APPENDIX 1

Detailed Methods

Overview

This eAppendix details the methodology used in assessing the cost-effectiveness of apixaban compared to usual care for the primary thromboprophylaxis of cancer patients.

Patient Characteristics

A total of 574 patients were included in the AVERT trial, recruited from 13 Canadian centres. The mean age was 61.5 years and 58.2% of patients were women. Gynecologic cancers accounted for 25.8% of patients, lymphoma for 25.3%, and pancreatic cancer for 13.6%. Patients remained on treatment for a median of 157 days (interquartile 78 to 168) in the apixaban group and 155 days (interquartile 83 to 168) in the placebo group.

Model Description

Patients with newly diagnosed cancer or cancer relapse after complete or partial remission, with a modified Khorana score of ≥2, entered the model in the state 'Primary thromboprophylaxis, without complications' where they received apixaban or placebo. Patients in this state were at risk of CRNMB, major bleeding (excluding ICH) and VTE. ICH was excluded from possible major bleeding events in this part of the model because no ICH events were observed in the AVERT trial, despite the inclusion of patients with primary brain tumours or intra-cranial metastases. Patients could remain in this state indefinitely or transition to 'CRNMB', 'major bleeding', or 'First VTE', based on the risk of developing each complication. Patients who transitioned to 'CRNMB' remained in this state for one cycle before moving back to 'Primary thromboprophylaxis, without complications'. Patients in the state 'CRNMB' were also at risk of a first VTE and major bleeding. Patients who transitioned to 'major bleeding' were at risk of a first VTE, based on the baseline VTE risk among cancer patients. Patients in the state 'Major bleeding' who did not experience subsequent complications moved to 'Off treatment', as primary thromboprophylaxis was discontinued for these patients. Patients in the state 'Off treatment' were at risk of CRNMB, major bleeding, and VTE, based on the baseline risk for these complications among cancer patients who do not receive primary thromboprophylaxis.

Patients who experienced a first VTE event entered the second part of the model. Patients in the state 'First VTE' were at risk of CRNMB, major bleeding, and ICH, based on the risk of these complications among cancer patients receiving a full-dose anticoagulant for VTE treatment. Patients in the state 'First VTE' who did not experience subsequent complications transitioned to 'Secondary thromboprophylaxis, without complications', where they received dalteparin at a reduced dose (150 units per Kg), per the CLOT trial regimen (14). Patients in the state 'Secondary thromboprophylaxis, without complications' were at risk of CRNMB, major bleeding, ICH, recurrent VTE, CTEPH, and PTS. Patients who experienced major bleeding or ICH did not resume anticoagulation treatment.

Patients who transitioned to 'ICH' were at risk of CRNMB, non-ICH major bleeding, and recurrent VTE, based on the risk of these complications among cancer patients with a history of VTE, who are not receiving anticoagulant treatment. The state 'ICH' was comprised of major ICH events (leading to important long-term disability) and minor ICH events (leading to no long-term disability). The proportion of patients experiencing major or minor ICH was taken from a large American

retrospective cohort of cancer patients who developed spontaneous ICH [1]. Patients who experienced major ICH and no subsequent complications transitioned to the 'Post-ICH' state, where they incurred post event management costs over their remaining lifetime, due to significant disability. Patients who experienced a minor ICH transitioned to 'Off treatment'.

Patients who suffered a recurrent VTE event were at risk of subsequent complications, based on the risk of complications among cancer patients who are treated with a dose escalation of dalteparin [2]. Patients who did not experience subsequent complications after a recurrent VTE event moved back to 'Secondary thromboprophylaxis, without complications'.

Patients who experienced CTEPH and PTS transitioned directly to 'post-CTEPH' and 'post-PTS' health states, respectively, where they incurred post-event management costs over their remaining lifetime.

Patients could transition to death at any point in time due to age-specific mortality, cancer or complications.

Input parameters
Transition Probabilities

Model Part 1

The baseline time-varying risk of VTE over a 6-month period from initiation of chemotherapy was derived using patient data from the placebo arm of the AVERT trial [3]. The VTE risk between 6 months to 5 years from initiation of chemotherapy was estimated as a weighted average of VTE risk by tumour type, with weights being the proportion of patients with each tumour type in the AVERT trial. The time-varying VTE risk for each tumor type was derived from published Kaplan Meir (KM) curves representing the cumulative VTE risk, stratified by tumor type, as reported in a study by Blix et al. [4]. The study estimated the cumulative incidence of VTE over 2 years from cancer diagnosis for each tumour type, with death as a competing risk. We extracted patient-level data from the KM curves using 'WebPlotDigitizer' [5]. The VTE risk was extrapolated to a period of up to 5 years by fitting parametric survival models (Weibull, Gompertz, and Exponential) to the digitized data. Model selection was based on Akaike information criterion (AIC) and Bayesian information criterion (BIC) values. The model with the lowest AIC and BIC values was selected. The VTE risk in the non-cancer population was applied after 5 years from initiation of chemotherapy. This last VTE risk was sourced from a retrospective cohort study that assessed the incidence of VTE in the province of Alberta, Canada, over one decade [6].

The baseline risk for a first VTE was also used to estimate the proportion of patients who transitioned from the states 'CRNMB', 'major bleeding', and 'off treatment' to 'first VTE', as there is a lack of evidence suggesting an increased VTE risk among cancer patients with a previous bleeding episode.

The baseline risk of CRNMB and major bleeding among ambulatory cancer patients receiving chemotherapy, with no prior history of VTE, was obtained from the placebo arm of the AVERT trial. The major bleeding risk in the non-cancer population was applied after 5 years from initiation of chemotherapy. This major bleeding risk was obtained from a meta-analysis of incidence rates of major bleeding in patients randomized to placebo or observation, following treatment of VTE [7].

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We assumed the risk of rebleed to be equal to the baseline risk of major bleeding, as existing studies reported an increased risk of rebleed only when anticoagulant treatment was resumed [8]. Our model, however, assumed that apixaban was discontinued if major bleeding occurred, based on the AVERT trial protocol.

A treatment discontinuation rate as a result of non-adherence or intolerance was estimated using data from the AVERT trial[3] and was applied to patients in both treatment arms.

Model Part 2

The risk of recurrent VTE, CRNMB, and major bleeding among cancer patients receiving dalteparin for the treatment of CAT was obtained from the per-protocol results of the HOKUSAI VTE Cancer trial [9]. The HOKUSAI VTE Cancer trial was chosen as the source for the risk of recurrent VTE, CRNMB, and major bleeding in cancer patients receiving anticoagulation treatment for CAT given the available length of follow up (up to 12 months), which is greater than other trials; the contemporaneity of the results, which better reflect the risk of complications in this patient population based on the current anti-neoplastic management options; and the similarity between the AVERT and HOKUSAI VTE Cancer patient populations (specifically, both trials included patients with primary brain tumors or brain metastases).

Additionally, we performed a scenario analysis where 50% of patients received LMWH and 50% received a direct oral Xa inhibitor for the treatment of CAT. The incidence of complications among patients treated with a direct oral Xa inhibitor was abstracted from the per-protocol results for the edoxaban treatment arm of the HOKUSAI VTE Cancer trial [9].

Given the rarity of ICH in HOKUSAI VTE Cancer, the risk of ICH among cancer patients who received dalteparin for the treatment of CAT was obtained from a systematic review and meta-analysis of studies assessing the safety of LMWH in this patient population [10].

Additionally, the risk of CTEPH among cancer patients on anticoagulant treatment for secondary thromboprophylaxis was abstracted from a meta-analysis of the incidence of CTEPH after acute PE [11]. The risk of PTS was obtained from the SOX trial, which evaluated the use of elastic compression stockings to prevent PTS among patients with a history of DVT [12].

The incidence of CRNMB, major bleeding and ICH among cancer patients who received a dose escalation of dalteparin to treat recurrent VTE was sourced from a cohort study evaluating the efficacy and safety of LMWH dose escalation in cancer patients with recurrent VTE [2], with the proportion of cancer patients with major and minor ICH determined as previously described [1].

The risk of CRNMB and major bleeding among cancer patients with a history of VTE who are off anticoagulation treatment was abstracted from the placebo arm of the AVERT trial. The risk of ICH among cancer patients with a history of VTE who are off-treatment was obtained from a cohort study that assessed the incidence of ICH in an Italian population-based stroke registry [13]. The risk of recurrent VTE among cancer patients with a history of VTE who are off-treatment was determined as a weighted average of recurrent VTE risk by tumor type (weights being the proportion of patients with each tumor type in the AVERT trial). The age-adjusted incidence of recurrent VTE for each tumor type was obtained from a cohort study based in the United Kingdom (UK) [14].

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The relative risk of VTE and CRNMB as a result of apixaban was derived from the AVERT trial using on-treatment analysis [3]. The AVERT trial was insufficiently powered to detect a difference in bleeding outcomes between the treatment arms. To account for this uncertainty, an estimate for the relative risk of major bleeding as a result of low-dose direct oral Xa inhibitor therapy was taken from a meta-analysis of AVERT and CASSINI, the two trials that evaluated the use of these agents for primary thromboprophylaxis among intermediate to high-risk ambulatory cancer patients [15]. The relative risk of complications as a result of apixaban was applied to the baseline risk of each complication for patients in the state 'Primary thromboprophylaxis, without complications'.

The HR for increased risk of death due to cancer was estimated as a weighted average of the age-standardized mortality rate by tumor type [16]. The proportion of patients with each tumor type in the AVERT trial was used as weights in the estimation of mortality due to cancer [3]. The HR for mortality due to cancer was applied to the age-adjusted mortality rate of the Canadian general population to determine the background mortality of patients in the model [17].

The HR for the risk of death due to VTE was extracted from a retrospective cohort study comparing survival of cancer patients with VTE to a matched cohort of cancer patients who did not have VTE, over one year [18]. The HR for mortality due to major bleeding in the model was estimated from a retrospective cohort study of patients who had gastrointestinal bleeding (GIB) [19]. The HR for mortality due to ICH was obtained from a cohort study that compared mortality between patients who survived a haemorrhagic stroke with a matched cohort from the general population [20]. The HR for mortality as a result of CTEPH was derived from a prospective cohort study evaluating long-term outcomes for patients diagnosed with CTEPH [21]. Excess mortality due to CTEPH was estimated as a ratio of mortality due to CTEPH and mortality for the general population [21].

Costs

Complications

The VTE cost was estimated as a weighted average of treatment costs of PE and DVT, where the proportion of patients with each VTE type in the AVERT trial was used as weights [3]. Resources required for the treatment of PE and DVT, such as the proportion of patients managed as inpatient and outpatient, typical diagnostic tests, outpatient physician consultations, mean inpatient length of stay, and number of inpatient physician consultations, were obtained from a Canadian cost-effectiveness study of oral anticoagulants for VTE treatment [22]. Based on consultations with clinical experts and the published guidelines for prevention and treatment of CAT, we used the cost of dalteparin to represent the cost of medication to treat and manage cancer patients with VTE in our primary analysis. Information on follow up outpatient visits for long-term management of cancer patients with a history of VTE was obtained through consultation with clinical experts. In the scenario analysis where 50% of patients with CAT received LMWH and 50% received a direct oral Xa inhibitor, we used the cost of edoxaban to represent the cost of oral anticoagulation treatment. Furthermore, the drug cost for the treatment of recurrent VTE was assumed to be 1.2 times that for a first VTE, based on the dose escalation to 125% of the weight-based LMWH usual dose for the treatment of breakthrough VTE on full-dose anticoagulation in cancer patients.

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The cost of treating major bleeding was calculated as a weighted average of treatment costs for each major bleeding type observed among patients in the AVERT trial [3]. The treatment costs for each major bleeding type included the cost of inpatient stay, a specialist consultation, and a follow up consultation. Data on resource use for treating a CRNMB episode was obtained from the published literature [22]. The cost of care per stay for an ICH event was extracted from a cohort study of ICH patients in a Canadian center [23]. Post event management costs for major ICH, as well as the treatment and long-term management costs for CTEPH and PTS, were sourced from published Canadian studies [22 24-26].

The costs of diagnostic tests and laboratory monitoring for long-term management of cancer patients who experienced VTE was obtained from an economic evaluation of the CLOT trial for secondary prophylaxis of VTE among cancer patients [27]. The unit costs of diagnostic tests to detect PE and DVT were obtained from published Canadian sources [22 28]. The unit costs of physician and specialist visits were extracted from the Ontario's Schedule of Benefits [29]. Per day hospital costs for patients diagnosed with PE and DVT were obtained from the Ontario Case Costing Initiative (OCCI) [28]. The inpatient costs for each type of major bleeding event observed in the AVERT trial was abstracted from the OCCI [28]. The daily acquisition costs of apixaban, dalteparin, and edoxaban were obtained from the Ontario Drug Benefit Formulary [30].

Health Utility Values

The baseline health utility value was calculated as a weighted average of utility values for cancer patients in remission by tumour type. The proportion of patients with each tumour type in the AVERT trial was used as weights in the estimation of the baseline utility value [3]. The utility values for remission according to each tumour type were obtained through a targeted literature search [31-47]. Where multiple utility values were available, each one was assessed regarding its applicability to our patient population and purpose, credibility, and consistency. Preference was therefore given to contemporary utility values taken from the Canadian setting.

An event specific disutility was applied to the baseline utility in patients who experienced a complication. The disutility value for VTE was estimated as a weighted average of disutility values for PE and DVT, where the proportion of patients with each VTE type in the AVERT trial was used as weights.

The disutility value for major bleeding was estimated from the disutility value for GI bleed. The disutility value for ICH was calculated as a weighted average of disutility values for minor and major ICH. The disutility values for PE, DVT, GI bleed, minor ICH, and major ICH were derived from a Canadian study that estimated utility values for patients with a history of VTE, using a standard gamble technique [48]. The disutility values for CRNMB were obtained from a UK-based study that reported EQ5D utility scores for a variety of chronic conditions [31]. The disutility value for CTEPH and the utility value for post-CTEPH were derived from a UK-based study that measured utility values for patients with pulmonary hypertension, using the Cambridge Pulmonary Hypertension Outcome Review (CAMPHOR) Utility Index [49]. The disutility values for PTS and post-PTS states were derived from a previous study that elicited utility values for PTS from volunteers and physicians, using the standard gamble technique [50].

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Previous studies on the cost-effectiveness of apixaban in non-cancer populations have accounted for a utility decrement as a result of administering apixaban. However, this value was derived from evidence on the reduction in quality of life as a result of warfarin for stroke prophylaxis in atrial fibrillation patients [51]. We derived a health utility decrement due to apixaban from the SF-36 data measured in the AVERT trial. However, no statistically significant reduction in utility as a result of apixaban was observed. As a result, this utility decrement was not applied in our model.

Table A1 Model Input Parameters and Key Assumptions

Parameter	Mean	SD/SE/(95% CI)	Reported Follow-Up Period (Years)	Source	Assumptions/ Notes
TRANSITION PROBABILITY					
Model Part 1 - Cancer patients on treatment for primary prophylaxis of VTE					
Baseline risk of primary VTE (0-6 months)	*Time variant risk*			AVERT trial, placebo arm; On-treatment analysis [3]	
Baseline risk of primary VTE (6 months - 5 years)	*Time variant risk*			Blix et al. [4]	
Baseline risk of primary VTE (>5 years)	0.0001		1.0	Alotaibi et al.; Data from Alberta, Canada [6]	Equal to that in the general population.
Baseline risk of major bleeding (0-5 years)	0.0109	0.0063	0.5	AVERT trial, placebo arm; On-treatment analysis [3]	
Baseline risk of major bleeding (>5 years)	0.0045	0.0009	1.0	Castellucci et al. [7]	Equal to that in the general population; Source - Systematic review and metanalysis of the literature to summarize the rates of major bleeding and fatal bleeding in patients randomized to placebo or observation during the secondary prevention of VTE.
Baseline risk of CRNMB	0.0509	0.0133	0.5	AVERT trial, placebo arm; On-treatment analysis [3]	
Drug discontinuation rate (unrelated to death/VTE/bleed), monthly	0.0590			AVERT trial data[52]	
Model Part 2					
For cancer patients with a history of VTE, <u>on treatment</u>					

for secondary prophylaxis of VTE					
Risk of CRNMB	0.1709	0.0167	1.0	After Primary VTE: HOKUSAI VTE Cancer trial; On-treatment analysis [9] After Recurrent VTE: Ihaddadene et al. [2]	
Risk of major bleeding (non- ICH)	0.0495	0.0096	1.0	After Primary VTE: HOKUSAI VTE Cancer trial; On-treatment analysis [9] After Recurrent VTE: Ihaddadene et al. [2]	
Risk of ICH	0.0036	0.0026	0.5	After Primary VTE: Roja-Hernandez et al. [10] After Recurrent VTE: Ihaddadene et al. [2]	
Risk of recurrent VTE	0.1345	0.0151	1.0	HOKUSAI VTE Cancer trial; On-treatment analysis [9]	
Risk of CTEPH	0.0320	0.0061	2.0	Ende-Verhaar et al. [11]	Only patients in state 'On treatment for secondary prophylaxis' can transition to CTEPH or PTS
Risk of PTS	0.1270	0.0168	2.0	SOX trial, placebo arm [12]	
For cancer patients with a history of VTE, who are <u>off treatment</u> for secondary thromboprophylaxis					
Risk of CRNMB	0.0509	0.0133	0.5	AVERT trial, placebo arm; On-treatment analysis [3]	
Risk of major bleeding (non-ICH)	0.0109	0.0063	0.5	AVERT trial, placebo arm; On-treatment analysis [3]	
Risk of ICH	0.0003	0.0001	1.0	Sacco et al. [13]	
Risk of recurrent VTE	0.0838	0.0086	1.0	Cohen et al. [14]	Calculated as a weighted average of recurrent VTE incidence by cancer type; Weights being proportion of each cancer type in the AVERT trial
Mortality Rates					

Baseline age-adjusted mortality for general population				Statistics Canada [17]	
Excess mortality due to cancer	10.97			Canadian Cancer Statistics, 2018 [16]	Weighted average of age-adjusted standardized mortality rate by tumour site; Weights being proportion of each cancer type in the AVERT trial
Excess mortality due to VTE	2.20	(2.05, 2.40)		Sorensen et al. [18] Follow up 1 year	
Excess mortality due to major bleeding	2.10	(1.60, 2.90)		Nagata et al. [19] Follow up 24.6 months	
Excess mortality due to ICH	2.60	(2.09, 3.24)		Gonzalez-Perez et al. [20]	
Excess mortality due to CTEPH	12.25	(10.27, 14.31)		Derived from Delcroix et al. [21]	Derived as a proportion of mortality for general population (Statistics Canada)
Relative Risk Due To Apixaban					
CRNMB	1.296	(0.663, 2.533)		Avert trial; On-treatment analysis [3]	
Major Bleeding	1.960	(0.800, 4.820)		Pooled from AVERT and CASSINI Trial, On-treatment analysis; Li et al. [15]	
VTE	0.143	(0.043, 0.477)		Avert trial; On-treatment analysis [3]	
Proportion of patients with ICH who have a major ICH	0.50			Murthy et al. [1]	
Proportion of patients who experience major bleeding and resume anticoagulation treatment	0.00			Li et al. [53]	
COSTS					
CRNMB treatment cost	383	122		CADTH report [22]	ER visit + ER physician consultation
Major bleeding treatment cost (Non-ICH)	9,191	2,424		Ontario Schedule of Benefits [29]; Ontario Case Costing Initiative [28]	Hospital costs + 1 initial specialist consultation + 1 follow-up specialist consultation. Hospital costs - weighted average of inpatient costs for hematuria, epistaxis (acute), vaginal bleeding, gastrointestinal bleeding; Sources for unit costs: Physician consultations - Ontario Schedule of Benefits,

					Hospital costs - Ontario Case Costing Initiative (2017/18)
ICH cost	16,962	16,705		Specogna et al. [23]	Setting - Canadian health system; Converted from US$ using OECD PPP converter; Includes major and minor IC bleed events.
Post-ICH Cost	756	± 25% of base case		Goeree et al. [24]; CADTH report [22]	
CTEPH treatment cost	91,412	± 25% of base case		Delcroix et al.[43]; CADTH report [22]	
Post-CTEPH management costs	140	± 25% of base case		CADTH report [22]	Warfarin monitoring + specialist visits
PTS treatment cost	8,181	± 25% of base case		Caprini et al. [25]; CADTH report [22]	
Post-PTS management cost	299	± 25% of base case		Caprini et al. [25]; CADTH report [22]	
Primary VTE treatment cost					
DVT outpatient cost	759			Resource use - CADTH report [22] Unit costs - Ontario Schedule of Benefits [29], Ontario Case Costing Initiative [28]	1 Doppler ultrasound 1 GP visit 1 specialist consultation 2 complete blood counts
DVT cost per inpatient day	1,558	(1000, 1,947)		Ontario Case Costing Initiative (2017/18) [28] Diagnosis codes - I801,I802,I803	
DVT length of stay	6.70	(5.00, 8.00)		CADTH report [22]	
DVT proportion managed as inpatient	0.19	(0.00, 0.40)			
PE outpatient cost	1,551			Resource use - CADTH report [22] Unit costs - Ontario Schedule of Benefits [29], Ontario Case Costing Initiative [28]	Diagnostics, 1 GP visit, 1 specialist visit, 2 blood counts, ER visit, ER physician fee Diagnostics - 1 ventilation perfusion lung scan (50%), 1 spiral CT scan (50%)
PE cost per inpatient day	1,655	(1000, 2,563)		Ontario Case Costing Initiative (2017/18) [28] Diagnosis codes - I26, I29	
PE length of stay	7.80	(6.00, 9.00)		CADTH report [22]	
PE proportion managed as inpatient	0.67	(0.30, 0.75)		CADTH report [22]	
Medication - LMWH	1221.58			Ontario Drug Benefit Formulary [30]	LMWH -Dalteparin at 200units per Kg for 4 weeks;
Medication - DOAC	274.60			Ontario Drug Benefit Formulary [30]	DOAC -Dalteparin at 200units per Kg for 5 days, then edoxaban 60mg daily for 25 days.

Recurrent VTE treatment cost	8,083				Hospital and outpatient costs assumed to be the same as that for primary VTE; medication dosage is 120% of that for primary VTE
Post VTE management costs - LMWH	937	± 25% of base case		Source: Ontario Schedule of Benefits [29], Dranitsaris et al. (for diagnostics, lab work, blood transfusions, unscheduled patient contact) [27], Ontario Drug formulary [30]	Monthly cost averaged over 5 years; Resource use: 0-6 months - Monthly physician visit + monthly cost of diagnostics, lab monitoring, blood transfusions, unscheduled patient contact + medication >6 months - Physician visit every 3 months + medication Medication - Dalteparin 150 units/kg daily
Post VTE management costs - DOAC	144	± 25% of base case		Source: Ontario Schedule of Benefits [29], Ontario Drug formulary [30]	Monthly cost averaged over 5 years; Resource use: 0-6 months - Monthly physician visit + medication >6 months - Physician visit every 3 months + medication Medication - Edoxaban 60mg daily
Apixaban, medication cost per month	98.02			Source: Ontario Drug formulary [30]	
UTILITY VALUES					
Baseline Health Utility Value for Cancer Patients	0.824	0.045		[31-47]	Weighted average of utility values for cancer patients in remission, by cancer site; Weights being the proportion of patients with each cancer type in the AVERT trial.
Disutility As A Result of Primary/Recurrent VTE	0.142	0.022		Hogg et al. [48]	Weighted average of disutility values for DVT and PE, with weights being the proportion of patients who have DVT and PE in the AVERT trial. Disutility estimated as difference between utility for the general population and utility value for patient with this condition; Utility for general population from Maddigan et al.
Disutility As A Result of CRNMB	0.013	0.003		Sullivan et al. [31]	
Disutility As A Result of MB (Non-ICH)	0.270	0.024		Hogg et al. [48]	Disutility estimated as difference between utility for the general population and utility value for patient with

					this condition; Utility for general population from Maddigan et al.
Disutility As A Result of Major ICH	0.770	0.166		Hogg et al. [48]	
Disutility As A Result of Minor ICH	0.170	0.094		Hogg et al. [48]	
Disutility As A Result of ICH (Weighted average of major and minor ICH)	0.470	0.130		Hogg et al. [48]	
Utility in Post ICH	0.150	0.166		Hogg et al. [48]	
Disutility As A Result of CTEPH	0.360	0.016		Meads et al. [49]; CADTH report [22]	Calculated as the difference between utility value for the general population and utility value for CTEPH
Utility in Post CTEPH State	0.560	0.016		Meads et al. [49]; CADTH report [22]	
Disutility As A Result of PTS	0.050	0.022		Lenert et al. [50]; Li et al. [53]	
Utility in Post PTS State	0.774	0.045		Lenert et al. [50]	Estimated as (Baseline utility for remission - Disutility as a result of PTS)

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