PHARMACOECONOMICS

First-Line Nivolumab Plus Ipilimumab with Chemotherapy for Advanced Non-Small-Cell Lung Cancer： A United States-Based Cost-effectiveness Analysis

Running Head: Cost-effectiveness NIC in NSCLC.

Youwen Zhu [1], Kun Liu [1], Libo Peng[2#]

corresponding author

Affiliations of authors:

1. Department of Oncology, Xiangya Hospital, Central South University, Changsha, Hunan 410008, China

2. Department of Oncology, The Central Hospital of Loudi, the University of South China, Loudi, Hunan 417000, China.

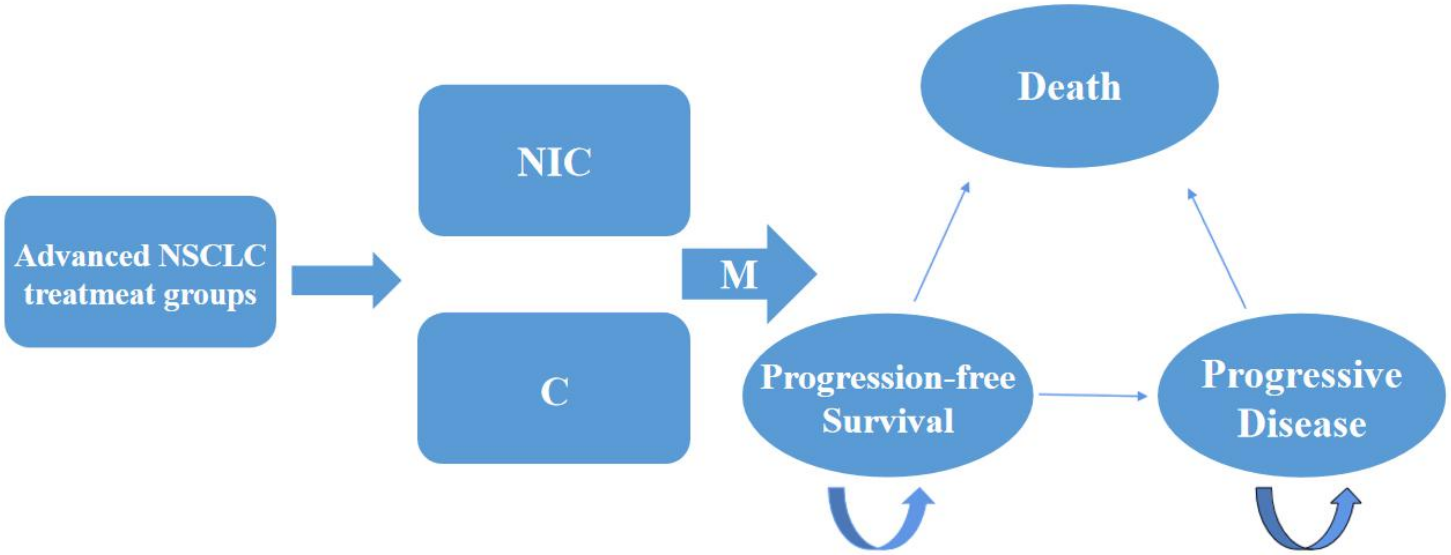
 # Correspondence to:

Libo Peng: Department of Oncology, The Central Hospital of Loudi Affiliated to the University of South China, Loudi, Hunan 417000, China.

E-mail: libopenghn@163.com

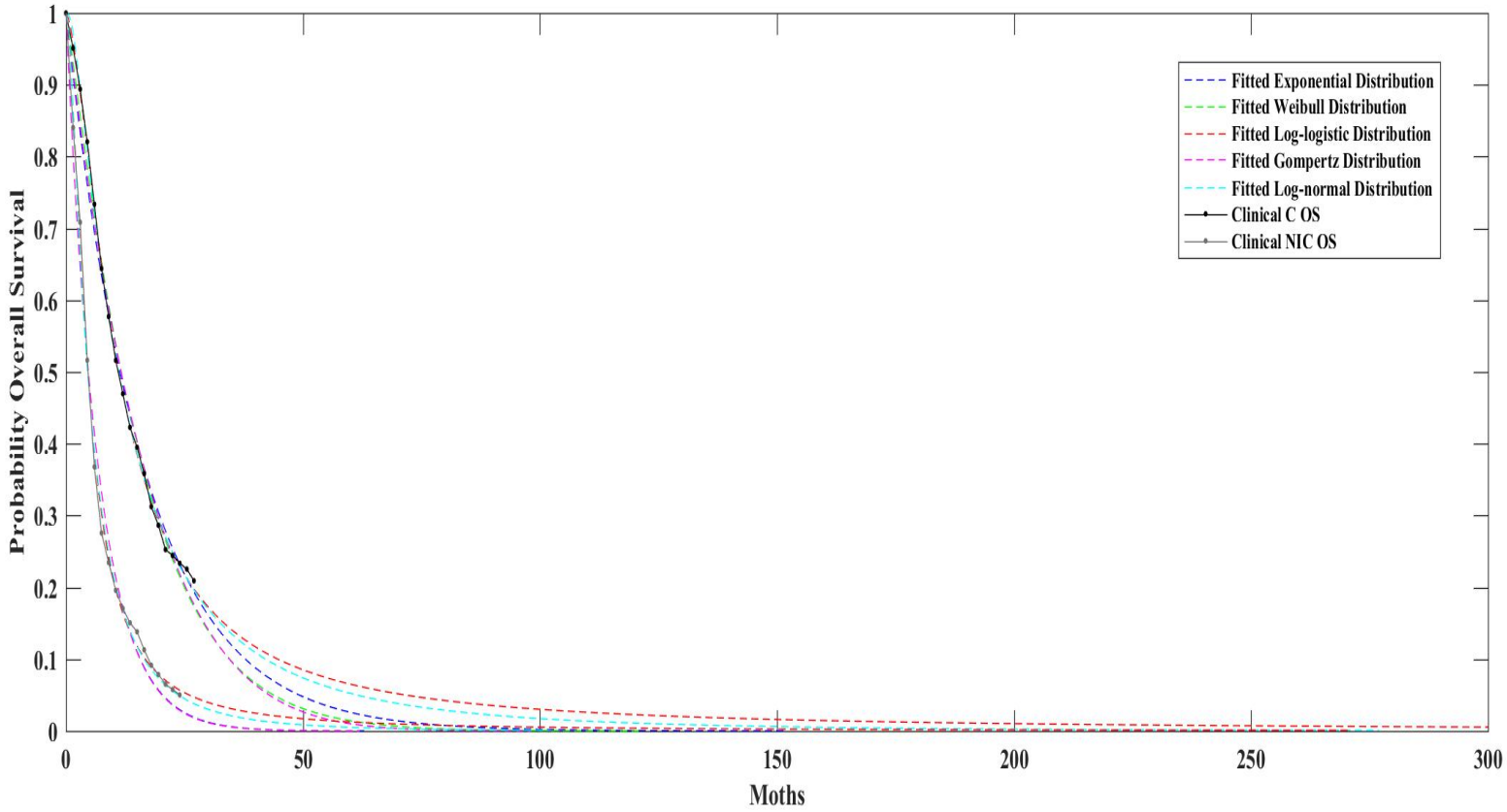
Supplementary Fig. 1. Markov states.
Supplementary Fig. 2. Kaplan-Meier curve fitting and extrapolation.
Supplementary Fig. 3. Probability sensitivity analysis scatter plot.
Supplementary Table 1. Drug dose and costs.
Supplementary Table 2. Results of subgroup analyses.
Supplementary Table 3. Summary of statistical goodness-of-fit of K-M curve in CheckMate 9LA trial.
Supplementary Table 4. CHEERS checklist.

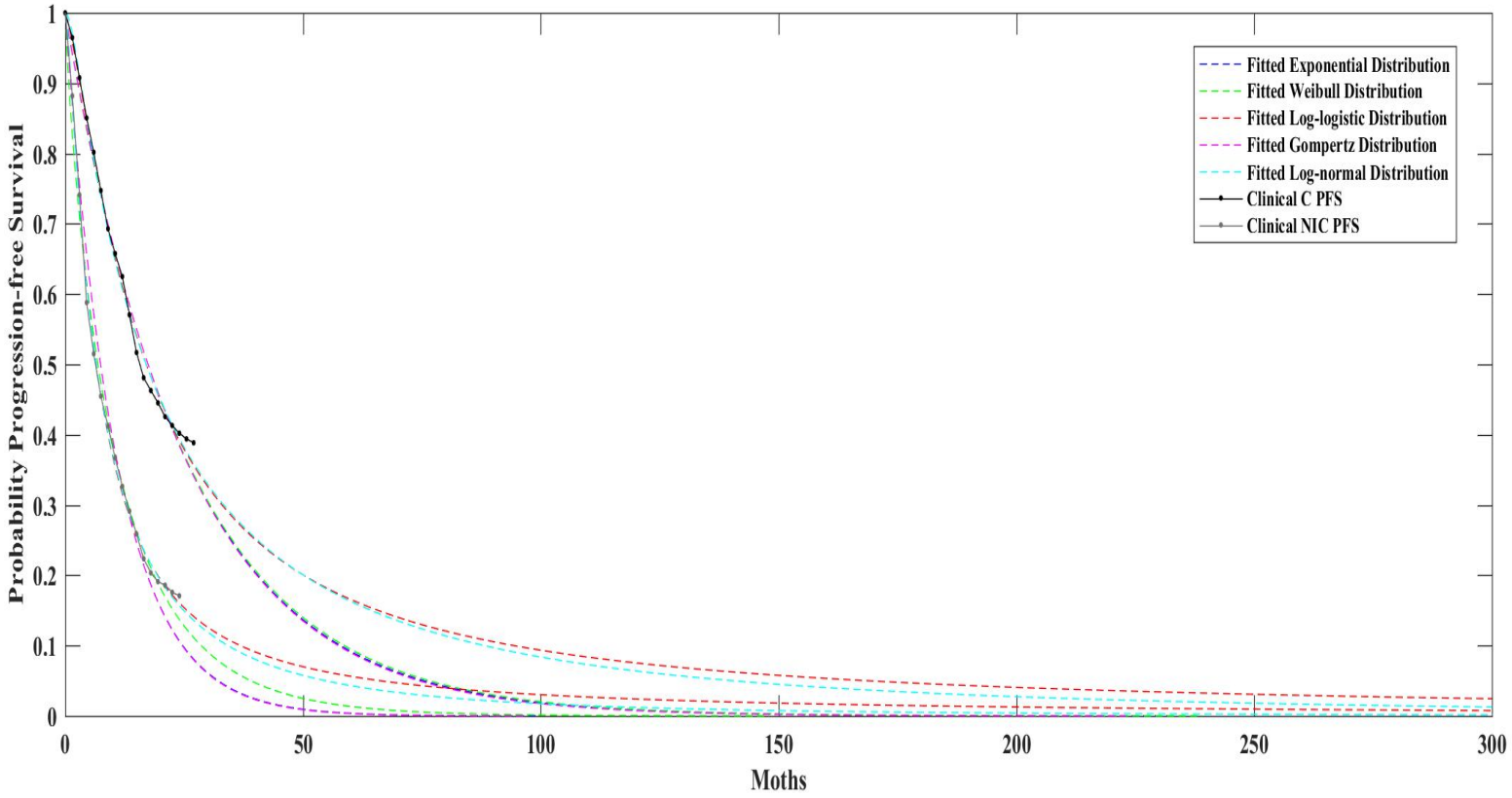
Supplementary Fig. 1. Markov states.



Abbreviation: NIC, nivolumab plus ipilimumab with two cycles of chemotherapy; C, chemotherapy; M, Markov.

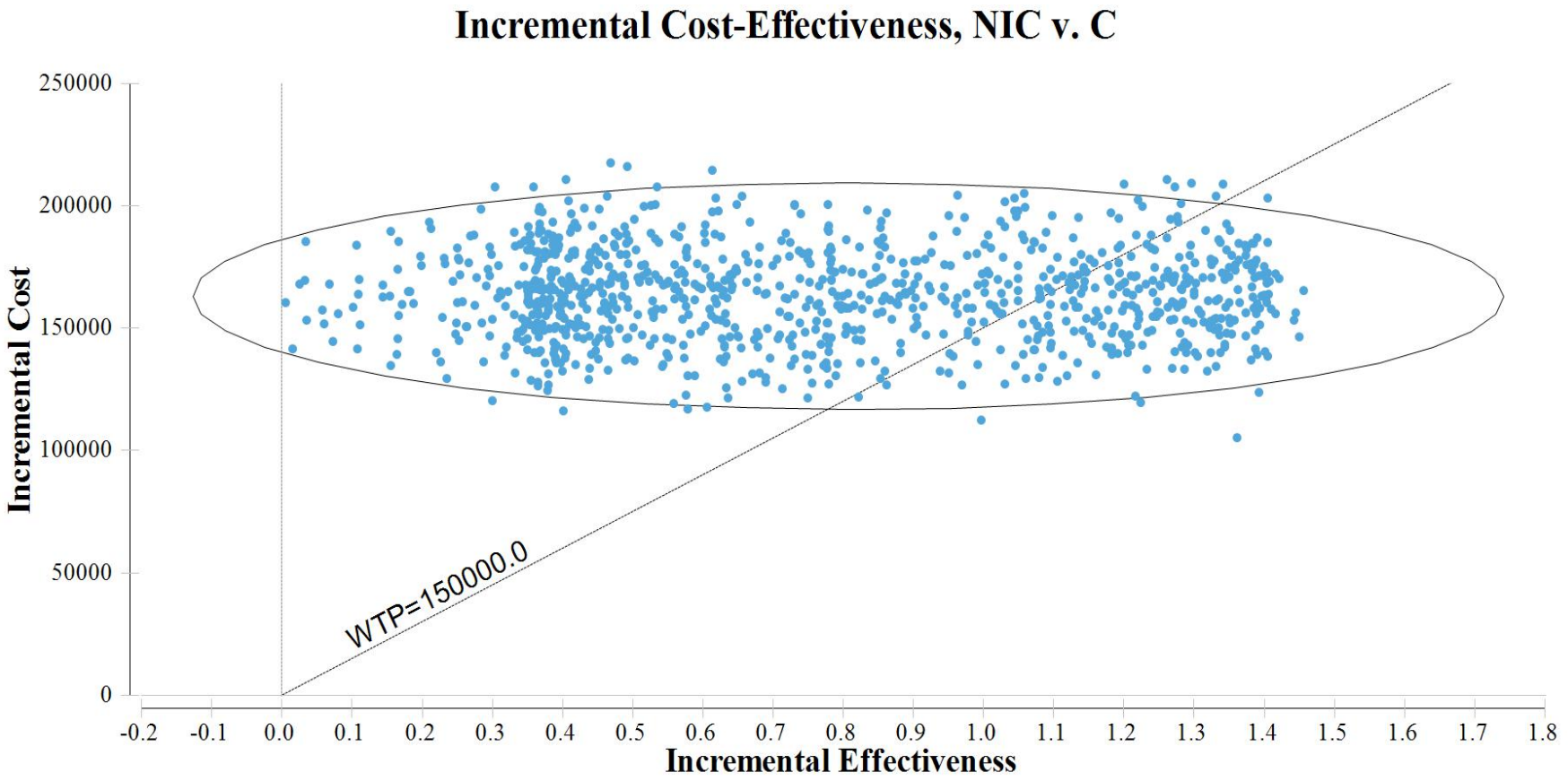
Supplementary Fig. 2. Kaplan-Meier curve fitting and extrapolation.





Abbreviation: NIC, nivolumab plus ipilimumab with two cycles of chemotherapy; OS, overall survival; PFS, progression-free survival.

Supplementary Fig. 3. Probability sensitivity analysis Scatter plot.



Abbreviation: NIC, nivolumab plus ipilimumab with two cycles of chemotherapy; C, chemotherapy; WTP, willingness-to-pay.

Each point in the diagram represents a simulation result of 10,000 Monte Carlo simulation. Ellipse represent the 95% CI and dotted line represent

WTP ($150,000/QALY). Points to the right of the dotted line are considered cost-effective.

Supplementary Table 1. Drug dose and costs

Drug	Dose	Unit costs($ per mg)	Costs for 1 model cycle ($, 6 weeks)
Nivolumab	360mg every 3 weeks	28.541	20,549.520
Ipilimumab	1mg/kg every 6 weeks	157.225	11,005.750
Carboplatin	carboplatin area under curve 6 every 3 weeks	0.054	63.450
Cisplatin	75 mg/m^2 every 3 weeks	0.168	46.368
Paclitaxel	200 mg/m^2 every 3 weeks	0.154	113.344

Pemetrexed	500 mg/m² every 3 weeks			7.319	13,466.96	

Supplementary Table 2. Results of subgroup analyses.

Subgroup	Simple size		OS HR (95% CI)	PFS HR (95% CI)	ICER per QALY	WTP $150 000/QALY
	NIC	C				
Age, years						
＜65	176	178	0.61 (0.47–0.80)	0.57 (0.45-0.74)	210,042	26.1%
≥65-75	148	147	0.62 (0.46–0.85)	0.75 (0.57-0.98)	199,835	33.4%
⩾75	37	33	1.21 (0.69–2.12)	1.17 (0.68-2.03)	-55,412,019	0%
Sex						
Male	252	252	0.66 (0.53–0.82)	0.64 (0.52-0.79)	230,964	17.1%
Female	109	106	0.68 (0.47–1.00)	0.82 (0.60-1.14)	221,879	26.8%

ECOG performance status						
0	113	1112	0.48 (0.32–0.71)	0.58 (0.42-0.79)	161,039	45.0%
1	247	245	0.75 (0.60–0.93)	0.75 (0.61-0.93)	271,327	6.3%
Smoking status						
Never smoker	46	52	1.14 (0.66–1.97)	1.42 (0.87-2.31)	3,544,367	0%
Current or former smoker	315	306	0.62 (0.45–0.86)	0.62 (0.52-0.75)	213,594	23.9%
Tumour histologic type						
Squamous	115	112	0.62 (0.45–0.86)	0.57 (0.42-0.78)	224,387	14.8%
Non-squamous	246	246	0.69 (0.55–0.87)	0.74 (0.60-0.92)	178,936	39.4%
Liver metastases						
Yes	68	86	0.83 (0.57–1.20)	0.94 (0.65-1.34)	312,657	4.4%
No	293	272	0.64 (0.51–0.80)	0.66 (0.54-0.81)	218,872	23.7%
Bone metastases						
Yes	97	110	0.74 (0.53–1.01)	0.80 (0.58-1.11)	216,233	18.0%
No	264	248	0.65 (0.51–0.82)	0.66 (0.54-0.81)	192,257	27.0%

CNS metastases						
Yes	64	58	0.38 (0.24–0.60)	0.42 (0.28-0.65)	142,030	51.2%
No	297	300	0.75 (0.61–0.92)	0.76 (0.63-0.92)	270,233	7.1%
PD-L1 expression subgroups						
＜1%	135	129	0.62 (0.45–0.85)	0.71 (0.53-0.94)	179,608	35.1%
⩾1%	103	204	0.64 (0.50–0.82)	0.67 (0.53-0.84)	208,910	23.4%
1-49%	127	106	0.61 (0.44–0.84)	0.69 (0.51-0.94)	177,625	35.8%
⩾50%	76	98	0.66 (0.44–0.99)	0.61 (0.42-0.89)	198,362	23.1%

Abbreviation: CI, confidence interval; ICER, incremental cost-effectiveness ratio; LY, life-year; OS HR, overall survival hazard ratio; PFS HR, progression-free survival hazard ratio; NIC, nivolumab plus ipilimumab with two cycles of chemotherapy; C, chemotherapy; QALY, quality-adjusted life-year; WTP, Willingness-to-pay; ECOG, Eastern Cooperative Oncology Group; PD-L1, programmed cell death-Ligand 1; CNS, central nervous system;

The subgroup sensitivity analyses revealed that the predicted ICERs of nivolumab plus ipilimumab with two cycles of chemotherapy being cost-effective compared with chemotherapy alone for patients with CNS metastase.

Supplementary Table 3. Summary of statistical goodness-of-fit of K-M curve in Checkmate 9LA trial.

Distribution	NIC OS		C OS		NIC PFS		C PFS	
	AIC	BIC	AIC	BIC	AIC	BIC	AIC	BIC
Exponential Distribution	61.89	62.72	36.20	37.15	40.02	40.85	25.41	26.35
Weibull Distribution	60.52	61.79	35.41	37.10	40.04	40.11	24.40	26.29
Gompertz Distribution	64.11	65.78	35.60	37.50	42.07	43.73	24.41	26.30
Log-logistic Distribution	59.67	61.34	35.27	37.16	39.90	41.56	24.33	26.22
Log-normal Distribution	60.49	62.16	35.22	37.11	39.94	41.61	24.27	26.16

Abbreviation: NIC, nivolumab plus ipilimumab with two cycles of chemotherapy; C, chemotherapy; OS, overall survival; PFS, Progression-free survival; AIC, Akaike's information criterion; BIC, Bayesian information criterion.

As for the ten curves listed in the table, the log-normal and log-logistic distribution had the lowest AIC and BIC. Actually, the visual fits of the ten curves (eFigure 2) showed that they extended tail, which would likely overestimate OS and PFS in the long term based on clinical experts' opinion.

Weibull distributions are flexible and widely used were matched to the number of patients in the three states over time, as its can

monotonically increase or decrease the hazard function, it is suitable for estimating the event that occurs in the early follow-up work period. Therefore, the Weibull distributions was likely to be the most reasonable parametric survival model.

Supplementary Table 4. CHEERS checklist.

Section/item	Item No	Recommendation	Reported on page No
Title and abstract			
Title	1	Identify the study as an economic evaluation or use more specific terms such as "cost-effectiveness analysis", and describe the interventions compared.	1
Abstract	2	Provide a structured summary of objectives, perspective, setting, methods (including study design and inputs), results (including base case and uncertainty analyses), and conclusions.	2
Introduction			
Background and objectives	3	Provide an explicit statement of the broader context for the study.	3-4
		Present the study question and its relevance for health policy or practice decisions.	
Methods			
Target population and subgroups	4	Describe characteristics of the base case population and subgroups analysed, including why they were chosen.	4
Setting and location	5	State relevant aspects of the system(s) in which the decision(s) need(s) to be made.	4
Study perspective	6	Describe the perspective of the study and relate this to the costs being evaluated.	
Comparators	7	Describe the interventions or strategies being compared and state why they were chosen.	4
Time horizon	8	State the time horizon(s) over which costs and consequences are being evaluated and say why appropriate.	4
Discount rate	9	Report the choice of discount rate(s) used for costs and outcomes and say why appropriate.	4
Choice of health	10	Describe what outcomes were used as the measure(s) of benefit in the evaluation and their relevance for	4

outcomes		the type of analysis performed.	
Measurement of effectiveness	11a	*Single study-based estimates:* Describe fully the design features of the single effectiveness study and why the single study was a sufficient source of clinical effectiveness data.	5
	11b	*Synthesis-based estimates:* Describe fully the methods used for identification of included studies and synthesis of clinical effectiveness data.	
Measurement and valuation of preference based outcomes	12	If applicable, describe the population and methods used to elicit preferences for outcomes.	Not applicable
Estimating resources and costs	13a	*Single study-based economic evaluation:* Describe approaches used to estimate resource use associated with the alternative interventions. Describe primary or secondary research methods for valuing each resource item in terms of its unit cost. Describe any adjustments made to approximate to opportunity costs.	6-7
	13b	*Model-based economic evaluation:* Describe approaches and data sources used to estimate resource use associated with model health states. Describe primary or secondary research methods for valuing each resource item in terms of its unit cost. Describe any adjustments made to approximate to opportunity costs.	
Currency, price date, and conversion	14	Report the dates of the estimated resource quantities and unit costs. Describe methods for adjusting estimated unit costs to the year of reported costs if necessary. Describe methods for converting costs into a common currency base and the exchange rate.	7
Choice of model	15	Describe and give reasons for the specific type of decision-analytical model used. Providing a figure to show model structure is strongly recommended.	4
Assumptions	16	Describe all structural or other assumptions underpinning the decision-analytical model.	5
Analytical methods	17	Describe all analytical methods supporting the evaluation. This could include methods for dealing with skewed, missing, or censored data; extrapolation methods; methods for pooling data; approaches to validate or make adjustments (such as half cycle corrections) to a model; and methods for handling population heterogeneity and uncertainty.	4-7
Results			
Study	18	Report the values, ranges, references, and, if used, probability distributions for all parameters. Report	7(Table 1)

parameters		reasons or sources for distributions used to represent uncertainty where appropriate. Providing a table to show the input values is strongly recommended.	
Incremental costs and outcomes	19	For each intervention, report mean values for the main categories of estimated costs and outcomes of interest, as well as mean differences between the comparator groups. If applicable, report incremental cost-effectiveness ratios.	8(Table 2)
Characterising uncertainty	20a	*Single study-based economic evaluation:* Describe the effects of sampling uncertainty for the estimated incremental cost and incremental effectiveness parameters, together with the impact of methodological assumptions (such as discount rate, study perspective).	4
	20b	*Model-based economic evaluation:* Describe the effects on the results of uncertainty for all input parameters, and uncertainty related to the structure of the model and assumptions.	
Characterising heterogeneity	21	If applicable, report differences in costs, outcomes, or cost-effectiveness that can be explained by variations between subgroups of patients with different baseline characteristics or other observed variability in effects that are not reducible by more information.	Not applicable
Discussion			
Study findings, limitations, generalisability, and current knowledge	22	Summarise key study findings and describe how they support the conclusions reached. Discuss limitations and the generalisability of the findings and how the findings fit with current knowledge.	10-12
Other			
Source of funding	23	Describe how the study was funded and the role of the funder in the identification, design, conduct, and reporting of the analysis. Describe other non-monetary sources of support.	Not applicable
Conflicts of interest	24	Describe any potential for conflict of interest of study contributors in accordance with journal policy. In the absence of a journal policy, we recommend authors comply with International Committee of Medical Journal Editors recommendations.	14-15