Appendix 1: Supplementary material

Identifying relevant literature

The aim of the literature searches was to supplement data identified from the original model publication,[1] by identifying recent literature reporting on efficacy, safety, and costs associated with MV in Canada. In combining data from the previous study with that from the Canadian setting, the aim was to provide a holistic view of data on PAV+ mode.

As the focus of the publication is an economic model, the intent of the searches was to obtain a representative assessment of additional data available on outcomes in the Canadian setting, thus they were performed pragmatically rather than systematically. That is, a structured literature search was conducted whereby one author screed title and abstracts as well as relevant full texts of the identified literature. Data extraction was then performed by all authors to ensure a high level of data accuracy. This approach differs to that of a traditional systematic literature review insofar as the title and abstracts and full texts were not reviewed independently by at least two authors.

To inform the model design and data analysis, a structured literature search of PubMed was performed using search terms detailed in **Table S1**. These were supplemented by hand searches of Google Scholar to identify relevant, non-PubMed-indexed clinical studies. The supplementary materials of included studies were also reviewed for relevant data.

Table S1 Structures searched in PubMed to identify relevant cost data

#	Aim	Search string	Hits
1	Country specific	canada[ad] OR "Canada"[tw] OR "Canadian"[tw] OR "Canadians"[tw] OR "Canada"[Mesh] OR "Alberta"[tw] OR "British Columbia"[tw] OR "Manitoba"[tw] OR "New Brunswick"[tw] OR "Newfoundland and Labrador"[tw] OR "Northwest Territories"[tw] OR "Nova Scotia"[tw] OR "Nunavut"[tw] OR "Ontario"[tw] OR "Prince Edward Island"[tw] OR "Quebec"[tw] OR "Saskatchewan"[tw] OR "Yukon Territory"[tw] OR "Toronto"[tw] OR "Ottawa"[tw] OR "Winnipeg"[tw] OR "Regina"[tw] OR "Edmonton"[tw] OR "Vancouver"[tw] OR "Montreal"[tw] OR "Saint John"[tw] OR "Halifax"[tw] OR "St John's"[tw] OR "Charlottetown"[tw] OR "Alberta"[ad] OR "British Columbia"[ad] OR "Manitoba"[ad] OR "New Brunswick"[ad] OR "Newfoundland and Labrador"[ad] OR "Northwest Territories"[ad] OR "Nova Scotia"[ad] OR "Nunavut"[ad] OR "Ontario"[ad] OR "Prince Edward Island"[ad] OR "Quebec"[ad] OR "Saskatchewan"[ad] OR "Yukon Territory"[ad] OR "Toronto"[ad] OR "Ottawa"[ad] OR "Winnipeg"[ad] OR "Regina"[ad] OR "Edmonton"[ad] OR "Vancouver"[ad] OR "Montreal"[ad] OR "Saint John"[ad] OR "Halifax"[ad] OR "St John's"[ad] OR "Charlottetown"[ad] OR "CADTH"[tw]	216,400
2	All cost studies	"Costs and Cost Analysis"[Mesh] OR "Cost-Benefit Analysis"[Mesh] OR "Cost of Illness"[Mesh] OR "Health Care Costs"[Mesh] OR "Cost Sharing"[Mesh] OR "Cost Savings"[Mesh] OR "Technology, High-Cost"[Mesh] OR "Cost Control"[Mesh] OR "Cost Allocation"[Mesh] OR "Direct Service Costs"[Mesh] OR "Hospital Costs"[Mesh] OR "Employer Health Costs"[Mesh] OR "Drug Costs"[Mesh] OR "Health Expenditures"[Mesh] OR "Health Resources/economics"[Mesh] OR "Economics, Hospital"[Mesh] OR "Economics, Medical"[Mesh] OR "Economics, Pharmaceutical"[Mesh] OR "Economics, Nursing"[Mesh] OR "Managed Care Programs"[Mesh] OR "Insurance, Physician Services"[Mesh] OR "Budgets"[Mesh] OR "Economics"[Mesh] OR "Commerce"[Mesh] OR Cost[tw] OR economic[tw] OR "Length of Stay/economics"[Mesh] OR "Length of Stay/statistics and numerical data"[Mesh] OR "Financial Management, Hospital"[Mesh] OR "Hospital Charges/statistics and numerical data"[Mesh] OR "Hospital Costs"[Mesh]	1,013,476

#	Aim	Search string	Hits
		OR "Economics, Hospital"[Mesh] OR "LOS"[tiab] OR ((USD[tw] OR CAD[tw] OR dollar[tw] OR dollars[tw]) AND (Cost[tw] OR price[tw] or expense[tw] OR burden[tw] OR "pricing"[tw] OR "prices"[tw])) OR (("Cost"[tw] OR spending[tw] OR "economic"[tiab] OR "Costs"[tw] OR "economics"[tiab]) AND ("Healthcare"[tiab] OR "health care"[tiab] or "medical"[tiab] OR treatment[tiab] OR hospital[tiab] OR hospitalization[tw] OR hospitalisation[tw] OR "health service"[tiab]))	
3	Studies since 2012	"2012/01/01"[PDAT]:"2018/05/01"[PDAT]	6,589,304
4	Recent cost studies	#1 AND #2 AND #3	6,942
5	Adverse events (AE) of interest	"Tracheotomy"[Mesh] OR "Tracheotomy"[tw] OR "Tracheostomy"[tw] OR "Pneumonia, Ventilator-Associated"[Mesh] OR VAP[tw] OR "ventilator-associated pneumonia"[tw] OR "Respiration, Artificial/adverse effects"[Mesh] OR "Respiration, Artificial/complications"[Mesh] OR "Respiration, Artificial/economics"[Mesh] OR "Respiration, Artificial/mortality"[Mesh] OR "Respiration, Artificial/statistics and numerical data"[Mesh] OR "Length of Stay/economics"[Mesh] OR synchrony[tw] OR synchronous[tw] OR asynchrony[tw] OR asynchronous[tw] OR ((LOS[tw] OR stay[tw]) AND (ICU[tw] OR "intensive care"[tw])) OR ((mortality[tw] OR death[tw] OR surviving[tw] OR survival[tw]) AND (ICU[tw] OR "intensive care"[tw] or "critically ill"[tw]))	160,942
6	Those reporting on assisted ventilation	"Respiration, Artificial"[Mesh] OR "High-Frequency Ventilation"[Mesh] OR "Interactive Ventilatory Support"[Mesh] OR "mechanical ventilation"[tw] OR "assisted ventilation"[tw] OR "proportional assist"[tw] OR "proportional-assist"[tw] OR PAV[tw] OR "PAV+"[tw] OR NAVA[tw] OR PSV[tw] OR "neurally adjusted"[tw] OR "artificial respiration"[tw] OR "artificial ventilation"[tw]	92,907
7	AEs and assisted ventilation	#5 AND #6	26,126
8	Cost of assisted ventilation	#4 AND #7	36

Literature search results

Regarding clinical effectiveness outcomes, the literature review identified seven clinical studies comparing PAV+ mode with PSV.[2–8] Of these, four covered the recovery phase of critical care, [2,3,5,7] three the weaning phase,[4,6,8] two were Canadian,[2,3] and one was not randomized.[7] A total of 271 patients were managed with PAV+ mode and 253 with PSV. Clinical and safety data of interest from these studies were extracted and used for meta-analysis.

Pragmatic meta-analysis

Methods

Given that the literature review which informed this meta-analysis was not conducted systematically (as noted in the section titled Identifying relevant literature), this meta-analysis is referred to as a pragmatic meta-analysis.

No individual study among those identified in the literature review presented robust clinical data on the required model inputs for the Canadian setting. In their absence, a pragmatic meta-analysis of results was conducted. Included studies were reviewed independently by both RS and KJB, with data extraction also performed independently by both authors. Where there was disagreement between included data, this was resolved by discussion. Unless already in the correct form for analysis, extracted data were converted to means and standard deviations according the method of Wan et al.[9]

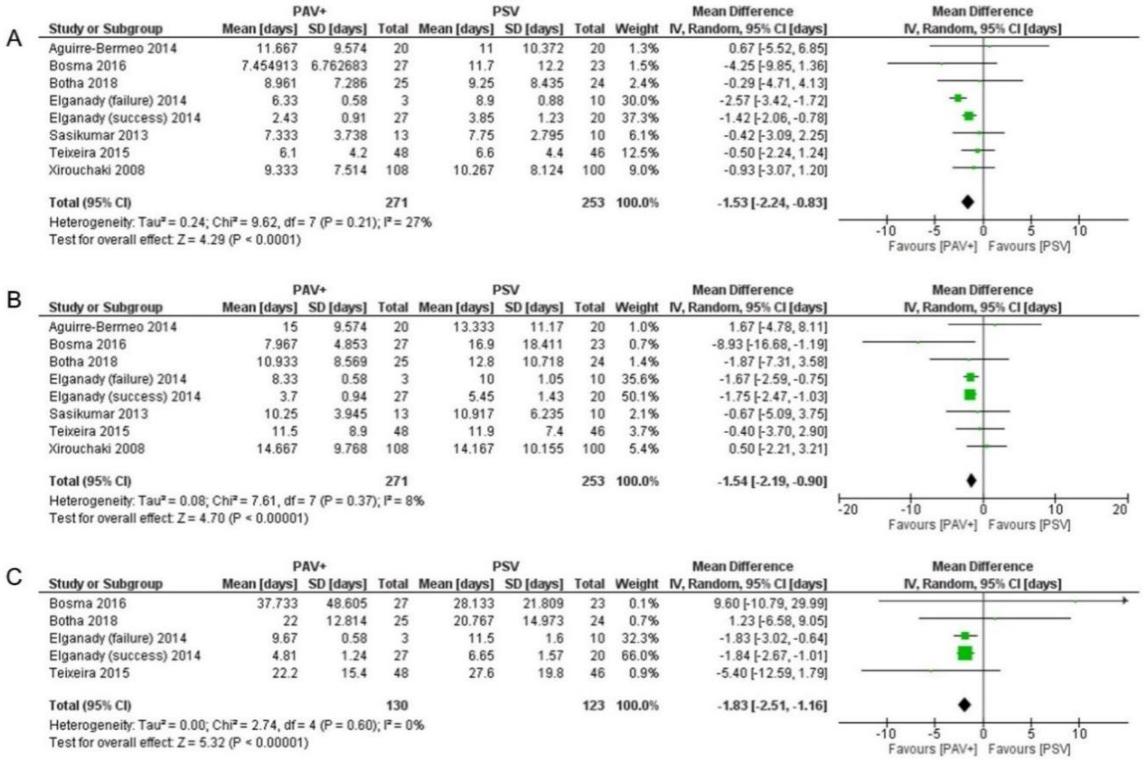
Data conversion (using R) and meta-analysis (using RevMan v5.3) were performed by JAD and outcomes checked by RS and KJB. In the meta-analysis, a random-effects model was used to account for low powered studies and potential differences in clinical practice between countries. Dichotomous outcomes were calculated as odds ratios or as Peto odds ratios for rare outcomes or where numerous groups had zero events. Uncertainty is taken to be the 95% confidence interval reported by RevMan v5.3.

Results

Data extraction resulted in sufficient data to assess all required endpoints for hospital time: total time on MV, ICU length of stay, and hospital length of stay. Total patient numbers were 524 for time on MV and in the ICU, and 253 for hospital length of stay. For each endpoint, heterogeneity was low ($I^2 \leq 24\%$) and PAV+ mode was associated with a significant reduction in time in each care setting. Meta-analysis results for these endpoints are shown in Figure S1.

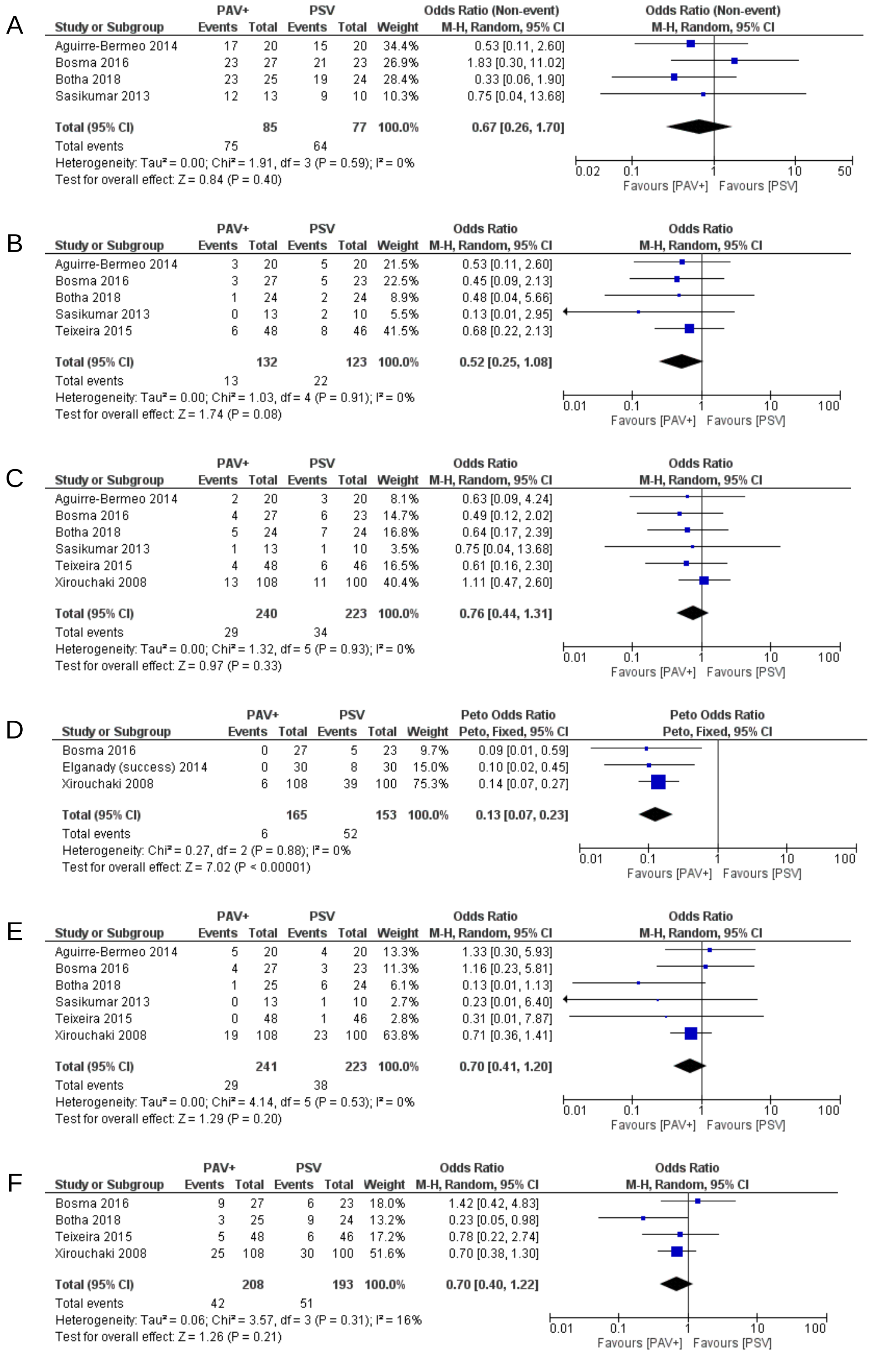
For dichotomous endpoints, six events had three or more studies reporting on the outcome: weaning success, extubation/liberation failure, need for tracheostomy, ICU mortality, hospital mortality, and asynchrony index ≥ 10. For all outcomes, heterogeneity of reported data was low ($I^2 \leq 16\%$). PAV+ mode was generally associated with improved outcomes, although not statistically significant (**Figure S2**), with the exception of asynchrony index ≥ 10, where PAV+ mode was significantly associated with decreased odds of asynchrony (OR 0.13, 0.07-0.23). The meta-analysis results represent the base-case inputs for our health-economic analysis and are summarized in **Table S2**.

Figure S1 Meta-analysis results for continuous outcomes



Results for time on MV (A), length of stay in the ICU (B) and length of stay in hospital (C) are shown. CI, confidence interval; IV, inverse variance; PAV+, proportional-assist ventilation with adjustable gain parameters; PSV, pressure support ventilation; SD, standard deviation.

Figure S2 Meta-analysis results for dichotomous outcomes



Results for weaning success (A), extubation/liberation failure (B), need for tracheostomy (C), asynchrony index ≥ 10 (D), ICU mortality (E) and overall hospital mortality (F) are shown. All are presented as odds ratios with random-effects models, except for odds of asynchrony index ≥ 10, calculated as Peto odds ratios since 2 of 3 PAV+ had zero events. CI, confidence interval; M-H, Mantel-Haenszel; PAV+, proportional-assist ventilation with adjustable gain parameters; PSV, pressure support ventilation; SD, standard deviation.

Table S2 Meta-analysis summary results

Outcome	PAV+		PSV		
Continuous	Mean (SD)	N	Mean (SD)	N	MD
Total time MV (days)	5.33 (0.96)	271	6.87 (1.08)	253	-1.53 [-2.24, -0.83]
ICU length of stay (days)	6.61 (0.83)	271	8.16 (1.05)	253	-1.54 [-2.19, -0.90]
Hospital length of stay (days)	6.69 (0.86)	130	8.53 (1.18)	123	-1.83 [-2.51, -1.16]
Dichotomous	Events	Total	Events	Total	OR
Successful weaning/liberation	75	85	64	77	1.49 [0.59, 3.79]
ICU mortality	29	241	38	223	0.70 [0.41, 1.20]
Hospital mortality	42	208	51	193	0.70 [0.40, 1.22]
Tracheostomy	29	240	34	223	0.76 [0.44, 1.31]
Extubation failure/re-intubation	13	132	22	123	0.52 [0.25, 1.08]
Asynchrony index >= 10	6	165	52	153	0.13 [0.07, 0.23]

Summary of inputs, after conversion to means and standard deviations where necessary, and results from the pragmatic meta-analysis. Results (MD or OR) are shown with 95% CIs. Mean (SD) values are weighted means, where the weight for each study is taken from the RevMan 5.3 output.
ICU, intensive care unit; MD, mean difference (PAV+ mode – PSV); MV, mechanical ventilation; OR, odds ratio (PAV+ mode relative to PSV); PAV+, proportional-assist ventilation with adjustable gain parameters; PSV, pressure support ventilation; SD, standard deviation.

Model transition matrix

The model transition matrix for the standard of care arm (PSV) is shown below (Table S3). The numbers in the table are probabilities and show the probability of moving from the health states listed in the left-most column to the health states listed along the top. Death is split out by ICU death, hospital death, and death (post discharge).

Table S3 Transition matrix for the standard of care arm.

To health state (columns); From health state (rows)

	IE < 10%	IE > 10%	VAP	SBT	Liberation	Hospital	Home	ICU death	Hospital death	Death
IE < 10%	0.6078	0.21689	0.01107	0.15394	0	0	0	0.0103	0	0
IE > 10%	0.63816	0.22773	0.01098	0.10511	0	0	0	0.01803	0	0
VAP	0.03534	0.09904	0.85532	0	0	0	0	0.0103	0	0
SBT	0.11618	0	0.01119	0	0.86233	0	0	0.0103	0	0
Liberation	0.04324	0	0	0	0.42251	0.52396	0	0.0103	0	0
Hospital	0	0	0	0	0	0.94425	0.05049	0	0.00526	0
Home	0	0	0	0		0	0.99963	0	0	0.00037
ICU death	0	0	0	0	0	0	0	1	0	0
Hospital death	0	0	0	0	0	0	0	0	1	0
Death	0	0	0	0	0	0	0	0	0	1

Model convergence

To assess the robustness of the model to changes in input parameters a convergence analysis was performed for both costs (Figure S3) and QALYs (Figure S4). These figures show that after circa 100 simulations the model has converged to a stable mean. As such, performing 2,000 simulations will likely show a large majority of the potential for variation within outcomes.

Figure S3 Convergence of cost estimates in the model

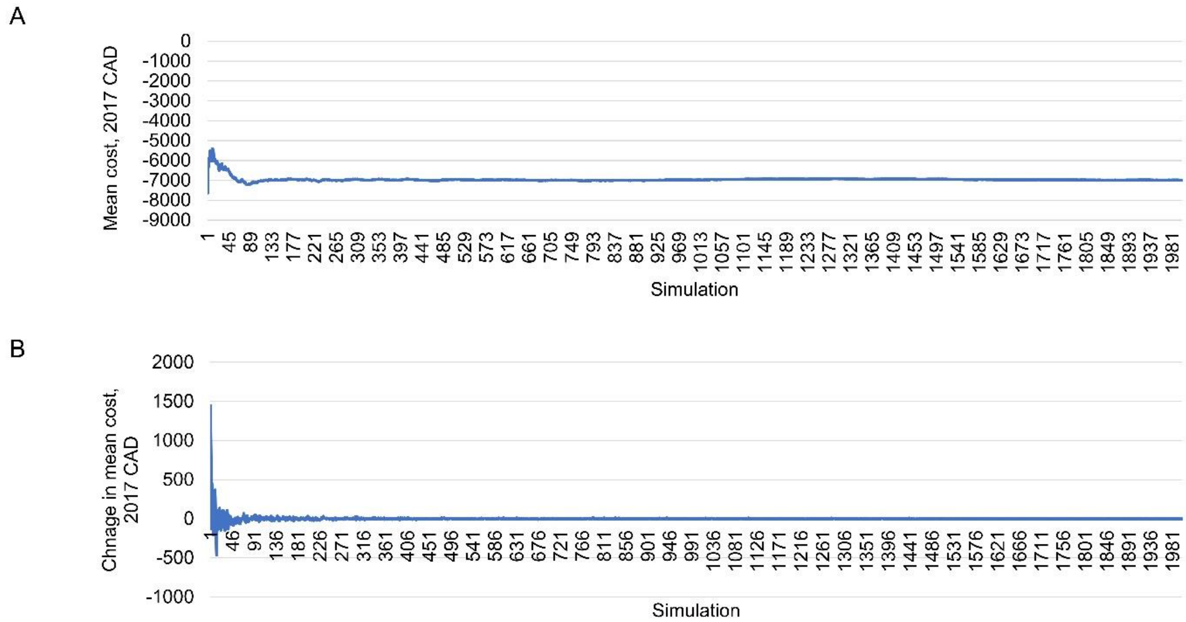
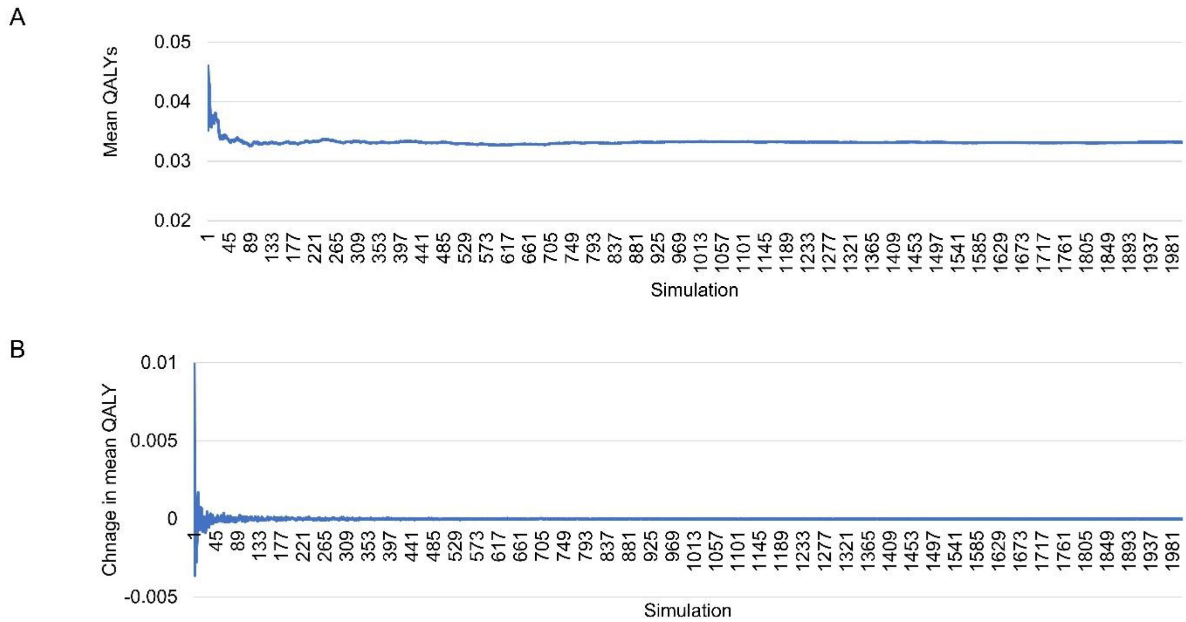


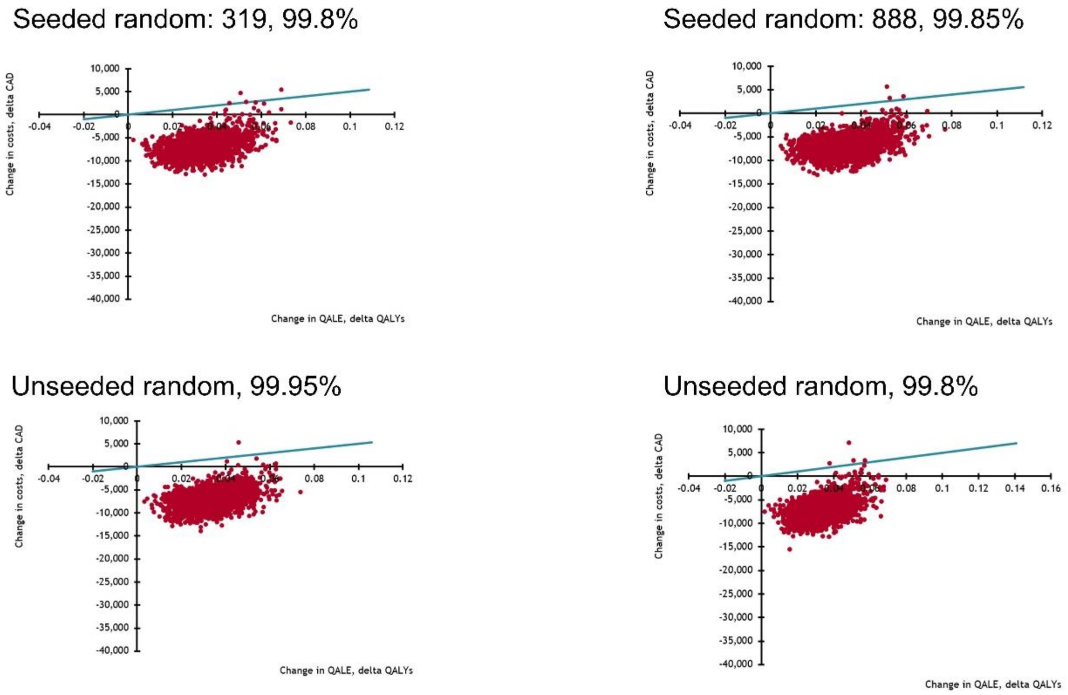
Figure S4 Convergence of QALY estimates in the model



Cost effectiveness

To assess whether use of a seeded random number could impact on the outcomes of the cost-effectiveness analysis, additional analyses were performed with different seeded random numbers (reproducible randomness) and with seeding of the random turned off (non-reproducible randomness, labelled as "unseeded" below). A seed of 50 was used in the base case analyses, here seeds of 319, 888, and unseeded (x2) were tested. In all cases, 99.8% or more of simulations were cost effective (Figure S5).

Figure S5 Examples of cost-effectiveness planes created through variation of the randomness



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