APPENDIX A: sensitivity analyses

Sub analysis for vaginal births only

Of the 305 523 individuals in the dataset with complete data, 300 214 were vaginal births. The sensitivity and specificity of the different diagnostic criteria for PPH treatment initiation were estimated to be different for this group, and so a sub analysis was run. The scenario parameters are in Table A1.

As with the main analysis, when only vaginal births were considered, lower blood loss thresholds resulted in greater impact, and scenarios using blood loss in combination with any other abnormal haemodynamic marker were more cost-effective than those using blood loss only. There was still large uncertainty (Figure A1). When the threshold of 300 ml blood loss in combination with any other abnormal haemodynamic marker was compared to the threshold of 500 ml blood loss alone, it was the preferred strategy for willingness-to-pay of > $230 per DALY averted.

Table A1: Vaginal birth sub analysis parameters.

Scenario name	Diagnostic criteria for treatment initiation	Sensitivity	Specificity
≥ 500 ml blood loss (comparator)	Blood loss ≥ 500 ml	72.8 (56.7, 84.6)	87.0 (82.1, 90.7)
≥ 450 ml blood loss	Blood loss ≥ 450 ml	73.4 (58.8, 84.3)	84.6 (79.5, 88.6)
≥ 400 ml blood loss	Blood loss ≥ 400 ml	76.0 (63.0, 85.6)	79.6 (72.1, 85.6)
≥ 350 ml blood loss	Blood loss ≥ 350 ml	77.1 (65.8, 85.5)	75.4 (67.1, 82.2)
≥ 300 ml blood loss	Blood loss ≥ 300 ml	80.1 (68.5, 88.2)	65.3 (51.8, 76.7)
≥ 450 ml blood loss + clinical marker(s)	450-499 ml blood loss + any other abnormal haemodynamic marker; or 500 ml alone*	81.2 (64.4, 91.2)	85.6 (81.3, 89.0)
≥ 400 ml blood loss + clinical marker(s)	400-499 ml blood loss + any other abnormal haemodynamic marker; or 500 ml alone*	83.3 (64.3, 93.2)	84.1 (79.4, 87.9)
≥ 350 ml blood loss + clinical marker(s)	350-499 ml blood loss + any other abnormal haemodynamic marker; or 500 ml alone*	85.2 (63.9, 94.9)	83.0 (78.2, 87.0)
≥ 300 ml blood loss + clinical marker(s)	300-499 ml blood loss + any other abnormal haemodynamic marker; or 500 ml alone*	89.9 (57.9, 98.3)	80.3 (73.9, 85.3)

*Point system (≥ 2 points) (blood loss ranging from lower bound to 499 ml = 1 point; pulse > 100 bpm or systolic < 100 mmHg or diastolic blood pressure < 60 mmHg or Shock Index > 1.0 = 1 point; blood loss ≥ 500 ml = 2 points)

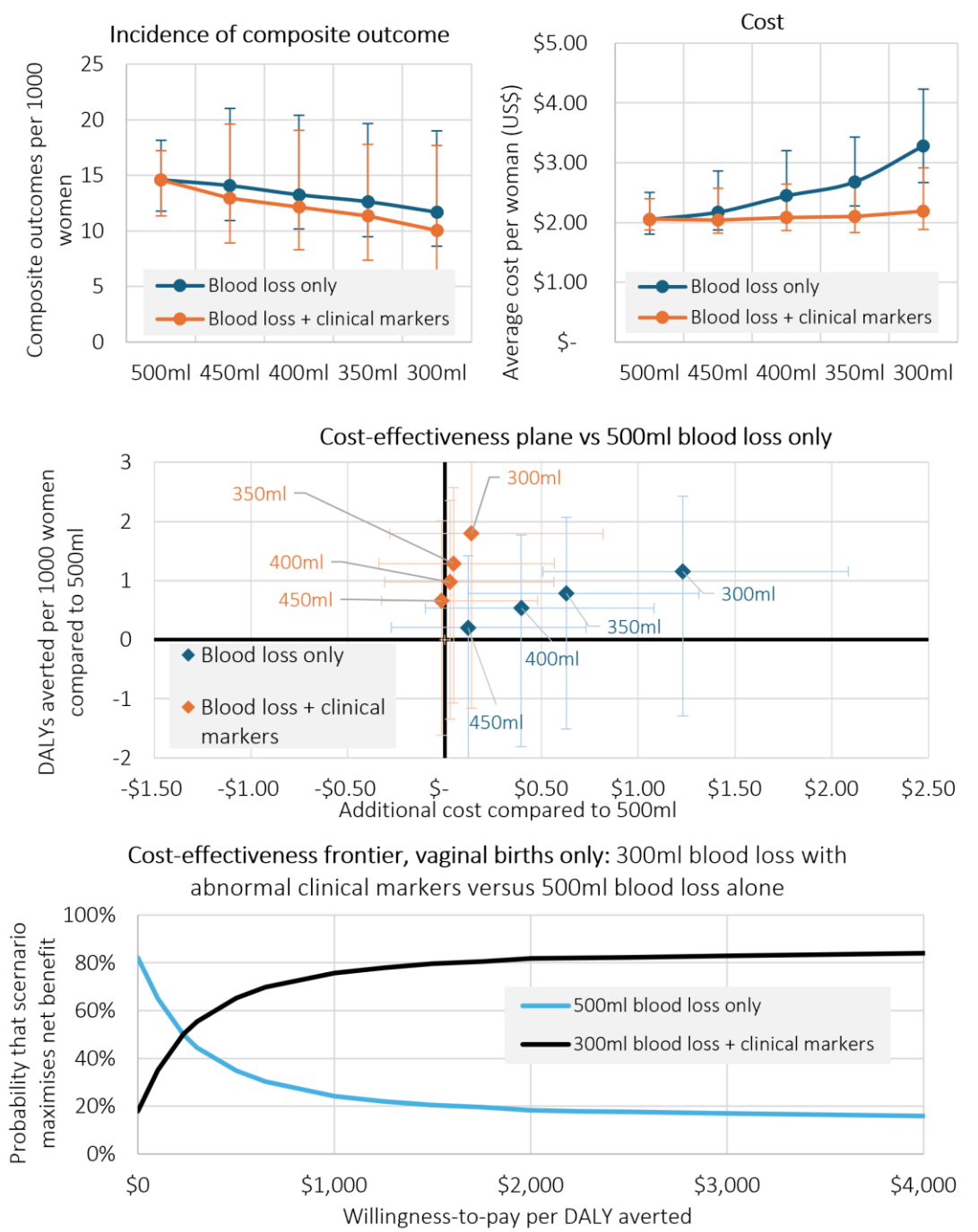

Figure A1: Sub-analysis considering vaginal births only. Model outcomes for blood loss thresholds alone ("blood loss only"), or blood loss thresholds in combination with any other abnormal haemodynamic marker ("blood loss + clinical markers"). Top left: incidence of composite outcome per 1000 women; top right: mean cost per woman (in 2022 US$); middle: disability-adjusted life years (DALYs) averted per 1000 women and difference in mean cost for scenarios compared to the 500 ml blood loss model; bottom: cost-effectiveness frontier, showing the probability that a scenario maximises net benefits for a given willingness-to-pay per DALY averted.

Sensitivity analysis for high-risk populations

When the incidence of the composite outcome was increased from 2.5% (as observed in the individual participant data) in the main analysis to 10%, then the impact of expanded treatment initiation criteria increased and additional costs were saved from composite outcomes averted. The lower blood loss thresholds were more cost-effective, and the lower blood loss thresholds in combination with any other abnormal haemodynamic marker were cost saving (Figure A2, Table A2). As per the main analysis, each scenario considering other abnormal haemodynamic markers remained more cost-effective than any of the blood loss only scenarios, due to reduced unnecessary treatment.

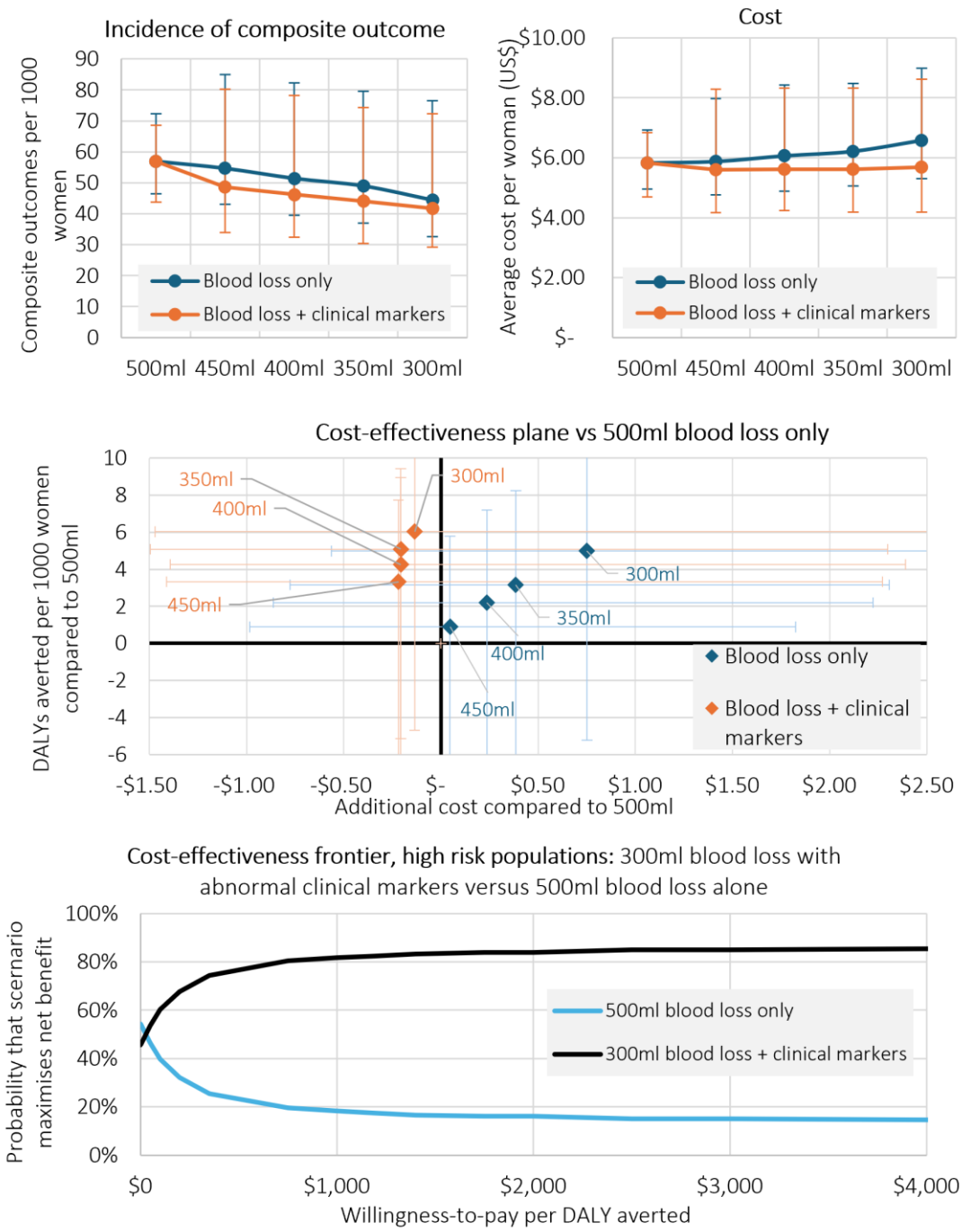

Figure A2: Sub-analysis for higher risk populations (10% incidence of composite outcome compared to 2.5% in main analysis). Model outcomes for blood loss thresholds alone ("blood loss only"), or blood loss thresholds in combination with any other abnormal haemodynamic marker ("blood loss + clinical markers"). Top left: incidence of composite outcome per 1000 women; top right: mean cost per woman (in 2022 US$); middle: composite outcomes averted per 1000 women and difference in mean cost for scenarios compared to the 500 ml blood loss model; bottom: cost-effectiveness frontier, showing the probability that a scenario maximises net benefits for a given willingness-to-pay per composite outcome averted.

Table A2: Results for sensitivity analysis for higher risk populations (10% incidence of composite outcome compared to 2.5% in main analysis).

Scenario	Incidence of composite outcome per 1000 women	Mean DALYs lost per 1000 women	Mean cost per woman (2022 US$)	Unnecessary treatments per 1000 women	Difference in composite outcomes per 1000 women, compared to 500 ml blood loss	Difference in DALYs per 1000 women, compared to 500 ml blood loss	Mean additional cost per woman compared to 500 ml blood loss (2022 US$)	Cost per DALY averted compared to 500 ml blood loss (2022 US$)
Blood loss								
≥ 500 ml blood loss	57.0 (46.4, 72.3)	22.5 (18.4, 28.7)	$5.83 ($4.96, $6.93)	174 (117, 241)				
≥ 450 ml blood loss	54.7 (43.0, 85.0)	21.6 (17.1, 33.7)	$5.87 ($4.76, $7.98)	205 (140, 280)	-2.3 (-14.7, 21.4)	-0.9 (-5.8, 8.5)	$0.05 (-$0.98, $1.82)	$51 (-$1576, $965)
≥ 400 ml blood loss	51.4 (39.5, 82.3)	20.3 (15.7, 32.6)	$6.06 ($4.89, $8.43)	267 (180, 366)	-5.6 (-18.1, 18.5)	-2.2 (-7.2, 7.3)	$0.24 (-$0.86, $2.22)	$107 (-$2394, $2956)
≥ 350 ml blood loss	49.0 (37.1, 79.6)	19.3 (14.7, 31.6)	$6.21 ($5.06, $8.47)	316 (216, 413)	-8.0 (-20.7, 15.9)	-3.2 (-8.2, 6.3)	$0.38 (-$0.78, $2.31)	$122 (-$3035, $2758)
≥ 300 ml blood loss	44.4 (32.6, 76.5)	17.5 (12.9, 30.3)	$6.58 ($5.30, $8.98)	409 (298, 529)	-12.6 (-25.9, 13.2)	-5.0 (-10.3, 5.2)	$0.75 (-$0.56, $2.78)	$151 (-$2963, $4383)
Blood loss + clinical marker(s)								
≥ 450 ml blood loss + clinical marker(s)	48.6 (34.0, 80.2)	19.2 (13.5, 31.7)	$5.61 ($4.17, $8.28)	237 (131, 359)	-8.4 (-19.4, 18.7)	-3.3 (-7.7, 7.4)	-$0.22 (-$1.41, $2.27)	-$66 (-$2572, $1720)
≥ 400 ml blood loss + clinical marker(s)	46.2 (32.5, 78.3)	18.2 (12.9, 31.0)	$5.62 ($4.25, $8.33)	268 (147, 401)	-10.8 (-22.6, 16.4)	-4.3 (-8.9, 6.4)	-$0.21 (-$1.39, $2.39)	-$48 (-$3246, $2946)
≥ 350 ml blood loss + clinical marker(s)	44.1 (30.4, 74.4)	17.4 (12.1, 29.4)	$5.62 ($4.18, $8.33)	278 (156, 426)	-12.9 (-23.9, 13.0)	-5.1 (-9.4, 5.1)	-$0.21 (-$1.50, $2.30)	-$41 (-$2815, $2177)
≥ 300 ml blood loss + clinical marker(s)	41.7 (29.3, 72.3)	16.5 (11.6, 28.6)	$5.69 ($4.19, $8.62)	321 (184, 468)	-15.3 (-26.5, 11.9)	-6.0 (-10.5, 4.7)	-$0.14 (-$1.47, $2.59)	-$23 (-$2470, $2375)

Sensitivity analysis excluding effects of early treatment

Without the early treatment effect, the impact of each scenario was reduced, and primarily a function of the scenario's sensitivity input parameters. The cost per composite outcome averted increased for all scenarios (Figure A3, Table A3).

As per the main analysis, each scenario considering other abnormal haemodynamic markers remained more cost-effective than any of the blood loss only scenarios, due to reduced unnecessary treatment.

When the threshold of 300 ml blood loss in combination with any other abnormal haemodynamic marker was compared to the threshold of 500 ml blood loss alone, it was the preferred strategy at a willingness-to-pay of >$861 per DALY averted.

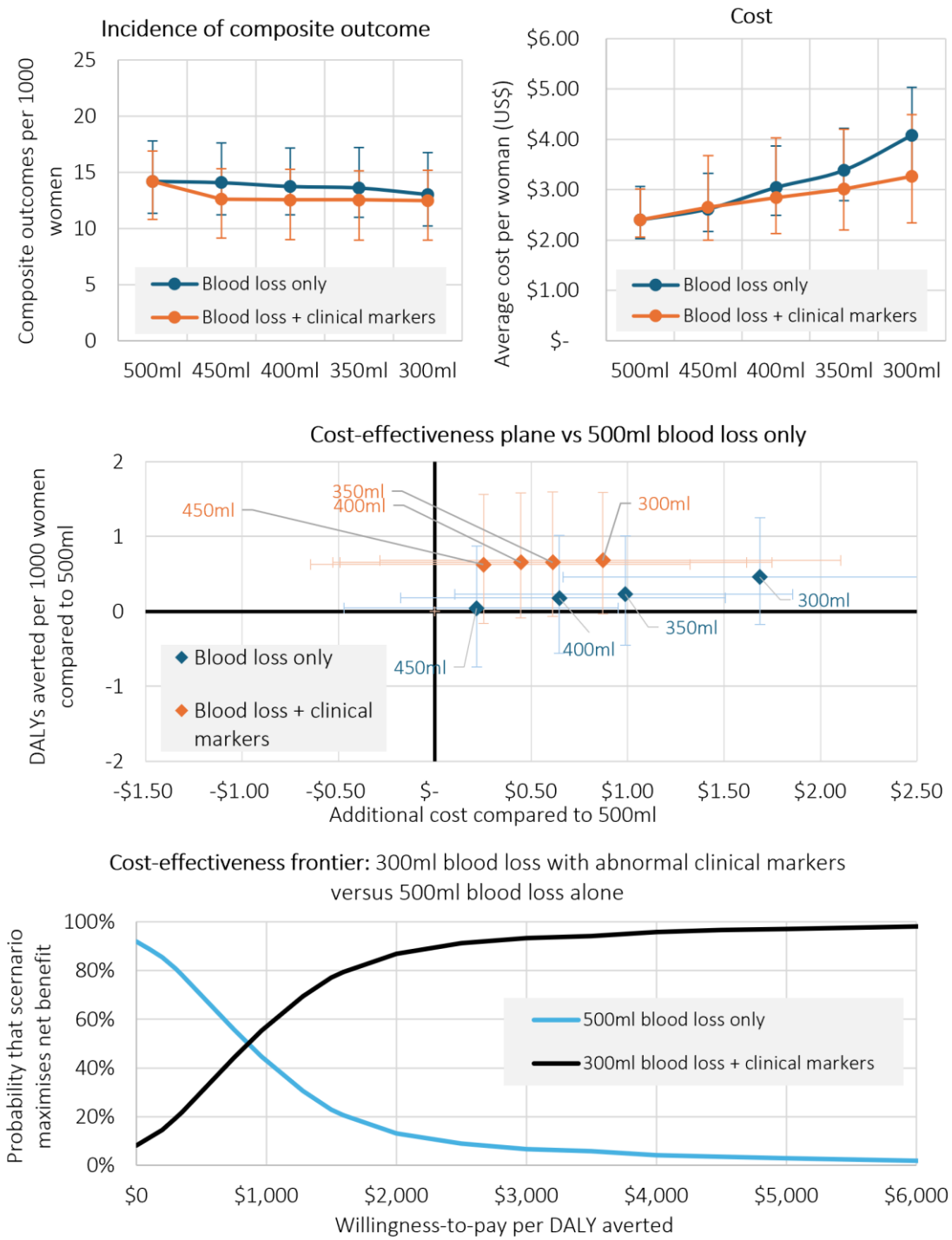

Figure A3: Sensitivity analysis excluding effects of early treatment. Model outcomes for blood loss thresholds alone ("blood loss only"), or blood loss thresholds in combination with any other abnormal haemodynamic marker ("blood loss + clinical markers"). Top left: incidence of composite outcome per 1000 women; top right: mean cost per woman (in 2022 US$); middle: composite outcomes averted per 1000 women and difference in mean cost for scenarios compared to the 500 ml blood loss model; bottom: cost-effectiveness frontier, showing the probability that a scenario maximises net benefits for a given willingness-to-pay per composite outcome averted.

Table A3: Results for sensitivity analysis excluding effects of early treatment.

Scenario	Incidence of composite outcome per 1000 women	Mean DALYs lost per 1000 women	Mean cost per woman (2022 US$)	Unnecessary treatments per 1000 women	Difference in composite outcomes per 1000 women, compared to 500 ml blood loss	Difference in DALYs per 1000 women, compared to 500 ml blood loss	Mean additional cost per woman compared to 500 ml blood loss (2022 US$)	Cost per DALY averted compared to 500 ml blood loss (2022 US$)
Blood loss								
≥ 500 ml blood loss	14.2 (11.4, 17.8)	5.6 (4.5, 7.1)	$2.40 ($2.02, $3.06)	189 (127, 261)				
≥ 450 ml blood loss	14.1 (11.2, 17.6)	5.6 (4.4, 7.0)	$2.62 ($2.17, $3.33)	222 (152, 304)	-0.1 (-2.2, 1.9)	0.0 (-0.9, 0.7)	$0.22 (-$0.47, $0.95)	$4872 (-$14892, $15711)
≥ 400 ml blood loss	13.7 (11.2, 17.2)	5.4 (4.4, 6.8)	$3.04 ($2.49, $3.87)	289 (196, 396)	-0.5 (-2.5, 1.4)	-0.2 (-1.0, 0.6)	$0.65 (-$0.18, $1.51)	$3615 (-$26983, $30478)
≥ 350 ml blood loss	13.6 (11.0, 17.2)	5.4 (4.4, 6.8)	$3.39 ($2.78, $4.22)	342 (235, 448)	-0.6 (-2.5, 1.1)	-0.2 (-1.0, 0.4)	$0.99 ($0.10, $1.86)	$4316 (-$29984, $39064)
≥ 300 ml blood loss	13.0 (10.2, 16.7)	5.1 (4.1, 6.6)	$4.08 ($3.29, $5.03)	444 (324, 574)	-1.2 (-3.1, 0.4)	-0.5 (-1.3, 0.2)	$1.69 ($0.66, $2.58)	$3682 (-$28407, $32645)
Blood loss + clinical marker(s)								
≥ 450 ml blood loss + clinical marker(s)	12.6 (9.1, 15.3)	5.0 (3.6, 6.1)	$2.65 ($2.00, $3.68)	253 (142, 387)	-1.6 (-4.0, 0.4)	-0.6 (-1.6, 0.2)	$0.25 (-$0.65, $1.32)	$404 (-$3130, $5654)
≥ 400 ml blood loss + clinical marker(s)	12.5 (9.0, 15.3)	5.0 (3.6, 6.0)	$2.84 ($2.13, $4.03)	287 (160, 433)	-1.7 (-4.0, 0.2)	-0.7 (-1.6, 0.1)	$0.45 (-$0.53, $1.62)	$684 (-$2112, $6126)
≥ 350 ml blood loss + clinical marker(s)	12.5 (9.0, 15.1)	5.0 (3.6, 6.0)	$3.01 ($2.20, $4.20)	298 (169, 459)	-1.7 (-4.0, 0.2)	-0.7 (-1.6, 0.1)	$0.61 (-$0.49, $1.75)	$936 (-$4369, $7957)
≥ 300 ml blood loss + clinical marker(s)	12.5 (8.9, 15.2)	4.9 (3.6, 6.0)	$3.27 ($2.34, $4.49)	345 (198, 506)	-1.7 (-4.0, 0.1)	-0.7 (-1.6, 0.0)	$0.87 (-$0.29, $2.11)	$1279 (-$3865, $10222)

APPENDIX B: Sensitivity analysis, treatment and composite outcome unit costs

Appendix B_unit cost sensitivity analysis.xlsx

APPENDIX C: Additional outputs

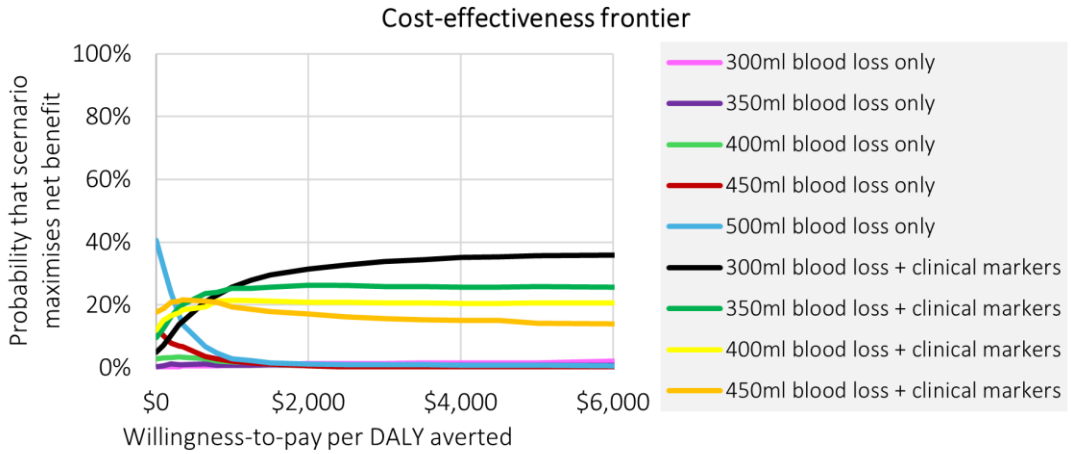

Figure C1: Cost-effectiveness frontier comparing all scenarios. Figure shows the probability that a scenario maximises net benefits for a given willingness-to-pay per composite outcome averted. Blood loss only – model outcomes for blood loss thresholds alone; blood loss + clinical markers – model outcomes for blood loss thresholds in combination with any other abnormal haemodynamic marker.

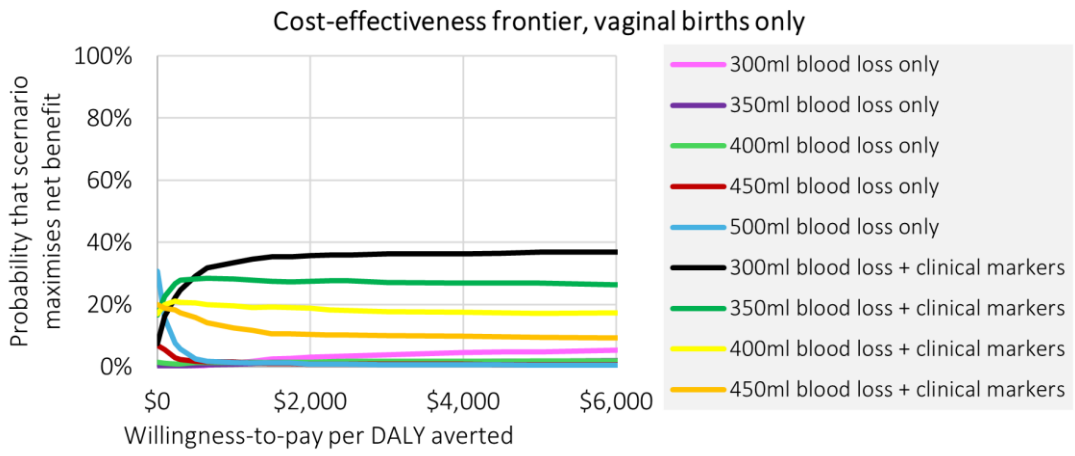

Figure C2: Cost-effectiveness frontier comparing all scenarios, vaginal births only. Figure shows the probability that a scenario maximises net benefits for a given willingness-to-pay per composite outcome averted. Blood loss only – model outcomes for blood loss thresholds alone; blood loss + clinical markers – model outcomes for blood loss thresholds in combination with any other abnormal haemodynamic marker.

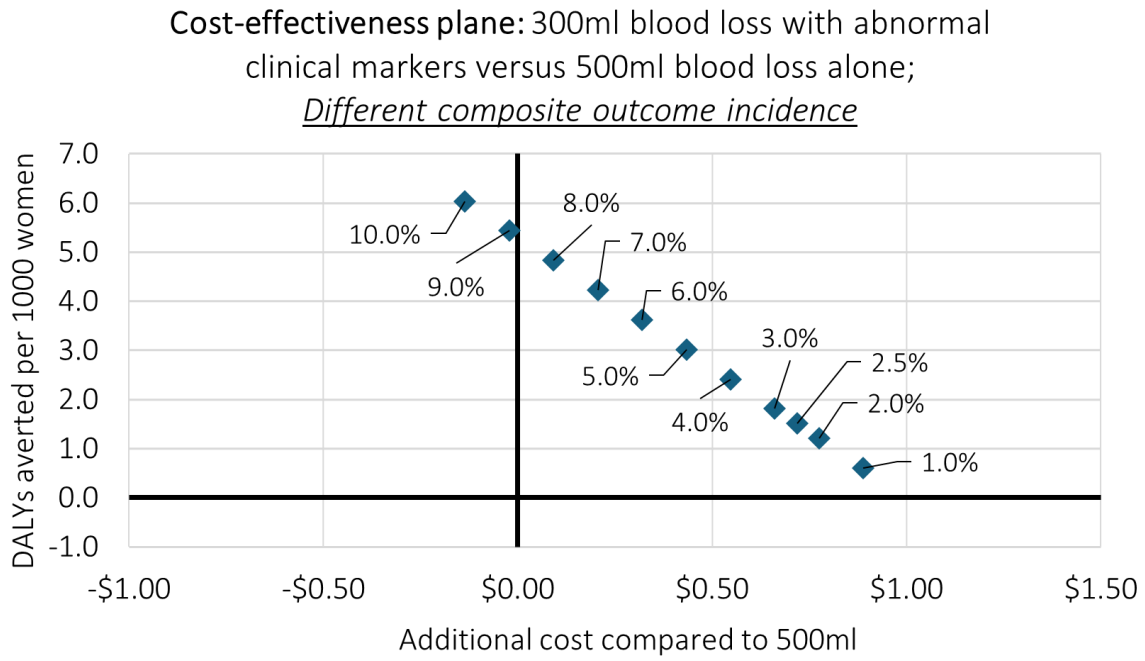

Figure C3: Cost-effectiveness plane for 300 ml blood loss + clinical markers compared to 500 ml blood loss only, different incidence of composite outcome.

Table C1: Cost per DALY averted as a percentage of GDP per capita for low- and middle-income countries. The 300 ml blood loss in combination with any other abnormal haemodynamic marker compared to the 500 ml blood loss alone.

			Scenario, compared to 500 ml blood loss alone	300 ml blood loss + clinical marker(s) (main analysis)	300 ml blood loss + clinical marker(s) (vaginal births only)
			ICER for scenario	$479	$77
Country ISO3	Country name	Income status	GDP per capita in 2022 (2022 US$)	ICER as a percentage of GDP per capita (main analysis)	ICER as a percentage of GDP per capita (vaginal births only)
Afghanistan	AFG	Low income	$357	134%	22%
Angola	AGO	Lower middle income	$2,930	16%	3%
Albania	ALB	Upper middle income	$6,846	7%	1%
Argentina	ARG	Upper middle income	$13,936	3%	1%
Armenia	ARM	Upper middle income	$6,572	7%	1%
Azerbaijan	AZE	Upper middle income	$7,771	6%	1%
Burundi	BDI	Low income	$251	191%	31%
Benin	BEN	Lower middle income	$1,265	38%	6%
Burkina Faso	BFA	Low income	$836	57%	9%
Bangladesh	BGD	Lower middle income	$2,716	18%	3%

Bosnia and Herzegovina	BIH	Upper middle income	$7,656	6%	1%
Belarus	BLR	Upper middle income	$7,995	6%	1%
Belize	BLZ	Upper middle income	$7,068	7%	1%
Bolivia	BOL	Lower middle income	$3,644	13%	2%
Brazil	BRA	Upper middle income	$9,281	5%	1%
Botswana	BWA	Upper middle income	$8,329	6%	1%
Central African Republic	CAF	Low income	$467	102%	16%
China	CHN	Upper middle income	$12,663	4%	1%
Cote d'Ivoire	CIV	Lower middle income	$2,309	21%	3%
Cameroon	CMR	Lower middle income	$1,605	30%	5%
Congo, Dem. Rep.	COD	Low income	$643	74%	12%
Congo, Rep.	COG	Lower middle income	$2,621	18%	3%
Colombia	COL	Upper middle income	$6,675	7%	1%
Comoros	COM	Lower middle income	$1,489	32%	5%
Cabo Verde	CPV	Lower middle income	$4,323	10%	2%
Costa Rica	CRI	Upper middle income	$13,626	3%	0%
Djibouti	DJI	Lower middle income	$3,231	13%	2%
Dominica	DMA	Upper middle income	$9,086	5%	1%
Dominican Republic	DOM	Upper middle income	$10,110	4%	1%
Algeria	DZA	Upper middle income	$4,962	9%	1%
Ecuador	ECU	Upper middle income	$6,541	7%	1%
Egypt, Arab Rep.	EGY	Lower middle income	$4,233	14%	2%
Ethiopia	ETH	Low income	$1,011	38%	6%
Fiji	FJI	Upper middle income	$5,405	8%	1%
Micronesia, Fed. Sts.	FSM	Lower middle income	$3,835	12%	2%
Gabon	GAB	Upper middle income	$8,409	6%	1%
Georgia	GEO	Upper middle income	$6,730	6%	1%
Ghana	GHA	Lower middle income	$2,240	21%	3%
Guinea	GIN	Lower middle income	$1,417	31%	5%
Gambia, The	GMB	Low income	$836	54%	9%
Guinea-Bissau	GNB	Low income	$853	50%	8%
Equatorial Guinea	GNQ	Upper middle income	$7,589	7%	1%
Grenada	GRD	Upper middle income	$10,474	4%	1%
Guatemala	GTM	Upper middle income	$5,358	8%	1%
Honduras	HND	Lower middle income	$3,003	15%	2%
Haiti	HTI	Lower middle income	$1,761	28%	5%
Indonesia	IDN	Upper middle income	$4,731	10%	2%
India	IND	Lower middle income	$2,353	19%	3%
Iran, Islamic Rep.	IRN	Upper middle income	$4,405	11%	2%
Iraq	IRQ	Upper middle income	$6,504	9%	1%
Jamaica	JAM	Upper middle income	$6,022	7%	1%
Jordan	JOR	Lower middle income	$4,332	11%	2%
Kazakhstan	KAZ	Upper middle income	$11,255	4%	1%
Kenya	KEN	Lower middle income	$2,110	25%	4%
Kyrgyz Republic	KGZ	Lower middle income	$1,740	24%	4%
Cambodia	KHM	Lower middle income	$2,325	20%	3%
Kiribati	KIR	Lower middle income	$2,076	23%	4%
Lao PDR	LAO	Lower middle income	$2,046	23%	4%
Liberia	LBR	Low income	$745	62%	10%
Libya	LBY	Upper middle income	$5,987	8%	1%
St. Lucia	LCA	Upper middle income	$13,104	4%	1%

Sri Lanka	LKA	Lower middle income	$3,343	13%	2%
Lesotho	LSO	Lower middle income	$1,030	52%	8%
Morocco	MAR	Lower middle income	$3,455	13%	2%
Moldova	MDA	Upper middle income	$5,738	7%	1%
Madagascar	MDG	Low income	$497	95%	15%
Maldives	MDV	Upper middle income	$11,786	4%	1%
Mexico	MEX	Upper middle income	$11,385	3%	1%
Marshall Islands	MHL	Upper middle income	$6,323	7%	1%
North Macedonia	MKD	Upper middle income	$7,606	6%	1%
Mali	MLI	Low income	$814	55%	9%
Myanmar	MMR	Lower middle income	$1,158	39%	6%
Montenegro	MNE	Upper middle income	$10,093	4%	1%
Mongolia	MNG	Upper middle income	$4,994	8%	1%
Mozambique	MOZ	Low income	$578	77%	12%
Mauritania	MRT	Lower middle income	$1,960	23%	4%
Mauritius	MUS	Upper middle income	$10,240	4%	1%
Malawi	MWI	Low income	$604	79%	13%
Malaysia	MYS	Upper middle income	$11,748	4%	1%
Namibia	NAM	Upper middle income	$4,349	11%	2%
Niger	NER	Low income	$610	74%	12%
Nigeria	NGA	Lower middle income	$2,139	30%	5%
Nicaragua	NIC	Lower middle income	$2,325	18%	3%
Nepal	NPL	Lower middle income	$1,386	35%	6%
Pakistan	PAK	Lower middle income	$1,538	35%	6%
Peru	PER	Upper middle income	$7,363	6%	1%
Philippines	PHL	Lower middle income	$3,548	13%	2%
Papua New Guinea	PNG	Lower middle income	$3,102	16%	3%
Paraguay	PRY	Upper middle income	$6,206	8%	1%
West Bank and Gaza	PSE	Lower middle income	$3,800	14%	2%
Rwanda	RWA	Low income	$975	47%	8%
Sudan	SDN	Low income	$1,046	22%	4%
Senegal	SEN	Lower middle income	$1,565	28%	5%
Solomon Islands	SLB	Lower middle income	$2,005	23%	4%
Sierra Leone	SLE	Low income	$860	63%	10%
El Salvador	SLV	Upper middle income	$5,094	9%	1%
Somalia	SOM	Low income	$573	80%	13%
Serbia	SRB	Upper middle income	$10,023	4%	1%
Sao Tome and Principe	STP	Lower middle income	$2,390	16%	3%
Suriname	SUR	Upper middle income	$6,084	9%	1%
Eswatini	SWZ	Lower middle income	$3,852	13%	2%
Chad	TCD	Low income	$672	70%	11%
Togo	TGO	Low income	$899	49%	8%
Thailand	THA	Upper middle income	$6,909	7%	1%
Tajikistan	TJK	Lower middle income	$1,052	41%	7%
Turkmenistan	TKM	Upper middle income	$8,156	6%	1%
Timor-Leste	TLS	Lower middle income	$2,343	32%	5%
Tunisia	TUN	Lower middle income	$3,678	12%	2%
Turkiye	TUR	Upper middle income	$10,675	4%	1%
Tuvalu	TUV	Upper middle income	$5,911	8%	1%
Tanzania	TZA	Lower middle income	$1,208	39%	6%
Uganda	UGA	Low income	$963	48%	8%
Ukraine	UKR	Upper middle income	$4,200	9%	2%

Uzbekistan	UZB	Lower middle income	$2,579	17%	3%
St. Vincent and the Grenadines	VCT	Upper middle income	$9,471	5%	1%
Viet Nam	VNM	Lower middle income	$4,116	11%	2%
Vanuatu	VUT	Lower middle income	$3,265	14%	2%
Samoa	WSM	Lower middle income	$3,869	11%	2%
Kosovo	XKX	Upper middle income	$5,291	8%	1%
Yemen, Rep.	YEM	Low income	$616	100%	16%
South Africa	ZAF	Upper middle income	$6,523	8%	1%
Zambia	ZMB	Lower middle income	$1,447	36%	6%
Zimbabwe	ZWE	Lower middle income	$2,041	22%	4%