Olaparib for maintenance treatment of *BRCA* 1 or 2 mutated, relapsed, platinum-sensitive ovarian, fallopian tube and peritoneal cancer in people whose relapsed disease has responded to platinum-based chemotherapy: A Single Technology Appraisal.

ERG addendum – analysis of olaparib PAS

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7th April 2015

Introduction

The original company's submission (CS) to NICE[1] included a Patient Access Scheme (PAS) submission[2] and a version of the company's model which incorporates the proposed PAS. At the time of writing the main ERG report,[3] this proposed PAS had not been signed off by the Department of Health and was therefore not considered by the ERG. The proposed PAS was later signed off by the Department of Health on the 26th March 2015. This addendum presents a re-analysis of the company's model which includes the PAS for olaparib. Issues surrounding the implementation of the PAS, beyond those which are directly relevant to the company's economic analysis, are not considered within this addendum.

Description of company's PAS submission

The company's PAS submission for olaparib[2] includes details of the nature of the PAS, issues around implementation and a re-analysis of the company's health economic model taking into account the PAS. The olaparib PAS is a "complex scheme" as defined by the PPRS. Under the olaparib PAS, the cost of olaparib for people who remain on treatment for more than [redacted] months will be met by the company.[2]

In line with the company's main submission,[1] the PAS submission includes the results of two economic evaluations which include the olaparib PAS:

- The base case economic evaluation of olaparib maintenance treatment versus routine surveillance in patients with *BRCAm* PSR ovarian cancer. This analysis excludes the costs of *BRCA* mutation testing and considers costs and benefits relating to the index *BRCAm* ovarian cancer patient only.
- A broader economic evaluation that also accounts for: (a) the costs of *BRCA* mutation testing in PSR ovarian cancer patients, and; (b) the costs and benefits of expanding *BRCA* mutation testing to family members of relapsed *BRCAm* ovarian cancer patients undergoing *BRCA* mutation testing as a prerequisite in consideration of olaparib as a potential treatment option. This analysis considers costs and benefits relating to the index *BRCAm* ovarian cancer patient and family members.

Implementation of the PAS within the company's model

The application of the PAS within the company's model is straightforward.

1. Beyond the PAS cut-off timepoint ([redacted] monthly cycles of treatment), the cost of olaparib maintenance therapy is set equal to zero.
2. A once-only per patient PAS implementation cost is applied (£68 per patient).
3. A monthly per patient PAS administration cost is applied (£68 per patient).

The assumptions underpinning the PAS implementation and administration costs are summarised in Table 1.

Table 1: Olaparib PAS implementation and operational costs (adapted from PAS submission[2])

Activity	NHS Staff Grade	Number of staff	Time per activity (mins)	Cost per hour	Cost per activity
1. Implementation of the PAS					
Pharmacy system set-up	6	1	15	£67	£17
Staff training - pharmacist	6	2	15	£67	£34
Patient registration	6	1	15	£67	£17
2. Administration of the PAS					
General scheme management (per ordering cycle)	6	1	15	£67	£17
Processing supplies – pharmacy staff	6	1	15	£67	£17
Financial and patient reconciliation	6	1	30	£67	£34
Total implementation costs per patient (first month only)					**£68**
Total administration costs per patient (per month)					**£68**

PAS – patient access scheme; mins - minutes

Company's results including the olaparib PAS

Central estimates of cost-effectiveness (including PAS)

Table 2 presents the company's base case cost-effectiveness results taking into account the PAS for olaparib.

Table 2: Company's base case results including the PAS for olaparib

Central estimates of cost-effectiveness (point estimates of parameters)							
Option	LYGs	QALYs	Costs	LYGs	Inc. QALYs	Inc. costs	ICER
Olaparib	3.55	2.58	£54,240.77	1.17	0.89	£44,343.16	**£49,826**
Routine surveillance	2.38	1.69	£9,897.60				
Central estimates of cost-effectiveness (expectation of the mean)							
Option	LYGs	QALYs	Costs	LYGs*	Inc. QALYs	Inc. costs	ICER
Olaparib	NR	NR	NR	NR	NR	NR	**£49,146**
Routine surveillance	NR	NR	NR	-	-	-	-

Inc. – incremental; LYG – life year gained; QALY – quality-adjusted life year; ICER – incremental cost-effectiveness ratio; NR – not reported

Based on the probabilistic version of the model, the ICER for olaparib versus routine surveillance is expected to be £49,146 per QALY gained. Estimates of costs and QALYs for each group generated using the probabilistic version of the model were not presented within the PAS submission.[2] The

deterministic version of the model, based on point estimates of parameters, produces a similar ICER for olaparib versus routine surveillance of £49,826 per QALY gained. Within this deterministic analysis, the QALY gain remains the same as the company's original base case analysis.

Company's uncertainty analysis results including the PAS for olaparib

Probabilistic sensitivity analysis (including PAS)

Figures 1 and 2 present a cost-effectiveness plane and a cost-effectiveness acceptability curve (CEAC) for olaparib versus routine surveillance, taking into account the PAS.

Figure 1: Cost-effectiveness plane for olaparib versus routine surveillance (reproduced from PAS submission[2])

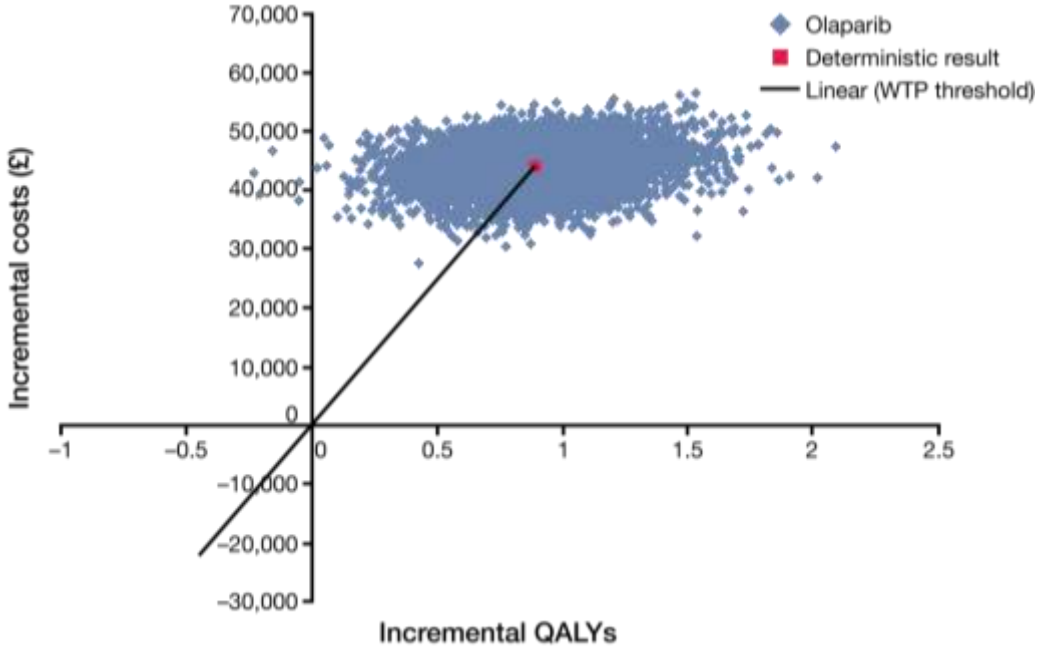
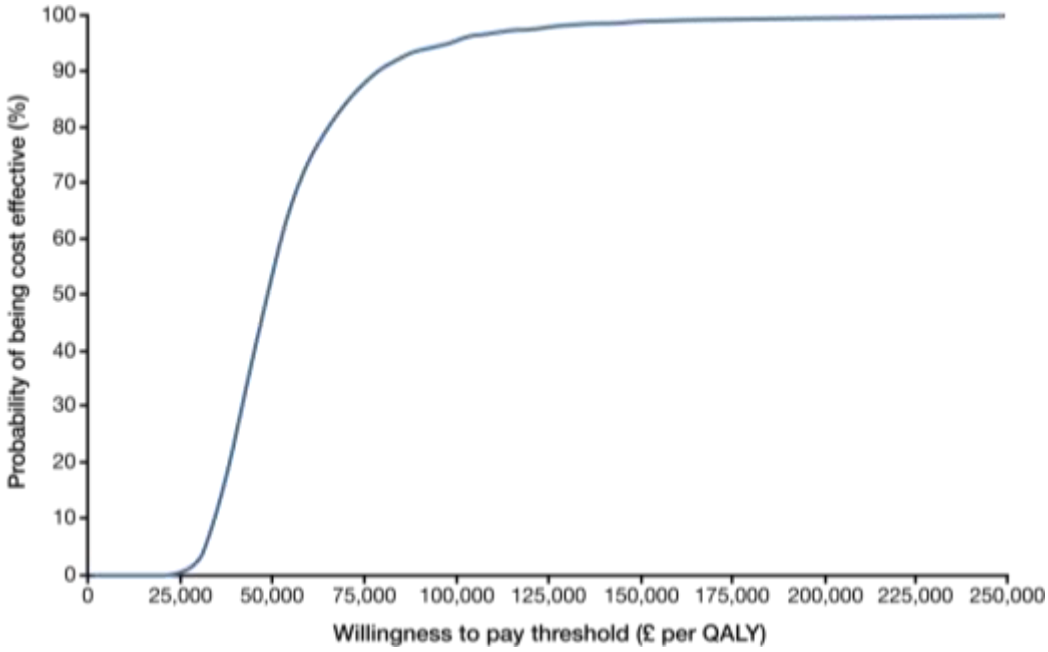


Figure 2: Cost-effectiveness acceptability curve for olaparib versus routine surveillance (reproduced from PAS submission[2])

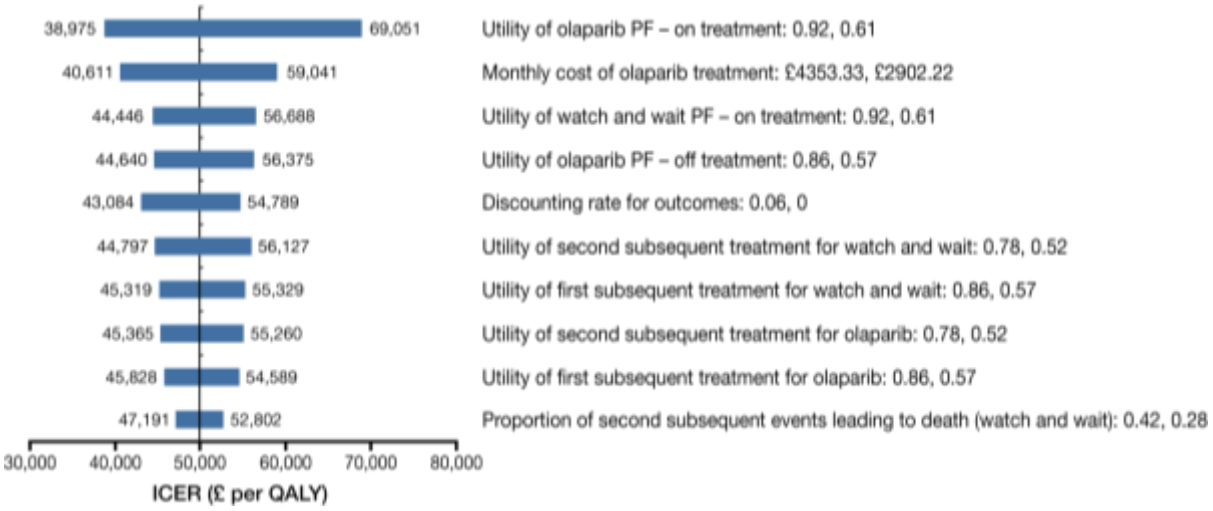


Assuming a willingness-to-pay threshold of £20,000 per QALY gained, the probability that olaparib produces more net benefit than routine surveillance is approximately zero. Assuming a willingness to pay threshold of £30,000 per QALY gained, the probability that olaparib produces more net benefit than routine surveillance is approximately 0.02. Assuming a willingness to pay threshold of £50,000 per QALY gained, the probability that olaparib produces more net benefit than routine surveillance is approximately 0.52.

Company's 1-way sensitivity analysis results (including PAS)

Figure 3 presents the company's one-way sensitivity analysis results.

Figure 3: One-way sensitivity analysis results (+/-20% deterministic mean, reproduced from PAS submission[2])



This analysis suggests that the utility values for patients receiving olaparib and routine surveillance, the monthly cost of olaparib treatment, the discount rate for health outcomes and the proportion of second subsequent events which are deaths are the most influential parameters within the model. The lowest ICER reported within the company's one-way sensitivity analysis is £38,975 per QALY gained (utility for olaparib, progression-free [on maintenance therapy] state =0.92); the highest ICER reported within the company's one-way sensitivity analysis is £69,051 per QALY gained (utility for olaparib, progression-free [on maintenance therapy] state =0.61).

Company's scenario analysis results (including PAS)

Table 3 presents the company's scenario analysis including the PAS for olaparib.

Table 3: Company's scenario analysis results (adapted from PAS submission[2])

Scenario	Olaparib		Routine surveillance		Incremental		
	QALYs	Costs	QALYs	Costs	Incremental QALYs	Incremental costs	ICER
Base case	2.58	£54,241	1.69	£9,898	0.89	£44,343	£49,826
TFST/D – PARPi adjusted, generalised gamma	2.65	£54,364	1.86	£10,320	0.79	£44,044	£55,892
TFST/D – trial-based, log normal	2.58	£54,241	1.94	£10,212	0.64	£44,029	£68,812
TFST/D – trial-based, generalised gamma	2.65	£54,364	2.11	£10,631	0.54	£43,734	£80,715
BRCA mutation population regression analysis	2.56	£54,241	1.69	£9,898	0.87	£44,343	£51,015
ITT population regression	2.56	£54,241	1.69	£9,898	0.88	£44,343	£50,602
Mean EQ-5D *BRCA* subpopulation	2.58	£54,241	1.69	£9,898	0.89	£44,343	£49,981
Costs of *BRCA* mutation testing included	2.58	£57,145	1.69	£9,898	0.89	£47,247	£53,089
Time horizon = 3 years	1.77	£49,839	1.46	£8,348	0.3	£41,491	£136,253
Time horizon = 5 years	2.22	£52,376	1.64	£9,582	0.58	£42,794	£73,361
Time horizon = 10 years	2.52	£53,946	1.69	£9,876	0.83	£44,069	£52,875

The company's scenario analysis suggests that the choice of survivor function for the first subsequent event has the propensity to substantially increase the ICER for olaparib versus routine surveillance. The use of the trial-based generalised gamma distribution increases the base case ICER from £49,826 per QALY gained to £80,715 per QALY gained. The choice of regression equation used in the mapping from the FACT-O to the EQ-5D does not substantially impact upon the ICER for olaparib versus routine surveillance; using alternative equations produces a range of ICERs from £49,826 per QALY gained to £51,015 per QALY gained. Including the cost of *BRCA* mutation testing increases the costs of olaparib by approximately £2,900, thereby leading to an ICER for olaparib versus routine surveillance of £53,089 per QALY gained. The use of a shorter time horizon increases the ICER for olaparib substantially. As noted in the main ERG report,[3] all of the ICERs presented in the company's scenario analyses are higher than the ICER produced using the company's base case scenario.

Company's analysis of the cost-effectiveness of olaparib which includes the wider costs and benefits of BRCA mutation testing for unaffected relatives (including PAS)

Table 4 summarises the results of the company's secondary analysis of the cost-effectiveness of olaparib plus the wider costs and benefits of *BRCAm* testing for unaffected relatives versus routine surveillance (without *BRCAm* testing for relatives). Within this analysis, the results for each family pedigree are equally weighted.

Table 4: Results of the company's secondary analysis of the cost-effectiveness of olaparib which includes the costs and benefits of *BRCA* mutation testing for unaffected relatives (adapted from PAS submission[2])

Pedigree	Unaffected relatives		Index case: Olaparib (vs 'watch and wait') *BRCA* mutation test costs excluded		Combined results (index case plus unaffected relatives)		
	Inc. costs	Inc. QALYs	Inc. costs	Inc. QALYs	Inc. costs	Inc. QALYs	Incremental cost per QALY gained
Pedigree 1	£52,047	1.263	£44,343	0.89	£50,506	1.19	£41,216
Pedigree 2	£51,313	1.552	£44,343	0.89	£49,919	1.42	£33,069
Pedigree 3	£51,684	1.487	£44,343	0.89	£50,216	1.37	£34,764
Pedigree 4	£51,682	1.239	£44,343	0.89	£50,214	1.17	£41,716
Pedigree 5	£51,177	1.312	£44,343	0.89	£49,810	1.23	£39,019
Average ICER across all 5 pedigrees							**£39,343**

Inc. – incremental; BRCA – Breast cancer susceptibility gene; QALY – quality-adjusted life year; ICER – incremental cost-effectiveness ratio

The results of the company's secondary analysis suggest that taking into account the wider benefits and costs of *BRCA* mutation testing improves the ICER for olaparib versus routine surveillance. Across the five individual pedigrees, the ICER for olaparib versus routine surveillance ranges from

£33,069 per QALY gained to £41,716 per QALY gained. Based on these five pedigrees, the company presents an average deterministic ICER for olaparib versus routine surveillance of £39,343 per QALY gained.

Additional work undertaken by the ERG

Verification of the application of the PAS within the company's model

The ERG confirms that the PAS has been implemented appropriately within the company's model. The ERG was able to reproduce the company's base case ICER, 1-way sensitivity analyses, scenario analyses and probabilistic sensitivity analyses using the PAS version of the company's model.

Additional exploratory and sensitivity analysis undertaken by the ERG

ERG-corrected base case using the company's model

Within the main ERG report, the ERG noted two apparent errors within the company's model.

1. *Risk of death.* Within the worksheet "Parameter data store", the model contains calculations of the proportion of first subsequent therapy events which were deaths. Cell C191 suggests that 2/52 (3.85%) first subsequent therapy events in the placebo group were deaths. However, according to Table 7.4 of the CS[1] the denominator should be 54, thereby suggesting a slightly lower probability of 3.70%.
2. *Frequency of follow-up visits for routine surveillance.* The original CS states *"Current UK follow up of patients on 'watch and wait' would be anticipated to be 3-monthly follow-up appointments, with blood tests to monitor the same parameters. It is therefore anticipated that an additional two appointments and blood tests will be required per quarter for patients on olaparib."* However, the model actually assumes that patients on routine surveillance in the progression-free state undergo monthly appointments.

In addition, the company's base case analysis did not include the costs of *BRCA* testing.

Table 5 presents revised estimates of the company's base case ICER incorporating the corrections to errors identified by the ERG and including the cost of *BRCA* mutation testing and the olaparib PAS.

Table 5: ERG-corrected base case ICER using the company's model (including PAS)

Central estimates of cost-effectiveness (expectation of the mean)							
Option	**LYGs***	**QALYs**	**Costs†**	**Inc. LYGs***	**Inc. QALYs**	**Inc. Costs**	**ICER**
Olaparib	-	2.61	£57,096	-	0.90	£48,299	**£53,374**
Routine surveillance	-	1.70	£8,796	-	-	-	-
Central estimates of cost-effectiveness (point estimates of parameters)							
Option	**LYGs**	**QALYs**	**Costs**	**Inc. LYGs**	**Inc. QALYs**	**Inc. Costs**	**ICER**
Olaparib	3.55	2.58	£57,145	1.17	0.89	£48,254	**£54,306**
Routine surveillance	2.38	1.69	£8,891	-	-	-	-

** life years gained are not reported as they are not recorded within the company's PSA sub-routine*
† Cost of BRCA mutation testing manually included in total expected cost of olaparib

Taking into account the ERG's corrections to the company's model, together with the PAS for olaparib, the probabilistic ICER for olaparib versus routine surveillance is estimated to be £53,374 per QALY gained. The analysis based on point estimates of parameters yields a similar ICER for olaparib versus routine surveillance of £54,306 per QALY gained.

Implied ICERs using ERG's partitioned survival model

As discussed in the main ERG report,[3] there appears to be a discrepancy between what was is being predicted by the company's model and what was observed within Study 19 (refer to ERG report[3] Section 5.3). Consequently, the ERG does not have confidence in the overall survival gains, or consequently, the QALY benefits, predicted for olaparib within the company's model. In order to examine the uncertainty around the expected survival benefits of olaparib, the ERG developed a partitioned survival model to estimate the range of potential QALY gains for olaparib versus routine surveillance taking account of the potential impact of placebo group crossover within Study 19. The results of this analysis were presented within Table 66 of the main ERG report.[3] This analysis suggested that the greatest discounted incremental QALY gain achievable using the ERG's model is approximately 0.52 QALYs. This scenario is based on the generalised gamma distribution for time to treatment discontinuation or death (TTD/D), the log normal distribution for time to first subsequent therapy or death (TFST/D) and the log normal distribution applied to the crossover site excluded (CSE) overall survival (OS) dataset. The most favourable incremental QALY estimate generated by the ERG's model is considerably lower than that produced by the company's model (ERG's model = 0.52 QALYs versus company's model = 0.90 QALYs). Given that the incremental cost for olaparib versus routine surveillance is almost entirely comprised of the additional acquisition costs associated with olaparib, applying the ERG-corrected base case incremental costs of £48,299 to the ERG's most optimistic incremental QALY gain for olaparib indicates that the ICER for olaparib versus routine surveillance is likely to be in excess of £92,214 per QALY gained, but may be considerably higher.

The ERG sought the views of three clinical experts (also authors of the ERG report) regarding their views on which of the extrapolated curves may be considered most plausible. The clinical advisors' preferences are summarised in Table 68 of the main ERG report and are reproduced in Table 6 below.

Table 6: Clinical advisors' preferred extrapolated curves

Respondent	Outcome	Preferred curve (s)	Reason given
Clinical advisor 1	TTD/D	Generalised gamma	*"Curves follow the data most accurately. Curves most clinically believable."*
	TFST/D	Generalised gamma	*"Curves represent an accurate overview of the individual data set (same number of "points" above and below the curves). Most clinically plausible."*
	RPSFTM-adjusted OS	Gamma	*"Most clinically "sensible", Closest representation of KM data. Extrapolation most believable."*
	CSE-adjusted OS	Gamma	*"Most feasible clinically. Curves follow data most accurately. Extrapolation most believable."*
Clinical advisor 2	TTD/D	Generalised gamma	*"Best fit with Kaplan-Meier, projected outcomes after 40 months look reasonable."*
	TFST/D	Generalised F	*"Best fit with Kaplan-Meier, projected outcomes after 40 months look reasonable.*
	RPSFTM-adjusted OS	Gamma	*"Best fit with Kaplan-Meier, projected outcomes after 40 months look reasonable. Doesn't produce an unlikely cross over between treatment arms."*
	CSE-adjusted OS	Gamma	*"Best fit with Kaplan-Meier, projected outcomes after 40 months look reasonable. Doesn't produce an unlikely cross over between treatment arms."*
Clinical advisor 3	TTD/D	Generalised gamma	*"Generalised f has an odd step, the others control drop to zero too quickly"*
	TFST/D	Generalised F	*"Looks to fit data better"*
	RPSFTM-adjusted OS	Log normal or generalised gamma	*"Very difficult as data curves so similar – log normal or generalised gamma looks better!"*
	CSE-adjusted OS	Gamma, log normal or log logistic	*"Even more difficult – coarser data similar curves. More realistic looking esp. time to reach near zero and fit to data."*

TTD/D - time to treatment discontinuation or death; TFST/D - time to first subsequent therapy or death; OS – overall survival; RPSFTM – rank preserving structural failure time model; CSE – crossover site excluded

Using the crossover-site excluded OS data, the first clinical advisor's preferred survival curves imply an incremental gain of 0.40 QALYs for olaparib versus routine surveillance. Assuming incremental costs of £48,299 for olaparib versus routine surveillance, this implies an ICER of £121,591 per QALY gained. Using the RPSFTM-adjusted OS data, the first clinical advisor's preferred survival curves imply an incremental gain of 0.28 QALYs for olaparib versus routine surveillance. Assuming incremental costs of £48,299 for olaparib versus routine surveillance, this implies an ICER of £171,176 per QALY gained.

Using the crossover-site excluded OS data, the second clinical advisor's preferred survival curves imply an incremental gain of 0.37 QALYs for olaparib versus routine surveillance. Assuming incremental costs of £48,299 for olaparib versus routine surveillance, this implies an ICER of £131,557 per QALY gained. Using the RPSFTM-adjusted OS data, the second clinical advisor's preferred survival curves imply an incremental gain of 0.25 QALYs for olaparib versus routine surveillance. Assuming incremental costs of £48,299 for olaparib versus routine surveillance, this implies an ICER of £190,973 per QALY gained.

The third clinical advisor's views were more tentative and did not indicate a single preferred curve for OS adjusted using either crossover method. This advisor stated a preference for the log normal and generalised gamma functions for the RPSFTM-adjusted OS data, and the gamma, log normal or log logistic functions for the crossover site excluded OS data. The resulting QALY gains implied by the clinical advisor's preferred survival functions range from -0.22 QALYs (RPSFTM-adjusted generalised gamma OS curve, olaparib dominated by routine surveillance) to 0.38 QALYs (CSE-adjusted log-logistic OS curve, implied ICER = £126,477 per QALY gained for olaparib versus routine surveillance).

References

(1) AstraZeneca UK Ltd. Olaparib as a monotherapy for the maintenance treatment of adult patients with platinum-sensitive relapsed (PSR) *BRCA*-mutated (germline and/or somatic) high-grade, serous epithelial ovarian, fallopian tube or primary peritoneal cancer who are in response (complete response or partial response) to platinum-based chemotherapy. Single Technology Appraisal. Company's submission to the National Institute for Health and Care Excellence. *AstraZeneca: Luton, UK* 2015.

(2) AstraZeneca Ltd UK. Olaparib as a monotherapy for the maintenance treatment of adult patients with platinum-sensitive relapsed (PSR) *BRCA*-mutated (germline and/or somatic) high-grade, serous epithelial ovarian, fallopian tube or primary peritoneal cancer who are in response (complete response or partial response) to platinum-based chemotherapy. Single Technology Appraisal. Patient Access Scheme submission. *AstraZeneca, Luton, UK* 2015.

(3) Tappenden P, Harnan S, Ren S, Thokala P, Wong R, Mukuria C et al. Olaparib for maintenance treatment of *BRCA* 1 or 2 mutated, relapsed, platinum-sensitive ovarian, fallopian tube and peritoneal cancer in people whose relapsed disease has responded to platinum-based chemotherapy: A Single Technology Appraisal. 2015. School of Health and Related Resarch.