (2002) Something old, something new, something borrowed, something blue: a framework for the marriage of health econometrics and cost-effectiveness analysis. Health Econ 11 (5):415-430. doi:10.1002/hec.678
27. Diggle P, Heagerty P, Liang K, Zeger S (2013) Analysis of longitudinal data. 2 edn. Oxford University Press, Oxford
28. Drummond MF, Stoddart GL, Torrance GW (2005) Methods for the economic evaluation for health care program. University Press, Oxford
29. Statistics Canada (2016) Average hourly wages of employees by selected characteristics and occupation, unadjusted data, by province (monthly) (Canada). http://www.statcan.gc.ca/tables-tableaux/sum-som/l01/cst01/labr69a-eng.htm. Accessed May 31 2016
30. O'Brien BJ, Rusthoven J, Rocchi A, Latreille J, Fine S, Vandenberg T, Laberge F (1993) Impact of chemotherapy-associated nausea and vomiting on patients' functional status and on costs: survey of five Canadian centres. CMAJ 149 (3):296-302
31. Lachaine J, Yelle L, Kaizer L, Dufour A, Hopkins S, Deuson R (2005) Chemotherapy-induced emesis: quality of life and economic impact in the context of current practice in Canada. Support Cancer Ther 2 (3):181-187. doi:10.3816/SCT.2005.n.011

32. Annemans L, Strens D, Lox E, Petit C, Malonne H (2008) Cost-effectiveness analysis of aprepitant in the prevention of chemotherapy-induced nausea and vomiting in Belgium. Support Care Cancer 16 (8):905-915. doi:10.1007/s00520-007-0349-1
33. Lordick F, Ehlken B, Ihbe-Heffinger A, Berger K, Krobot KJ, Pellissier J, Davies G, Deuson R (2007) Health outcomes and cost-effectiveness of aprepitant in outpatients receiving antiemetic prophylaxis for highly emetogenic chemotherapy in Germany. Eur J Cancer 43 (2):299-307. doi:10.1016/j.ejca.2006.09.019
34. Chan SL, Jen J, Burke T, Pellissier J (2014) Economic analysis of aprepitant-containing regimen to prevent chemotherapy-induced nausea and vomiting in patients receiving highly emetogenic chemotherapy in Hong Kong. Asia Pac J Clin Oncol 10 (1):80-91. doi:10.1111/ajco.12170
35. Moore S, Tumeh J, Wojtanowski S, Flowers C (2007) Cost-effectiveness of aprepitant for the prevention of chemotherapy-induced nausea and vomiting associated with highly emetogenic chemotherapy. Value Health 10 (1):23-31. doi:10.1111/j.1524-4733.2006.00141.x
36. Dranitsaris G, Leung P (2004) Using decision modeling to determine pricing of new pharmaceuticals: the case of neurokinin-1 receptor antagonist antiemetics for cancer chemotherapy. Int J Technol Assess Health Care 20 (3):289-295
37. Aapro M, Molassiotis A, Dicato M, Pelaez I, Rodriguez-Lescure A, Pastorelli D, Ma L, Burke T, Gu A, Gascon P, Roila F (2012) The effect of guideline-consistent antiemetic therapy on chemotherapy-induced nausea and vomiting (CINV): the Pan European Emesis Registry (PEER). Ann Oncol 23 (8):1986-1992. doi:10.1093/annonc/mds021

Table 1. Input parameters used for a cost-utility analysis

Variable	Value	Source
Cost		
Antiemetic agent/rescue therapy ($ per dose)		
– Dexamethasone 10 mg	5.48	Ontario Drug Benefit formulary (2016)
– Dexamethasone 4 mg	0.08	
– Ondansetron 8 mg	7.44	
– Aprepitant Tri-pack (80/125 mg)	34.39	
– Olanzapine 2.5 mg	0.49	
– Methotrimeprazine*	0.28	
– Metoclopramide 10 mg	0.07	
– Prochlorperazine 10 mg	0.22	
Chemotherapy agent ($ per cycle)		
– 5-fluorouracil, doxorubicin and cyclophosphamide (FAC)	229.36	Mittman et al. (2010)
– Doxorubicin and cyclophosphamide (AC)	324.75	Younis et al. (2008)
– 5-flurouracil, epirubicin and cyclophosphamide (FEC)	895.33	Younis et al. (2011)
Hospitalization ($ per admission)		
– Nausea	3,226.10	Ontario Case Costing Initiative (2012)
– Vomiting	3,602.21	Ontario Case Costing Initiative (2012)
Medical oncologist visit ($ per visit)		
– Initial visit	157	Ontario Schedule of Benefits for Physician Services (2015)
– Follow-up visit	31	
Productivity loss		
– Number of lost hour per chemotherapy-induced nausea vomiting episode	2.75	O'Brien et al. (1993)
– Average wage ($)	26.91	Statistics Canada (2016)
Utility values		
– No nausea or vomiting	0.82	Grunberg et al. (2009)
– Nausea without vomiting	0.60	
– Vomiting without nausea	0.55	
– Experience nausea and vomiting	0.42	

Table 2. Cost, quality-adjusted life year and incremental cost-effectiveness ratios

Variable	RMG group (n=154)	PC group (n=170)	Mean difference (95% CI)
Unadjusted cost ($), mean (SD)			
– Medication	788.33 (282.44)	739.30 (280.75)	49.03 (15.16, 80.16)
– Hospital	6.48 (144.56)	19.61 (265.32)	-13.13 (-39.22, 12.89)
– Physician	68.39 (58.04)	69.01 (58.12)	-0.63 (-7.52, 5.81)
– Productivity loss	78.91 (75.17)	108.92 (86.37)	-30.02 (-40.01, -20.57)
– Total health system cost	863.19 (330.02)	828.02 (384.40)	35.15 (-8.84, 76.68)
– Total societal cost	942.10 (354.64)	937.03 (400.62)	5.07 (-40.79, 50.50)
Unadjusted QALYs	0.0152 (0.0069)	0.0134 (0.0068)	0.0018 (0.0011, 0.0027)
Adjusted* incremental cost, mean (95% CI)			
– Health system's perspective	$49.19 ($24.87, $73.08)		
– Societal perspective	$20.58 (-$4.52, $47.07)		
Adjusted* incremental QALY, mean (95% CI)	0.0016 (0.0009, 0.0022)		
Cost ($) per QALY gained			
– Health system's perspective	30,864.28 (14,718.98, 62,789.04)		
– Societal perspective	12,914.65 (-2,570.40, 41,042.95)		

* adjusted for age, type and the number of chemotherapy agents, history of motion or morning sickness, alcohol intake per day, and presence of comorbidity

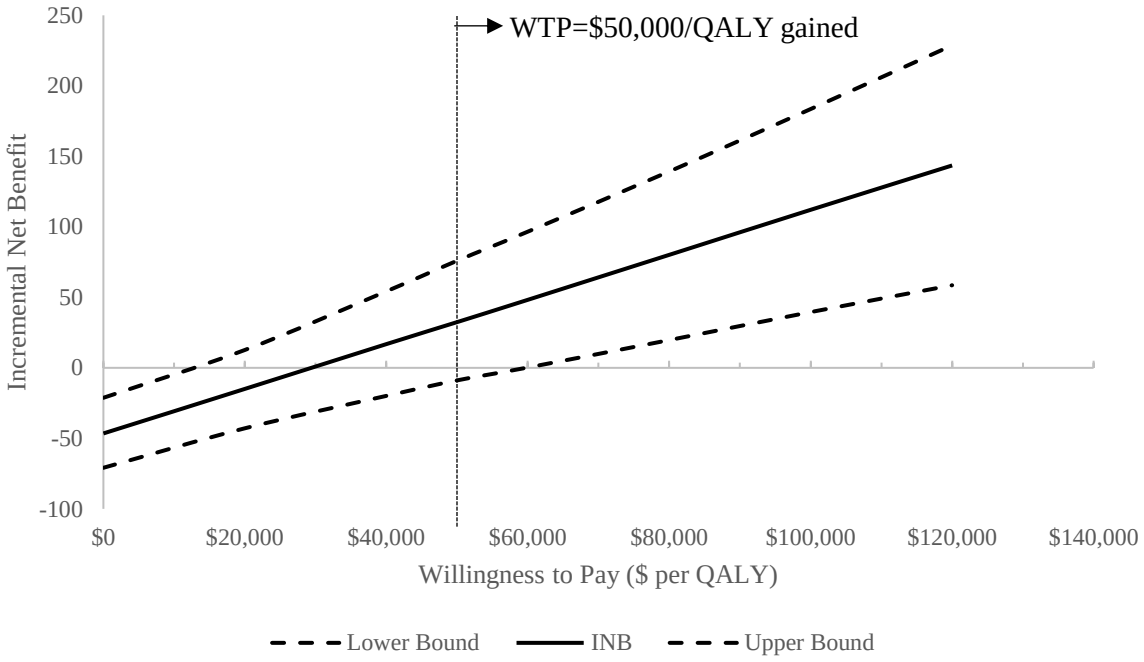


Figure 1a. Estimated incremental net benefit from the health system's perspective as a function of willingness to pay values

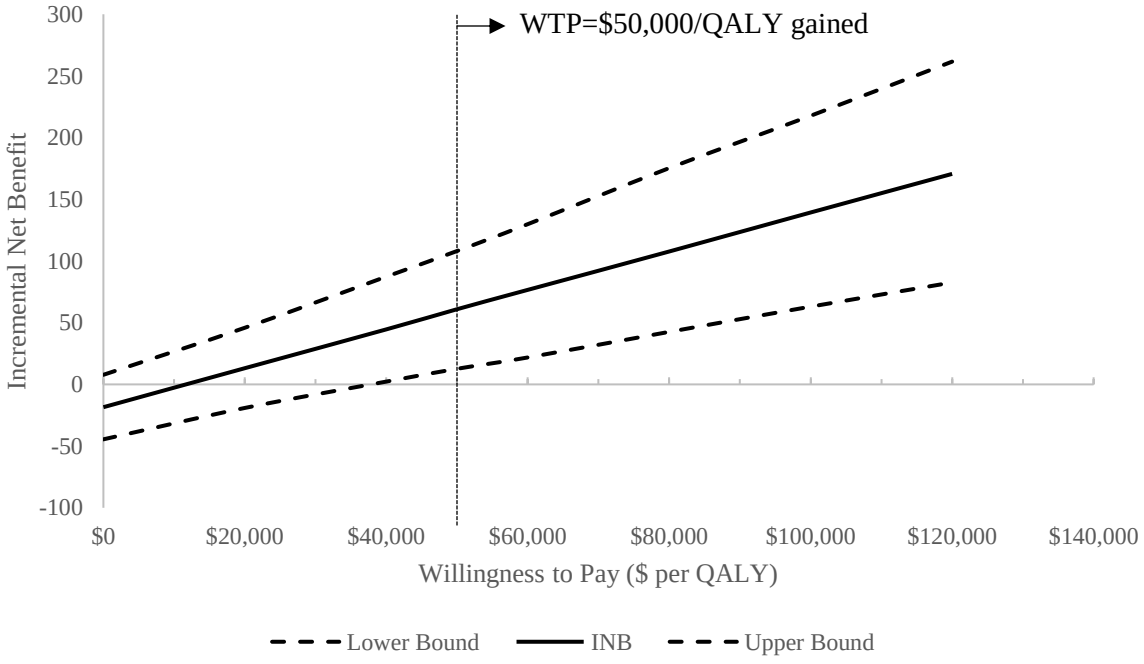


Figure 1b. Estimated incremental net benefit from the societal perspective as a function of willingness to pay values

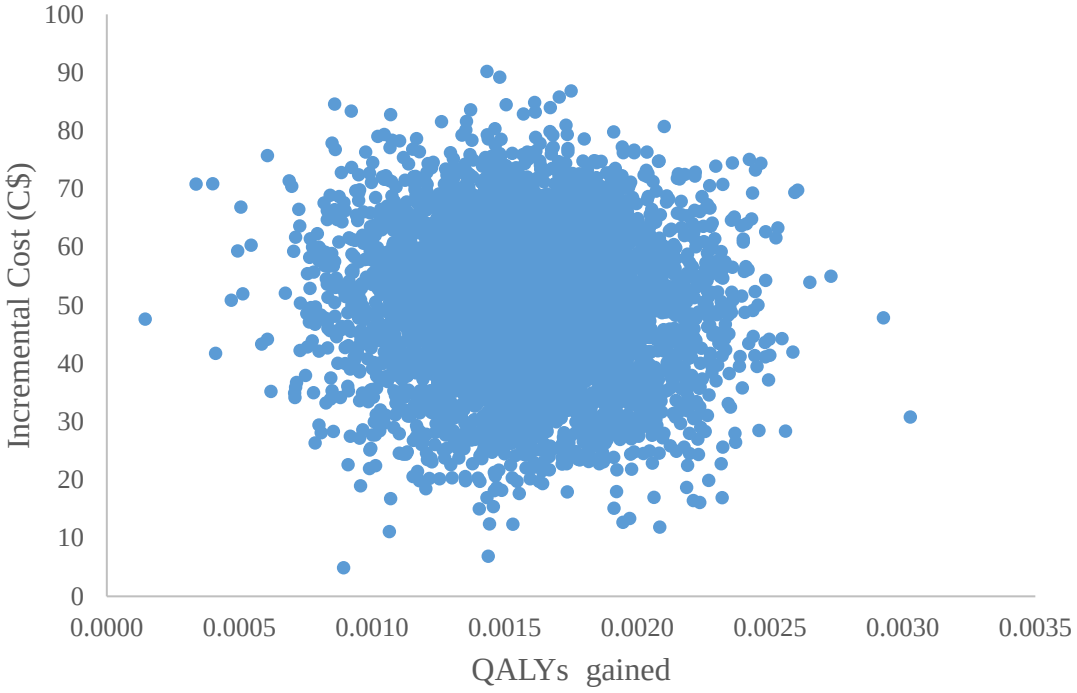


Figure 2a. Cost-effectiveness plane representing estimated cost per QALY from the healthcare system's perspective

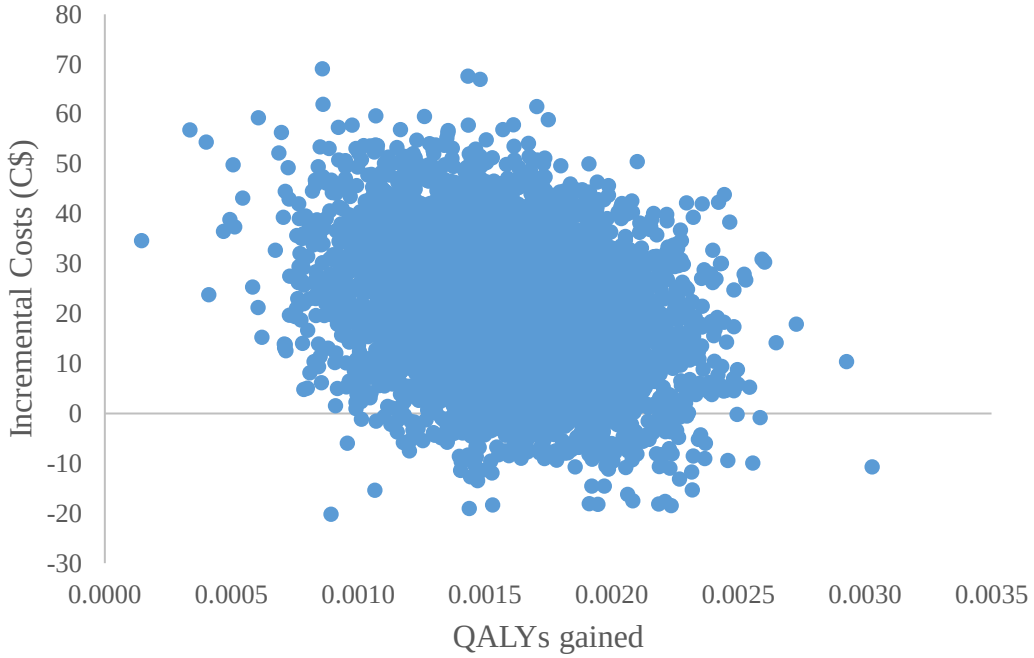


Figure 2b. Cost-effectiveness plane representing estimated cost per QALY from the societal perspective

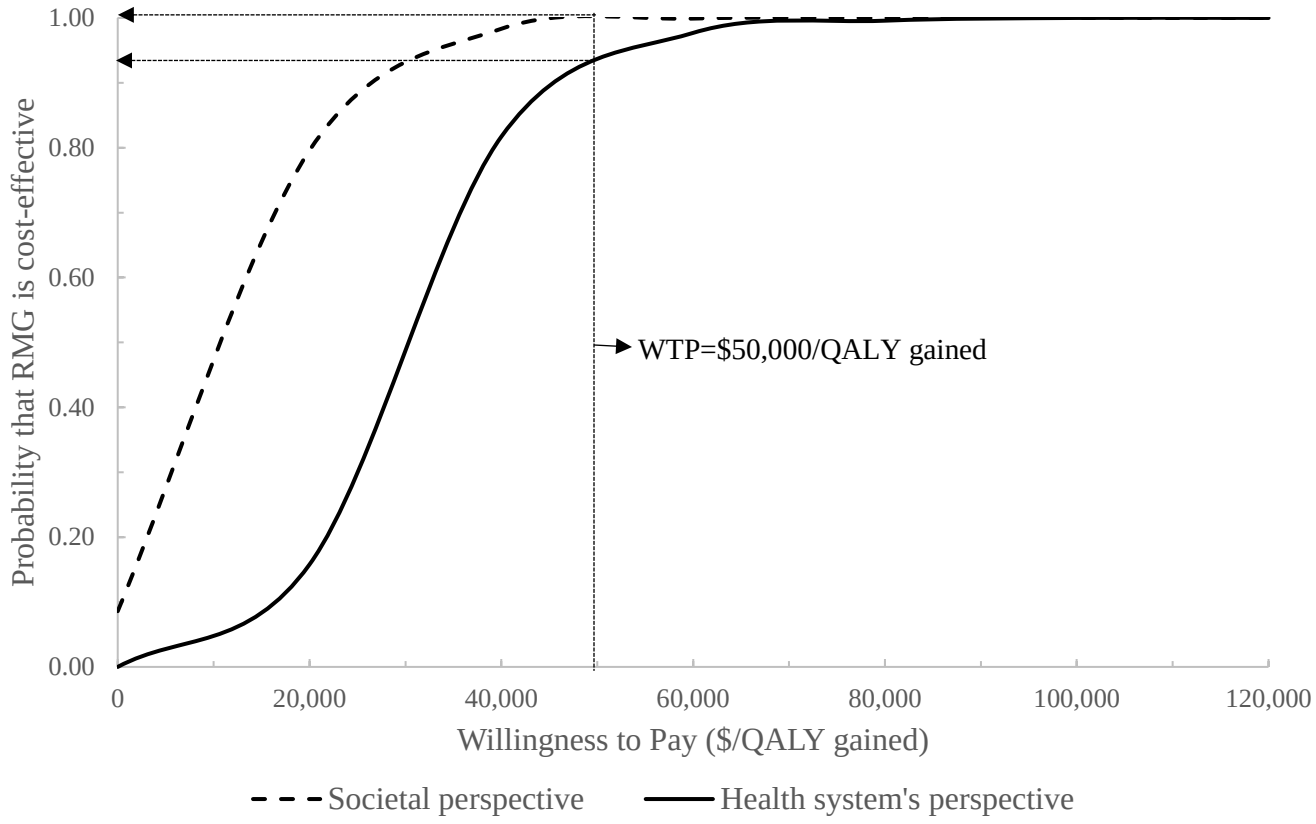


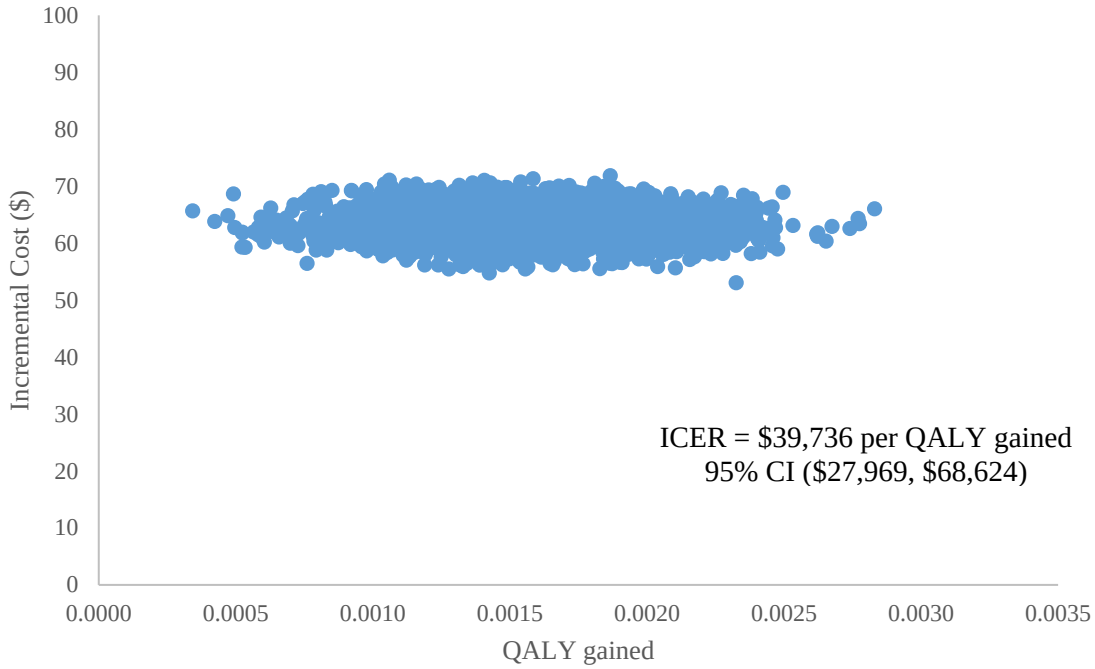
Figure 3. Cost-effectiveness acceptability curve showing the probability that the risk-guided antiemetic prophylaxis is cost-effective over a range of willingness to pay values

Appendix 1. Risk scoring system for acute and delayed chemotherapy-induced nausea and vomiting (CINV) [1,2]

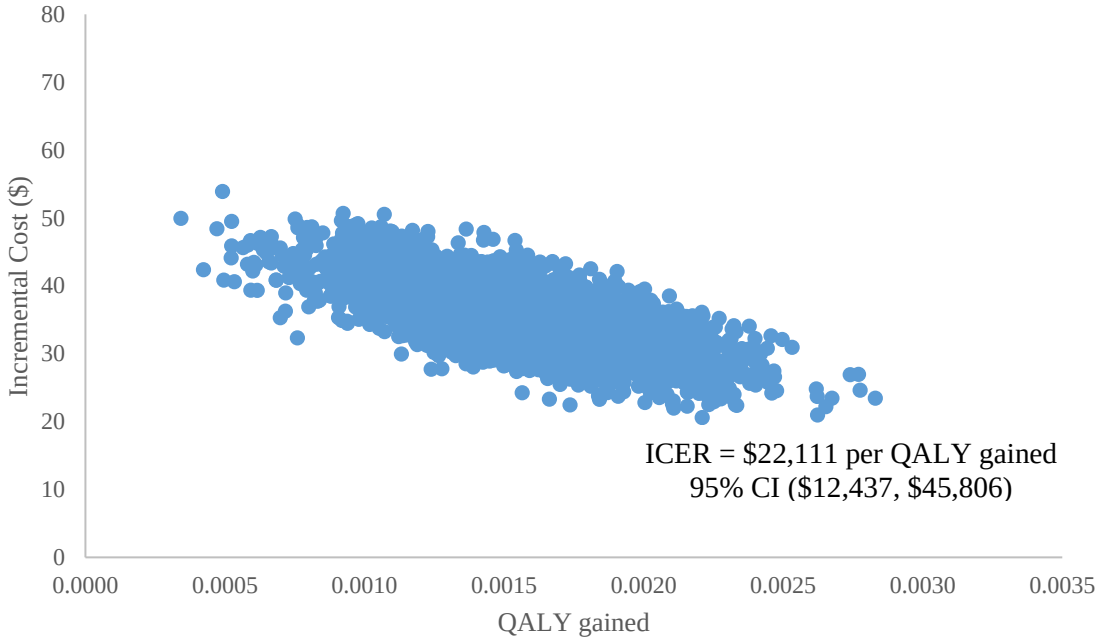
Acute CINV Risk Index	Delayed CINV Risk Index
Start at base score of 10 • If the patient is between 40 to 60 years of age, subtract 3 • If the patient is ≥ 60 years, subtract 4 • If the patient has existing comorbidity (e.g. cardiovascular disease, diabetes, gastrointestinal, musculoskeletal, thyroid, other), subtract 2 • If the patient consumes at least one alcoholic drink per day, subtract 1 • If the patient is about to receive cycle 3 or beyond, subtract 1 • If the disease site is gynecological and gastrointestinal, subtract 2 • If the patient is about to receive anthracycline based chemotherapy, add 1 • If the patient is about to receive platinum based chemotherapy, add 3 • If the patient has disease stage I or II, add 1 • If the patient is taking non prescribed treatments for emesis control at home, add 2	**Start at base score of 20** • If the patient is ≤ 40 years, add 8 • If the patient received a 5HT3 anti-emetic ± dexamethasone post chemo, add 5 • If the patient had prior nausea/vomiting before starting the current chemo, add 14 • If the patient had morning sickness during a pregnancy (if applicable), add 7 • If the patient is taking non prescribed anti-emetics at home, add 23 • If the patient had ≥ one vomiting episode during the first 24 hours post chemo, add 7 • If the patient is about to receive cycle 3 or beyond, subtract 7 • For every hour the patient slept on the night before chemo, subtract 1

Appendix 2. Antiemetic schedule for the Risk Model Generated Arm

Emesis Regimen Escalation	Day of Chemotherapy	8hrs Post Chemo	Day 2-3 Post Chemo
Level-0	Dexamethasone 10mg PO Ondansetron 8mg PO	Dexamethasone 4mg PO Ondansetron 8mg PO	Dexamethasone 4mg PO twice daily Ondansetron 8mg PO twice daily
Level-1	Dexamethasone 12mg IV Ondansetron 8mg PO Aprepitant 125mg PO	Ondansetron 8mg PO	Aprepitant 80mg PO daily
Level-2	Dexamethasone 12mg IV Ondansetron 8mg PO Aprepitant 125mg PO	Ondansetron 8mg PO	Aprepitant 80mg PO daily Dexamethasone 8mg PO daily
Level-3	Dexamethasone 12mg IV Ondansetron 8mg PO Aprepitant 125mg PO	Ondansetron 8mg PO Dexamethasone 8mg PO Olanzapine 2.5mg PO	Aprepitant 80mg PO daily Dexamethasone 8mg PO daily Olanzapine PO 2.5mg daily for 7 days total



Appendix 3a. Results of scenario analyses when hospital cost was excluded. Cost-effectiveness plane estimated from the healthcare system's perspective



Appendix 3b. Results of scenario analyses when hospital cost was excluded. Cost-effectiveness plane estimated from the societal perspective

Note: ICER, incremental cost-effectiveness ratio

References

1. Dranitsaris G, Joy A, Young S, Clemons M, Callaghan W, Petrella T (2009) Identifying patients at high risk for nausea and vomiting after chemotherapy: the development of a practical prediction tool I. J Support Oncol 7:W1–8
2. Petrella T, Clemons M, Joy A, Young S, Callaghan W, Dranitsaris G (2009) Identifying patients at high risk for nausea and vomiting after chemotherapy: the development of a practical prediction tool II. J Support Oncol 7:W9–16