

pan-Canadian Oncology Drug Review Final Economic Guidance Report

Gemtuzumab Ozogamicin (Mylotarg) for Acute Myeloid Leukemia

April 2, 2020

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FUNDING

The pan-Canadian Oncology Drug Review is funded collectively by the provinces and territories, with the exception of Quebec, which does not participate in pCODR at this time.

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REFERENCES

1 ECONOMIC GUIDANCE IN BRIEF

1.1 Submitted Economic Evaluation

The economic analysis submitted to pCODR by Pfizer compared gemtuzumab ozogamicin (GO) in combination therapy with SOC (daunorubicin and cytarabine) versus standard of care for the treatment of adult patients with previously untreated, de novo CD33-positive acute myeloid leukemia, except acute promyelocytic leukemia (APL).

GO received Health Canada approval for the following indication in November 2019:

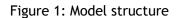
• In combination therapy with daunorubicin and cytarabine for the treatment of adult patients with previously untreated, de novo CD33-positive AML, except APL.

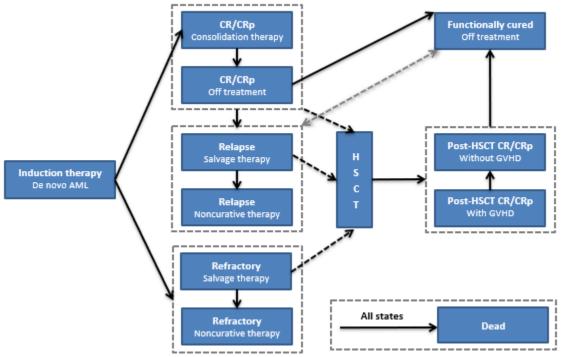
The requested listing criteria for gemtuzumab ozogamicin plus SOC are aligned with the Health Canada indication and the ALFA-0701 study population. Specifically, the requested reimbursement criteria are.

Funding Request/Patient Population Modelled	GO in combination therapy with SOC (daunorubicin and cytarabine) for the treatment of adult patients with previously untreated, de novo CD33-positive acute myeloid leukemia, except acute promyelocytic leukemia (APL). This aligns with the patient population that the economic model is built on.				
Type of Analysis	CEA/CUA				
Type of Model	Markov cohort state-transition				
Comparator	SOC: daunorubicin and cytarabine				
Year of costs	2019				
Time Horizon	40 years (lifetime)				
Perspective	Canadian publicly funded health care system				
Cost of Gemtuzumab ozogamicin (GO)	The recommended dose of GO is 3 mg/m ² /dose (up to a maximum of one 4.5-mg vial) infused over a 2 hour period on days 1, 4, and 7 in combination with daunorubicin 60 mg/m ² /day infused over 30 minutes on days 1-3 and cytarabine 200 mg/m ² /day by continuous infusion on days 1-7. GO should not be administered during second				
	induction therapy. Consolidation Up to 2 consolidation courses of intravenous daunorubicin (60 mg/m ² for 1 day [first course] or 2 days [second course]) in combination with intravenous cytarabine (1000 mg/m ² per 12 hours, infused over 2 hours on days 1-4) with intravenous GO (3 mg/m ² /dose infused over 2				

Table 1. Submitted Economic Model

	hours up to a maximum dose of one 4.5-mg vial				
	on day 1) are recommended.				
	 \$20,000.00 per vial of 4.5 mg 				
Cost of SOC: daunorubicin and cytarabine	Daunorubicin:				
	 \$91.00 per vial of 20 mg 				
	Cytarabine:				
	• \$5.09 per vial of 100 mg				
	• \$76.85 per vial of 500 mg				
	• \$153.25 per vial of 1,000 mg				
	• \$306.50 per vial of 2,000 mg				
Model Structure	Cohort state-transition with 5 health states: 1)				
	AML diagnosis/induction, 2) complete remission				
	(including consolidation and beyond), 3)				
	relapse/refractory (secondary				
	therapy/reinduction), 4) stem-cell therapy, and				
	5) mortality.				
	(Figure 1)				
Key Data Sources	Clinical data were obtained from the ALFA-0701				
	study and were used in the model; Other external				
	sources:				
	Utility values applied in each health state for the				
	reference case were obtained from Forsythe et				
	al. (2018);				
	Drug costs Pfizer (GO) and Delta PA Ontario form				
	(2019) (1 st line and subsequent lines of				
	treatments);				
	Hematopoietic Stem-Cell Transplantation Costs:				
	Interprovincial Billing Rates for High Cost				
	Procedures Effective;				
	Disease Management costs: Ontario Case Costing;				
	OHIP Schedule of Benefits (2015); OHIP Schedule				
	of Benefits (2015); Ontario Nurses' Association				
	collective agreement (2019); Ontario Schedule of				
	Benefits (2019); Manitoba Physician's Manual				
	(2019).				
	Adverse events costs: Ontario Case Costing.				
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Abbreviations: AML = acute myeloid leukemia; CR = complete remission; CRp = complete remission with incomplete platelet recovery; GVHD = graft versus host disease; HSCT = hematopoietic stem-cell transplantation.

1.2 Clinical Considerations

According to the pCODR Clinical Guidance Panel (CGP), this comparison is appropriate.

- Relevant issues identified included:
 - The Clinical Guidance Panel concluded that there is a net clinical benefit to Gemtuzumab Ozogamicin(GO) in the management of previously untreated, newly diagnosed adult individuals with AML who are candidates for intensive, curative intent remission induction and consolidation therapy *and* who have genetically favourable risk, intermediate risk, or unknown risk AML using the International System for Human Cytogenetic Nomenclature, NCCN, or ELN classification systems.

As requested by the review team, a sensitivity analysis was provided by the sponsor for the subgroup of patients presenting favourable, intermediate and unknown risk. The submitted ICER was lower than the base-case result. Re-analysis was performed by the EGP.

- The CGP advise that patients who are proven to be CD33-negative at time of diagnosis are unlikely to derive clinically meaningful benefit from the addition of GO. As such, the CGP recommends against the use of GO in this setting.

The review team requested a subgroup analysis for patients with CD33 positive. The sponsor responded that the test was absent in 28% of the patients, as such, no sensitivity

analysis was performed for patients with CD33 positive only. No re-analyses were performed by the EGP.

Summary of registered clinician input relevant to the economic analysis

One joint clinician input on behalf of six oncologists and two pharmacists from the Pediatric Oncology Group of Ontario (POGO), and three inputs from individual clinicians were provided for this submission. A total of nine oncologists and two clinical pharmacists provided input on behalf of the provinces of Ontario, British Columbia and Alberta.

- The clinicians seemed not to support age as an eligibility criterion for GO. For example, exclusion of patients less than 15 years or over 70 years was generally not supported.
 - The economic model was based on adult patients only. No subgroup analysis was provided for pediatric patients or for patients 70 years and older.
- Clinicians expressed uncertainty extending the use of GO to patients with therapy-related AML (t-AML), as they were not included in the ALFA-0701 trial; however, POGO suggested that GO may be suitable for t-AML patients as they may have received significant doses of anthracycline in previous lines of therapy that may disqualify them from then receiving daunorubicin. All clinicians agreed that there is no data to support using GO in combination with midostaurin and chemotherapy for newly diagnosed FLT3-mutated AML patients.
 - The economic model did not account for t-AML patients or for GO in combination with midostaurin and chemotherapy.
- Benefit of gemtuzumab ozogamicin was suggested to be greatest for patients with low risk AML. However, all patients were stated to benefit from the treatment. As gemtuzumab ozogamicin would be added to an existing treatment combination, it would not replace any other treatments for AML patients in the front-line setting.
 - The economic model included a subgroup analysis for patients with favourable, intermediate and unknown risk.
- Cytogenetic testing is performed for AML patients as part of standard of care; as this test is already conducted for patients, no additional testing costs would be required.
 - The economic model accounted for the cytogenetic testing costs.

Summary of patient input relevant to the economic analysis

One patient with AML had experience with GO and had accessed the treatment through a clinical trial. The treatment process was described as convenient as they were able to receive treatment at their local hospital. However, the patient was removed from the trial due to side effects; specifically, the patient experience thrombocytopenia that "slowed platelet recovery after each chemo session" resulting in their removal from the trial.

Overall, patients with AML value having additional and effective treatment options, reduced side effects and improved quality of life and sense of independence

Summary of Provincial Advisory Group (PAG) input relevant to the economic analysis PAG identified the following as factors that could impact the implementation: Clinical factors:

- Use of gemtuzumab ozogamicin (GO) in combination with other treatments Economic factors:
 - Monitoring and supportive care for hepatotoxicity and hematological toxicities

• Additional resources (chemotherapy chair, pharmacy preparation and nursing)

The EGP noted that no particular specification was done by the sponsor in the model for GO group, regarding the hepatotoxicity and hematological toxicities or additional resources used in GO group. The EGP performed no re-analysis as the model didn't allow alterations of these.

1.3 Submitted and EGP Reanalysis Estimates

A cohort state-transition model was developed by the sponsor to capture health states and events that occur throughout the entire disease course and that impact costs and outcomes. The model included several health states: induction therapy, CR/CRp (includes two sub-states: consolidation therapy and off treatment), relapse (includes two sub-states; salvage therapy and noncurative therapy), refractory (includes two sub-states; salvage therapy and noncurative therapy), refractory (includes two sub-states: with and without GVHD), functionally cured (off treatment), and death. The model had a cycle length of 1 month and a lifetime (40-year) time horizon. Response rates and survival data from the ALFA-0701 study were used to inform health state transitions. Adverse event rates were also obtained from this study. Utility values were obtained from the published literature.

The reference case analysis was conducted from the perspective of the Canadian publicly funded health care system using Ontario costs. Costs and outcomes were discounted at 1.5% annually. The reference case analysis was conducted probabilistically, and some probabilistic scenario analyses were conducted to assess uncertainty and to test alternative data sources and assumptions.

There were several concerns and limitations of the model identified by the EGP, which are listed below:

Overall, the submitted model was very complex, and lack transparency. Probabilistic sensitivity analyses (PSA) were performed by the sponsor to evaluate some assumptions used in the model. However, some important uncertainties are present in the model related to the population heterogeneity, i.e. patients with CD33 negative, as well as to the long-term extrapolation of the OS, time horizon, and utilities (affected by the toxicity of the treatments). In addition, the model did not account for additional cost of monitoring and supportive care for hepatotoxicity (note: VOD was included) and hematological toxicities, or for additional resources, in term of chemotherapy chair, pharmacy preparation and nursing in GO group (e.g. adverse events of special interest [refer to clinical guidance report] or grade 1/2 adverse events). These were not tested by the sponsor.

Population heterogeneity

The review team requested subgroup analyses for patients with a favourable, intermediate, and unknown cytogenetic risk, and for patients with CD33 positive. A sensitivity analysis was performed by the sponsor to test validity of the results in favourable, intermediate, and unknown cytogenic risk patients. Yet, no sensitivity analysis was performed for patients with CD33 positive, as the test was absent in 28% of patients. No re-analyses were performed by the EGP.

Probability of death

Survival Beyond ALFA-0701 Follow-up Period

Based on best visual fit, statistical fit, and clinical opinion, the preferred MCM curves used in the base case were MCM log-normal, for both RFS and OS. For OS (refractory) the Gompertz parametric model was selected. The EGP performed re-analyses for alternative models, yet, the impact was minimal (results not shown).

Post-Hematopoietic Stem-Cell Transplantation (HSCT) Survival Adjustment

Analyses of post-HSCT OS in the ALFA-0701 study were performed from the time of HSCT. The OS after HSCT was considered to be similar for all patients, regardless of whether the HSCT followed first- or second-line CR or CRp and the chemotherapies received or whether the patients were refractory to induction therapy or relapsed. The CGP did not agree with this assumption, rather the CGP expected that the timing of HSCT impacts the survival. For instance, patients having had an HSCT following a first-line CR/CRp will have a better survival than after a second-line CR/CRp.

In addition, adjustments are included in the model to increase the predicted survival for patients after HSCT and reduce the predicted survival for patients who do not receive HSCT, proportionally, such that the total number of deaths remains the same. The adjustment is performed based on a cured proportion of patients calculated from the ALFA-0701 study. Post-HSCT OS was 42.2% at the end of study follow-up, which is incorporated in the model as proportion of patients being cured after transplantation. When the survival of the HSCT patients has dropped to 42.2%, as predicted by the OS curves, adjusted general population mortality rates are applied to these patients. The additional deaths that would have occurred for the HSCT patients had the cure rate not been applied are instead taken from the patients who did not receive HSCT.

The impact of this assumption is unknown. Since the percentage of patients receiving HSCT is higher in SOC group than in GO, the EGP anticipates that the ICER was not underestimated. No reanalyses were performed by the EGP.

Proportion of patients being cured after HSCT

Both CGP and EGP did not agree with the assumption that 42% of patients at the end of the study are cured. As shown in the Figure 8, after 3 years only 12 patients are still followed (alive) and this number decreased to only 1 patient after 4 years. Due to the limited number of patients, both CGP and EGP considered this assumption inappropriate. When this assumption was removed, the ICER presented only a small variation.

Cost of subsequent line of treatment

Relapsed or refractory patients can receive high-intensity salvage therapy with curative intent. The reference-case value for the proportion of patients with relapsed or refractory disease who received salvage therapy was assumed to be 60% based on clinical estimates.

Relapsed and refractory patients who are not deemed fit enough to receive salvage therapy instead receive noncurative therapies (including best supportive care) and palliative care. The model considered hydroxycarbamide, low-dose cytarabine, and azacitidine in a 40:40:20 ratio. Patients who received salvage therapy and did not go on to receive an HSCT move to best supportive care only (hydroxycarbamide). The EGP performed re-analyses for alternative ratios, such as 60:20:20, 45:45:10, etc., yet, the impact on the ICER was minimal.

Hematopoietic stem-cell transplantation probabilities (HSCT)

HSCT probabilities were calculated for the CR or CRp and refractory health states from pooled data in the ALFA-0701 study. HSCT for CR or CRp (without relapse) patients were the same between arms in the ALFA-0701 study, and therefore, pooling is clinically accurate. The sponsor stated the following: '*Although GO was not expected to impact the probability of HSCT for patients who relapsed, GO prevents relapses; therefore, the total number of HSCTs for relapse patients was expected to be lower for GO'*. Both CGP and EGP agreed with this statement, however, the submitted model assumed a higher percent of patients receiving HSCT in SOC

compared to GO group for patients with a relapse. The review team disagreed with this assumption, and considered equal probabilities of HSCT from year 1 to year 5. In addition, the CGP considered that the percentage of patients assumed to receive HSCT in the model was too low and did not reflect the current clinical practice. Alternative percentages in year 1 to year 3 were considered by the EGP for both groups, respectively: 20%, 20%, 10%.

Health-related quality of life

Health-related quality of life data were not collected during the ALFA-0701 study. The utilities values were considered the same in both groups.

The disutility associated with these events were not presented. Yet, the sponsor referred to McKenzie and Van der Pol, 2009 mapping algorithm (base case scenario) and Proskorovsky, 2014 mapping algorithm (sensitivity analysis scenario). The model on Excel file was based on a disutility value of 0.021 (base-case), and 0.024 (scenario analysis), respectively, for all the adverse events, except for Veno-occlusive disease for which this value was 0.208.

Time horizon

The sponsor considered a time horizon of 40 years, and no sensitivity analysis were performed. Both CGP and EGP considered the time horizon excessive, especially considering uncertainties related to OS extrapolation. The EGP performed re-analyses for time horizons of 5-, 10-, 15years. The EGP noted that a time horizon of 15 years was considered in the base case of the midostaurin pCODR review in patients newly diagnosed and untreated AML. Both CGP and EGP agreed on a 15-year time horizon.

Estimates (range/point)	Submitted	EGP Reanalysis
ΔE (LY)	1.28	-
Progression-free	-	-
Post-progression	-	-
ΔE (QALY)	1.02	0.73
Progression-free	-	-
Post-progression	-	-
ΔC (\$)	\$57,194	\$75,302
ICER estimate (\$/QALY)	\$56,255	\$102,938

Table 2. Submitted and EGP Reanalysis Estimates (probabilistic)

1.4 Detailed Highlights of the EGP Reanalysis

Although some of the queries raised by the review team have been addressed by the sponsor, there were two remaining assumptions with unknown impact on the ICER and no re-analyses were possible. These were in relation with the post-hematopoietic stem-cell transplantation (HSCT) survival adjustment, as follow:

1) The OS after HSCT was considered to be similar for all patients, regardless of whether the HSCT followed first- or second-line CR or CRp and the chemotherapies received or whether the patients were refractory to induction therapy or relapsed.

2) Adjustments are included in the model to increase the predicted survival for patients after HSCT and reduce the predicted survival for patients who do not receive HSCT, proportionally.

In addition to the sensitivity analyses provided by the sponsor at the review team request, the EGP made the following changes to the submitted economic model:

- **Time horizon** was set to 5, 10, 15, 20 and 30 years. Both CGP and EGP agreed that the most appropriate time horizon is 15 years. This assure comparability to Midostaurin pCODR review in patients newly diagnosed with AML.
- **Probabilities of Hematopoietic stem-cell transplantation (HSCT)** for patients having relapsed were considered the same in both GO and SOC groups.
- Alternative **percentage of patients receiving subsequent line of treatment** (salvage therapy or non-curative intent therapy) as well as the **type of therapies**, were considered by the EGP. The impact on the ICER was minimal, as such, the results are not shown.

Overall the ICER estimated by the EGP is higher than the ICER estimated by the sponsor.

One-way and multi-way sensitivity analyses					
Description of Reanalysis	ΔC	∆E QALYs	ΔE LYs	ICUR (QALY)	∆ from baseline submitted ICER
Deterministic					
Baseline (Sponsor's best case)	\$54,189	1.04	1.28	\$52,290	
Parameter 1: time horizon of 5 y	\$52,320	0.27	0.31	\$194,981	\$142,691
time horizon of 10 y	\$53,877	0.54	0.64	\$100,076	\$47,816
time horizon of 15 y	\$54,127	0.76	0.90	\$71,557	\$19,267
time horizon of 20 y	\$54,177	0.91	1.09	\$59,746	\$7,456
time horizon of 30 y	\$54,189	1.03	1.26	\$52,821	\$531
Parameter 2: 1) % of HSCT for relapse patients is equal in both GO and SOC groups (values as in SOC group)	\$77,020	1.06	1.28	\$72,425	\$20,135
2) % of HSCT for relapse patients is equal in both GO and SOC groups (values chosen by the EGP) (20%, 20% and 10% in y1 to y3)	\$68,666	1.03	1.28	\$66,908	\$14,618
EGP's Reanalysis for the Best Cas	e Estimate (Determinis	tic and Prob		
Description of Reanalysis	ΔC	∆E QALYs	∆E LYs	ICUR	∆ from baseline submitted ICER
Baseline (Sponsor's best case) (Deterministic)	\$54,189	1.04	1.28	\$52,290	
Baseline (Sponsor's best case) (Probabilistic)	\$57,194	1.02	1.25	\$56,255	
Population: Favourable, intermediate and unknown cytogenetics (Sponsor's scenario analysis) (Deterministic)	\$51,963	1.51	1.88	\$34,367	-\$17,923

Table 3. EGP Reanalysis Estimates (Deterministic and Probabilistic)

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Population: Favourable, intermediate and unknown cytogenetics (Sponsor's scenario analysis) (Probabilistic)	\$56,958	1.512	1.871	\$37,661	\$14,629
	[EGP b	est estimat	e]		
Best case estimate of above 1 and 2 parameters					
Parameter 1: time horizon 15 years and 2.1): % of HSCT for relapse patients equal in both groups (values as in SOC group) (deterministic)	\$76.958	0.78	0.90	\$98,217	\$45,927
Parameter 1: time horizon 15 years and 2.1): % of HSCT for relapse patients equal in both groups (values as in SOC group) (probabilistic)	\$75,302	0.73	NA	\$102,938	\$46,683
EGP's Reanalysis for Base (Parameter 1: time horizon 15 years + Parameter 2.1): % of HSCT for relapse patients equal in both groups (values as in SOC group) + Parameter 3: population Favourable, intermediate, and unknown cytogenetics (deterministic)	\$51,874	1.06	1.26	\$49,096	-\$3,194
Parameter 1: time horizon 15 years + Parameter 2.1): % of HSCT for relapse patients equal in both groups (values as in SOC group) + Parameter 3: population Favourable, intermediate, and unknown cytogenetics(values as in SOC group) (probabilistic)	\$55,761	1.024	1.218	\$54,440	-\$1,815

1.5 Evaluation of Submitted Budget Impact Analysis

The factors that most influence the budget impact analysis include: number of patients eligible to be treated with GO and the extent of market expansion. The BIA was based on the projected number of patients in Canada who would be expected to start GO.

The CGP considered the assumptions made to estimate the number of eligible patients appropriate. However, both CGP and EGP considered the market share of Y1 to Y3 underestimated. Alternative market share was used by the EGP which yielded a higher budget impact over a 3-year period compared to the sponsor's estimate.

1.6 Conclusions

The EGP's best estimate of ΔC and ΔE for GO + SOC when compared to SOC is \$102,938 /QALY.

• Two assumptions made on the OS after HSCT might affect the ICER, yet, their magnitude is unknown. These were:

1) The OS after HSCT was considered to be similar for all patients, regardless of whether the HSCT followed first- or second-line CR or CRp and the chemotherapies received or whether the patients were refractory to induction therapy or relapsed.

2) Adjustments are included in the model to increase the predicted survival for patients after HSCT and reduce the predicted survival for patients who do not receive HSCT, proportionally.

- An extra cost might be required for additional monitoring and supportive care for hepatotoxicity and hematological toxicities, or for additional resources, in term of chemotherapy chair, pharmacy preparation and nursing in the GO group(e.g. adverse events of special interest[refer to clinical guidance report] or grade 1/2 adverse events). The EGP predicts that the ICER is underestimated.
- The extra cost of GO is \$75,302 (Δ C). The percentage of patients receiving HSCT after relapse is the main factor which affected the Δ C.
- The extra clinical effect of GO is 0.73 QALY(ΔE). The time horizon is the main factor which affected the ΔE .
- Finally, excluding patients with adverse cytogenetics AML led to a decrease of the ICER by half (\$54,440/QALY versus \$102,938/QALY)

Overall conclusions of the submitted model:

The submitted model was very complex and lack transparency. It included many appropriate assumptions, but some uncertainty remained and were not tested by sensitivity analyses. An important driver in this economic evaluation was the time-horizon which was considered to be too long by both the CGP and EGP, considering increased uncertainty related to clinical benefits over longer time horizons. In addition, the model did not allow one to conduct re-analyses on patients with CD33 positive patients only or to account for additional cost of monitoring and supportive care for hepatotoxicity and hematological toxicities, or for additional resources, in term of chemotherapy chair, pharmacy preparation and nursing in GO group (e.g. adverse events of special interest [refer to clinical guidance report] or grade 1/2 adverse events). The EGP considers that ICER might be underestimated. Finally, the percentage of patients receiving HSCT was low and did not reflect the current clinical practice. The EGP's re-analyses on higher percentage of HSCT demonstrated little variation on the ICER.

2 DETAILED TECHNICAL REPORT

This section outlines the technical details of the pCODR Economic Guidance Panel's evaluation of the economic evidence that is summarized in Section 1. In accordance with the *Disclosure of Information Guidelines for the CADTH Pan-Canadian Oncology Drug Review*, this section is not eligible for disclosure. It was provided to the pCODR Expert Review Committee (pERC) for their deliberations and the participating drug programs for their information.

3 ABOUT THIS DOCUMENT

This Economic Guidance Report was prepared by the pCODR Economic Guidance Panel and supported by the pCODR Leukemia Clinical Guidance Panel and the pCODR Methods Team. This document is intended to advise the pCODR Expert Review Committee (pERC) regarding resource implications and the cost-effectiveness of GO for AML. A full assessment of the clinical evidence of GO for AML is beyond the scope of this report and is addressed by the relevant pCODR Clinical Guidance Report. Details of the pCODR review process can be found on the pCODR website (www.cadth.ca/pcodr).

pCODR considers it essential that pERC recommendations be based on information that can be publicly disclosed. Information included in the Economic Guidance Report was handled in accordance with the *pCODR Disclosure of Information Guidelines*. There was no non-disclosable information in the Economic Guidance Report provided to pERC for their deliberations.

This Final Economic Guidance Report is publicly posted at the same time that a pERC Final Recommendation is issued. The Final Economic Guidance Report supersedes the Initial Economic Guidance Report.

The Economic Guidance Panel is comprised of economists selected from a pool of panel members established by the pCODR Secretariat. The panel members were selected by the pCODR secretariat, as outlined in the pCODR Nomination/Application Information Package and the Economic Guidance Panel Terms of Reference, which are available on the pCODR website (<u>www.cadth.ca/pcodr</u>). Final selection of the pool of Economic Guidance Panel members was made by the pERC Chair in consultation with the pCODR Executive Director. The Economic Guidance Panel is editorially independent of the provincial and territorial Ministries of Health and the provincial cancer agencies.

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Sections 1 & 2

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