Economic Analysis of Alvimopan for Prevention and Management of Post-operative Ileus

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Short Title:
Economic Analysis of Alvimopan for POI

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Conflicts of interest:

Daniel Touchette, PharmD, MA, assumes responsibility as the submission’s guarantor. Dr. Touchette was involved in the conception and initiation of the analysis, and in preparation of the manuscript. Dr. Touchette has no conflicts of interest to report.

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Funda Tiryaki, PharmD, MS was involved in the development of the analysis and in substantially editing the manuscript. Dr. Tiryaki has no conflicts of interest to report.

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Abstract

Objective: To determine whether alvimopan for prevention of post-operative ileus (POI) among patients undergoing small- or large-bowel resection via laparotomy is associated with lower total costs compared to standard post-operative care.

Methods: We constructed a formal decision model from the healthcare system perspective. Clinical outcomes (time to discharge order written [DCO], post-operative nasogastric tube insertion, POI-related readmission within 7 days, nausea and vomiting) were obtained from meta-analyses of published studies. Cost inputs included drugs, nursing labor, readmission, and hospitalization. Costs were assessed by determining the net cost of alvimopan use and subsequent reduction in length of stay (LOS). Sensitivity analyses and a scenario analysis were conducted.

Results: The costs for alvimopan were $570 based on an average of 9.5 doses. Given the 18.4-hour mean reduction in DCO, the use of alvimopan reduced hospitalization costs by $2,021. The mean difference in overall cost of care was $1,168 (95% certainty interval: $-437 to $5,879), favoring the use of alvimopan. In sensitivity analyses, the association of alvimopan with lower costs was robust to several changes in key parameters including the cost and number of doses of alvimopan, DCO, readmission rates, and hospitalization cost. In scenario analyses, alvimopan use yielded a cost saving of $897 when no difference in readmission rates was assumed and a net cost of $278 when no difference in
DCO was assumed. In the scenario analysis using data from a study that did not enforce opioid use, alvimopan resulted in a cost-saving of $65 per patient.

**Conclusion:** For the base case, alvimopan was cost-saving for prevention of POI among patients undergoing bowel resection via laparotomy, although these potential cost-savings were highly dependent on a difference in DCO. This finding is not applicable to the less-invasive laparoscopic surgical approach for which quality data on alvimopan use are lacking. Limitations of this analysis included the use of DCO as a proxy for LOS and difficulty interpreting study results due to inconsistent reporting and conduct of the clinical trials evaluating alvimopan.
Introduction

Post-operative ileus (POI) is defined as "a transient cessation of co-ordinated bowel motility after surgical intervention, which prevents effective transit of intestinal contents and/or tolerance of oral intake."\(^1\) POI is common in surgeries in which the bowel or nearby structures are manipulated during surgery. Clinical symptoms include delayed and incomplete gastric emptying, abdominal distension, pain, nausea, and vomiting. Complications include atelectasis, pneumonia, and delayed enteral nutrition, ambulation, and wound healing.\(^2-4\) Recovery time varies from days to weeks. Recovery is complicated by the use of opioids, which can also decrease gastric motility. POI is responsible for causing considerable morbidity in some patients.

POI is a major contributor to delaying hospital discharge after abdominal surgery, increasing length of stay (LOS) by approximately two to three days.\(^5\) In one analysis, 3% of patients undergoing colon and rectum operations were readmitted for bowel obstruction and ileus.\(^6\) POI significant enough to be coded in billing records has been associated with substantial increases in length of stay and $8,000-$10,000 per patient in additional cost.\(^7,8\) Overall, POI is estimated to cost the US healthcare system an estimated $1.46 billion annually.

Alvimopan is a peripherally acting μ-opioid antagonist that has been demonstrated to accelerate upper and lower gastrointestinal (GI) recovery following bowel surgery in patients expected to receive opioids for postoperative pain management.\(^9-14\) Specifically,
alvimopan has been shown to reduce the need for nasogastric tube reinsertion and the incidence of nausea and vomiting in patients undergoing laparotomy.\textsuperscript{9-14} Alvimopan has also been found to decrease time to discharge order written (DCO).\textsuperscript{9,11-13} While readmissions due to POI were not statistically significantly different in any of the clinical trials, alvimopan reduced the proportion of patients requiring hospitalization for any cause in a pooled analysis.\textsuperscript{10} However, with an estimated cost of up to $840 per patient, using alvimopan typically results in a substantial addition to the immediate cost of therapy.\textsuperscript{15,16} As a result of this immediate cost, a potential for cardiovascular complications with long term use, and concerns about off-label use institutions may restrict or refuse the use of alvimopan.\textsuperscript{17}

At the time of undertaking this study, we had identified only a single economic analysis of alvimopan in the literature.\textsuperscript{18} By comparing only the cost of alvimopan and the cost-offsets associated with a reduced LOS, this analysis showed that alvimopan would be expected to reduce costs. However, significant limitations existed in the methodology used in this analysis, bringing into question the validity of the report’s results. Most importantly, there was a lack of clarity as to how the cost analysis was developed and the results were not explored sufficiently by sensitivity analyses.

Given the cost of alvimopan and the need for a more detailed, comprehensive cost-consequence analysis for formulary decision-makers, we developed a decision model designed to assess total costs and cost offsets associated with alvimopan use in patients
Methods

We constructed a formal decision model to assess costs from the healthcare system perspective. We adhered to the methods recommended by the Panel on Cost-Effectiveness in Health and Medicine and guidelines from the International Society for Pharmacoeconomic and Outcomes Research.\textsuperscript{19}

Comparators

In this analysis, we compared a standardized, accelerated post-operative care pathway (usual care) to usual care plus alvimopan. The standardized accelerated post-operative care pathway consisted of the removal of nasogastric tube no later than noon on post-operative day one, introduction of liquid diet and ambulation on post-operative day one, and introduction of solid food by post-operative day two. This multimodal approach to accelerate recovery is currently regarded as best practice in post-operative management of patients undergoing major bowel surgeries.\textsuperscript{20-23} The alvimopan comparison arm was based on the following regimen: alvimopan 12 mg administered 30 minutes to 5 hours prior to surgery, followed by subsequent maintenance dose of 12 mg given every 12 hours for a maximum of 7 days post-operatively (15 maximum total doses).

Patient Population
We performed the analysis targeting patients undergoing partial small- or large-bowel resection with primary anastomosis via laparotomy and scheduled to receive post-operative pain management with intravenous (IV) opioid-based patient-controlled analgesia. The time horizon considered for this evaluation was the duration of hospitalization.

Model Design

We used a decision tree (Figure 1) to assess the net cost of using alvimopan 12mg versus usual care. The design of both comparison arms is identical. Based on the published results of four randomized clinical trials, we identified LOS as a primary cost driver in our model. However, time to DCO was used as a proxy for LOS in all four clinical trials. We therefore had to use time to DCO in our model rather than the preferable terminal outcome, LOS. From those studies, we also identified adverse outcomes associated with a considerable cost (i.e. a cost sufficient to potentially alter the expected value of alvimopan in the decision model) and included them in the decision tree. Specifically, we included post-operative nasogastric tube insertion (NGT), POI-related readmission within 7 days, nausea, and vomiting. Other clinical outcomes of the trials such as all-cause readmission within 10 days, time to recovery of gastrointestinal (GI) function, and time to readiness for discharge were originally considered, but were determined to be irrelevant or have insufficient evidence linking them to important clinical or economic terminal outcomes. In particular, the time to GI recovery was measured as a composite endpoint defined as the later of the following events: tolerance of solid food, first bowel movement, or first flatus. We deemed that this composite
outcome served as an intermediate to LOS and did not add information beyond our existing proxy for LOS.

Model Inputs

We conducted a thorough literature review via PubMed to September 10, 2011 (no starting date specified) using the following search terms: *alvimopan*, *phase III trial*, *bowel, resection, postoperative, ileus*. First, published randomized clinical trials of alvimopan were obtained and reviewed. We then identified two meta-analyses and a pooled analysis of the trials to support our model inputs of the clinical outcomes. Clinical inputs were selected from the Delaney meta-analysis, as this analysis likely presents the most accurate estimates available for the effectiveness of alvimopan. Table 1 shows the estimates and proportions reported by each of the studies for outcomes relevant to the model. Table 2 shows the inputs actually used in the base case of the model and the associated sources.

Alvimopan drug cost was estimated using 80% of the average wholesale price (AWP) reported in the 2010 Red Book. In the base-case analysis, the mean number of alvimopan doses (9.5) observed in the Delaney analysis was used. Costs of POI-related readmission and per-day hospitalization (used to calculate the cost-saving associated with the reduction in time to DCO) were taken from a systematic review of published studies on the economic burden of POI. To estimate resources utilized in NGT insertion, we solicited information regarding equipment used (BARD tube and suction canister) and nursing time required from an expert panel of four surgical nurses. The total cost of
nursing labor was determined by multiplying average salaries (as reported by the US Bureau of Labor Statistics)\textsuperscript{25} by the duration of time to perform insertion obtained from surveying a panel of experts. For the purpose of our decision model, costs associated with nausea and vomiting were assumed to involve only the anti-emetic drug costs and excluded nominal costs such as emesis basins. Given the current guideline recommendations to use an anti-emetic agent from a different pharmacologic class in patients with post-operative nausea and vomiting who fail on the first drug,\textsuperscript{27} we assumed ondansetron and prochlorperazine, both generically available, as the anti-emetic agents used in nausea and vomiting, respectively, and estimated these generic drug prices based on 50\% of the AWP.\textsuperscript{16} All cost data was inflation adjusted to the end of 2010 using the consumer price index for medical care or hospital and related services.\textsuperscript{25}

Sensitivity Analyses

We performed various sensitivity analyses to account for uncertainty in the model assumptions and to address the variability of published data. We did several one-way and multi-way sensitivity analyses over low and high estimates of select variables (see Table 2). Each variable was subjected to a one-way sensitivity analysis. The range over which each variable was varied was chosen based on the 95\% confidence interval as reported in the studies that provided the base-case estimates. Where confidence intervals were not available (i.e. doses of alvimopan), we chose the triangular distribution and inputted the range from the Delaney trial for the extreme values (i.e. 1-15 doses).\textsuperscript{10} Specifically, we used the following distributions: beta for event probabilities, log-normal for hospital costs including readmission and nursing time, triangular for number of doses
of alvimopan, and normal for the difference in time to DCO between the alvimopan and usual care arms. Monte Carlo simulation was then used to evaluate the overall uncertainty of the model result in the base case. All analyses were performed using TreeAge Pro® 2009.

In addition, several scenario analyses were conducted to address shortcomings identified in the literature supporting alvimopan use. A European study assessing alvimopan use in post-operative ileus observed a much lower efficacy of alvimopan than did the other three international studies. Due to potential heterogeneity in the results, specifically a lower utilization of opioids and differences in the European healthcare system (demonstrated by a longer time to discharge), all European study subjects were omitted from subsequent meta-analyses. We therefore conducted two scenario analyses using estimates from one European study to populate the model. In the first scenario analysis, only the base case estimates for number of alvimopan doses, DCO, and the probabilities of nausea and vomiting were replaced with those from the European study. Since NGT reinsertion and readmission for post-op ileus were not evaluated in the European Phase III trial, the probabilities of the outcomes were set equal to the base-case alvimopan values, using estimates from the Delaney meta-analysis. In the second scenario analysis, we assumed that alvimopan produced no benefit with respect to reducing the need for NGT reinsertion or post-op ileus-related readmission and the model inputs were set equal to the usual care. These two scenarios represent the two possible extremes for the effectiveness of alvimopan.
Results

Base Case

In the base-case model, the added drug costs for alvimopan were estimated at $570 per person and there was an estimated cost offset of $2,021 resulting from reduced LOS (as proxied by DCO) with alvimopan use. Additional cost offsets were realized by reductions in the need for gastric tube reinsertion, nausea, vomiting, and post-operative ileus related readmissions. Overall, the use of alvimopan resulted in a total cost of $11,084. In comparison, usual care resulted in a total cost of $12,271. Hence in the base-case, alvimopan use was associated with an average savings of $1,187 per person.

Sensitivity Analyses on the Base Case

The stability of the base-case depended primarily on two variables: cost of a hospital day, and mean time to discharge. The mean cost of a hospital day created the most variability in the model. Usual care became the preferred option (i.e. total cost less than alvimopan) when the cost of a hospital day was reduced below a threshold of $362 per day. Similarly, when the difference in DCO between alvimopan and usual care was reduced to 3.5 hours, usual care became the less costly preferred option. Other variables - the cost and probability of POI-related readmission, and the number of doses and cost of alvimopan - but were not able to change the base case results when varied in a univariate manner.

The Monte Carlo simulation conducted on the base-case resulted in a mean and median difference in costs of $1,168 and $630, respectively. The 95% certainty interval (i.e. the interval containing 95% of the observations, removing 2.5% of the observations from
each tail of the distribution) was -$437 to $5,879. The 80% certainty interval ranged from -$194 to $3,008 and 19.6% of all observations fell below $0. Given our distribution inputs for the Monte Carlo simulation, it was not certain that alvimopan would be truly cost-saving.

Scenario Analysis
When model inputs for number of alvimopan doses, DCO, probability of experiencing nausea, and probability of vomiting were set to values observed in the European phase III trial, the use of alvimopan resulted in a total cost of $18,084 compared with the usual care cost of $18,149 (difference = $65). When the other model inputs of NGT reinsertion and probability of readmission were set equal to the base-case values for usual care (i.e. no difference observed), the use of alvimopan resulted in a total cost of $18,375, more costly than usual care by $226.

Discussion
Our analysis provides a much more detailed and comprehensive breakdown of the overall costs associated with alvimopan than the previously published analyses. In our base-case analysis, alvimopan was likely cost-saving as was the case in two previously published cost analyses. Alvimopan achieves a net cost-saving in our model, provided time to discharge is reduced by an average of at least 3.5 hours. However, in the Monte Carlo simulations, the 80% certainty interval included $0, indicating a potential that alvimopan may not be cost-saving given uncertainty in the underlying parameters of the
model. Furthermore, when looking at our scenario analysis including the results of the European phase III study, it appeared that alvimopan could potentially increase the total cost of care. This has important policy implications for institutions that do not uniformly enforce opioid PCA for post-operative pain management, as described below.

Our analysis is primarily limited by the strength of the data available in existing publications. The meta-analysis conducted by Delaney et al. well described statistical methods, including an analysis of the between-treatment effects among the three included clinical trials. The second pooled analysis included an additional study, but did not sufficiently describe the methods used for pooling data or whether any validity analyses were conducted. However, both pooled analyses excluded a large European phase III study in which alvimopan outcomes were not as favorable as in North American studies. Inclusion of this study’s findings would have reduced the differences seen between alvimopan and usual care in LOS considerably, possibly but not likely impacting the statistical significance of the findings.

Furthermore, inconsistencies in the numbers of included subjects between the two pooled analyses bring into question the validity of these results. Specifically, the number of subjects and reasons for exclusion in the pooled analysis by Delaney et al. appear well documented (see Table 1). The pooled results and economic analysis by Bell et al. includes an additional study by Ludwig et al. when compared with Delaney et al., but the total number of subjects analyzed is greater than that of both the Delaney pooled analysis and Ludwig trials combined. In addition, the reported rates of nausea and vomiting do
not appear consistent between the pooled analyses, even with the addition of the Ludwig data. Because of these limitations in the Bell manuscript, we chose to use the results of the Delaney pooled analysis as the base-case inputs for our model.

As stated in previous reports, clinical practice differed between the United States (US) and European hospitals in these clinical trials, with a differing utilization of opioids and a longer hospital length of stay in the European study subjects. Clinical practice and hospital length of stay has likewise been shown to differ substantially between Canadian and US hospitals. Despite these differences, Canadian study subjects remained in the pooled analyses while those in the European study were excluded. Furthermore, there are significant issues with using randomized clinical trials in economic analyses that have not been addressed in sensitivity analyses by Bell. Clinical trials notoriously attempt to standardize care in ways that are different from usual clinical practice to reduce heterogeneity and improve the effect size. The North American studies mandated use of opioid patient-controlled analgesia (PCA) as well as placing restrictions on non-opioid analgesics, while promoting discharge following achievement of the gastrointestinal recovery outcomes. Further, acute pain services promoting and monitoring PCA are widely present in many larger urban European hospitals. Given this, differences observed in the European study may have had more to do with the study design that allowed more freedom for variability in pain management than with regional discrepancies in clinical practice. Given the uncertainty raised by this possibility, we chose to conduct an additional scenario analysis using data from the European study to
provide formulary decision-makers with additional information on which to base their decision.24

Alvimopan was compared with the standard of care for managing POI in clinical trials, namely nasogastric tube insertion, early administration of intravenous fluids and solid food, and encouraging early ambulation. In recent studies, chewing gum has been shown to improve time to first bowel movement, and reduce hospital length of stay following appendectomy,36 radical cystectomy for bladder cancer,37 and abdominal surgery.38 Results of a meta-analysis suggest that given its safety profile and beneficial effects, chewing gum should be offered to select patients after assessment of mental status and aspiration risk.38 Studies are needed to assess if alvimopan is superior to chewing gum or if the addition of alvimopan to chewing gum results in further LOS reductions or other benefits.

The use of laparoscopy, a less invasive surgical procedure, has also been shown to reduce postoperative surgical complications including GI recovery time, vomiting, and hospital length of stay.15,39,40 Decreased manipulation of the bowels and less pain and subsequent opioid use are likely factors in these findings. In the phase III clinical trials evaluating alvimopan, only subjects who underwent laparotomy were enrolled. One retrospective analysis evaluating the use of alvimopan in subjects undergoing either open or laparoscopic bowel resection suggested that similar benefits may be observed in subjects undergoing laparoscopic surgery.28 However, this study utilized an open label design with a retrospective analysis with insufficient sample size (given the results observed in
prospective clinical trials) and had substantial and important differences in baseline subject characteristics. Non-opioid use was higher in the alvimopan group, and total exposure to opioids (i.e. total dose given) was not controlled for in the analyses. Given these serious limitations, it remains unclear whether alvimopan results in improvements in POI-related outcomes in subjects undergoing laparoscopic surgery.

Limitations

There are several important limitations to our pharmacoeconomic analysis. As mentioned above, inconsistent reporting of clinical and economic outcomes in meta-analyses, differences in the conduct of clinical trials, and difficulty interpreting these results were a major concern. In an effort to overcome these limitations, we made a written request for data from the manufacturers of alvimopan (Entereg®), but received no response.[personal communication, June 1, 2010] Without access to primary data from the clinical trials, we attempted to address these issues using sensitivity analyses to provide formulary administrators with the most information possible on which to base their decisions.

We were unable to quantify benefits of alvimopan in terms of an effectiveness or utility measure such as quality-adjusted life-years gained, due to relatively minor impact of the drug on outcomes that affect these measures. There may be willingness by some to pay an additional amount for a medication that decreases vomiting and improves patient satisfaction by reducing the need for NGT, rehospitalization, and decreased LOS. However, due to the small potential gains associated in these outcomes by alvimopan, these benefits were not included in our analysis.
We did not consider the potential increased risk of bowel perforation or other adverse events in our analysis.\textsuperscript{41} Most documented adverse events associated with alvimopan use appeared to be either minor or no different from control subjects. In the case of bowel perforation, this rare event is unlikely to significantly affect the economic analysis, but should be considered carefully by clinicians as it changes the risk-benefit ratio of alvimopan. More research is needed to determine the incidence, severity, and consequences of this potentially serious complication.

Finally, a factor limiting the accuracy of these findings pertained to the use of time to discharge order (DCO) instead of the actual time to discharge. This was necessary due to the use of this surrogate marker in the primary sources of data. Although it is not clear that this difference biases the results in any way, using the actual time to discharge would have been a more appropriate way to determine changes in the LOS.

**Conclusion**

Alvimopan is a potentially useful medication in the treatment of patients undergoing bowel resection surgery via laparotomy. The medication is likely to reduce hospital length of stay and total cost of care in this population, although limitations exist in published reports that raise questions regarding the certainty of these findings. Research
is needed to determine the effects of alvimopan when chewing gum is used as part of the post-surgical regimen or when surgery is performed using laparoscopic procedures.
References

Table 1. Outcomes reported in phase III clinical studies of alvimopan and pooled analyses results

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<tr>
<th></th>
<th>Delaney⁹</th>
<th>Ludwig¹¹</th>
<th>Viscusi¹²</th>
<th>Wolff¹⁴</th>
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⁹Methods for pooling data not given. Includes only bowel surgery subjects. Includes Delaney, Ludwig, Viscusi, and Wolff studies.

¹¹Excludes subjects undergoing total abdominal hysterectomy. Includes Delaney, Viscusi, and Wolff studies.

¹²Time to DCO written not provided for each treatment group. Mean study time to DCO presented, along with difference. Mean value provided for reference.

¹³POI-specific readmission rates not reported. Values are total readmission rates.

Abbreviations:

UC = usual care
A12 = alvimopan 12 mg two hours before surgery and then twice daily
DCO = discharge order written
POI = post-operative ileus
NGT = nasogastric tube
NR = not reported
Table 2. Inputs used for base-case and sensitivity analyses

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<td></td>
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</tr>
<tr>
<td>A12</td>
<td>1.00</td>
<td>0.26</td>
<td>1.70</td>
<td>1.00</td>
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<tr>
<td>UC</td>
<td>2.00</td>
<td>0.97</td>
<td>3.05</td>
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<tr>
<td><strong>Cost inputs</strong></td>
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<tr>
<td>Alvimopan 12 mg</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cost per dose ($)</td>
<td>60.00</td>
<td>37.50</td>
<td>75.00</td>
<td>60.00</td>
</tr>
<tr>
<td>Number of doses</td>
<td>9.5</td>
<td>5.0</td>
<td>14.0</td>
<td>11.6</td>
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<tr>
<td>NGT reinsertion</td>
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<tr>
<td>Nursing wage ($ per hour)</td>
<td>31.31</td>
<td>25.00</td>
<td>50.00</td>
<td>31.31</td>
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<tr>
<td>Nursing time (h)</td>
<td>0.26</td>
<td>0.18</td>
<td>0.34</td>
<td>0.26</td>
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<tr>
<td>NGT ($)^a</td>
<td>12.59</td>
<td>7.78</td>
<td>20.73</td>
<td>12.59</td>
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<td>Nausea treatment</td>
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<tr>
<td>Ondansetron ($ per dose)^b</td>
<td>0.56</td>
<td>0.56</td>
<td>1.20</td>
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<td>Vomiting treatment</td>
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<td>Prochlorperazine ($ per dose)^b</td>
<td>1.5</td>
<td>1.50</td>
<td>1.80</td>
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<tr>
<td>Post-op hospitalization cost ($ per day)</td>
<td>1,910</td>
<td>192</td>
<td>7,755</td>
<td>1,910</td>
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Readmission cost ($)\textsuperscript{c}  29,094  6,365  109,187  29,094  Goldstein\textsuperscript{a}; Iyer\textsuperscript{b}

\textsuperscript{a}Includes BARD tube and suction canister
\textsuperscript{b}Costs of nausea and vomiting were assumed to only consider anti-emetic agents
\textsuperscript{c}POI-related readmission within 7 days

Abbreviations:
UC = usual care
A12 = alvimopan 12 mg two hours before surgery and then twice daily
DCO = discharge order written
POI = post-operative ileus
NGT = nasogastric tube
NR = not reported
Figure 1. Decision analysis model