Cost effectiveness analysis of maintenance therapy based on the molecular profile in newly diagnosed advanced ovarian cancer patients in India

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SUMMARY

INTRODUCTION: Ovarian cancer has the highest fatality amongst all gynaecological malignancies. This study aims to evaluate the cost effectiveness of molecular-driven maintenance therapy in the newly diagnosed advanced ovarian cancer (AOC) after response to first line platinum-based chemotherapy in India.

METHODS: Maintenance therapy was assessed for three different molecular profiles including BRCA mutated (BRCAm) AOC, homologous recombinant deficient (HRD) positive BRCA wild type (BRCAwt) AOC, and BRCAwt HRD unknown or negative patients. Maintenance therapy options consisted of poly-ADP ribose polymerase inhibitors (PARPi) – olaparib, rucaparib and niraparib, compared to routine surveillance for BRCAm and HRD positive patients, while single agent bevacizumab was evaluated for patients BRCAwt HRD unknown or negative patient group. A state-transition model was developed to assess the incremental cost per quality adjusted life year (QALY) gained with a given treatment option, as compared against the next best alternative. The cost-effectiveness was determined using a willingness to pay (WTP) threshold of 1-time per capita gross domestic product (GDP) (₹ 171,498) in India.

RESULTS: For patients with BRCAm, generic olaparib incurs an incremental cost of ₹ 82,711 per QALY gained when compared to routine surveillance and was found to be cost effective in the Indian setting. For HRD positive patients, none of the evaluated PARPi was cost effective when compared to routine surveillance. However, a price reduction of 23% for the generic olaparib, can make it cost effective. For patients BRCAwt, bevacizumab was not considered to be a cost-effective option as compared to routine surveillance.

CONCLUSION: Generic olaparib at the current prices is cost effective for maintenance therapy in BRCAm newly diagnosed AOC patients in India and should be included along with molecular testing in India's government funded health insurance scheme to make it accessible among BRCAm AOC patients.

INTRODUCTION

Ovarian cancer (OC) is the eighth most common cancer among women and accounted for 4.7% of cancer deaths worldwide (1). In India, the age-adjusted incidence of OC has been reported to range from 0.9 to 8.4 per 100,000 women (2). An area of concern in the management of OC in India is the poor survival, with 5-year survival of 46% (3). One of the major reasons for the same is that majority of the patients (62%) present in advanced stages (Stage III and IV) when prognosis is poor (4). In an attempt to improve outcomes in AOC, there has been incorporation of maintenance therapy following primary treatment.

Various agents have been tried as maintenance therapy for AOC, but those which have shown significant efficacy include vascular endothelial growth factor inhibitor bevacizumab and poly-ADP-ribose polymerase inhibitors (PARPi). Bevacizumab maintenance is associated with an improved median progression free survival (PFS) of 2-4 months (5). A recent meta-analysis which analysed the efficacy of maintenance PARPi in patients with newly diagnosed AOC found that median PFS was significantly better in patients with a breast cancer gene mutation (BRCAm) (45.7 versus 17.7 months), homologous recombination deficiency (HRD positive) excluding BRCAm (22.3 versus 13.1 months), but not in HRD negative (15 versus 11.3 months) when compared with placebo (6). There have been no direct comparisons between the efficacy of various PARPi including olaparib, niraparib, rucaparib, veliparib etc and these are considered to have equal effectiveness and choice of therapy may be influenced by the clinical profile, genetic profile, toxicity and cost.

Current guidelines (7,8) recommend maintenance therapy after first line systemic therapy for patients of high grade serous or grade 2/3 endometroid, stage III-IV OC who are in complete response or partial response. Despite the proven efficacy of maintenance therapy in AOC, its use remains limited due to the high costs associated with these drugs. Various cost effectiveness studies for maintenance PARPi in the first line setting for AOC have been published in the past with heterogenous results. Olaparib with bevacizumab when compared to bevacizumab alone was cost effective in Spain (9) but not found to be cost effective from the US healthcare perspective (10). Olaparib alone when compared to routine surveillance was not found to be cost effective in Malaysia (11) but was cost effective in Singapore (12). Another study from the US healthcare perspective reported that at the current price, primary maintenance therapy is not cost effective, regardless of the molecular signature (13).

In view of the high burden of the disease, multiple drugs available for different molecular profiles, significant costs associated with these drugs, heterogeneity in previously reported cost effectiveness analysis, and recently introduced generic versions of olaparib in India, there is an urgent need to conduct an economic evaluation to justify its value for money. Therefore, the current paper aims to assess the cost effectiveness of maintenance therapy with olaparib, rucaparib and niraparib in AOC patients in India with BRCAm and HRD positive (BRCAwt), when compared to routine surveillance. In addition, we evaluated the use of bevacizumab in patients with BRCAwt and unknown or negative HRD status.

METHODOLOGY

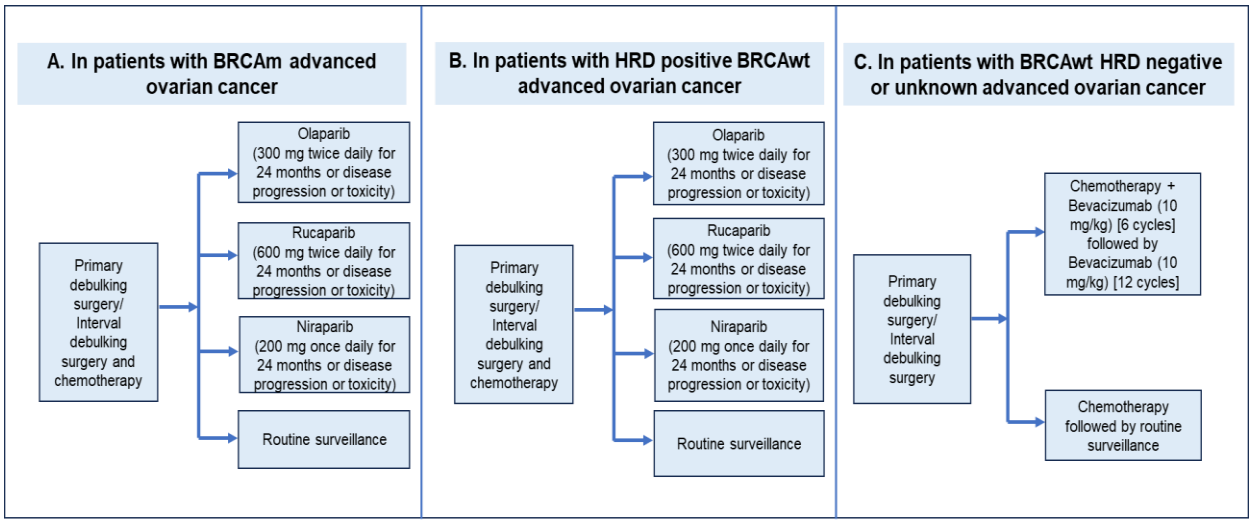
Model Overview

Overview of Population Groups and Treatment strategies

A hypothetical cohort of newly diagnosed advanced (stage III and IV) high grade ovarian tumors who underwent primary or interval debulking surgery with platinum-based chemotherapy in the neoadjuvant and/or adjuvant setting and showed complete or partial response entered the model in the PFS state. Once in the PFS state the patients could receive maintenance therapy based on their molecular profile. Three different sub-groups were analysed based on the molecular profile:

1. Patients with BRCAm could receive either olaparib, rucaparib, niraparib or be kept on routine surveillance without any maintenance therapy.
2. HRD positive BRCAwt (henceforth referred to as HRD positive) patients could receive either olaparib, rucaparib, niraparib or be kept on routine surveillance without any maintenance therapy.
3. Patients BRCAwt and HRD negative/ unknown (henceforth referred to as patients BRCAwt) could either receive maintenance treatment with bevacizumab or be kept on routine surveillance without any maintenance therapy.

Figure 1. Treatment strategies based on the molecular profile of the patients with advanced ovarian cancer after response to first line platinum-based chemotherapy



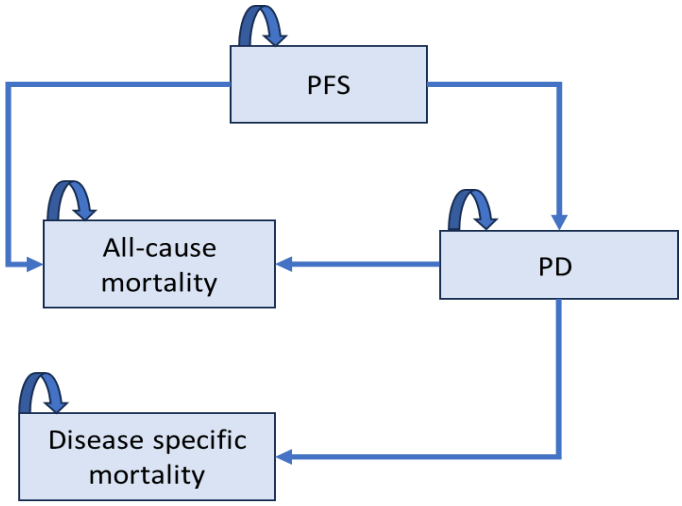
We adhered to the methodological guidelines outlined in the Indian reference case for conducting economic evaluations (14), and the consolidated health economic evaluation reporting standards (CHEERS) checklist (15) for comprehensive conduct and description of the study (Table S4).

Model structure

A *de novo* state-transition model (STM) was developed in Microsoft Excel to estimate the lifetime costs and health consequences in patients with newly diagnosed AOC (Stage III/ IV). Individual models were developed based on the molecular profile. The model started at the age

of 50 years, considering the mean age of AOC in India (16). The models consisted of four mutually exclusive health states: progression free state (PFS), progressive disease (PD), all-cause mortality (ACM), and disease specific mortality (DSM) (Figure 2). The outcomes were evaluated in terms of life-years (LYs) and quality-adjusted life-years (QALYs). The cycle length was one month and future costs as well as outcomes were discounted at 3% annually (14). Based on the Indian methodological guidelines for conducting HTA, an abridged societal perspective was considered for the economic evaluation, implying that we considered health system costs, as well as direct medical and non-medical out-of-pocket expenditure borne by the patients to access treatment (14). The indirect costs associated with lost productivity were not included in the analysis.

Figure 2. Schematic diagram for state transition model



PFS: Progression-free survival PD: Progressive Disease

Based on clinical response to maintenance therapy, patients in PFS could continue to be in the same state or could progress to PD state. Patients in the PD state were assumed to receive the second-line therapy or best supportive care (BSC). BSC included symptomatic management of pain, discharge/ bleeding per vaginum, recurrent ascites, nausea, anorexia, gastritis, bowel obstruction etc. Based on response to second line therapy, patients could either die due to disease specific or ACM or could receive third line therapy or BSC. Probability of progression from PD state after receiving second line or third line chemotherapy or BSC were independent of the type of maintenance therapy and patient sub-groups. Details of second line, third line and subsequent treatment are provided in Table S1. Patients from both PFS or PD could die from ACM. However, it was assumed that only patients from PD state could have DSM.

Clinical effectiveness and transition probabilities

To acquire efficacy and transition probabilities through various health states after administration of olaparib, niraparib and rucaparib, in BRCAm and HRD positive AOC patients, data were used from SOLO-1, PRIMA, and ATHENA-MONO trials respectively (17-

19). For use of maintenance bevacizumab in patients BRCAwt, data was used from POALA-1 (20).

Probabilities for remaining in PFS health state were estimated for each cycle using the PFS curves reported in these trials. Estimation of survival beyond the follow-up period necessitated the use of extrapolation beyond the trial period using standard methods. The PFS survival data for bevacizumab were extracted from the Kaplan-Meier (KM) curve reported in the PAOLA-1 trial, using web-based digitizer software (21). Similarly, PFS survival data for olaparib, rucaparib in BRCAm AOC were derived from SOLO-1, and ATHENA-MONO trial-based KM curves, respectively (17, 19). The KM curve specific to niraparib in BRCAm patients was acquired from a systematic review by Gulia et al and digitized to extract the PFS survival data (6). Survival data for niraparib in HRD positive AOC were obtained from digitization of PFS curves reported by the PRIMA trial (18), while KM curve constructed by Gulia et al was used to extract the PFS values for rucaparib in HRD positive AOC (6). Since the SOLO-1 study included only patients with germline BRCA1 or BRCA2 mutation, PFS gradient was computed using data from ATHENA-MONO (19) and SOLO-1 (17) trial, to determine monthly progression probabilities following receipt of olaparib maintenance therapy in HRD positive AOC.

Using these reconstructed KM curve probabilities and published number of patients at risk, we created the individual patient level data for all the competing maintenance therapy arms in different AOC groups. This reconstructed individual patient-level data from the trials were subsequently fitted to five standard parametric models (exponential, Weibull, Gompertz, log-normal, and log-logistic) using STATA 13. The choice of a suitable distribution was determined through visual inspection and the assessment of goodness of fit, including Akaike and Bayesian information criteria. Finally, the monthly probabilities were calculated using the standard extrapolation technique (21). Table 1 depicts the results of fitting parametric survival curves. Figures S1-S6 present the empirical and fitted survival curves for time-to-progression for the considered first line maintenance therapies.

The probability to remain in PFS in case of routine surveillance for comparison in the AOC BRCAwt subgroup was calculated through pooled analysis of digitized data from PFS curves for debulking surgery in combination with carboplatin-paclitaxel chemotherapy, using a random effects model. The PFS curves were obtained from individual RCTs (EORTC-55971, CHORUS, and JGOG0602 trials), which were sourced from a systematic review (22). Likewise, the six-monthly PFS probability for placebo as maintenance therapy in BRCAm AOC, were calculated through meta-analysis of time-to-progression probabilities from SOLO-1, PRIMA, and ATHENA-MONO trials; while that in the HRD positive AOC, was synthesized using data from PRIMA, and ATHENA-MONO trials, using the random effects model (17-19).

The probability of DSM for patients in the PD state following primary maintenance, second- or third-line chemotherapy or BSC was obtained from published Indian study, which evaluated 10-year survival outcome in advanced-stage AOC (23). Age-specific ACM rates were obtained from Indian Sample Registration System lifetables (24).

Specific incidence rates for adverse events of grade three or more in olaparib, niraparib, rucaparib, and bevacizumab, as well as dose modification and drug discontinuation rates were obtained from the SOLO-1, PRIMA, ATHENA-MONO, and PAOLA-1 trials, respectively (17-20).

Utility value parameters

The state wise utility values for PFS and post-progressive health states were obtained from primary data collection from 192 stage III/ IV ovarian cancer patients, collected as part of a multi-centric cross-sectional nationally representative Indian study undertaken across seven major cancer hospitals in six Indian states (25). The patients were administered the EQ-5D-5L tool, and India specific tariff values were used for estimating the utility score for the health states (26). The detailed input parameters are shown in Table 1.

Table 1: Input parameters to determine effectiveness of different treatment arms

Input parameter	Value	Standard error	Distribution	Source
Median age	50 years	-		(16)
Annual discount rate	3%	-		(14)
PFS for olaparib in BRCAm ovarian cancer	λ: 4.0372 γ: 0.3213	λ: 0.1113 γ: 0.0716	Log-normal	(17)
PFS for niraparib in BRCAm ovarian cancer	λ: 3.1902 γ: -0.0954	λ: 0.1288 γ: 0.1124	Log-normal	(18)
PFS for rucaparib in BRCAm ovarian cancer	λ: 3.7247 γ: -0.3125	λ: 0.1946 γ: 0.1601	Log-logistic	(19)
PFS for bevacizumab	λ: 0.0112 γ: 0.411	λ: 0.0037 γ: 0.0706	Weibull	(20)
PFS for niraparib in HRD positive ovarian cancer*	λ: 3.1174 γ: 0.2450	λ: 0.1544 γ: 0.1029	Log-normal	(18)
PFS for rucaparib in HRD positive ovarian cancer*	λ: 2.9901 γ: 0.0682	λ: 0.1284 γ: 0.1052	Log-normal	(19)
Routine surveillance (AOC BRCAwt)	0.935	0.0232	Beta	(22)
Age specific mortality (annual)				
55-59 years	0.008	6.34232E-05	Beta	(24)
60-64 years	0.013	9.13868E-05	Beta	
65-69 years	0.018	0.00014	Beta	
Death due to disease in PD state (monthly)	0.027	0.00158	Beta	(23)
Health related quality of life value				
PFS	0.68	0.039	Beta	(25)
PD	0.65	0.038	Beta	

*BRCAwt, PFS: Progression-free survival, PD: Progressive state, HRD: Homologous recombinant deficiency

Costs

The health system as well as direct medical and non-medical out-of-pocket costs related to treatment were determined using standard sources (Table 2). The costs of debulking surgery, and each cycle of carboplatin-paclitaxel chemotherapy, as well costs for second, and third-line treatment were obtained from the national health insurance scheme (*Ayushman Bharat-Pradhan Mantri Jan Arogya Yojna*) reimbursement rates (27). The reimbursement rates include the drug acquisition and administration costs, and cost of management of acute adverse events. The market prices of olaparib, and rucaparib were used for the analysis (Table 2). The cost of 1 mg/kg molecule of bevacizumab biosimilar was acquired from Rajasthan Medical Services Corporation rates and the final cost of the required drug in each cycle was calculated based on quantity of drug required as per the average weight of an adult female in India from the report of expert group on nutrient requirements for Indians, 2020 (28). The recommended doses for bevacizumab as per the guidelines for use in primary treatment and maintenance of AOC ranges from 7.5mg/kg -15mg/kg for 18-22 cycles (7). In our analysis we included the cost of 18 cycles of Bevacizumab at 15mg/kg at similar efficacy as reported in PAOLA-1 (20). We relied on consultations with the private suppliers to obtain the price quotations of niraparib in India.

The costs of out-patient department (OPD) consultations, diagnostic and laboratory investigations, and follow up were also incorporated. The costs of diagnostics were majorly obtained from the central government health scheme rates and included radiology, tumor markers, haematology, biochemistry profile, cytology and histopathology (29). The market prices of CA19.9, BRCA test and HRD test were used, which were further verified by the clinical experts (Table 2). Cost for surgery and platinum based first line chemotherapy was included. For the maintenance treatment arms including olaparib, rucaparib, niraparib and bevacizumab, drug acquisition costs, drug administration cost for bevacizumab, direct patient OOP expenditure per OPD consultation, management of grade 3-4 adverse events (AEs) and the cost of routine follow-up was included. The direct non-medical out-of-pocket expenditures were derived from primary data of CaDCQoL study in India (25). For patients in the surveillance arms routine follow up costs were estimated using the standard treatment guidelines, and the state procurement medicine prices obtained from the National Health System Cost Database for India, and from the Jan Aushadi Kendra List (30, 31). The details of cost included are provided in Table 2, Table S1. All the costs are reported in Indian rupees and US dollars. A conversion rate for the year 2022 of $1 = INR 78.60, as reported by the World Bank, was used (32).

Table 2. Input parameters used to determine costs in different treatment arms

Input parameter	Base case Value (SE) In INR	Base case Value (SE) In USD	Distribution	Source
Costs of diagnostics				
CECT abdomen and pelvis	4500 (1299)	57.3 (16.5)	Gamma	(29)
CECT chest	2875 (829)	37.6 (10.5)	Gamma	
MRI abdomen and pelvis	5000 (1444)	63.6 (18.4)	Gamma	
CA125 test	400 (115)	5.1 (1.5)	Gamma	

CEA test	298 (86)	3.8 (1.1)	Gamma	
HCG test	340 (98)	4.3 (1.2)	Gamma	
AFP test	345 (100)	4.4 (1.3)	Gamma	
LDH test	371 (107)	4.7 (1.4)	Gamma	
CBC	155 (45)	2.0 (0.6)	Gamma	
RFT	261 (75)	3.3 (1.0)	Gamma	
LFT	275 (79)	3.5 (1.0)	Gamma	
Biopsy	1362 (393)	17.3 (5.0)	Gamma	
FNAC	1045 (302)	13.3 (3.8)	Gamma	
Ascitic cytology	100 (29)	1.3 (0.4)	Gamma	
Coagulogram	650 (188)	8.3 (2.4)	Gamma	
ECG	50 (14)	0.6 (0.2)	Gamma	
Serum electrolytes	460 (133)	5.9 (1.7)	Gamma	
PET scan	14663 (4234)	186.6 (53.9)	Gamma	
CA19.9	1106 (319)	14.1 (4.1)	Gamma	(33)
BRCA 1/2 test	12500 (3608)	159.0 (45.9)	Gamma	(34)
HRD test	50000 (14434)	636.1 (183.6)	Gamma	(35)
Cost of treatment				
OPD visit	266.2 (77)	3.4 (1.0)	Gamma	(36)
Hysterectomy	72588 (20954)	923.5 (266.6)	Gamma	(27)
Injection Paclitaxel 175mg/m^2 and Injection Carboplatin AUC 5 (per cycle)	14850 (4287)	188.9 (54.5)	Gamma	
Bevacizumab per mg	26.96 (8)	0.3 (0.1)	Gamma	(37)
Olaparib 300 mg (per cycle)	15000 (4330)	190.8 (55.1)	Gamma	(38)
Rucaparib 600 mg (per cycle)	72396 (20899)	921.1 (265.9)	Gamma	(39)
Niraparib 200 mg (per cycle)	571429 (164957)	7270.1 (2098.7)	Gamma	Expert consultation
Second line/ third line/ subsequent treatment- per cycle cost				
Injection Paclitaxel 175mg/m^2 and Injection Carboplatin AUC 5	14850 (4287)	188.9 (54.5)	Gamma	(27)
Injection Gemcitabine 1gm/m^2 D1, D8 and Injection Carboplatin AUC 5 3 weekly	13900 (4013)	176.8 (51.1)	Gamma	
Injection Liposomal doxorubicin 30 mg/m^2 and Injection Carboplatin AUC 5 3 weekly	17200 (4965)	218.8 (63.2)	Gamma	
Injection Docetaxel 75mg/m^2 x 3 weekly	8500 (2454)	108.1 (31.2)	Gamma	
Injection Gemcitabine 1gm/m^2 D1, D8, D15 x 3 weekly	9000 (2598)	114.5 (33.1)	Gamma	
Injection Liposomal doxorubicin 40mg/m^2 x 3 weekly	17950 (5182)	228.4 (65.9)	Gamma	

Injection Topotecan 1.5mg/m^2 D1-3 x 3 weekly	24600 (7010)	313.0 (89.2)	Gamma	
Tab Etoposide 50mg	3400 (981)	43.3 (12.5)	Gamma	
Cost of management of side effects (per cycle)				
Anaemia (blood transfusion)	2100 (606)	26.7 (7.7)	Gamma	(27)
Anaemia (iron folic acid tablets)	2.56 (0.73)	0.03 (0.01)	Gamma	(37)
Lymphopenia (Day care treatment)	12558 (3265)	159.8 (41.5)	Gamma	(29), (39)
Neutropenia (Indoor)	28625 (8263)	364.2 (105.1)	Gamma	(29), (40), (41)
Neutropenia (Outdoor)	12601 (3638)	160.3 (46.3)	Gamma	(29), (41), (42)
Hypertension	1315 (380)	16.7 (4.8)	Gamma	29), (37)
Diarrhoea	20 (6)	0.3 (0.1)	Gamma	(30)
Thrombocytopenia	12700 (3666)	161.6 (46.6)	Gamma	29)
Cost of best supportive care (in one cycle)				
Pain	379	4.8 (1.4)	Gamma	(37)
Recurrent ascites	4202	53.3 (15.4)	Gamma	(27)
Bloating	36	0.5 (0.1)	Gamma	(31)
Loss of appetite	695	8.8 (2.6)	Gamma	(37)
Constipation	82	1.0 (0.3)	Gamma	
Nausea	99	1.3 (0.4)	Gamma	(31)
Bleeding per vaginum	741	9.4 (2.7)	Gamma	(37)
Discharge per vaginum	221	2.8 (0.8)	Gamma	
Intestinal obstruction (IV antibiotics)	14700	187.0 (54.0)	Gamma	(27)
Intestinal obstruction (colostomy)	20000	254.5 (73.5)	Gamma	
Non-medical expenditure				
PFS	2287	29.1 (8.4)	Gamma	(25)
PD	4548	57.9 (16.7)	Gamma	

CECT: Contrast-enhanced computed tomography; CEA: Carcinoembryonic antigen test; AFP: Alpha fetoprotein test; LDH: Lactate dehydrogenase test; CBC: Complete Blood count; RFT: Renal Function test; LFT: Liver function test; FNAC: Fine needle aspiration cytology; ECG: Electrocardiogram; PET: Positron emission tomography; PFS: Progression-free survival state; PD: Progressive disease state

Sensitivity analysis

Probabilistic Sensitivity Analysis (PSA) was undertaken to assess the effect of joint parameter uncertainty for each arm using relevant distributions (Table 1-2). Under PSA, all cost parameters were assigned gamma distribution, while utility values and probabilities/proportions were assigned beta distribution. The uncertainty range was derived from primary data using the reported standard errors. However, if such estimates were not available, the monthly clinical parameters, mortality risks, and utility values were varied by ±10%, while costs were varied by ±50%. Based on 1000 Monte Carlo simulations, median value of incremental cost-effectiveness ratio (ICER) along with 2.5^{th} and 97.5^{th} percentile were computed and reported. Price threshold analysis was undertaken to understand the effect of varying the prices of drugs on ICER values.

The comparative cost-effectiveness was assessed in terms of incremental cost per QALY gained, using one-time gross domestic product (GDP) threshold of 2022-23 (INR 1,71,498; US$2,182) (14). Dominance and extended analyses were conducted, comparing each treatment arm against the next best alternative to evaluate the comparative cost-effectiveness among different treatment arms, using R Shiny app and commands for ICER calculator.

Ethical approval

Ethical approval was obtained from the Institutional Ethics Committee of Post Graduate Institute of Medical Education and Research, India.

Role of the funding source

The study was funded by the Department of Health Research, Ministry of Health and Family Welfare, Government of India vide grant number 11011/02/2023-HR. The funders had no role in the design, data collection, analysis, and interpretation, or preparation of this manuscript.

RESULTS

Table 3 enlists the median lifetime costs and QALYs per patient in different competing scenarios. Bevacizumab was associated with marginal gain of 0.061 QALYs with incremental cost of ₹ 384,746 in AOC patients BRCAwt, when compared to routine surveillance (Table 4). Administration of rucaparib and niraparib maintenance therapy were dominated strategies, due to lower lifetime QALY per case of BRCAm AOC with higher lifetime costs, in comparison to olaparib (Table 3). Olaparib use led to gain of 3.71 life years and 2.55 QALYs at an additional cost of ₹209,271, making it cost-effective as a maintenance therapy in BRCAm AOC.

Likewise, rucaparib was dominated by olaparib due to associated lower QALYs gained at higher costs in HRD positive AOC. Both olaparib and niraparib resulted in higher QALY gains with additional costs, however, both the strategies were not cost-effective for use in HRD positive AOC, considering WTP threshold of one-time per capita GDP of India (Table 4).

Table 3. Discounted lifetime costs and health outcomes per person in advanced ovarian cancer

AOC BRCAwt[#]	Discounted life years*	Discounted QALY*	Discounted cost (₹)*
Routine surveillance	3.89 (3.26-5.28)	2.59 (2.12- 3.60)	600,865 (491,341- 706,474)
Chemotherapy with Bevacizumab followed by Bevacizumab	3.97 (3.71-4.27)	2.65 (2.37-2.94)	985,611 (697,949- 1,155,372)
AOC with BRCAm			
Routine surveillance	4.18 (3.72- 4.76)	2.79 (2.37- 3.23)	547,723 (452,699- 656,230)
Olaparib	7.90 (7.47- 8.35)	5.34 (4.74- 5.95)	757,993 (596,657- 992,340)
Rucaparib	6.90 (6.48- 7.30)	4.65 (4.17-5.14)	1,838,294 (1,167,687- 2,871,565)
Niraparib	5.12 (4.80- 5.45)	3.43 (3.09-3.77)	10,253,444 (5,815,105- 16,901,379)
HRD positive AOC			
Routine surveillance	4.27 (3.69- 5.02)	2.85 (2.42- 3.42)	581,692 (485,032- 693,884)
Olaparib	5.29 (4.95- 5.64)	3.54 (3.19- 3.91)	763,033 (621,845- 964,860)

Rucaparib	4.60 (4.30- 4.92)	3.07 (2.78- 3.39)	1,607,719 ((1,065,312- 2,388,467)
Niraparib	5.51 (5.14- 5.90)	3.70 (3.33- 4.11)	9,545,702 (5,489,030- 15,587,088)

*Values indicate median estimates, while values in parentheses indicate values at 2.5th and 97.5th percentile, #: with unknown HRD status ##: BRCAwt AOC: Advanced Ovarian Cancer, HRD: Homologous Recombinant Deficiency

Table 4. Cost-effectiveness of maintenance therapy for advanced ovarian cancer

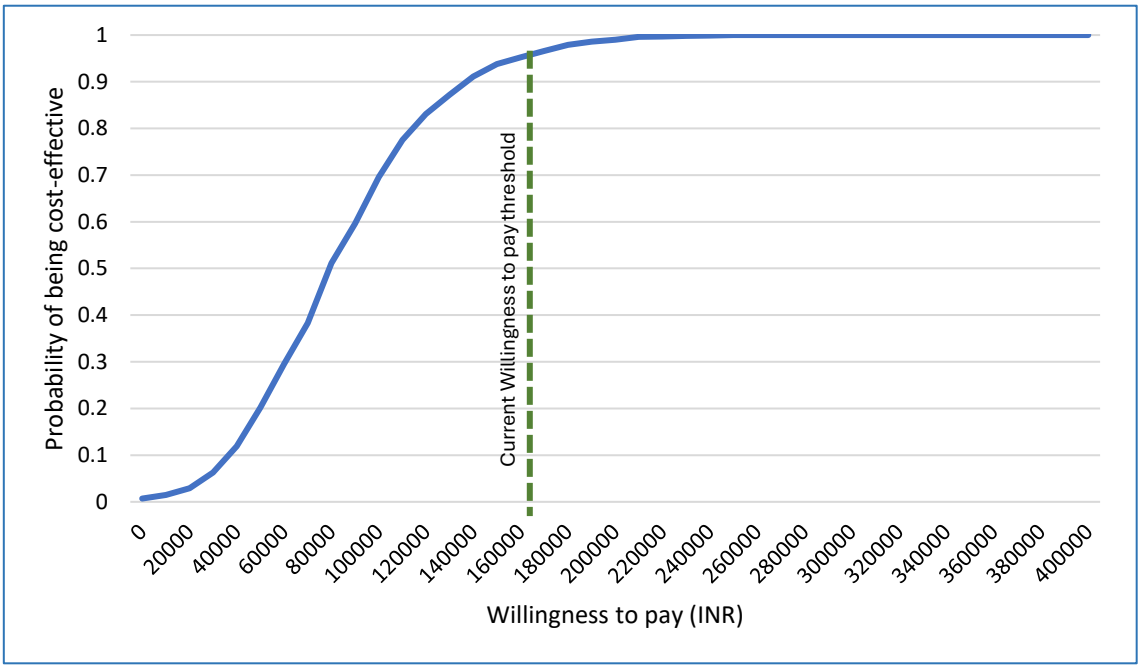
AOC BRCAwt[#]	Incremental LY*	Incremental QALY*	Incremental cost (₹)*	Incremental cost/ QALY gained*	Status
Routine surveillance					
Chemotherapy with Bevacizumab followed by Bevacizumab	0.09 (-1.26- 0.64)	0.061 (-0.86- 0.44)	384,746 (159,830- 513,613)	40,00,279[&]	WTP exceeded
AOC with BRCAm					
Routine surveillance					
Olaparib (comparison- routine surveillance)	3.71 (3.00- 4.32)	2.55 (1.96- 3.13)	2,09,271 (36,646- 418,663)	82,711 (14,151- 170,315)	Cost-effective
Rucaparib	-	-	-	-	Dominated
Niraparib	-	-	-	-	Dominated
HRD positive AOC[##]					
Routine surveillance					
Olaparib (comparison- routine surveillance)	1.01 (0.3- 1.60)	0.68 (0.21- 1.10)	177,984 (28,496- 354,952)	248,842 (53,699- 877,448)	WTP exceeded
Niraparib (comparison- olaparib)	0.22 (-0.17- 0.62)	0.15 (-0.11- 0.43)	8,730,209 (4,673,103- 14,845,785)	45,025,242 (-72,0,422,458- 636,921,450)	WTP exceeded
Rucaparib	-	-	-	-	Dominated

*Values indicate median estimates, while values in parentheses indicate values at 2.5th and 97.5th percentile; WTP: Willingness to pay threshold, #: with unknown HRD status ##: BRCAwt AOC: Advanced Ovarian Cancer, HRD: Homologous Recombinant Deficiency &2.5th and 97.5th percentile values not reported since the values lied in different quadrants of the cost-effectiveness plane (Figure-S7)

Probabilistic Sensitivity Analysis

At the current willingness-to-pay threshold of one-time GDP per capita, the probability of olaparib maintenance therapy being cost-effective was 97.5% for BRCAm AOC and 23% for HRD positive AOC (Figures 5 and S10).

Figure 5. Probability of olaparib being cost-effective in BRCAm patients compared to routine surveillance



Price Threshold analysis

We found that a 23% reduction in the price of olaparib (from the base case price of ₹15,000) would make it cost-effective for use in HRD positive patients (Figure S11). At current prices, using rucaparib as a maintenance therapy for ovarian cancer is not a cost-effective strategy compared to other PARPi. However, to replace routine surveillance with rucaparib maintenance therapy, a price reduction of 73% and 91% would be necessary to ensure value for money in ovarian cancer with a BRCAm and HRD positive tumor, respectively (Figure S12). Likewise, niraparib becomes cost-effective compared to routine surveillance in HRD positive and BRCAm ovarian cancer at per tablet price of ₹397 (98% price reduction) and ₹283 (98.5% price reduction), respectively.

Model Validation

We used the TECH-VER checklist for technical verification of the model (43). Our study found the 3-year and 5-year survival rates were 45% and 33%, respectively in the routine surveillance scenario. These model outcomes corroborate with the findings from a systematic review that reported a 3-year and 5-year survival rates of 46% and 36%, respectively in Indian patients with ovarian cancer (44). The model derived median survival time was similar to that reported by a 10-year prospective cohort study in AOC (45). Furthermore, the median PFS in different maintenance therapies was in concurrence with the data from the randomized controlled trials (Table S2).

DISCUSSION

Our study concludes that at the current cost effectiveness threshold in India (₹ 171,498), only generic olaparib maintenance treatment was found to be cost effective at the current prices as compared to routine surveillance for BRCAm patients. For the HRD positive subgroup, none of the three PARPi analysed were found to be cost effective. However, if the cost of generic olaparib is reduced by 23%, olaparib becomes cost effective for maintenance treatment of HRD positive patients in India. For patients of BRCAwt, use of single agent bevacizumab was not found to be cost effective when compared to routine surveillance. This was in lines with the evidence from Italy (46), USA (47), and Singapore (12). Our findings on QALY gains associated with the use of olaparib in BRCAm patients aligned with the existing literature (Table S3).

To the best of our knowledge, we could not find any published cost effectiveness analysis for the PARPi rucaparib in the first line maintenance treatment of AOC. This may be because the efficacy of rucaparib in the first line setting was reported recently in the ATHENA-MONO trial (19). However, evaluation of rucaparib is important from the Indian perspective as other than olaparib, rucaparib is the only PARPi available in India. In our study rucaparib was dominated by olaparib for both BRCAm and HRD positive patients as it produced lower QALYs (4.65 and 3.07 for BRCAm and HRD respectively) at higher costs.

The low probability of bevacizumab to be cost effective results from the minimal gain in QALYs (2.65 versus 2.59) when compared with routine surveillance. A previous cost utility analysis on the use of bevacizumab for primary treatment and maintenance of AOC reported an ICER of $632,571/ progression-free year saved (48). Another recent cost effectiveness analysis which found bevacizumab to be not cost effective, reported an ICER of $557,865/ progression-free year saved (13).

With the advent of newer expensive drugs being added in the oncology management every day, it is important to take value-based decisions for incorporation of these into routine clinical care to rationalize the spending in health care (49). Though clinical guidelines continue to recommend maintenance therapy in the primary setting for AOC, it is important to consider the efficiency question before deciding whether to include such a therapy for public financing. Based on our analysis, generic olaparib maintenance treatment should be included in the health benefit package (HBP) under India's publicly funded health insurance program *Ayushman Bharat Pradhan Mantri Jan Aarogya Yojna* (AB-PMJAY).

This molecular profile based personalized cost-effective approach also signifies the need for biomarker testing including BRCAm and HRD status. This testing is expensive in the Indian context and is not funded by any of the available HBPs under PMJAY. This molecular testing for ovarian cancers should be made widely available and accessible, to help in cost effective decision making for maintenance treatment of AOC.

Strengths and Limitations

Firstly, our study analysed different molecular profiles, and multiple available drugs in the Indian context. Secondly, we assessed the cost effectiveness of rucaparib in the first line maintenance treatment which has not been done previously. Thirdly, we have used updated data from all recently published trials to obtain survival benefit. Fourthly, we obtained the cancer-specific OOPE and quality of life estimates from multicentric nationally representative Indian study. Lastly, we comprehensively incorporated the costs of second line, third line and subsequent treatment along with costs of palliative management and best supportive care and used real world cost data to populate our models.

There are certain limitations in our analysis. Firstly, cost of only grade 3-4 adverse effect management was included in the analysis. Secondly, we did not consider the disutility associated with adverse events separately, as QoL data was obtained from the CaDCQoL study where 99% of the AOC patients had already reported having adverse effects. Thirdly, though we used the updated trial data, we had to extrapolate the survival data beyond the follow-up duration of the trial. However, we validated our modelled results with observed epidemiological and clinical studies and found good concordance. Fourthly, due to non-availability of direct comparisons between various PARPi, in various molecular subtypes, cross trail data was used for comparison of efficacy between them. Our short-term and long-term modelled survival outcomes are in close range with the observed reported data from Indian patients. Lastly, since niraparib is not currently available in India, its cost was estimated as per the consultations with the private suppliers. The eventual price may be different depending on volume of sales. However, we significantly varied the price in sensitivity analysis.

Conclusions and Policy Implications

The results of the present study help in the selection of the cost-effective maintenance therapy for patients with AOC after response to first line therapy in the Indian context. Olaparib was found to be a cost-effective therapy for BRCAm patients while none of the analysed PARPi were found to be cost effective for the HRD positive subgroup. A price reduction of 23% may provide a value for money in use of olaparib for HRD positive subgroup. Findings from our study could help both physicians and policy makers in clinical practice, reimbursement policy and drug pricing for this high burden malignancy with expensive management.

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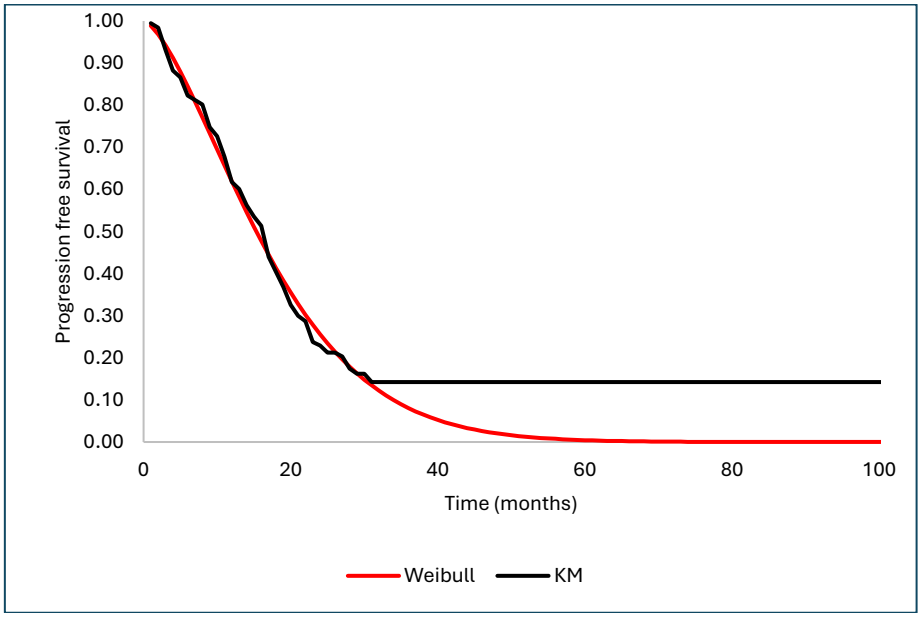
Supplementary Material

Contents

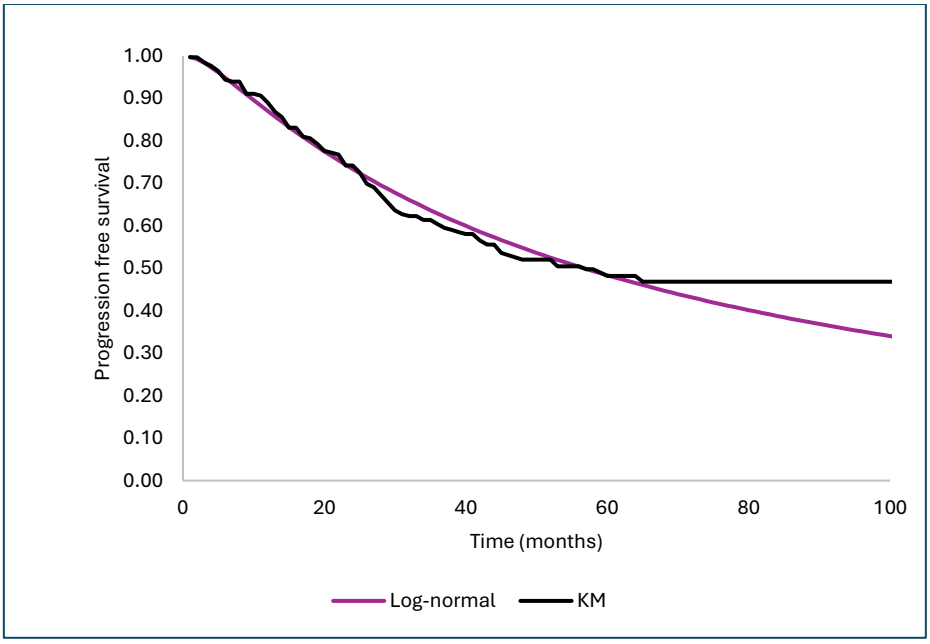
Section A. Reconstructed PFS curves

Figure S1. Bevacizumab (Advanced ovarian cancer without BRCAm)



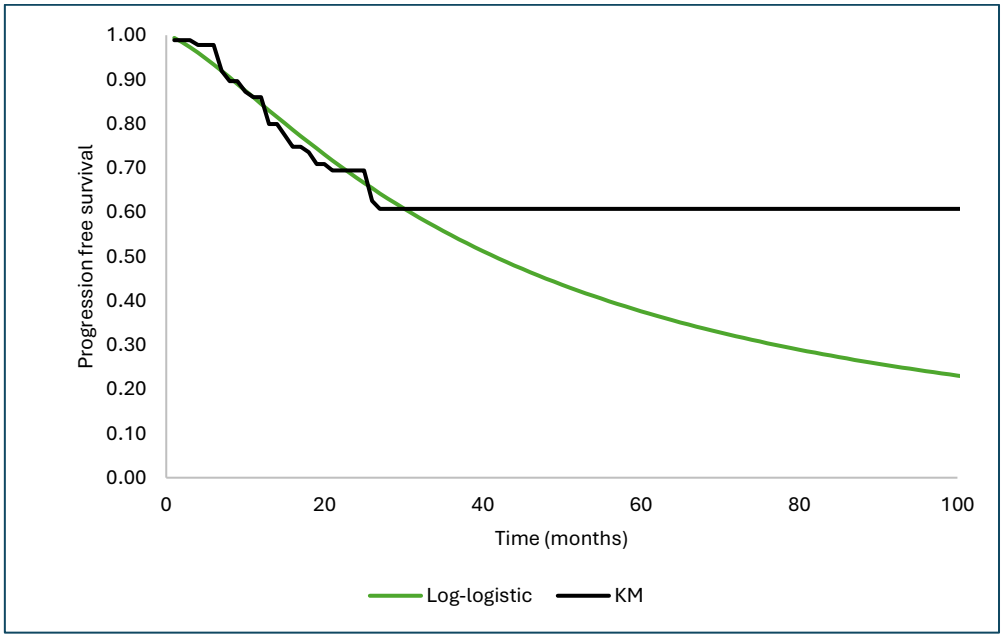
Distribution	AIC	BIC
Exponential	479.9037	483.1455
Weibull	**453.2519**	**459.7354**
Gompertz	460.4865	466.97
Log-normal	468.1199	474.6034
Log-logistic	459.2952	465.7786

Figure S2. Olaparib (BRCAm advanced ovarian cancer)



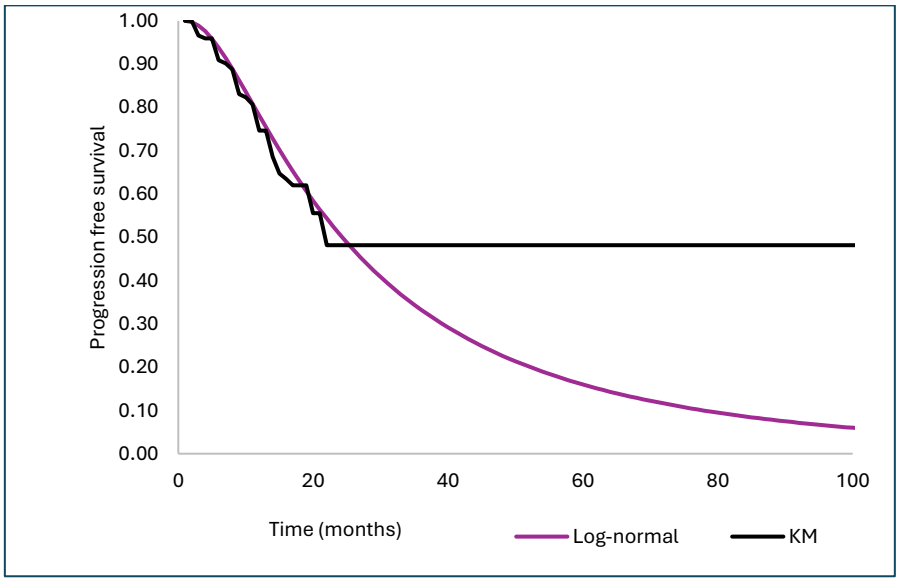
Distribution	AIC	BIC
Exponential	586.897	590.4577
Weibull	588.298	595.4194
Gompertz	587.7015	594.8229
Log-normal	**579.5925**	**586.7139**
Log-logistic	581.2338	588.3551

Figure S3. Rucaparib (BRCAm advanced ovarian cancer)



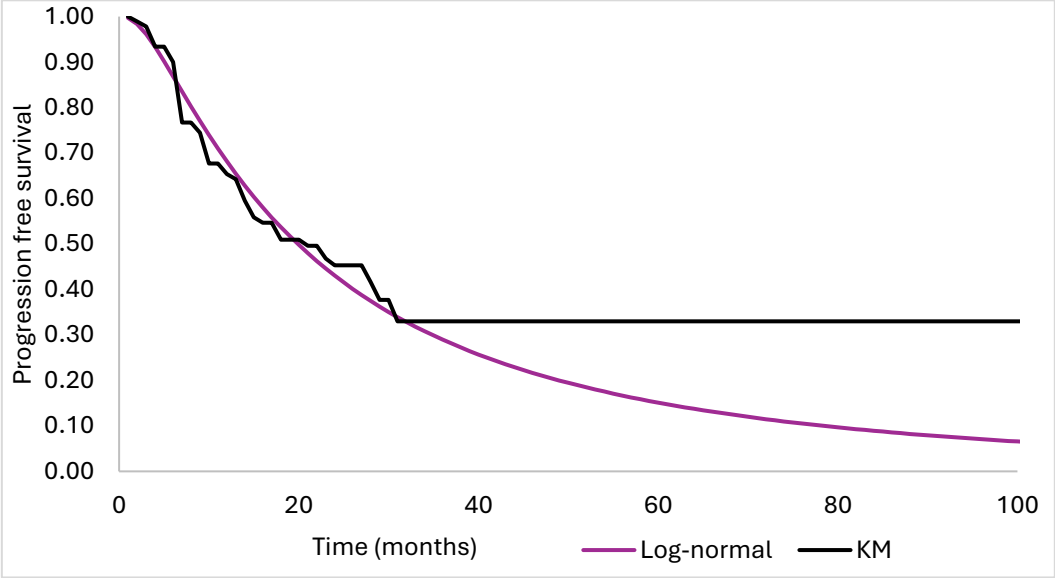
Distribution	AIC	BIC
Exponential	167.6819	170.1928
Weibull	168.5629	173.5846
Gompertz	169.6192	174.6409
Log-normal	169.1216	174.1434
Log-logistic	**167.4546**	**172.4763**

Figure S4. Niraparib (BRCAm advanced ovarian cancer)



Distribution	AIC	BIC
Exponential	227.9193	230.9432
Weibull	214.5932	220.641
Gompertz	221.0165	227.0643
Log-normal	**211.5831**	**217.6308**
Log-logistic	213.0542	219.1019

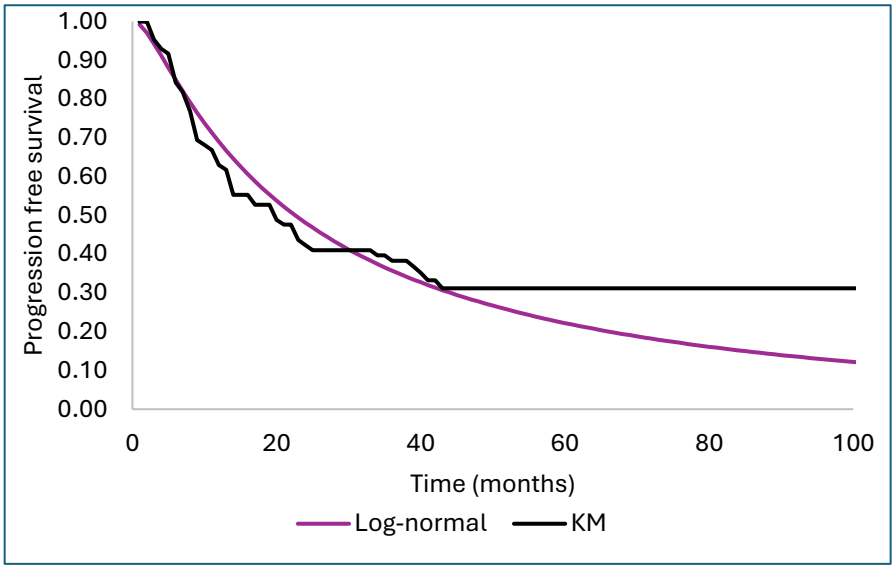
Figure S5. Rucaparib (HRD positive advanced ovarian cancer)



Distribution	AIC	BIC
Exponential	227.0542	229.5975
Weibull	226.349	231.4356
Gompertz	228.9203	234.0069

Log-normal	**218.8351**	**223.9216**
Log-logistic	221.9215	227.0081

Figure S6. Niraparib (HRD positive advanced ovarian cancer)



Distribution	**AIC**	**BIC**
Exponential	338.7175	341.8533
Weibull	339.5305	345.8021
Gompertz	340.7171	346.9887
Log-normal	**335.0171**	**341.2887**
Log-logistic	337.2886	343.5602

Section B. Details of second line, third line, and fourth line treatments

The table S1 provides the details of second-, third-, and fourth-line treatment considered in the model, based on standard treatment guidelines, validated by clinical consultations.

Table S1. Details of second-, third-, and fourth- line treatments

Second Line treatment (Platinum sensitive)	Proportion of patients on different treatment regimens
Injection Paclitaxel@175mg/m^2 + Injection Carboplatin AUC 5 x 3 weekly x 6 cycles	60%
Injection Gemcitabine@ 1gm/m2 D1, D8 + Injection Carboplatin AUC 5 x 3 weekly x 6 cycles	20%
Injection Liposomal doxorubicin @ 30 mg/m2 + Injection Carboplatin AUC 5 x 3 weekly x 6 cycles	20%
Additional Bevacizumab 7.5 mg/ kg (30%) *9 cycles	30%
Second Line treatment (Platinum resistant)	
Injection Docetaxel 75mg/m^2 x 3 weekly x 6 cycles	30%

Injection Gemcitabine 1gm/m^2 D1, D8 x 3 weekly x 6 cycles	30%
Injection Liposomal doxorubicin 40mg/m^2 * 28 days x 6 cycles	30%
Injection Topotecan 1.5mg/m^2 D1-5 x 3 weekly x 6 cycles	10%
Third Line treatment (Both platinum sensitive and resistant)	
Injection Docetaxel 75mg/m^2 x 3 weekly x 6 cycles	5%
Injection Gemcitabine 1gm/m^2 D1, D8, D15 x 3 weekly x 6 cycles	40%
Injection Liposomal doxorubicin 40mg/m^2 x 3 weekly x 6 cycles	40%
Injection Topotecan 1.5mg/m^2 D1-3 x 3 weekly x 6 cycles	10%
Tab Endoxan 50mg OD D1-D21 every 28 days	5%
Fourth Line treatment (Both platinum sensitive and resistant)	
Injection Docetaxel 75mg/m^2 x 3 weekly x 6 cycles	5%
Injection Gemcitabine@ 1gm/m^2 D1, D8, D15 x 3 weekly x 6 cycles	20%
Injection Liposomal doxorubicin 40mg/m^2 x 3 weekly x 6 cycles	20%
Injection Topotecan 1.5mg/m^2 D1-3 x 3 weekly x 6 cycles	40%
Tab Etoposide 50mg OD/Tab Endoxan 50mg OD	15%

It was considered that diagnostic tests (complete blood count, renal function test, liver function test) would be conducted prior to each OPD visit for treatment. Additionally, echocardiography was considered for patients on liposomal doxorubicin. The CA125 test was considered in each alternate cycle of treatment. Furthermore, it was anticipated that 90% of patients would undergo a contrast-enhanced computed tomography (CECT) scan of the abdomen, pelvis, and chest, while 10% would receive a positron emission tomography (PET) scan after three cycles of treatment. Following six cycles, it was expected that 50% of the patients would have a CECT scan of the abdomen, pelvis, and chest, with the remaining 50% undergoing a PET scan. It was assumed that patient follow-up would include quarterly outpatient department (OPD) visits with CA125 testing during the first and second years following the completion of treatment. In the third year, follow-up visits would occur every six months, while from the fourth year onward, patients would attend annual OPD visits for clinical examination.

Section C. Cost-effectiveness plane

Figure S7. Bevacizumab in comparison to routine surveillance in BRCAwt advanced ovarian cancer

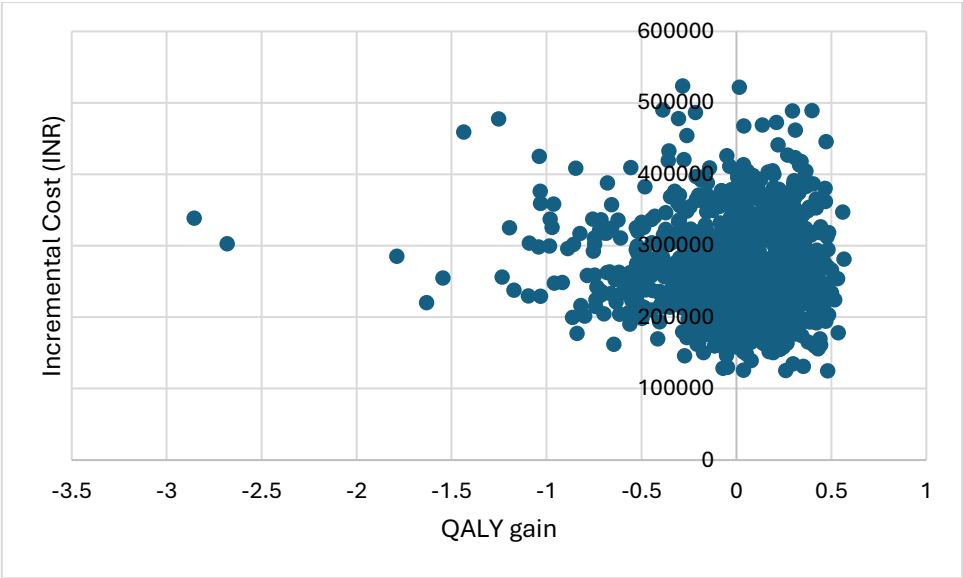


Figure S8. Olaparib in comparison to routine surveillance in BRCAm advanced ovarian cancer

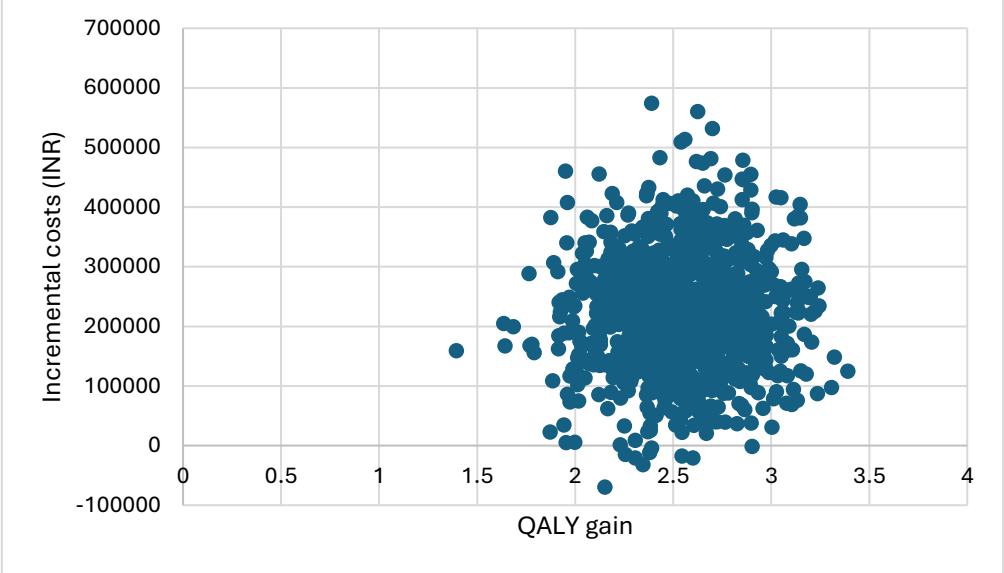
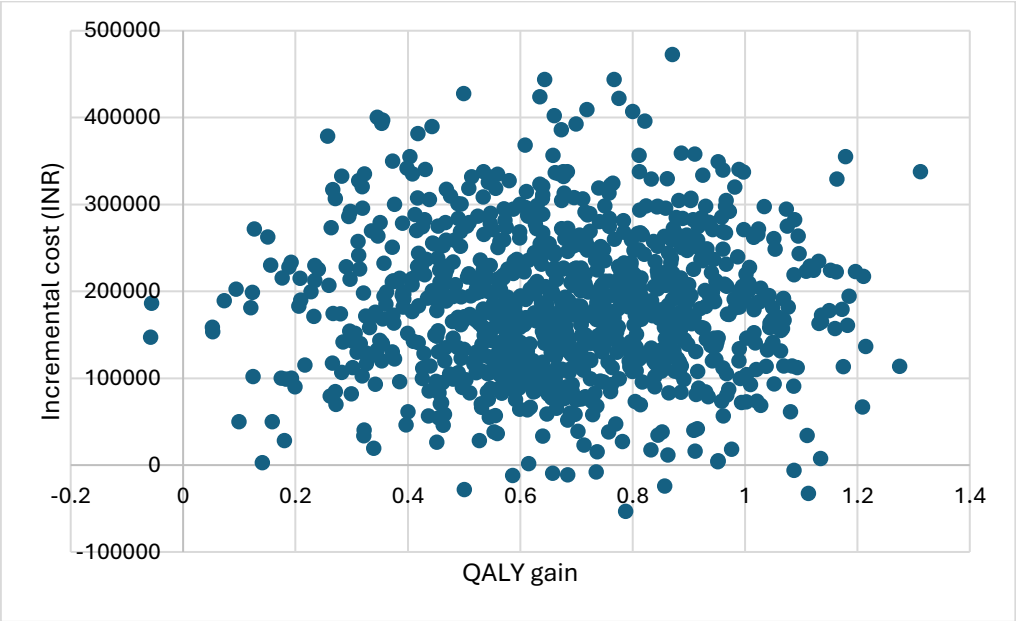
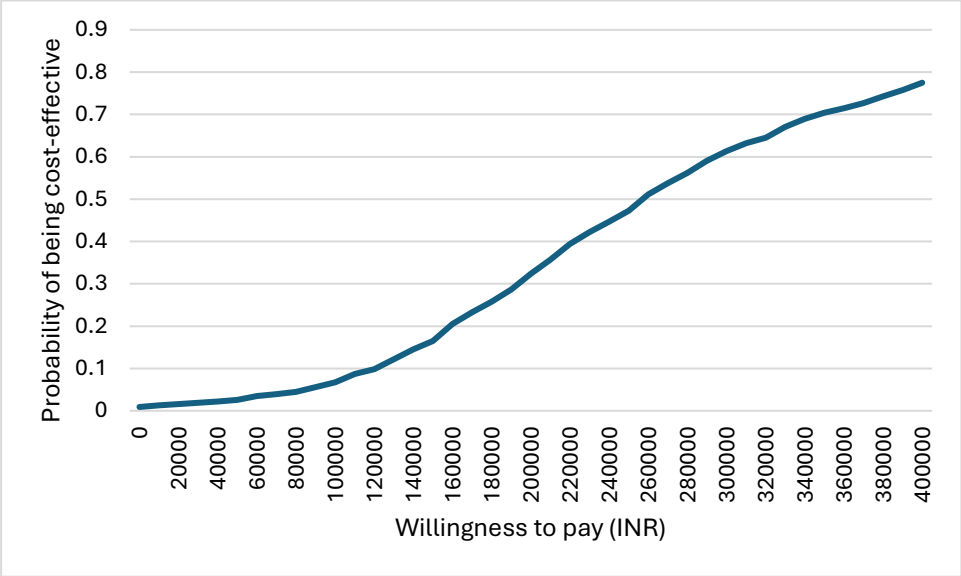


Figure S9. Olaparib in comparison to routine surveillance in HRD positive BRCAwt advanced ovarian cancer



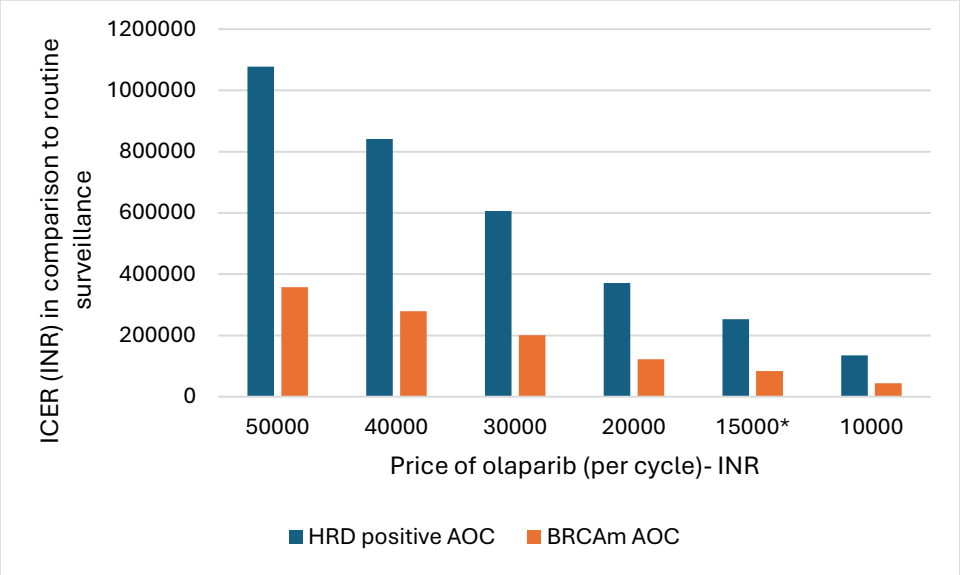
Section D. Cost-effectiveness acceptability curve

Figure S10. Probability of olaparib being cost-effective in HRD positive BRCAwt advanced ovarian cancer patients compared to routine surveillance



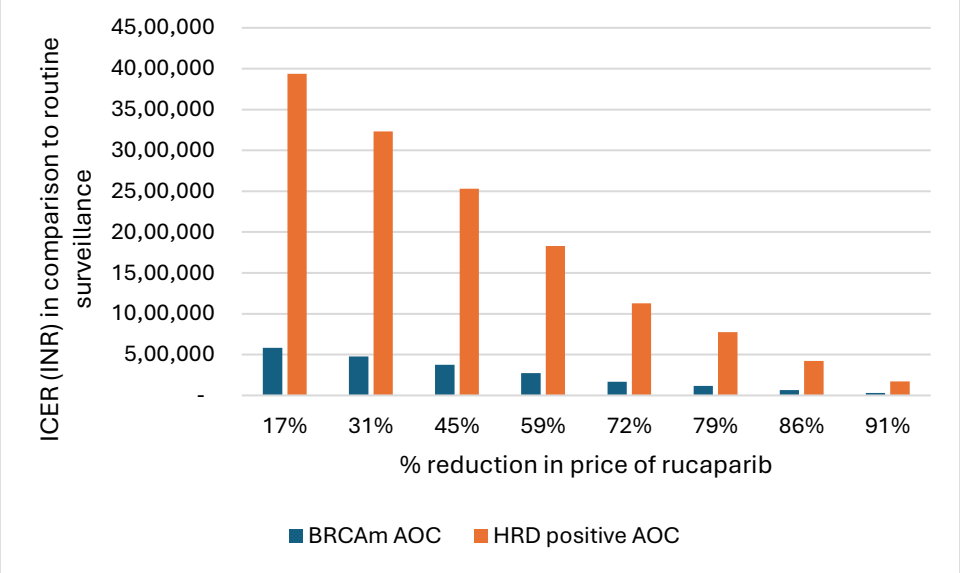
Section E. Price-threshold analysis

Figure S11. Price-threshold analysis for olaparib



*Base case price, WTP: INR 1,71,498

Figure S12. Price-threshold analysis for rucaparib



Section F. Comparison of model derived Progression free survival in different strategies

Figure S13. PFS in treatment arms in BRCAwt advanced ovarian cancer patients

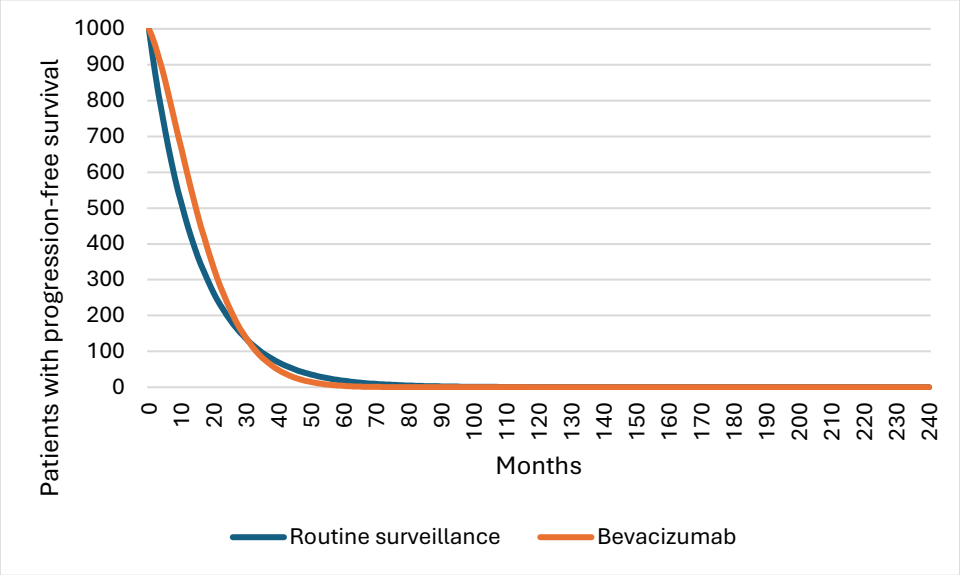


Figure S14. PFS in treatment arms in BRCAm advanced ovarian cancer patients

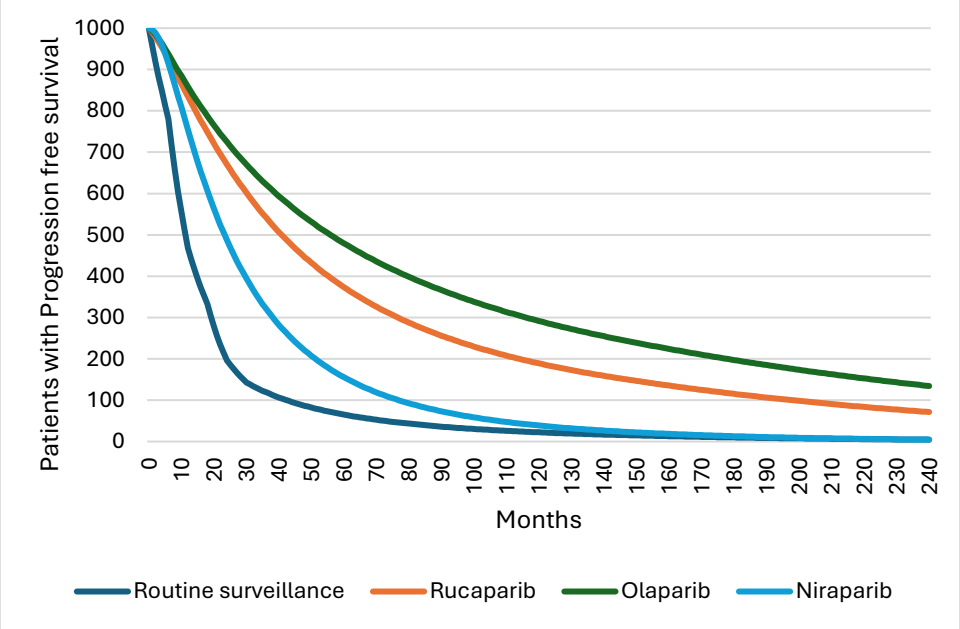
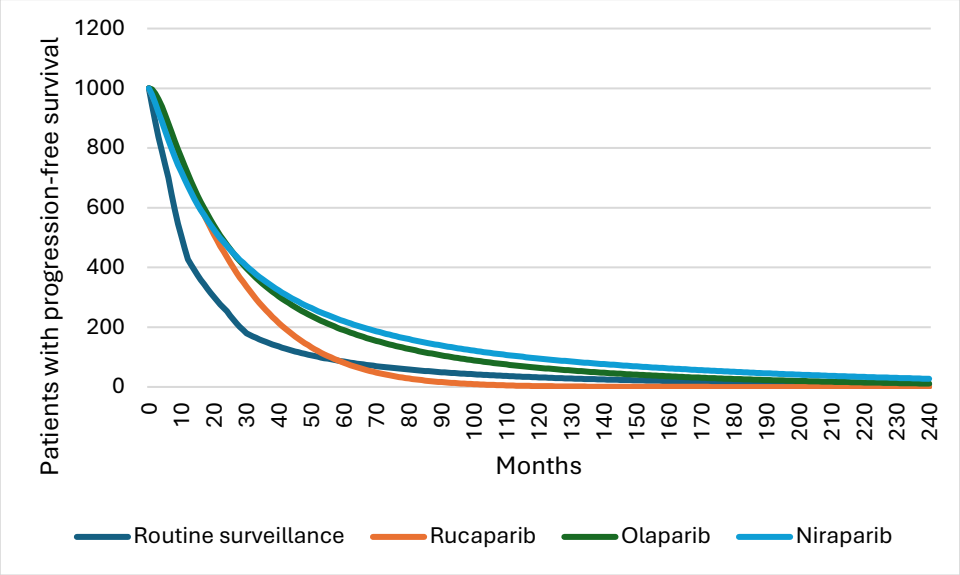


Figure S15. PFS in treatment arms in HRD positive BRCAwt advanced ovarian cancer patients



Section G. Model validation and comparison with published literature

Table S2. Median Progression free survival and overall survival from the present study and published randomized controlled trials

	Median PFS (months)			Median OS (months)		
BRCAwt patients	Model	Studies	Reference	Model	Studies	Reference
Routine surveillance	11	11-17	[1]	41	22.6- 49	[1]
Bevacizumab	15	16	[2]	44		
BRCAm patients						
Routine surveillance	13	13-15	[3,4]	54		
Olaparib	56	56	[3]	95		
Rucaparib	41			80		
Niraparib	24	24.5	[4]	58		
HRD positive patients						
Routine surveillance	11	11	[4,5]	50		
Olaparib	23			59		
Rucaparib	21	20	[5]	54		
Niraparib	22	19.4	[4]	60		

Table S3. Incremental QALYs by use of Olaparib compared to routine surveillance in BRCAm advanced ovarian cancer (Current study versus published cost-effectiveness analysis)

	Incremental QALYs
Current study (India)	2.55
Yong et al (Malaysia) [6]	2.76
Muston et al (USA) [7]	2.93
Tan et al (Singapore) [8]	2.85
Moya- Alarcon et al (Spain) [9]	2.00
Armeni et al (Italy) [10]	2.41

Table S4. CHEERS Checklist

	Item	Guidance for Reporting	Reported in section
TITLE			
Title	1	Identify the study as an economic evaluation and specify the interventions being compared.	Page 1
ABSTRACT			
Abstract	2	Provide a structured summary that highlights context, key methods, results and alternative analyses.	Page 1
INTRODUCTION			
Background and objectives	3	Give the context for the study, the study question and its practical relevance for decision making in policy or practice.	Page 2, 3
METHODS			
Health economic analysis plan	4	Indicate whether a health economic analysis plan was developed and where available.	
Study population	5	Describe characteristics of the study population (such as age range, demographics, socioeconomic, or clinical characteristics).	Page 3,4
Setting and location	6	Provide relevant contextual information that may influence findings.	Page 3,4
Comparators	7	Describe the interventions or strategies being compared and why chosen.	Page 2,3
Perspective	8	State the perspective(s) adopted by the study and why chosen.	Page 4
Time horizon	9	State the time horizon for the study and why appropriate.	Page 4
Discount rate	10	Report the discount rate(s) and reason chosen.	Page 4
Selection of outcomes	11	Describe what outcomes were used as the measure(s) of benefit(s) and harm(s).	Page 7
Measurement of outcomes	12	Describe how outcomes used to capture benefit(s) and harm(s) were measured.	Page 5-7

Valuation of outcomes	13	Describe the population and methods used to measure and value outcomes.	Page 5-7
Measurement and valuation of resources and costs	14	Describe how costs were valued.	Page 8-10
Currency, price date, and conversion	15	Report the dates of the estimated resource quantities and unit costs, plus the currency and year of conversion.	Page 8
Rationale and description of model	16	If modelling is used, describe in detail and why used. Report if the model is publicly available and where it can be accessed.	
Analytics and assumptions	17	Describe any methods for analysing or statistically transforming data, any extrapolation methods, and approaches for validating any model used.	Page 5,6, 16
Characterizing heterogeneity	18	Describe any methods used for estimating how the results of the study vary for sub-groups.	
Characterizing distributional effects	19	Describe how impacts are distributed across different individuals or adjustments made to reflect priority populations.	
Characterizing uncertainty	20	Describe methods to characterize any sources of uncertainty in the analysis.	
Approach to engagement with patients and others affected by the study	21	Describe any approaches to engage patients or service recipients, the general public, communities, or stakeholders (e.g., clinicians or payers) in the design of the study.	
RESULTS			
Study parameters	22	Report all analytic inputs (e.g., values, ranges, references) including uncertainty or distributional assumptions.	Page 7,9,10
Summary of main results	23	Report the mean values for the main categories of costs and outcomes of interest and summarise them in the most appropriate overall measure.	Page 11,12
Effect of uncertainty	24	Describe how uncertainty about analytic judgments, inputs, or projections affect findings. Report the effect of choice of discount rate and time horizon, if applicable.	
Effect of engagement with patients and others affected by the study	25	Report on any difference patient/service recipient, general public, community, or stakeholder involvement made to the approach or findings of the study	
DISCUSSION			
Study findings, limitations, generalizability, and current knowledge	26	Report key findings, limitations, ethical or equity considerations not captured, and how these could impact patients, policy, or practice.	Page 14-16
OTHER RELEVANT INFORMATION			
Source of funding	27	Describe how the study was funded and any role of	Page 11

		the funder in the identification, design, conduct, and reporting of the analysis	
Conflicts of interest	28	Report authors conflicts of interest according to journal or International Committee of Medical Journal Editors requirements.	

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