Sevelamer in Patients with End-stage Renal Disease: A Systematic Review and Economic Evaluation
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Sevelamer in Patients with End-stage Renal Disease: A Systematic Review and Economic Evaluation

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Authorship

Bruce Culleton provided input on the report’s conception and design, the interpretation of analysis, and the revision of the report for intellectual content.

Scott Klarenbach provided input into the economic model design elements, with specific input into cost categories, and sensitivity analysis and interpretation of the results of the model. He assisted with the revisions of multiple versions of the manuscript, and approved the final version.
Helen Lee conducted the literature review, modelling, data analysis, and budget impact analysis.

Braden Manns acted as the primary author of the report. He developed and supervised the economic evaluation, and he supervised the content development of the overall report.

Fiona Shrive participated in the decision analysis, and the technical side of modelling. She provided general input into the report.

Marcello Tonelli contributed to the drafting of the protocol, the search strategy, and the analysis. He drafted and critically revised the report, and approved the final version.

Natasha Wiebe coordinated the project and project personnel. She contributed to the design methodology and statistical analysis. She also drafted some sections of the report, and critically revised others.

**Conflicts of Interest**

David Mendelssohn, MD, has served on advisory boards, and has received speaker fees from Genzyme, and from many others, including Baxter, Ortho Biotech, Amgen, Roche, and several antihypertensive companies.

None of the report authors declared any conflicts of interest.
Sevelamer in Patients with End-stage Renal Disease: A Systematic Review and Economic Evaluation

Technology
Sevelamer hydrochloride oral capsule.

Condition
Patients with end-stage renal disease (ESRD) and hyperphosphatemia

Issue
Traditional (calcium-based) phosphate binders may not be perceived as suitable for controlling hyperphosphatemia in all patients because of theoretical concerns about their use, and dose-limiting hypercalcemia. Sevelamer is the first non-calcium-based phosphate binder to receive Health Canada approval. Given a large differential cost between this new agent and traditional therapies, the appropriate use of this new therapy requires examination.

Methods and Results
We did a systematic review to identify relevant literature, by searching multiple databases using a defined strategy, and by hand searching relevant journals. Evidence of efficacy was determined from randomized controlled trials (RCTs). Evidence of harm was determined from trials or registries where data was gathered prospectively. Ten RCTs with a total of 3,025 participants were included in the efficacy analysis; 28 prospective trials with a total of 3,983 participants were identified and eligible for the review of harm. One unpublished, randomized, unblinded study of 2,103 dialysis patients was designed to measure overall survival and cardiovascular mortality.

Implications for Decision Making
- Sevelamer has no demonstrated effect on health outcomes compared with calcium-based phosphate binders. There was no convincing evidence that substituting sevelamer for calcium-based binders reduced all-cause mortality, cardiovascular mortality, hospitalization, or the frequency of symptomatic bone disease, and no evidence that sevelamer improved quality of life. Sevelamer therapy results in a smaller decrease in phosphate levels, and fewer episodes of hypercalcemia of unknown clinical significance, compared with calcium-based phosphate binders.
- There is uncertainty regarding the cost effectiveness of sevelamer. Even if sevelamer is assumed to be more effective than calcium-based phosphate binders, it is associated with a cost per quality-adjusted life year gained ranging from $127,000 to $278,100. It is possible that sevelamer use, restricted to patients ≥65 years old, might be more economically efficient, but improved effectiveness in this group requires confirmation from future studies.
- Funding sevelamer will require additional resources. The difference in cost per patient between calcium carbonate and sevelamer at usual daily doses is $4,127 annually. Substituting sevelamer for calcium carbonate for all patients with ESRD in Canada would increase expenditures by $70,620,616 annually. Restricting access to those ≥65 years old, or based on biochemical criteria, results in increased expenditures between $14,712,628 and $36,016,514.

This summary is based on a comprehensive health technology assessment available from CADTH’s web site (www.cadth.ca): Manns B, Tonelli M, Shrive F, Wiebe N, Klarenbach S, Lee H, Culleton B. Sevelamer in patients with end-stage renal disease: a systematic review and economic evaluation

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CADTH is an independent, not-for-profit organization that supports informed health care decision making by providing unbiased, reliable information about health technologies.
EXECUTIVE SUMMARY

The Issue
Most end-stage renal disease (ESRD) patients require oral calcium-based phosphate binders with meals. Calcium-based phosphate binders may be unsuitable for controlling hyperphosphatemia in some patients, because of dose-limiting hypercalcemia and dietary non-compliance. Attention has also been focused on the potential for adverse cardiovascular effects resulting from their use. Although oral phosphate binders reduce serum phosphate levels, an association has been reported between the cumulative dose of oral calcium-based phosphate binders and the extent of vascular calcification, which in turn may be associated with mortality in ESRD. Non-calcium based phosphate binders have been developed for use in patients with ESRD to treat hyperphosphatemia. Sevelamer is the first such agent to be approved by Health Canada. Given a large differential cost between this agent and traditional therapies, the appropriate use of this therapy requires examination.

Objectives
Our objectives were to perform a systematic review of the efficacy and harm of sevelamer, and to conduct a primary economic evaluation and budget impact analysis of its use when compared with calcium-based phosphate binders, in patients with ESRD, who are on dialysis.

Systematic Review of Efficacy and Harm

Methods: Using two search terms, sevelamer and Renagel, we conducted a comprehensive search to identify all relevant studies of sevelamer use. We assessed the study quality of randomized controlled trials (RCTs), using a condensed version of the Chalmers Index, and a standard data extraction method to record the data elements of interest into a database. We assessed the following outcomes: mortality (all-cause, and cardiovascular); cardiovascular events; hospitalizations; quality of life; levels of serum phosphate, calcium, parathyroid hormone (PTH), bicarbonate, calcium-phosphate product; and occurrence of adverse events. Because of the differences expected between trials, we decided a priori to combine results in a conservative fashion using a random effects model.

Result: We identified 10 primary publications of RCTs with a total of 3,025 participants eligible for efficacy analysis. Eight RCTs reported serum phosphate and calcium levels, and four reported all-cause mortality.

In analyses pooling, the eight studies reporting on serum phosphate and calcium levels (2,445 participants), the overall control of phosphate was better with calcium-based phosphate binders by 0.09 mmol/L [95% confidence interval (CI) 0.02 to 0.16]. On-treatment calcium-phosphate product was not significantly different in patients receiving calcium-based phosphate binders [weighted mean difference (WMD) 0.09 mmol²/L², −0.07 to 0.25]. The overall WMD in serum calcium was lower with sevelamer therapy by 0.10 mmol/L (−0.12 to −0.07). In the four RCTs that reported all-cause mortality (2,302 participants), the duration of follow-up varied from two to 45 months. The overall risk difference for all cause mortality in these four trials was not significantly different (−1%, 95% CI −4 to 2). The finding of improved survival among patients >65 years old, and those treated for >2 years in the DCOR study secondary analyses requires confirmation in a subsequent randomized trial.

We also identified 28 publications of prospective trials (16 RCTs and 12 single-arm trials) with a total of 3,983 participants eligible for harm analysis. In three RCTs that reported serious adverse events (SAEs) (2,185 participants), there was a non-significant lower risk of SAEs in patients receiving calcium-based
phosphate binders (13% lower, 95% CI –2 to 29). We found no studies examining the efficacy of sevelamer specifically in ESRD patients with concomitant hyperphosphatemia and hypercalcemia—the type of patient for whom sevelamer is funded in many provinces. There are no data indicating that such a strategy will reduce mortality or morbidity in these patients.

**Economic Analysis**

**Methods:** In the base-case analysis, we evaluated a simulated cohort of Canadian dialysis patients. We compared sevelamer with calcium carbonate, using a provincial health care ministry and a lifetime perspective. We used a Markov model, and to account for modelling uncertainty, we considered four modelling strategies. Given that the primary DCOR analysis compared survival without stratifying by time on therapy, our primary analysis used this estimate of sevelamer’s efficacy [a constant relative risk of 0.91 overall (model 1)]. Because no statistically significant benefit was seen in the DCOR primary analysis, we also presented the results of a cost minimization analysis (model 2). Given that the assumption of constant proportional hazards was not met in the DCOR primary analysis, we performed an exploratory analysis in which survival data were modelled separately for the period before and after two years (model 3). Given that the DCOR investigators reported an interaction between treatment efficacy and patient age (<65 or ≥65 years), we also performed an exploratory analysis modelling the efficacy of patients aged <65 and ≥65 separately (model 4). In each model, data on the effectiveness of sevelamer, in comparison with calcium-based phosphate binders, were taken from the DCOR study.

**Results:** In the base-case analysis, considering model 1, the use of sevelamer, in comparison to calcium, was associated with a cost per quality-adjusted life year (QALY) gained of $157,500 overall. In model 2, we repeated the overall analysis considering no survival or hospitalization advantage for sevelamer, demonstrating that the use of sevelamer resulted in an incremental cost of $17,000. In models 3 and 4, which assumed sevelamer to be more effective than calcium-based phosphate binders, the use of sevelamer was associated with a cost per QALY gained ranging from $127,000 to $278,100.

One of six pre-specified subgroup analyses suggested that the effect of sevelamer on mortality was modified by patient age. A statistically significant reduction in mortality was reported in patients ≥65 years old. The use of sevelamer exclusively in patients ≥65 years old was associated with a cost per QALY gained of $105,500. Although restricting the use of sevelamer to patients ≥65 years old may improve economic efficiency, the effectiveness of sevelamer in this group is uncertain.

The probabilistic sensitivity analysis revealed that there was significant uncertainty in the cost per QALY gained, regardless of the model considered. Significant uncertainty exists with respect to the cost effectiveness of sevelamer. As we found no data on the effectiveness of sevelamer in patients with co-existent hyperphosphatemia and hypercalcemia, we could not evaluate the cost effectiveness of targeting the prescription of sevelamer to such patients.

**Health Services Impact**

If all Canadian ESRD patients received sevelamer, drug expenditures could increase by $70,620,600 annually. If funding was restricted to those ≥65 years old, then drug expenditures could increase by $36,065,400 annually. Current restrictions limiting sevelamer use to patients with co-existent hyperphosphatemia and hypercalcemia may result in expenditures between $14,712,628 and $36,016,514 in Canada. We found no RCT evidence to support the use of sevelamer in these patients.
Conclusions

Compared with calcium-based phosphate binders, there was no evidence that sevelamer reduced all-cause mortality, cardiovascular mortality, hospitalization, or the frequency of symptomatic bone disease, and no evidence that sevelamer improved quality of life. Based on available evidence, the use of sevelamer, in comparison with calcium, in patients with ESRD who are on dialysis, is associated with similar to slightly higher phosphate levels, similar calcium phosphate product levels, and slightly lower serum calcium levels. The only study that investigated whether sevelamer reduces mortality and morbidity compared with calcium had methodological limitations, including lack of blinding, and substantial loss to follow-up. Overall mortality was not significantly different between sevelamer and calcium-based phosphate binders in this study, and the methodological concerns raise questions about the validity of the purported benefit in the pre-specified group of patients aged ≥65 years. The results of these secondary analyses require confirmation in future randomized studies.

Based on the available evidence, the use of sevelamer results in similar to slightly higher phosphate levels; similar calcium phosphate product levels; and slightly lower calcium levels, compared with calcium-based phosphate binders. The risk of SAEs was non-significantly lower in patients receiving calcium-based phosphate binders (13% lower, 95% CI −2 to 29), compared with those receiving sevelamer. The routine use of sevelamer in patients with ESRD is not supported by available data.

Even assuming that sevelamer is associated with a clinical benefit, as we did in our primary economic evaluation, the cost per QALY gained for treating all patients with ESRD, with sevelamer compared to calcium-based phosphate binders, may be perceived as excessive depending on what a decision maker is willing to pay for a QALY. Although lower, the cost per QALY gained for treating easily identifiable patient groups (i.e., age ≥65 years) exceeds $100,000 per QALY, and is based on considerable clinical uncertainty. If the effectiveness of sevelamer were confirmed in this group in a subsequent study, then its use in patients >65 years old should be reconsidered.

Many provinces fund sevelamer for patients with ESRD, with specific abnormalities in mineral metabolism (most commonly the co-existence of hyperphosphatemia and hypercalcemia). There are no data to support that such a strategy will reduce mortality or morbidity in these patients, and the cost effectiveness of this approach is unknown. Because calcium-based phosphate binders reduce serum phosphate levels to the same extent as sevelamer, it is unlikely that sevelamer will be more cost effective in this patient group.
# ABBREVIATIONS

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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</thead>
<tbody>
<tr>
<td>AE</td>
<td>adverse event</td>
</tr>
<tr>
<td>CORR</td>
<td>Canadian Organ Replacement Registry</td>
</tr>
<tr>
<td>CVD</td>
<td>cardiovascular disease</td>
</tr>
<tr>
<td>CKD</td>
<td>chronic kidney disease</td>
</tr>
<tr>
<td>CI</td>
<td>confidence interval</td>
</tr>
<tr>
<td>DCOR</td>
<td>Dialysis Clinical Outcomes Revisited</td>
</tr>
<tr>
<td>ESRD</td>
<td>end-stage renal disease</td>
</tr>
<tr>
<td>ICER</td>
<td>incremental cost effectiveness ratio</td>
</tr>
<tr>
<td>iPTH</td>
<td>intact parathyroid hormone</td>
</tr>
<tr>
<td>K/DOQI</td>
<td>Kidney Dialysis Outcomes and Quality Initiative</td>
</tr>
<tr>
<td>QALY</td>
<td>quality-adjusted life year</td>
</tr>
<tr>
<td>RCT</td>
<td>randomized controlled trial</td>
</tr>
<tr>
<td>RR</td>
<td>relative risk</td>
</tr>
<tr>
<td>RD</td>
<td>risk difference</td>
</tr>
<tr>
<td>SAE</td>
<td>serious adverse event</td>
</tr>
<tr>
<td>SD</td>
<td>standard deviation</td>
</tr>
<tr>
<td>USRDS</td>
<td>United States Renal Database System</td>
</tr>
<tr>
<td>WMD</td>
<td>weighted mean difference</td>
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</table>
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1 INTRODUCTION

1.1 Background

In 2002, 60% of the approximately 27,000 patients with end-stage renal disease (ESRD), in Canada, were treated with dialysis. Patients with ESRD have high mortality rates, and abnormal mineral metabolism, including hyperphosphatemia and hypocalcemia. Observational data have linked abnormal mineral metabolism, such as hyperphosphatemia, to adverse clinical outcomes, including mortality, in patients with ESRD. Higher levels of serum phosphate are associated with worse outcomes, but it is less clear whether better control of hyperphosphatemia would reduce morbidity or mortality in ESRD.

The treatment for hyperphosphatemia in ESRD has focused on the use of oral calcium-based phosphate binders taken at mealtimes. Dietary phosphate binders are used by virtually all ESRD patients. Calcium-based phosphate binders have been used as first-line therapy, because they correct hypocalcemia in addition to reducing serum phosphate levels, and because they are inexpensive.(1)

The use of calcium-based phosphate binders can be limited when hypercalcemia is present. Although the extent of this problem is poorly defined in epidemiological terms, this limitation does occur in daily clinical practice. This has led to the use of magnesium- and aluminium-containing oral phosphate binders, and recently, to the use of oral phosphate binders such as sevelamer, which do not contain calcium, magnesium, or aluminium.(2) Recent practice guidelines recommend the use of sevelamer in several common clinical situations.(2)

1.2 Overview of the Technology

Sevelamer hydrochloride is a non-absorbed polymer of allylamine that binds phosphate ions, preventing intestinal absorption of ingested phosphate. It is available as a 400 mg or an 800 mg capsule-shaped film-coated tablet containing sevelamer hydrochloride, and non-medicinal ingredients including colloidal silicon dioxide, diacetylated monoglyceride, hypromellose, iron oxide black ink, and stearic acid. The Health Canada-approved indication for sevelamer is for the control of hyperphosphatemia in patients with ESRD, who are on hemodialysis.

2 THE ISSUE

Most patients with ESRD require oral calcium-based phosphate binders with meals. Calcium-based phosphate binders may be unsuitable for controlling hyperphosphatemia in some patients, because of dose-limiting hypercalcemia and dietary non-compliance. Attention has also been focused on the potential for adverse cardiovascular effects resulting from their use. Although oral phosphate binders reduce serum phosphate levels, an association has been reported between the cumulative dose of oral calcium-based phosphate binders and the extent of vascular calcification, which in turn may be associated with mortality in ESRD. The relevance of this has not been tested in controlled trials. Non-calcium based phosphate binders have been developed for use in patients with ESRD to treat hyperphosphatemia. Sevelamer is the first such agent to be approved by Health Canada. Given a large differential cost between this agent and traditional therapies, the appropriate use of this therapy requires examination.
3 OBJECTIVES

Our objectives were to perform a systematic review of the efficacy and harm of sevelamer, and to conduct a primary economic evaluation and budget impact analysis of its use when compared with calcium-based phosphate binders, in patients with ESRD, who are on dialysis.

The report will address the following research questions:

• What is the overall clinical impact (benefit and harm) of using sevelamer compared with calcium based phosphate binders or placebo in adult patients with ESRD, who are on dialysis?
• What is the cost effectiveness of sevelamer compared with calcium phosphate binders, in patients with ESRD, who are on dialysis, in a Canadian setting?
• What is the financial impact on the Canadian health care system of funding sevelamer for all ESRD patients, restricting funding to those aged ≥65 years, or restricting funding based on the presence of clinical criteria (i.e., biochemical abnormalities)?

4 SYSTEMATIC REVIEW

4.1 Methods

This study was conducted and reported in accordance with available guidelines.(3,4)

4.1.1 Literature search strategy

We conducted a comprehensive search to identify all relevant trials or registries of sevelamer use. Articles in all languages were considered, regardless of publication status. MEDLINE® (1966 to November 1, 2005), EMBASE® (1988 to November 1, 2005), all EBM Reviews, the National Health Service Economic Evaluation Database, TOXNET, BIOSIS Previews®, and other grey literature sources (n=43) were searched. Two search terms, sevelamer and Renagel, were used to identify all relevant trials; and the drug number 182683-00-7 was used in MEDLINE and EMBASE. The sources searched and strategies used are listed in Appendix 1. The reference lists were evaluated by two reviewers (MT, and a second reviewer) to identify pertinent trials. Any trial considered to be relevant by one or both reviewers was retrieved for examination.

4.1.2 Selection criteria and method

Each potentially relevant study was independently assessed by two reviewers (MO, and a second reviewer) for inclusion in the review, using pre-determined eligibility criteria and a printed form (Appendix 3). For assessing efficacy, trials meeting the following criteria were eligible for inclusion:

• study design: randomized controlled trials (RCTs), parallel and crossover
• population: adults with ESRD (chronic kidney disease, on dialysis, or kidney transplant recipients)
• intervention: sevelamer
• comparator: calcium-based phosphate binder (alone or in combination with other agents) or placebo
• outcomes: clinical outcomes (e.g., mortality, serum phosphate).
For assessing harm, trials meeting the following criteria were eligible for inclusion:
- study design: prospective trial or registry
- population: adult patients with ESRD
- intervention: sevelamer
- comparator: none required
- outcomes: any adverse event (AE) outcomes (e.g., gastrointestinal complaints, infection).

Disagreements were resolved with a third party through consensus. Disagreements arose with 2% of the articles considered for efficacy, and with 7% of the articles considered for harm.

4.1.3 Data extraction strategy

We used a standard data extraction method (Appendices 3 and 4) to record the following properties of each trial into a database: trial characteristics (country, design, sample size, and duration of therapy); participants (age, gender, cause of renal disease, and dialysis modality); therapeutic intervention (dose and co-interventions); control regimen (therapy, dose, and co-interventions), outcomes (primary outcome, timing of outcomes, and types of AEs); and results. A second reviewer (NW) checked the extracted data for accuracy. In cases where necessary data (e.g., deaths) were missing from the studies, we requested additional information from the authors.

We assessed the following outcomes: mortality (all-cause, and cardiovascular), cardiovascular disease (CVD) events; hospitalizations (number and total length of stay); health-related quality of life; and levels of serum phosphate, serum calcium, serum parathyroid hormone (PTH), serum bicarbonate, and serum calcium-phosphate product. We also assessed episodes of hypercalcemia (serum calcium above the upper limit of normal, regardless of duration) and symptomatic bone disease (bone disease and fractures).

We considered AEs to be serious if the authors described the event as serious, or if it was the reason given for withdrawal from a trial. All other AEs were considered non-serious. Gastrointestinal complaints included any of the following: bloating, nausea, epigastric pain, abdominal pain and distension, vomiting, diarrhea, flatulence, dyspepsia, eructation, heartburn, constipation, and indigestion. Infection included upper respiratory tract infection, sepsis, and pneumonia. We also collected data on episodes of chest pain and hypotension.

4.1.4 Strategy for quality assessment

We assessed the study quality of all RCTs using a condensed version of the Chalmers Index,(5) and previously validated items known to be associated with study quality (method of randomization, double-blinding, description of withdrawals and dropouts, and allocation concealment) (Appendix 4).(6,7) The Chalmers Index summarizes quality in three sections: trial design (participant selection, description of treatment, randomization, blinding, losses to follow-up, and compliance), statistical analysis (sample size estimation, handling of missing data, types of models, side effect report, and multiple testing), and presentation of results [accession dates, duration of follow-up, and confidence intervals (CIs)]. We also extracted data on the funding source, given its potential to introduce bias.(8) We did not assess single-arm trials for quality, although two RCTs eligible only for harm outcomes were assessed.(9,10)
4.1.5 Data analysis methods

We analyzed data using Review Manager 4.2.7 (Oxford, England) and Stata 8.2 (College Station, Texas). We substituted missing final value standard deviations (SDs) with the maximum of other included study SDs. Change-from-baseline SDs were calculated using a correlation of 0.5. We used the weighted mean difference (WMD) to pool results for continuous efficacy outcomes (e.g., serum phosphate and serum calcium). For trials with <100 participants, we used change-from-baseline results in place of final value results. Pooling methods that account for the within-patient correlation from crossover trials were used to combine crossover and parallel continuous trial data. For dichotomous outcomes (efficacy and harm) with many zero events cells, we used the risk difference (RD) to pool results, because the odds ratio and the relative risks (RRs) would exclude studies where total events sum to zero. In crossover trials, data from the first period (i.e., before the crossover) were used for non-reversible outcomes such as mortality. First-period data were approximated for all other dichotomous outcomes because the carryover effect was reported to be absent.

Because of the differences expected between trials, we decided a priori to combine results using a random effects model. Statistical heterogeneity was quantified using the I² statistic. The I² statistic approximates the per cent of total variation (within- and between-study) due to between-study variation. We planned a priori to examine the association between certain variables (age, gender, diabetic status, type of calcium-based phosphate binder, dose of sevelamer, duration of follow-up, cause of ESRD, and quality criteria), and the effect of sevelamer on the outcomes. However, too few trials were included to perform meta-regressions. In sensitivity analyses, we assessed the influence of loss to follow-up on dichotomous outcomes using a best case or worst case scenario. Publication bias was assessed using weighted regression.

For AE rates, we used data from single-arm trials and the sevelamer arm(s) of RCTs. Where total AEs were unreported but specific event tabulations were reported; we took the uncombined maximum number of specific events as the total number of events, to keep our rate estimates conservative. AE rates were not pooled, because the quality of reporting was poor (e.g., descriptions of ascertainment and event severity were absent), thereby increasing the heterogeneity between trials.

4.2 Results

4.2.1 Quantity of research available

Figure 1 shows the trial flow among the studies considered for inclusion. Multiple publications were excluded from the singular count of included trials, because they were secondary publications of a previous report. Relevant and unique results were included in this report. Publications by Koiwa et al. and Koiwa et al. were excluded, because the time of randomization occurred after subjects had been treated with sevelamer for four weeks. Hervas et al. was excluded, because several statistical inconsistencies could not be reconciled. Several trials accrued many of the same participants, and were included in each outcome once.

4.2.2 Trial characteristics

We identified 10 primary publications of RCTs with a total of 3,025 participants who were eligible for efficacy analysis; one was an abstract, and a second was a poster. Eight RCTs (2,924 participants) compared sevelamer with calcium acetate, calcium carbonate, or
either (based on physician preference). (20, 34, 35) One RCT compared sevelamer with placebo (30) and the remaining compared combinations of sevelamer and calcium-based phosphate binders. (10, 36) Two were randomized crossover trials with reportedly no carryover effect. (33, 40) One had no baseline washout period. (39) One accrued only new dialysis patients. (34) All were hemodialysis patients, except in one study, where it was unclear. (39) Although we tried to extract data on the funding of studies, we did not identify any that were conducted using public funds. Studies that reported their funding sources were exclusively funded by the manufacturer.

Twenty-eight prospective trials, with a total of 3,983 participants, were eligible for the review of harm. (9, 10, 20, 30, 31, 33-55) Most (n=16) were single-arm trials. No registries were identified. Two trials studied peritoneal dialysis patients; (42, 50) both were conducted in Spain, and one was published in Spanish. The demographic and clinical characteristics are described in Table 1.

Few quality or validity tools discriminate between single-arm trials. Because they lack a control group, inferences regarding effect size cannot be drawn from these studies. The quality assessment of the included RCTs is shown in Table 2. Of the 12 RCTs, 10 were included in the assessment of efficacy, and all were included in the assessment of harm. The reporting of study design was weak in several areas. Non-eligible patients were not described in nine of the 12 trials. Double-blind treatment assignment was reported in two trials. (30, 38) The description of withdrawals and dropouts was incomplete or unreported in eight trials. Furthermore, the percentage of loss to follow-up was >10% in six of eight trials (Table 2) (percentage of loss to follow-up could not be calculated from the remaining four trials), and three of the 12 RCTs reported their sample size calculation. Four trials reported an intention to treat design, and one trial reported a method for handling missing data. Two RCTs reported side effects adequately (the number and type of side effect was listed individually, and by treatment group). Under presentation of results, the dates of accrual or follow-up were reported in half of the RCTs (n=6), and confidence intervals were reported for the primary outcome in two of the 12 RCTs. None of the RCTs reported a public source of funding.

4.2.3 Data analyses and synthesis

To assess the potential for publication bias in RCTs, we used results from the most frequent treatment comparison (sevelamer versus calcium-based phosphate binders), and the most frequent outcome studied (serum phosphate). Publication bias is often assessed using a funnel plot. A funnel plot is a scatter plot of a measure of each study’s precision (y axis) against each study’s treatment effect (x axis). Precision may be the inverse of the study’s standard error or sample size. Because small studies have less precision and large studies have more, the scatter should form an inverted funnel. We expect publication bias when small positive studies are missing, causing the funnel plot to appear asymmetrical. Our funnel plot appeared symmetrical (Figure 2), and the weighted regression test detected no statistical evidence of publication bias (bias=-0.4, p=0.73).

4.3 Sevelamer versus Calcium-Based Phosphate Binders

4.3.1 Mortality

Four RCTs, with 2,302 participants, reported all-cause mortality. The duration of follow-up varied from two to 45 months. One RCT (35) specified all-cause mortality as the primary outcome. The overall risk difference was non-significant (~1%, 95% CI –4 to 2) (Figure 3). No qualitative trend was apparent; two RCTs favoured sevelamer compared with calcium-based phosphate binders, and
the per cent of heterogeneity due to between-study variance (I²=0%) was non-existent. Two RCTs
with 93% of the weight did not follow all participants until the end of the study or death. (20,35) Both
these RCTs had >10% losses to follow-up. Three RCTs, with 2,102 participants, reported
cardiovascular mortality. The overall risk difference was non-significant (−1%, −4 to 2) (Figure 4),
and between-study heterogeneity was absent.

4.3.2 Hospitalizations

Two RCTs reported the number of days of hospitalization, but these results could not be pooled
because of differences in the reporting. Chertow et al. (20) reported the number of patients
hospitalized during the 52-week trial. The difference was non-significant (total 567 versus 980 days;
p=0.23; 200 participants), but favoured sevelamer therapy. Suki et al. (35) reported the number of
days hospitalized per patient year; this difference was non-significant (median 5.0 versus 5.8 days;
p=0.09; 2,040 participants), but also favoured sevelamer therapy.

4.3.3 Health-related quality of life

No RCTs reported a measure of health-related quality of life.

4.3.4 Reporting of other clinical outcomes

No RCTs reported CVD events, or the frequency of symptomatic bone disease such as fractures or
bone pain.

4.3.5 Serum measures

Eight RCTs, with 2,445 participants, reported levels of serum phosphate, serum calcium, and intact
parathyroid hormone (iPTH). The duration of follow-up ranged from eight weeks to 45 months. In pooled
analyses, the overall control of serum phosphate was significantly better with calcium-based phosphate
binders by 0.09 mmol/L (95% CI 0.02 to 0.16) (Figure 5), and the between-study heterogeneity was large
(I²=60%). All RCTs favoured calcium-based phosphate binders. The overall WMD in serum calcium was
significantly lower with sevelamer therapy by 0.10 mmol/L (−0.12 to −0.07) (Figure 6). Between-study
variance was also large (I²=61%). The data for iPTH were skewed, so the results could not be combined
(Figure 7). The mean (or median) differences of iPTH ranged from 0.7 to 9.5 pmol/L. All RCTs
demonstrated a numerically lower mean level of on-treatment iPTH (or in some cases, a smaller increase
in PTH) in the calcium groups, although only two were statistically significant.

Seven RCTs, with 2,215 participants, reported levels of serum calcium-phosphate product. On-treatment
calcium-phosphate product was non-significantly lower in patients receiving calcium-based phosphate
binders (WMD 0.09 mmol²/L², −0.07 to 0.25) (Figure 8), and the between-study heterogeneity was large
(I²=55%). Three RCTs, with 322 participants, reported levels of serum bicarbonate. The overall WMD
was significant, and was lower with sevelamer therapy by 2.7 mmol/L (−3.5 to −1.9; I²=0%) (Figure 9).
4.3.6 AEs

Sixteen sevelamer trials (RCTs and single-arm trials), with 1,813 participants, reported serious AEs (Table 3). The frequencies of SAEs ranged from 2% to 33% for an approximate median duration of follow-up of two years. The median frequency of SAEs was 15%. Non-serious AEs were reported in eight trials with 617 participants (Table 3). The median frequency of non-serious AEs was 25% (range six to 58) for a median follow-up of eight weeks. The frequency of serious adverse gastrointestinal events ranged from 5% to 40% (median eight weeks of follow-up), and the frequency of non-serious gastrointestinal events ranged from 6% to 58% (median 24 weeks) in the 19 trials (939 participants) where it was reported (Table 4). Three trials with 260 participants reported chest pain; one trial (n=34; median follow-up six months) reported one incident as serious, while the other two trials reported frequencies of 7% and 8% (median follow-up eight weeks), but did not distinguish between serious and non-serious events. Two trials reported that infection occurred in 7% and 9% of participants respectively (of 226 participants; median eight weeks). One trial reported a 5% frequency of hypotension (eight weeks).

Controlled comparisons of AEs were less frequent. Three RCTs, with 2,185 participants reported SAE totals. The risk difference was non-significant (13% lower in patients receiving calcium-based phosphate binders, 95% CI −2 to 29; I²=78%) (Figure 10); all three RCTs favoured calcium-based phosphate binders. Two RCTs, plus a report(22) of the Treat-to-Goal RCT with 211 participants reported all AEs. This risk difference was non-significant (−2%, −14 to 10) (Figure 11). One of these RCTs favoured calcium-based phosphate binders. One report (31 participants) of serious gastrointestinal complaints found a significant risk difference of 33% (9% to 58%) favouring calcium-based phosphate binders. Three reports (211 participants) of gastrointestinal complaints found an overall non-significant difference of 1% (−13 to 11) (Figure 12) with no between-study heterogeneity.

4.3.7 Hypercalcemia

The hypercalcemic rate for 12 sevelamer trials (RCTs and single-arm trials; 626 participants; median 12 weeks) (Table 5) was a median of 11%, and ranged from zero to 36. Six RCTs (538 participants) reported the numbers of patients who became hypercalcemic during follow-up. The overall risk difference of 22% (95% CI 16 to 29; I²=0%) (Figure 13) was significant, and favoured sevelamer therapy. The number needed to harm (i.e., to result in one participant experiencing ≥1 episode of hypercalcemia) was five (three to six). The median duration of hypercalcemia or its clinical consequences were not reported for any trial.

4.3.8 Sevelamer versus other comparators

One small RCT,(30) of an eight week duration, with 36 participants, compared sevelamer with placebo, and found a significant difference favouring sevelamer on serum phosphate, but not on serum calcium, serum bicarbonate, or any AEs.

Another RCT,(10) with 71 participants (55 completing the trial), compared sevelamer with sevelamer plus calcium carbonate during a 12-week treatment period. The changes in levels of serum phosphate and serum calcium phosphate product were not significantly different between treatment groups. The rates of AEs were also deemed to be similar. Conversely, the per-protocol analysis found a significant difference on serum calcium favouring the sevelamer group; the intention to treat analysis reported a p value of 0.09. Among non-users of vitamin D, the combined use of sevelamer plus calcium carbonate, compared with sevelamer alone, resulted in a significantly lower mean PTH (−115 versus −22 pg/mL, p=0.006).
Iwasaki et al. (36) compared 3.0 g per day of sevelamer to 2.25 g per day, both with a therapeutic dosage of calcium carbonate. This was an eight-week study, which 51 out of 65 participants completed (21 from the 3.0 g per day group, and 30 from the 2.25 g per day). The authors found no significant differences between groups on the rates of AEs (although those not completing the study were excluded in the AE analysis). The authors did not compare the groups directly on efficacy outcomes, but reported significant changes from baseline on levels of serum phosphate, serum calcium, and serum calcium-phosphate product for the high dose group, and a significant change from baseline on serum calcium for the low dose group. Our calculations found no significant differences between groups.

Akizawa et al. (9) randomized 94 patients to receive one of four dosages of sevelamer (1.5 g/day, 3.0 g/day, 6.0 g/day, or 7.5 g/day). No comparisons between groups were reported, other than noting that the reduction in serum phosphate depended on dosage.

4.3.9 Sevelamer in patients with co-existent hyperphosphatemia and hypercalcemia

Many provinces fund sevelamer for ESRD patients who have specific abnormalities in mineral metabolism (most commonly concomitant hyperphosphatemia and hypercalcemia). We found no randomized studies that examined the effectiveness of sevelamer in ESRD patients with co-existent hyperphosphatemia and hypercalcemia. There are no data indicating that such a strategy will reduce mortality or morbidity among these patients.

4.3.10 Supplemental issues

Our systematic review was conducted in accordance with published guidelines. Although we made every attempt to include all studies (including those not published in peer reviewed journals), additional studies may remain unidentified. As with all meta-analyses, our findings are limited by the quality of the studies. Although we had access to the DCOR poster presented at the American Society of Nephrology meeting in late 2005, it would have been preferable to have access to the peer-reviewed report or the trial report.

The DCOR study (35) is the only study with enough statistical power to investigate whether sevelamer reduces mortality and morbidity compared with calcium-based phosphate binders. Although the study has not yet been published in a peer reviewed journal, it has been presented at scientific meetings, and has received coverage in the lay press.

This randomized, unblinded study allocated 2,103 dialysis patients at 75 US centres to receive sevelamer, or calcium-based phosphate binders. All patients were treated with hemodialysis. The intended duration of follow-up was two years, but it was extended for an additional year after a recommendation from the Data Management Committee, based on lower than expected mortality at an interim analysis. (35) The maximum follow-up time was 3½ years. Among participants, 48% (47% of sevelamer recipients, and 49% of calcium recipients) dropped out of the study early, and information about clinical events for these patients after loss to follow-up is unavailable.

The primary analysis from DCOR did not show a difference in survival between patients treated with sevelamer, and those receiving calcium-based phosphate binders (RR 0.91, p=0.30). There was also no difference in cardiovascular mortality (RR 0.92, p=0.48). In secondary analyses stratified for duration of therapy and age, sevelamer was associated with better survival in patients treated for ≥2 years, and those aged ≥65 years.
Six tests for interaction (specified a priori) were performed to evaluate whether the effect of sevelamer was dependent on the presence of selected baseline patient characteristics. Of these, the interaction with patient age (<65 years or ≥65 years) was statistically significant. Corrections for multiple comparisons were not performed. The RR of mortality for sevelamer compared with calcium-based phosphate binders was 1.14 (0.88, 1.49) for patients aged <65 years, and 0.78 (0.62, 0.97) for patients aged ≥65 years. The results of this secondary analysis require confirmation in future studies.

The assumption of constant proportional hazards was not met in the primary analysis. As a result, the authors performed a post-hoc analysis, which presents survival data separately for patients who were followed for <2 years (or died before the end of the second year), and those who were followed for >2 years (who by definition, had not died in the first two years). In patients followed for <2 years, the RR of mortality for sevelamer compared with calcium-based phosphate binders was 1.08 (0.89, 1.32), as opposed to 0.66 (0.48, 0.94), in patients surviving for >2 years. It is difficult to draw any conclusions from analyses that define subgroups based on post-randomization events. The balance introduced by randomization at study entry may no longer be present by two years, resulting in a biased comparison between the treatment groups. Because 52% of patients completed this unblinded study, the differential loss to follow-up between the two study arms may have led to a spurious finding of reduced mortality with sevelamer. The high frequency of loss to follow-up means that a significant increase in mortality due to sevelamer cannot be excluded. Because it cannot be predicted accurately which patients will survive >2 years, this group cannot be selected for the targeted prescription of sevelamer. Moreover, advocating such targeted prescription would raise ethical issues. The findings of this post-hoc analysis are of uncertain clinical significance, are prone to bias, and would be difficult to implement.

The DCOR study, while large and randomized, has several methodological limitations, including the lack of blinding, significant loss to follow-up, and analytical issues that raise concerns about the validity of the purported benefit in patients who had been treated for ≥2 years, or were ≥65 years old. The results of these secondary analyses require confirmation in future randomized studies.

5 ECONOMIC ANALYSIS

5.1 Review of Economic Studies

We sought to conduct a systematic review of existing economic evaluations of sevelamer in patients with ESRD, before determining the need to conduct a primary economic evaluation of our own.

5.1.1 Methods for review of economic studies

A protocol for the systematic review was written a priori and followed throughout the process.

a) Literature search strategy

Given the broad search terms that were used for the clinical systematic review, we screened all studies that were retrieved for eligibility in the economic review (Appendix 1); 436 studies were screened for eligibility.

b) Study selection criteria

A study was eligible for inclusion in the systematic review of economic evaluations if it met each of the following criteria: it was a complete economic evaluation (i.e., determined the input of sevelamer
to costs and health benefits), it included adult patients with ESRD, and it compared sevelamer to any alternative phosphate binder. We decided to base our conclusions on Canadian studies, and economic evaluations that were based on clinical endpoints from RCTs, unless none were identified.

c) **Selection method**
Two reviewers (BM, FS) applied the eligibility criteria to the title of each citation, and the abstract. Where disagreements occurred, a full-text hard copy of the article was retrieved. Two reviewers (BM, FS) applied the eligibility criteria to the full-text papers. For inclusion in the review, the study had to satisfy all the selection criteria. Disagreements between the reviewers were resolved by consensus.

d) **Data extraction strategy**
Two reviewers (BM, FS) used a standard data extraction form (Appendix 5) to independently extract and document relevant information on author, title, type of program, intervention, comparators, study population and size, study design, time horizon, perspective, data sources for effects, data sources for costs, discounting, health-related quality of life, currency, year, base-case incremental cost effectiveness ratio (ICER) results or incremental net benefit, sensitivity analysis, and conclusions.

e) **Study quality assessment**
The quality of each study included in the systematic review was independently assessed by two reviewers (BM, FS) using a checklist adapted from the *British Medical Journal* (Appendix 5). (56)

f) **Data analysis methods**
Given that only one study met the inclusion criteria, the results were synthesized qualitatively, highlighting the impact of sevelamer on the direction and magnitude of health outcomes, costs, and the cost effectiveness ratio.

5.1.2 Results

Five full-text articles were thought to be potentially relevant after a review of titles and abstracts. (57-61) Of the five articles, one study, by Huybrechts *et al.*, met our inclusion and exclusion criteria. (61) The remaining five were not full economic evaluations. We found no Canadian studies, and the only analysis that met the inclusion criteria (61) used clinical data from a randomized trial that measured surrogate endpoints. (20) Because a randomized study that reports clinical outcomes (i.e., the DCOR study) is available, the results of the study by Huybrechts *et al.* (61) are unlikely to influence the results of this report.

5.1.3 Discussion

In the study by Huybrechts *et al.* (61) the research objective, although not clearly stated, appeared to involve the calculation of the ICER for sevelamer compared with calcium-based phosphate binders, specifically calcium acetate, in American patients with ESRD. The use of sevelamer (intervention) was compared with calcium acetate (comparator) in patients with ESRD (target population). A cost effectiveness study was performed, reporting a cost per life year gained, and a cost per cardiovascular event avoided. The perspective adopted was that of a health care payer, and the time horizon considered was the patient’s lifetime. Costs and benefits were discounted at an annual rate of 3%. This work received financial support from Genzyme, the company marketing sevelamer.

Huybrechts *et al.* used a discrete event simulation model, a form of mathematical modelling. Data on the clinical effectiveness of sevelamer were taken from the Treat-To-Goal study (20) a randomized trial comparing the effect of sevelamer to calcium-based phosphate binders on the progression of coronary and aortic calcification during one year in patients with ESRD. Using these data, the investigators
projected what would likely happen to calcification scores, during a one-year period, for a hypothetical cohort of American ESRD patients. Based on the modelled calcification scores at one year for patients treated with sevelamer or calcium-based phosphate binders, the investigators then modelled the cardiovascular outcomes expected for these patients. This was based on a study of ESRD patients in France, which assessed long-term survival and risk for cardiovascular events for patients with different calcification scores. The baseline risk of events was based on patients whose characteristics were typical of the US Renal Database System (USRDS) cohort (mean age 54, 60% male, 6% smokers), and baseline survival data were taken from the USRDS. Drug costs were obtained from the 2002 Wholesale Acquisition Cost list. Costs for cardiovascular complications were obtained from a resource-use database capturing hospital discharge abstracts in California, Florida, Maryland, Massachusetts, and Washington. Dialysis costs were excluded from base case analyses.

The base case analysis resulted in a cost per life year gained of US$1,641. When discounting was applied, the cost per life year gained increased to US$2,219. The cost per cardiovascular event prevented was reported to be US$4,448. Sensitivity analyses were completed. When the effectiveness of sevelamer was varied in the 95% CI, the cost per life year gained varied between US$20,000 per life year, when the lower 95% CI bound (sevelamer less effective) was modelled, and a cost-savings when the upper bound was applied (sevelamer more effective). When dialysis costs were included in the total patient costs for the additional survivors, the cost per life year gained was US$59,000.

The authors state that in a population of ESRD patients, similar to those modelled in this analysis, sevelamer would prevent nine cardiovascular events, and save 18 life years per 100 patients treated at an incremental cost effectiveness of <US$2,500 per discounted life year gained.(61) The authors acknowledge that the validity of this model is based on the assumption that a reduction in calcification score would equate to a reduction in cardiovascular (clinical) events. Thus, the calcification score was used as a surrogate outcome for hard clinical outcomes.

With long-term data available from a randomized study on the effectiveness of sevelamer on clinical outcomes, the results of this economic evaluation(61) have limited applicability. We present the results of a primary economic evaluation that we performed, comparing sevelamer and calcium-based phosphate binders in patients with ESRD.

5.2 Introduction to Economic Analysis

An economic evaluation is the comparative analysis of alternative health care interventions in terms of their relative costs (resource use) and effectiveness (health effects). In the planning of health services, the aim of an economic evaluation is to ensure that the benefits from health care programs implemented are greater than the opportunity costs of such programs.(62) The question under consideration (i.e., whether and for whom sevelamer should be funded in the Canadian health care system) addresses a question of allocation efficiency (i.e., do we allocate scarce resources toward the use of sevelamer in ESRD patients, or to another health-promoting activity). When addressing such questions, a cost benefit analysis, or a cost utility analysis [a form of cost effectiveness analysis(63)] can be used. We chose to use a cost utility analysis, where health benefits are expressed as healthy years or QALYs, to determine the economic efficiency of sevelamer for use in ESRD.

There are two methods of performing a cost utility analysis: alongside a clinical trial, or using decision analytic modelling.(64) For several reasons, including the fact that randomized trials are typically of short duration, most cost utility analyses combine the use of decision analytic modelling,
with data taken from randomized trials and observational cohorts. The most important data input into a decision analysis is the measure of effectiveness of the intervention, in this case, the effectiveness of sevelamer. The effectiveness of interventions can be determined by the impact of a therapy on clinical endpoints (i.e., mortality, quality of life, clinical events such as the need for dialysis, or development of a myocardial infarction) or surrogate endpoints, which are indirect measures of clinically relevant endpoints. Given the drawbacks of surrogate endpoints, when assessing the cost effectiveness of interventions, it is optimal (and many analysts argue it is mandatory) to have data on the effectiveness of the intervention with respect to clinical endpoints.\textsuperscript{(64,65)\textsuperscript{12}}

Thus, when modelling the cost effectiveness of sevelamer compared with calcium-based phosphate binders in patients with ESRD on dialysis, we used input data from randomized trials that assessed the effectiveness of sevelamer on clinical endpoints.

5.3 Clinical Data Relevant to this Economic Analysis

One randomized trial assessed the impact of sevelamer on relevant clinical endpoints (i.e., mortality). The DCOR study was started in 2001 to evaluate whether sevelamer was associated with lower mortality and morbidity compared with calcium-based phosphate binders.\textsuperscript{(35)} Given a lower than expected mortality rate noted at an interim analysis, the follow-up was extended for an additional year. Of the patients in the study, 48% dropped out early, and information on clinical events for these patients after study withdrawal is unavailable.

The unpublished DCOR study reported efficacy in several ways. In the a priori stated primary analysis, there was no difference in overall survival for patients treated with sevelamer compared with those receiving calcium-based phosphate binders (RR 0.91, \( p=0.30 \)). In secondary analyses, stratified for time on therapy and age, sevelamer was associated with better survival in patients treated for \( \geq 2 \) years and those aged \( \geq 65 \). Because the \( p \) value was \( >0.05 \), the null hypothesis of no difference between sevelamer and calcium-based phosphate binders cannot be rejected, and therefore this randomized trial suggests that sevelamer does not significantly influence mortality in dialysis patients.

The study authors note that because the assumption of constant proportional hazards was not met in the primary analysis, survival data are presented separately for patients who were followed for \(<2\) years (or who died before the end of the second year), and those who were followed for \(>2\) years (who by definition, had not died in the first two years). In patients followed for \(<2\) years, the RR of mortality for sevelamer compared with calcium-based phosphate binders was 1.08 (95% CI 0.89, 1.32), as opposed to 0.66 (95% CI 0.48, 0.94) in patients surviving for \(>2\) years. Because only 52% of patients completed this unblinded study, a differential loss to follow-up may have occurred in the two study groups, raising concerns that the balance introduced by randomization at study entry was absent after two years. It would be difficult to reliably predict which patients will survive \(>2\) years, and to select this group for the targeted prescription of sevelamer.

Despite the methodological drawbacks of the DCOR study, and the resultant uncertainty in the effectiveness of sevelamer, it is a large randomized clinical trial performed in North American hemodialysis patients, and the sole trial with enough statistical power to determine the impact of sevelamer on a clinical endpoint. For the primary economic analysis that follows, the effectiveness data for sevelamer were taken exclusively from the DCOR study. Thus, the results of this economic analysis represent a best case scenario for sevelamer.
5.4 Primary Economic Evaluation

Given that we did not identify any economic evaluations that adequately addressed our study question, we conducted our own primary economic evaluation.

5.4.1 Methods for primary economic evaluation

a) Objective
Our objective was to determine the cost effectiveness of sevelamer compared with calcium-based phosphate binders, in patients with ESRD, who are on dialysis, in a Canadian setting.

b) Population
In the base-case analysis, we evaluated a simulated cohort of dialysis patients with ESRD who were ≥18 years old, and whose characteristics were representative of typical Canadian patients.

Information for the population of interest was taken from the Canadian Organ Replacement Registry (CORR), which collects information on Canadian patients undergoing dialysis or transplantation. CORR releases a semi-annual report on aggregate data about mortality, use of dialysis modality, and rate of transplantation.(66) Data are not reported for specific age groups. For another analysis, CORR provided data from a random sample of approximately 37% of patients starting renal replacement in Canada between January 1, 1996, and December 31, 2000.(67) After excluding children (age<18 years, n=117), we performed analyses on the resulting dataset, which included clinical and demographic data, geographical location, dialysis modality, and whether the patient died or received a transplant after ≤6 years of follow-up ending on December 31, 2002. This is an appropriate comparative group given that sevelamer would not have been used in most of these patients. Using this dataset, we accurately determined the probabilities of patients <65 years old and ≥65 years old moving between the states of alive on dialysis, alive with a transplant, and dead.(67)

c) Treatment comparators
We sought to compare sevelamer with the most commonly used phosphate binder for patients with ESRD in Canada, calcium carbonate.(1) This was one of the calcium-based phosphate binders used as standard care for many patients enrolled in sevelamer clinical trials, including DCOR. Alternative phosphate binders are used rarely in Canadian ESRD patients (i.e., magnesium-based phosphate binders), they do not constitute usual care, and their relative effectiveness for clinical or surrogate outcomes is unknown in comparison with sevelamer.

d) Analytical approach
To calculate the cost effectiveness of sevelamer, we used a Markov model, adapted from previous analyses(68,69) that have modelled the cost effectiveness of therapies for patients with ESRD. We stratified patients by age (<65 years, or ≥65 years) and considered yearly transitions between three clinical states: alive on dialysis, alive with a transplant, and dead (Figure 14). The starting point of the model was based on a cohort of Canadian dialysis patients(67) who were stratified by age (<65 years, or ≥65 years). In cycles subsequent to transplant, patients could die, return to hemodialysis, or continue with a functioning transplant. The primary analysis was continued until <1% of the cohort remained alive. The model outputs were QALYs, life years gained, costs, and the cost per QALY gained. QALYs were estimated by multiplying the number of cycles spent by the average patient in each clinical state by the utility associated with the state. Base case analyses were done using a Markov cohort analysis; second order Monte Carlo simulation was performed in the sensitivity analysis. All analyses were performed using Treeage Pro 2005 (Treeage Software, Inc., Williamstown US).
e) **Audience and perspective**
The target audience for this study includes provincial drug benefit plans, provincial health ministries, and regional renal programs. The primary perspective was that of a Canadian publicly funded health care system. This is consistent with the recommendations in the third edition of the CADTH guidelines,(70) and seems reasonable given the absence of data as to whether sevelamer has an impact on the indirect costs experienced by patients.(35)

f) **Time horizon**
In the primary analysis, a lifetime time horizon was considered. This is consistent with CADTH guidelines.(70) To reflect the maximum follow-up of 3½ years from the DCOR clinical trial, and to avoid the need for extrapolation of future benefits associated with sevelamer, we considered a four-year time horizon in the sensitivity analysis.

g) **Clinical effects of patients treated with calcium-based phosphate binders**
Baseline transition probabilities and clinical effects appear in Table 6. The probabilities of mortality and transplantation (i.e., the probability of transition from one predefined state to another in the model) for the calcium-based treatment strategy were based on the observed rates in our Canadian patient cohort, stratified by age (n=7,034).(67) The mortality rates for patients <65 years and ≥65 years were taken from individual patient data for all dialysis patients in the four-year cohort. Given the high baseline mortality rate for all patients, mortality was not adjusted in each group (<65 years or ≥65 years) to account for increasing age during modelling. These rates represent the mortality rates observed in Canadian dialysis patients more accurately than the rates observed in the control arm of the DCOR study.

h) **Evidence of efficacy of sevelamer**
The relative survival for patients treated with sevelamer, compared with calcium-based phosphate binders, was taken from the DCOR study. This unpublished study reported efficacy in several ways. Given the results, and the suggestion of differential benefit based on length of follow-up and patient age, it is unclear how best to model the efficacy of sevelamer for patients overall. We considered several strategies, and developed an a priori analysis plan. The analytic strategies used, which consider ways of modelling the efficacy of sevelamer, appear in Table 7. Given that the primary DCOR analysis compared survival without stratifying by time on therapy, our primary analysis used this estimate of sevelamer’s efficacy (a constant RR over time of 0.91 for all age groups) [model 1 (primary)]. Because there was no statistically significant benefit seen for the primary analysis, we also present the results of a cost minimization analysis [model 2 (cost minimization)] (Table 7). Given that the assumption of constant proportional hazards was not met in the primary analysis, we performed an exploratory analysis in which survival data were modelled separately for the period before and after two years [model 3 (mortality over time)]. The DCOR investigators reported an interaction between treatment efficacy and patient age (<65 years or ≥65 years), and we also performed an exploratory analysis modelling the efficacy of patients aged <65 years or ≥65 years [model 4 (mortality by age)].

If our model is valid and technically accurate, models 1 and 4 will predict mortality in a similar fashion during the four-year study period. Using a lifetime analysis (the base case time horizon), even these models may differ when modelling the cost effectiveness of sevelamer for patients overall. In all base case models, we assume that the RR continues throughout the patient’s lifetime, but in a subsequent secondary analysis, we assume no survival benefit beyond four years. Although CADTH guidelines suggest modelling effectiveness rather than efficacy,(70) in this case, no data on effectiveness are available. Through a sensitivity analysis, we considered different estimates of efficacy based on the 95% CI.
i) **Other clinical effects**

**Transplantation:** Transplant rates for patients aged <65 years and ≥65 years were derived for mortality using the same cohort (Table 6).(67) The survival of transplant patients, and transplant failure necessitating a return to dialysis, were estimated from a contemporary cohort of North American patients. We assumed transplant failure and survival to be similar for patients treated with calcium-based phosphate binders and sevelamer.

**Health-related quality of life:** A focused literature search was done to obtain estimates of utility scores for contemporary Canadian dialysis and transplant patients (Table 8). The following inclusion criteria were followed: studies were performed in Canada, studies used a valid measure of patient utility, and studies focused on ESRD patients receiving dialysis or transplant. When determining which study results to use as the base case value, we favoured studies that were done in unselected patient populations, and were performed more recently. Three studies were found.(71-73) Base case analyses use the results of a contemporary cohort of ESRD patients,(71) who were followed for up to 18 months. Secondary analyses use the results from Laupacis et al.,(72) because these patients are not representative of the overall cohort of patients likely to receive sevelamer as they tended to be healthier, given that this study only enrolled patients who were transplant candidates. Given that quality of life was not reported in the DCOR study, or any other sevelamer study, we assumed similar utility values for patients treated with calcium-based phosphate binders and sevelamer.

j) **Costs**

**Drug:** The baseline estimates of cost are included in Table 9. The average daily consumption of sevelamer and calcium-based phosphate binders was not reported in the DCOR study. In the primary analysis, the cost of sevelamer and calcium carbonate was estimated based on the average doses (sevelamer 6.5 g per day; calcium carbonate 4.3 g per day) consumed in the Treat-to-Goal study,(20) the second largest clinical trial of sevelamer. The costs of calcium carbonate and sevelamer were taken from provincial formularies, excluding dispensing fees, because in provinces where both medications are covered through prescription drug insurance, the dispensing fees would be similar.

Consistent with clinical practice, we assumed that laboratory monitoring would not be influenced by the use of either medication. The costs of medication-related complications are assumed to be captured in the hospitalization category (i.e., cost category 2).

**Other costs:** As the primary analysis took the perspective of the publicly funded health care system, it included direct costs to the publicly funded health care system, direct costs to patients and their families, and time costs to patients and their families.(70) Costs that are only relevant from a societal perspective (i.e., due to lost productivity) were excluded from the analysis, given that there is no evidence that they differ based on treatment strategy. All costs are reported in Canadian dollars, and were inflated to 2004 costs using the consumer price index for health care goods in Canada.(74)

**Drug costs:** The costs of sevelamer and of its comparator, calcium-based phosphate binders (cost category 1), were determined. The impact of provincial variation in costs, if any, was assessed.

**Hospitalization costs:** Given that it has been reported that sevelamer may reduce the incidence of hospitalization, the cost of annual hospitalization for ESRD patients (cost category 2) was determined, based on recent Canadian data, and supplemented by data retrieved in a focused literature review (Table 8). To determine the average annual cost, information on the annual frequency of hospitalization and mean cost per hospital stay was required (Table 8). The DCOR study is the only one that has reported the impact of
sevelamer on frequency of hospitalization. Overall, the number of hospitalizations (per patient year) was not significantly reduced from 2.3±4.9 to 2.1±4.4 (p=0.06) for patients treated with sevelamer. The benefit seemed greater in patients aged ≥65 years, although formal significance testing to confirm the differential benefit in this group was not presented.

**Associated health care costs:** Given that any therapy that extends life will increase the cost of associated health care (i.e., dialysis and transplant care), we also estimated the cost of ongoing dialysis and transplant therapy (cost category 3). This has been estimated in detail in Canada, though other estimates were sought using a focused literature search (Table 8). A systematic review was not performed for the estimates. A focused literature search was done to identify studies that estimated the cost of hospitalization, dialysis, and transplantation for Canadian ESRD patients. The inclusion criteria specified studies with inpatient and outpatient costs; studies that were performed in Canada; and transplantation studies that reported costs for the first year and subsequent years separately. When determining which study results to use as the base case value, we favoured studies that were done in unselected patient populations, and were performed more recently. Costs (Table 8) were inflated to 2004 values using the consumer price index.

Methodological controversy exists as to which costs to include in economic evaluations that are performed regarding ESRD. For the primary analysis (i.e., publicly funded health care system), we considered costs that fall in categories 1 to 3.(75) Given the magnitude of dialysis and transplant costs (category 3), interventions for patients that improve survival without reducing the need for dialysis, will be associated with a cost utility ratio at least as great as that of dialysis. The magnitude of the cost utility ratio for inexpensive therapies that improve the survival of ESRD patients may be more dependent on the estimate used for future dialysis costs, rather than the costs and benefits that are directly related to the intervention.(75) The inclusion of such costs (which is methodologically correct) in economic evaluations may mitigate the acceptance of interventions that improve patient survival. In a sensitivity analysis, we explored the cost per QALY gained, considering only the costs in categories 1 and 2.

**k) Subgroup analysis based on patient age**

The DCOR study identified six groups a priori for which analyses were planned. A significant interaction was noted for one group (between treatment and age <65 years or ≥65 years). Patients <65 years experienced a non-statistically significant rise in mortality [RR 1.14 (95% CI 0.88 to 1.49)], while those ≥65 years experienced significantly lower mortality [RR 0.78 (95% CI 0.62 to 0.97)]. Although the statistical significance of the test for interaction was not corrected for multiple comparisons, this raises the possibility that sevelamer is more effective in older patients. Thus, we modelled the cost effectiveness of sevelamer in patients aged ≥65 years.

**l) Assumptions**

- Our baseline comparison was between sevelamer and calcium carbonate, the most frequently used calcium-based phosphate binder in Canada.(1) While it could be argued that magnesium-based phosphate binders are a reasonable comparator, they are rarely used in clinical practice (because of concerns about safety), and we are unaware of data comparing their efficacy for clinical outcomes to that of sevelamer. Another relevant comparison might have been between sevelamer and calcium acetate (which is used infrequently in Canada). However, whether the efficacy of sevelamer in DCOR depended on the type of calcium-based phosphate binders was not reported. Some have suggested that an alternative strategy would be a combination of sevelamer and calcium-based phosphate binders. While we
considered the effectiveness of such a strategy (on phosphate and calcium levels) in the systematic review, the effectiveness in terms of hard clinical endpoints is unknown; and therefore, it was not modelled as a strategy in the economic evaluation.

- We considered the baseline mortality rate from a Canadian cohort of ESRD patients on dialysis (rather than using estimates from the control group in the DCOR study). This improves the external generalizability of the results of the economic evaluation, because patients in randomized trials may be healthier than those in the general population.
- We used the RR of mortality with sevelamer as noted in the DCOR study, including the RR of mortality in relevant subgroups. Subgroups were determined based on the findings as presented in DCOR. Appropriate consideration was given to the possibility of bias resulting from subgroup analyses.
- We assumed that the efficacy of sevelamer was similar in Canadian ESRD patients. While there are differences in ESRD patients in Canada and the US (slightly lower mortality rates for ESRD patients in Canada; different treatment patterns in Canada, including more time on dialysis per week), we assumed that the relative efficacy of sevelamer would be similar.
- We assumed that the efficacy of sevelamer would continue for the life of the dialysis patient. Because clinical trial data are only available to four years, scenarios where efficacy is lost after four years were also modelled.
- We used transplant rates and mortality data from the same Canadian registry. We modelled different rates of transplantation for patients aged <65 years or ≥65 years.
- We assumed that the hospitalization rates that were observed in the trial were a true reflection of the effectiveness of sevelamer. Given that the study was not blinded, and investigators knew which patients were on active therapy, differences in hospitalization may have resulted from bias.
- We modelled adherence to therapy as was done in the DCOR clinical trial. Given that the results of the clinical trial were reported as intention to treat, for the mortality rates observed, we considered that some patients were not adherent with therapy, and therefore, did not receive sevelamer. In the primary analysis, the cost of sevelamer was calculated based on the average dose consumed in the Treat-to-Goal study, the second largest clinical trial of sevelamer. In the sensitivity analysis, the average dose of sevelamer (and cost) was reduced to account for the doses potentially taken by patients, and the failure by some patients to use sevelamer.

m) Sensitivity analysis
We performed one-way sensitivity analyses, varying the values for uncertain variables between the ranges noted in Tables 6 to 8. We performed analyses modelling the efficacy of sevelamer in different ways (Table 7). Scenario analyses were also performed assessing the efficacy of sevelamer in patients aged >65 years, and analyses considering different time horizons.

The standard method of expressing uncertainty in classical statistics is through the use of measures of variance, such as the 95% CI, around a mean for normally distributed variables. This approach is problematic in economic evaluation, and has led to the use of other methods designed to deal with and express analytical uncertainty (77,78). For instance, uncertainty that exists in probability estimates, or estimates of clinical effectiveness or cost, are usually considered with a sensitivity analysis.

The classical univariate sensitivity analysis has been criticized, because it only considers the uncertainty in one (or two) variables at a time, and it may underestimate the uncertainty in a cost effectiveness ratio (77,78). As a result, some analysts have tried to construct 95% CIs around cost effectiveness ratios (78). This presents a statistical challenge, because incremental costs (the numerator) and incremental life years gained (the denominator) may not be normally distributed, and
usually do not meet the assumption of independence.(78) It may be difficult for decision makers to interpret the results of an economic analysis in the context of 95% CIs.(78) Others have argued against the use of CIs for cost effectiveness ratios, and have recommended the use of Monte Carlo simulation as performed in this analysis.(79,80)

Monte Carlo simulation enables the simultaneous sensitivity analysis of all uncertain variables. It does so by replacing estimates of probabilities, utilities, and costs with probability distributions that are based on the reported means and variances of each variable.(80-82) The analysis is then repeated 25,000 times, sampling different values from the appropriate distributions for each variable. In this way, a statistical distribution is built around the ICER, giving a better reflection of the uncertainty inherent in the analysis.

With Monte Carlo simulation, one can also consider the uncertainty with respect to the maximum cost per QALY gained that decision makers would find acceptable (i.e., some decision makers will choose only to fund therapies associated with cost per QALY gained <$20,000;(83) others, with larger budgets, may choose to fund therapies with cost per QALY gained up to $50,000 to $100,000). This is displayed as a cost effectiveness acceptability curve showing the probability that a therapy is associated with a cost per QALY gained lower than a range of displayed maximum cost effectiveness ratios.

We performed Monte Carlo simulation for our overall model (Figure 14), and for patients aged ≥65 years. Statistical distributions were created around all the variables for which significant measurement uncertainty existed, and for which distributions could be estimated (Tables 6 and 8).

**n) Health services and budget impact**

A health services and budget impact analysis was performed using demographic, epidemiologic, clinical, and economic data. Demographic data by provincial distribution were modelled to capture the budgetary impact in Canada. Epidemiologic data for Canada were taken from the CORR registry (most recent report 2002-2003), which tracks data on all patients with ESRD in Canada.

The potential economic impact of sevelamer use in Canada was considered according to potential funding strategies, including:

- no funding of sevelamer
- funding of sevelamer for all patients with ESRD
- restricted funding of sevelamer based on defined patient groups (i.e., age ≥65 years)
- restricted funding of sevelamer for patients with defined abnormalities of mineral metabolism such as coexistent hyperphosphatemia and hypercalcemia (i.e., as is done in several provinces through restricted listing criteria).

The budgetary impact on health care sectors (i.e., increase to drug costs; possible decrease to hospital sector) was noted.

**5.4.2 Results**

**a) Model validity**

Consistent with the results of published guidelines,(84-86) before the use of this decision model, we ensured that the results made sense, and could be explained intuitively. We also assessed for logical inconsistencies through the evaluation of our model under hypothetical conditions, to determine that our models had face validity. We also confirmed, using rigorous testing, that the mathematical calculations were accurate, and consistent with the specifications of the model (i.e., internal validity).
We determined that our model had predictive validity by comparing model outputs (a function of input variables and model structure) with observed data from the DCOR study. We did this by creating survival curves with models 1 and 4 (using survival probabilities taken from DCOR), and confirmed these to be nearly identical to those reported in the DCOR study (data not shown).

As a final validity check, we tested to see whether the model outputs returned by models 1 and 4 were similar throughout the DCOR study. Because the survival estimates for both models were taken from DCOR, and the survival estimate for patients overall (model 1) is composed solely of the survival estimates for the age groups (model 4), properly functioning versions of models 1 and 4 should produce similar outputs (Table 11). This comprehensive validation process increases confidence in each model.

b) Base case analysis
In the base case analysis, which used a lifetime horizon (model 1 primary), the use of sevelamer, in comparison with calcium-based phosphate binders, resulted in an incremental cost of $33,000 and an increase in QALYs of 0.211, resulting in a cost per QALY gained of $157,500 overall (Table 10).

Given that the effect of sevelamer on mortality and hospitalization was not statistically significant compared with calcium-based phosphate binders in the DCOR study (p=0.30, and p=0.06 respectively), we repeated our analysis considering no survival or hospitalization advantage for sevelamer (RR 1.0 for both outcomes). In this analysis (model 2 cost minimization) (Table 7), the use of sevelamer, in comparison with calcium-based phosphate binders, resulted in an incremental cost of $17,000, but, as expected, no increase in quality-adjusted life years (Table 10). The total incremental cost is lower for this model, given that additional life years (which generate additional related health care costs) are not generated. The incremental cost in model 2 represents expenditure on sevelamer alone.

Given that the DCOR study suggested a differential patient benefit based on length of follow-up and age, we also considered other methods of modelling efficacy. The DCOR investigators stated that the assumption of constant proportional hazards was not met in the primary analysis. In model 3 (mortality over time) (Table 7), we modelled the effectiveness of sevelamer differently for the first two years, compared with year 3 and onward. This resulted in an incremental cost per QALY gained for sevelamer, compared with calcium-based phosphate binders overall, of $127,000 (Table 10). An interaction was noted in DCOR between treatment efficacy and patient age (<65 years or ≥65 years), and in model 4 (mortality by age) (Table 7), which modelled the efficacy of patients aged <65 years and ≥65 years separately. The incremental cost per QALY gained overall was $278,100 (Table 10).

c) Scenario analyses
Given that there is uncertainty about the long-term benefits of sevelamer, and that some feel uncomfortable extrapolating the long-term impact of a therapy beyond the time horizon of the longest available clinical trial, we repeated the analyses for each model during a four-year time horizon, consistent with the DCOR (where the maximum follow-up was 3½ years). The cost per QALY gained varied between $380,400 and $2.4 million for models 1, 3, and 4 (Table 11). The significant increase in the cost per QALY gained for all models reflects the fact that additional survivors have not had enough time to accrue additional life years during the shorter time horizon of this analysis.

Even inexpensive treatments in the ESRD population that extend life may be associated with a substantial cost per QALY gained,(75) because of the high costs of dialysis that are incurred for additional survivors. We analyzed models 1, 3, and 4, excluding the related health care costs associated with dialysis and transplantation. The cost per QALY gained varied from $43,800 to $186,800 (Table 12).
An interaction was noted in DCOR between treatment efficacy and patient age (<65 years or ≥65 years), with patients ≥65 years experiencing a statistically significant benefit. Assuming that sevelamer resulted in a differential reduction in mortality in patients ≥65 years of age, its use was associated with a cost per QALY gained of $105,500 (Table 13). Excluding the costs of dialysis and transplantation, including only patients ≥65 years, and using model 4, the cost per QALY gained becomes $23,300 (Table 12).

As we found no data on the effectiveness of sevelamer in patients with co-existent hyperphosphatemia and hypercalcemia, we could not evaluate the cost effectiveness of targeting the prescription of sevelamer to such patients, although this indication is funded by several provinces.

d) Sensitivity analysis

Univariate sensitivity analysis: In Table 14, the results of sensitivity analyses conducted using model 1, is reported. Generally, the results of the analysis were robust to clinically plausible changes in all uncertain variables. Varying the RR of mortality for sevelamer to the reported lower limit of the 95% CI (0.77) resulted in a cost per QALY gained of $121,500, while increasing the RR of mortality for sevelamer to the upper limit of the 95% CI (1.08) resulted in sevelamer reducing the total number of QALYs experienced by patients, but also leading to lower total expenditures, given that a lower proportion of patients were alive to incur related health care costs (i.e. dialysis).

Varying the baseline annual mortality risk for dialysis patients (within the 95% CI for Canadian dialysis patients) and transplant patients (within a plausible range) did not result in a significant change in the cost per QALY gained. When we replaced the baseline annual death risk for dialysis patients <65 years or ≥65 years with the higher rates reported for American dialysis patients aged 50 years to 69 years (164 per 1,000 patient years), and those ≥70 years (349 per 1,000 patient years) (estimates based on USRDS data); the cost per QALY gained overall was $138,300. Excluding the impact of quality of life (but using baseline mortality rates from the Canadian cohort), the use of sevelamer, compared with calcium-based phosphate binders, results in a cost per life year gained of $102,600.

When the cost of hospitalization or the effect of sevelamer on mortality and hospitalization were changed within clinically plausible ranges, there was no significant change in the cost per QALY gained. This resulted from two competing effects on the ICER. When the RR of hospitalization and mortality was reduced from 0.91 to 0.6825, the cost per QALY gained decreased to $92,800 (Table 14). It would be expected that if the cost per hospitalization increased, then sevelamer, even when keeping the RR of hospitalization constant, would be more cost effective (i.e., have a lower cost per QALY gained). This effect was nearly balanced by the countering increase in costs incurred by the increased number of survivors (who lived longer and thus incurred additional dialysis-related costs). The net effect of changing the baseline frequency or cost of hospitalizations was insignificant, suggesting that the results of our analysis are applicable to countries, such as the US, where hospitalization costs are higher.

Reductions in the price of sevelamer by 25% or 50% resulted in a cost per QALY gained for sevelamer of $135,800 and $114,100 respectively. Similarly, if the average daily dose of sevelamer was reduced or increased by 25%, the cost per QALY gained for sevelamer was $135,800 and $179,200 respectively.

There was no evidence that sevelamer reduces the indirect costs borne by the patient, and alternative perspectives were not considered in the sensitivity analysis.
e) **Probabilistic sensitivity analysis**

**ICER scatterplots:** With second order Monte Carlo simulation, Figure 15 presents scatter plots highlighting the uncertainty in the ICER when the uncertainty in all variables is considered simultaneously. In all models and groups considered, there is significant uncertainty in the 95% confidence ellipse, with a significant proportion of simulations falling into each quadrant of the cost effectiveness plane.

**Cost effectiveness acceptability curves:** Figure 16 displays the cost effectiveness acceptability curves for model 1 (panel A), all models simultaneously (panel B), and the group of patients ≥65 years (panel C). The probability that the use of sevelamer would be cost effective (i.e., more effective; either cost saving or associated with a cost per QALY gained below the threshold) if a decision maker was willing to pay only $50,000 or $100,000 per QALY gained and considering model A, is 15% or 32% respectively. Considering the group of patients ≥65 years separately, the probability that the use of sevelamer would be cost effective if a decision maker was willing to pay only $50,000 or $100,000 per QALY gained is 21% or 44% respectively.

In Figure 16, we present a cost effectiveness acceptability curve for the group of patients ≥65 years, excluding the costs of dialysis and transplantation (panel D). In this analysis, which is favourable to sevelamer, the probability that its use would be cost effective, if a decision maker was willing to pay only $50,000 or $100,000 per QALY gained, is 58% or 71%.

### 6 HEALTH SERVICES IMPACT

#### 6.1 Population Impact

The prevalence of ESRD in Canada is tracked by the CORR, which publishes semi-annual reports documenting trends in prevalence and treatment of patients who receive dialysis or transplantation. On December 31, 2002 in Canada, the overall rate of ESRD instances requiring dialysis was 545.8 per million (17,116 persons on dialysis throughout Canada).

The Health Canada approved indication for sevelamer is the control of hyperphosphatemia in patients with ESRD on hemodialysis, though nephrologists who prescribe sevelamer are unlikely to distinguish between its use in hemodialysis or peritoneal dialysis. We assume that sevelamer would be equally likely to be used by hemodialysis and peritoneal dialysis patients. We also assume that it will not be used in patients with chronic kidney disease who are not yet on dialysis. Because there are several fold more patients with chronic kidney disease (CKD) than ESRD, the drug’s use in patients with CKD could have significant resource implications, without evidence of clear benefit.

We consider three potential scenarios in which sevelamer could be used and funded. In the first scenario, sevelamer could be funded for all patients with ESRD, regardless of dialysis modality, age, or other restrictions.

Second, given that a secondary analysis of DCOR suggested that its use might be more beneficial in patients ≥65 years, we consider a scenario in which funding is restricted to patients ≥65 years.

The third scenario of reimbursement is based on clinical criteria. Many of the provinces, except Alberta, fund sevelamer for ESRD patients who have specific abnormalities in mineral metabolism (most commonly, the co-existence of hyperphosphatemia and hypercalcemia). Analyses provided by...
the manufacturer suggest that 20.8% of Canadian patients with ESRD are receiving sevelamer. Other authors have suggested that its use could become more widespread if prescribing falls in line with clinical practice guidelines. The K/DOQI guidelines on Bone Metabolism and Disease in Chronic Kidney Disease(2) recommend the use of sevelamer in several clinical situations based on the presence of defined laboratory abnormalities. Using local laboratory data and a clinical database of patients receiving dialysis in southern Alberta, Manns et al. estimated that 51% of patients would meet the K/DOQI criteria for the use of sevelamer.(1,2) Although subsequent Canadian clinical practice guidelines do not recommend the use of sevelamer,(87) the K/DOQI guidelines have a wide following among Canadian clinical nephrologists.

Table 15 reports the number of patients with ESRD who would potentially receive sevelamer.

### 6.2 Budget Impact

We considered the budget impact from the perspective of provincial drug plans (in which case, we only consider the projected incremental increase in the drug budget), and from provincial health ministries (in which case, we also consider potential changes in costs in other health care sectors).

The most common phosphate binder prescribed in Canada is calcium carbonate, with an average daily cost of $0.23 (based on an average required dose of 4.3 g).(20) Although infrequently used, magnesium-based phosphate binders are also inexpensive. Based on an average daily dose of 6.5 per day, the average daily cost of sevelamer is $12.52.

Table 16 reports the projected increase in cost, based on the number of patients with ESRD in each Canadian province, and in Canada overall, for patients aged ≥65 years, and in scenarios that restrict use based on defined laboratory abnormalities. Table 17 considers the perspective of a provincial health ministry, and takes into account potential savings in hospitalization with sevelamer use, and potential increases in related health care costs (i.e., dialysis costs) due to additional survivors resulting from use of sevelamer. This reduction in hospitalization (and the improvement in survival) was not statistically significant in DCOR, and this analysis is therefore exploratory.

### 6.3 Efficiency versus Equity

Trade-offs between the goals of efficiency (cost effectiveness) and equity (fairness) occur when resource allocation decisions are made. The possible reimbursement options for sevelamer would be not to list, to list for all patients with ESRD, or to list with restrictions based on age or other biochemical criteria. Although it could be argued that sevelamer should be funded based on equity, there are several definitions of equity. Some define it as equal treatment for all; others have described the concept of equal treatment for equal need, sometimes qualified to mean equal treatment for equal need for those who have equal capacity to benefit.(88) Using the latter definition, restricted funding strategies do not necessarily violate the principle of equity. For example, restricting funding to patients most likely to benefit from sevelamer (i.e., those ≥65 years) could assist renal programs in maximizing clinical benefit in their allotted budget. This strategy may enable unused funds to be spent on other cost effective therapies for patients with ESRD. If the opportunity cost of funding sevelamer is thought to be too high in any patient group, then directing resources to unfunded interventions that are more economically efficient in ESRD care may maximize health among patients with ESRD more effectively.
When considering these issues, one must also acknowledge the clinical uncertainty with respect to the effectiveness of sevelamer, and the risk to the budget of provincial drug plans (Table 16). If one were to accept that sevelamer was only effective in patients $\geq 65$ years, then there would be no equity issues with restricting funding to patients $\geq 65$ years, because no clinical benefit was noted among patients $<65$ years in the DCOR study.

### 7 DISCUSSION

#### 7.1 Summary of Results

##### 7.1.1 Systematic review of clinical effectiveness of sevelamer

We performed a systematic review of sevelamer in patients with ESRD, which included a total of nearly 4,000 participants drawn from 28 studies. Compared with oral calcium-based phosphate binders, there was no evidence that sevelamer reduced all-cause mortality, cardiovascular mortality, hospitalization, or the frequency of symptomatic bone disease, and there was no evidence that sevelamer improved quality of life. Sevelamer therapy results in a smaller increase in serum calcium levels, and fewer episodes of hypercalcemia. Sevelamer seems to be slightly inferior to oral calcium-based phosphate binders in the control of hyperphosphatemia, although the clinical significance of the difference (about 0.1 mmol/L) is likely small. Sevelamer therapy also leads to lower serum bicarbonate levels (approximately 2.7 mmol/L), which is of uncertain clinical significance, but warrants examination. The comparative efficacy of sevelamer for the control of hyperparathyroidism could not be assessed.

Safety analyses show that the incidence of AEs among sevelamer recipients is relatively high (median frequencies of serious and non-serious AEs are 15% and 25% respectively), but this must be interpreted in the context of the clinical population. Although there was between-trial heterogeneity in the frequency of AEs, this is expected given the variable duration of follow-up and the different clinical populations. When data from RCTs were pooled, the risk of serious AEs was non-significantly different between patients receiving sevelamer and calcium-based phosphate binders, although there was a trend to increased risk with sevelamer (13% higher; 95% CI 2% lower to 29% higher). Unfortunately, the clinical significance of these AEs (and their impact on quality of life) cannot be assessed from the available data.

The populations studied include patients treated with hemodialysis or peritoneal dialysis, drawn from a range of countries and practice settings. Therefore, the findings of this report are likely to be externally valid, although the two largest RCTs were conducted among American hemodialysis patients. The internal validity of the available data is less certain. The overall quality of trial conduct and reporting was low, with one study describing adequate allocation concealment, uncommon use of an intention to treat design, infrequent blinding of care providers or outcome assessors, and considerable loss to follow-up in most studies. The two largest RCTs had loss to follow-up $>20\%$, which can introduce significant bias.

The link between oral calcium-based phosphate binders, vascular and cardiac calcification, and adverse clinical outcomes in dialysis patients is appealing, but is not supported by data from controlled studies. Also, as shown by this review, there is no evidence that substituting sevelamer for calcium-based phosphate binders will improve clinically meaningful outcomes. The reductions in
serum bicarbonate, and a trend toward an increased risk of serious AEs with sevelamer treatment warrant scrutiny, and raise the possibility that sevelamer might adversely affect the quality of life in ESRD patients (a hypothesis that we could not address in our review). We found no studies that examined the effectiveness of sevelamer in ESRD patients with concomitant hyperphosphatemia and hypercalcemia—the type of patient for whom sevelamer is funded in many provinces. Therefore, available clinical practice guidelines,(2) which limit the total daily dose of oral calcium-based phosphate binders, and recommend the preferential use of sevelamer, do not seem to be supported by available data.

On the other hand, the available studies cannot exclude a clinically relevant beneficial effect of sevelamer, especially in certain clinical populations. Although we do not believe that the subgroup analysis performed by the DCOR investigators necessarily shows that sevelamer improves outcomes in older patients, future trials should study patients >65 years to address this possibility. Given that sevelamer may reduce the risk of hypercalcemia compared with calcium-based phosphate binders, patients with higher levels of serum calcium at baseline also appear worthy of a study. Future RCTs should also try to address deficits in trial quality and reporting.

In summary, we found no evidence that sevelamer improves clinically relevant outcomes in ESRD patients, compared with calcium-based phosphate binders. Although sevelamer provides comparable control of serum phosphate levels with a lower risk of hypercalcemia than calcium-based phosphate binders, it also seems to result in significantly reduced serum bicarbonate levels, and perhaps contribute to an increased risk of serious AEs. The only RCT that measured clinical endpoints was the DCOR study. While this study was large and randomized, it had several methodological limitations, including the lack of blinding, significant loss to follow-up, and analytical issues that raise concerns about the validity of the purported benefit in patients who had been treated for >2 years, or were aged >65 years. While intriguing, the results of these secondary analyses require confirmation in future randomized studies.

7.1.2 Economic Evaluation

Given that the primary analysis of the DCOR study showed no statistically significant difference in mortality, the most straightforward conclusion would be that sevelamer did not improve clinical outcomes, and perform a cost minimization analysis (in which sevelamer resulted in an incremental cost of $17,000 per patient, but no increase in QALYs). To avoid prematurely discarding the possibility that sevelamer is an economically efficient treatment, and is consistent with guidelines for economic analyses, we considered several modelling strategies. In the base case analysis (model 1 primary), the use of sevelamer, in comparison to calcium-based phosphate binders, was associated with a cost per QALY gained of $157,500 overall. In model 3 (mortality over time), where we modelled the efficacy of sevelamer differently for the first two years, compared with year 3 and onward, sevelamer use was associated with a cost per QALY gained of $127,000. In model 4, (mortality by age), which modelled the efficacy of patients aged <65 years and ≥65 years separately, the incremental cost per QALY gained for patients overall was $278,100.

Considering only the models that assume sevelamer to be more effective than calcium-based phosphate binders, the use of sevelamer was associated with a cost per QALY gained ranging from $127,000 to $278,100. The cost per QALY gained for sevelamer is partly due to the observation that therapies prolonging life in ESRD patients without reducing the need for dialysis, significantly increase related health care costs, such as those for dialysis.(75) Controversy exists as to whether such costs for related health care should be included in economic evaluations of ESRD patients. For instance, interventions for dialysis patients that improve survival without reducing the need for
dialysis (even those that incur little or no cost) will be associated with a cost utility ratio at least as great as that of dialysis. The inclusion of such related costs in economic evaluations may mitigate the acceptance of interventions that improve patient survival. The aim of an economic evaluation is to ensure that the benefits from health care programs implemented are greater than the opportunity costs.(62) The question is should the Canadian health system allocate scarce health care resources toward the use of sevelamer in ESRD patients, or to another health promoting activity in or outside ESRD care. When addressing such a question, it becomes clear that to compare two potential interventions, the impact of these interventions on related health care costs, and on drug costs and health outcomes, must be considered. While this issue makes it unlikely for interventions that improve survival (without improving quality of life or reducing quality of life) to attain the usual cost per QALY thresholds of $50,000 or $100,000, it does not detract from the concept of opportunity cost, which must be considered when allocating health care resources to new interventions.

Even when these related health care costs are excluded (which would be inconsistent with accepted practice for economic evaluation), the cost per QALY gained for sevelamer varied between $43,800 and $186,800. The lower end of this range represents an optimistic estimate of the cost effectiveness of sevelamer.

An interaction was noted in DCOR between treatment efficacy and patient age (<65 years or ≥65 years), with patients ≥65 years experiencing a statistically significant reduction in mortality. Accepting the limitations of subgroup analysis, and assuming this result to be accurate, the use of sevelamer in patients ≥65 years (and assuming a RR of mortality of 0.78) was associated with a cost per QALY gained of $105,500. Excluding the costs of dialysis and transplantation, and including only patients ≥65 years, the cost per QALY gained becomes $23,300, which represents an optimistic and potentially unrealistic estimate of the cost effectiveness of sevelamer. Although sevelamer use that is restricted to patients ≥65 years might be more economically efficient, there remains uncertainty about its effectiveness in this group.

Univariate sensitivity analysis showed that uncertainty in variables did not generally lead to quantitatively significant differences in the cost per QALY gained for sevelamer, with the exception of uncertainty in effectiveness. The DCOR study does not exclude the possibility that sevelamer improves clinical outcomes. When uncertainty in all variables was considered simultaneously using Monte Carlo simulation, this led to significant variability in the cost per QALY gained, with the results of many simulations overlapping all four quadrants of the cost effectiveness plane, regardless of the model. Significant uncertainty exists with respect to the cost effectiveness of sevelamer.

This is the only study to model the cost effectiveness of sevelamer using clinical rather than surrogate endpoints. In the only other full economic evaluation of sevelamer performed in patients with ESRD, Huybrecht et al.(61) modelled the cost effectiveness of sevelamer using efficacy data taken from the Treat-to-Goal study, which suggested that sevelamer reduced coronary artery calcification, an unproven surrogate endpoint for mortality in ESRD patients. Based on the ability of sevelamer to reduce coronary artery calcification, and assuming that this would reduce subsequent mortality and cardiovascular disease, including hospitalization and associated costs, the authors suggested that the use of sevelamer was cost effective. Reducing vascular calcification has not been shown to reduce mortality, so the results of this cost effectiveness study, although using the best available data at the time that it was published, are less valid than the present study’s results.

Regardless of the model considered, the cost per QALY gained for treating all ESRD patients with sevelamer, compared with calcium-based phosphate binders, may be perceived as excessive. Although lower, the cost per QALY gained for treating easily identifiable patient groups (i.e., age ≥65 years) may be perceived as excessive, particularly given the clinical uncertainty in this group.
Many provinces fund sevelamer for patients with ESRD with specific abnormalities in mineral metabolism (most commonly the co-existence of hyperphosphatemia and hypercalcemia). There are no data to support that such a strategy will reduce mortality or morbidity in these patients, and consequently the cost effectiveness of this approach is unknown.

### 7.2 Study Limitations

#### 7.2.1 Systematic review of clinical effectiveness of sevelamer

This is the most comprehensive systematic review of the clinical and safety effects of sevelamer. Previous reviews have been narrative, unable to include as many studies, or both. Our findings and the strength of our conclusions are limited by the available evidence. There is a relative paucity of large RCTs that address this clinical topic, and the quality of the available trials is poor. Also, our pooled results are prone to the limitations of meta-analysis. We took care to reduce the likelihood of bias by following recommendations for the conduct of systematic reviews, including an a priori review protocol, using a defined, comprehensive literature search strategy designed by an expert librarian, performing quality assessment and data extraction with duplicate reviewers, and using rigorous statistical methodology. These steps reduce our susceptibility to bias and lead to robust conclusions.

#### 7.2.2 Economic Evaluation

Uncertainty remains as to the most appropriate method of modelling the effectiveness of sevelamer in the overall group of patients with ESRD. It is reassuring that the results of the models are generally consistent across a spectrum of sensitivity analyses.

The cost effectiveness of sevelamer may be improved if its use significantly reduces the cost of hospitalization. While we modelled a reduction in the frequency (and thus cost) of hospitalization in our analyses, the actual reduction in hospitalization costs will await further DCOR analyses based on Medicare data that are unavailable now. The model may require refinement, although it is unlikely to result in significant changes in the cost per QALY gained.

Because of the lack of data about the impact of sevelamer on patient-related costs (i.e., time off work to receive medical care, productivity losses), analyses using a full societal perspective were not presented. If hospitalization is reduced by the use of sevelamer, then one could speculate that its use may reduce the indirect costs related to the need for caregiver time, or loss of a patient’s productive time. The magnitude of this change is likely to be small, in comparison with the overall cost of hospitalization. Given that relatively large changes in the cost of hospitalization had minimal impact in the sensitivity analysis (Table 14); it is unlikely that adopting a broader societal perspective would significantly change the results of this analysis.

### 7.3 Health Services Impact

The most recent CORR report indicates that in 2002, there were >17,000 patients with ESRD in Canada, 51% of whom were ≥65 years of age. Virtually all patients with ESRD require phosphate binders. The difference in cost between calcium carbonate and sevelamer at usual daily doses is $4,127 more for sevelamer annually.

Assuming that all patients with ESRD in Canada receive sevelamer, drug expenditures could increase by $70,620,616 annually. If funding were restricted to those ≥65 years, then drug expenditures could
increase by $36,065,366 annually. Restrictions in many provinces, which limit sevelamer use to patients based on defined biochemical criteria, may result in expenditures between $14,712,628 and $36,016,514.

Phosphate binders are also used in patients with CKD who are not yet on dialysis. Sevelamer does not have a Health Canada indication for use in patients with CKD. When considering the budget impact of sevelamer, we assumed that it would not be used in patients with CKD who are not yet on dialysis. However, given interest in early prevention and that patients with CKD are several fold more prevalent than those with ESRD, its use in the CKD population could have significant resource implications, without benefit to patients.

7.4 Knowledge Gaps

Given the methodological limitations of the DCOR study, the purported benefit of sevelamer in ESRD patients who have been treated for >2 years, or were aged ≥65 years is uncertain. The results of these secondary analyses require confirmation in future randomized studies.

No studies have addressed whether the addition of sevelamer in patients who meet certain laboratory criteria (i.e. hypercalcemia) is of any clinical benefit. Before the use of sevelamer becomes widespread in this patient group, clinical trials demonstrating benefit for these patients should be completed.

8 CONCLUSIONS

Compared with oral calcium-based phosphate binders, there was no evidence that sevelamer reduced all-cause mortality, cardiovascular mortality, hospitalization, or the frequency of symptomatic bone disease, and that sevelamer improved quality of life. The only study that investigated whether sevelamer reduces mortality and morbidity compared with calcium had methodological limitations, including lack of blinding, and substantial loss to follow-up. The overall mortality was not significantly different between sevelamer and calcium-based phosphate binders in this study, and the methodological concerns raise questions about the validity of the purported benefit in the pre-specified group of patients aged ≥65 years. The results of these secondary analyses require confirmation in future randomized studies.

Based on the available evidence, the use of sevelamer results in similar to slightly higher phosphate levels; similar calcium phosphate product levels; and slightly lower calcium levels, compared with calcium-based phosphate binders. The risk of SAEs was non-significantly lower in patients receiving calcium-based phosphate binders (13% lower, 95% CI −2 to 29), compared with those receiving sevelamer. The routine use of sevelamer in patients with ESRD is not supported by available data.

Even assuming that sevelamer is associated with a clinical benefit, as we did in our primary economic evaluation, the cost per QALY gained for treating all patients with ESRD, with sevelamer compared to calcium-based phosphate binders, may be perceived as excessive depending on what a decision maker is willing to pay for a QALY. Although lower, the cost per QALY gained for treating easily identifiable patient groups (i.e., age ≥65 years) exceeds $100,000 per QALY, and is based on considerable clinical uncertainty. If the effectiveness of sevelamer were confirmed in this group in a subsequent study, then its use in patients >65 years should be reconsidered.
Many provinces fund sevelamer for patients with ESRD, with specific abnormalities in mineral metabolism (most commonly the co-existence of hyperphosphatemia and hypercalcemia). There are no data to support that such a strategy will reduce mortality or morbidity in these patients, and the cost effectiveness of this approach is unknown. Because calcium-based phosphate binders reduce serum phosphate levels to the same extent as sevelamer, it is unlikely that sevelamer will be more cost effective in this patient group.

9 REFERENCES


Guidelines for the economic evaluation of health technologies: Canada. 3rd ed. Ottawa: Canadian Agency for Drugs and Technologies in Health; 2006.


APPENDICES

Available from CADTH’s web site
www.cadth.ca