Additional file 1:

This appendix formed part of the original submission. We post it as supplied by the authors.

Supplement to: Zhen-Hao Wu, Yu-Jing An, Zhen-Xing Chu, et al. Cost-effectiveness of self-sampling and enhanced strategies for HPV prevention among men who have sex with men in China: a modelling study.

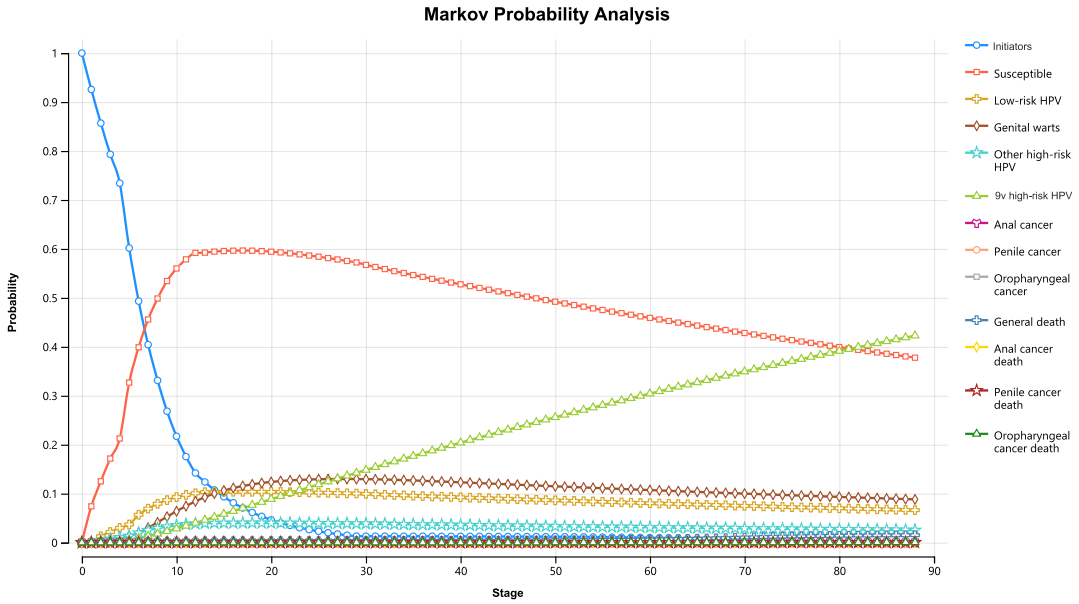
Contents

Supplementary materials

1 Model structure

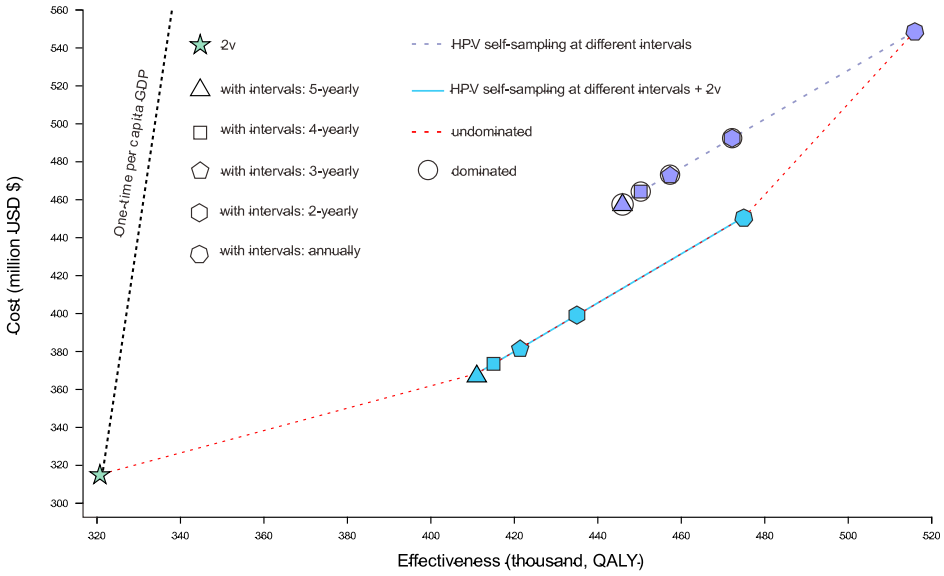
In the model simulation (Fig. 1), each susceptible individual could become infected with either low-risk or high-risk subtypes of the HPV at varying transmission rates, leading them to transition into the corresponding states of low-risk or high-risk HPV infection, respectively. Individuals persistently infected with low-risk HPV may develop genital warts, while those who do not will clear the infection and return to a susceptible state. Those affected by genital warts are likely to recover with appropriate treatment. Conversely, persistent infection with high-risk HPV can potentially lead to anal cancer, penile cancer, or oropharyngeal cancer. In our model, individuals were assumed to not experience complete recovery from cancerization once it occurs. Upon reaching the status of anal cancer, penile cancer, and oropharyngeal cancer individuals will receive cancer therapy but face the risk of mortality. In the model, the status of anal cancer, penile cancer, and oropharyngeal cancer were presumed to exclude precancerous lesions related to anal cancer [22].

Additional file 1: Fig. S1: Model structure

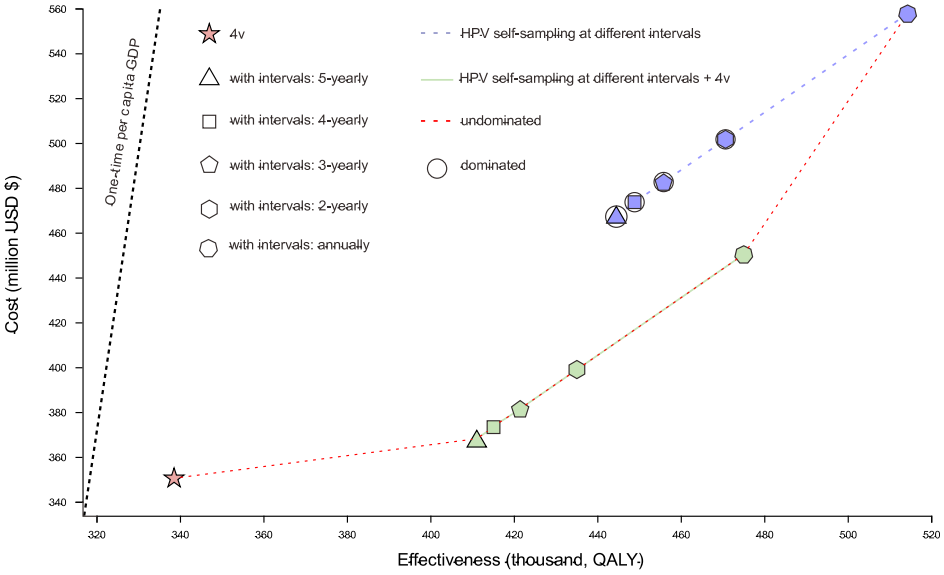


Additional file 1: Fig. S2: Markov state probs curve.

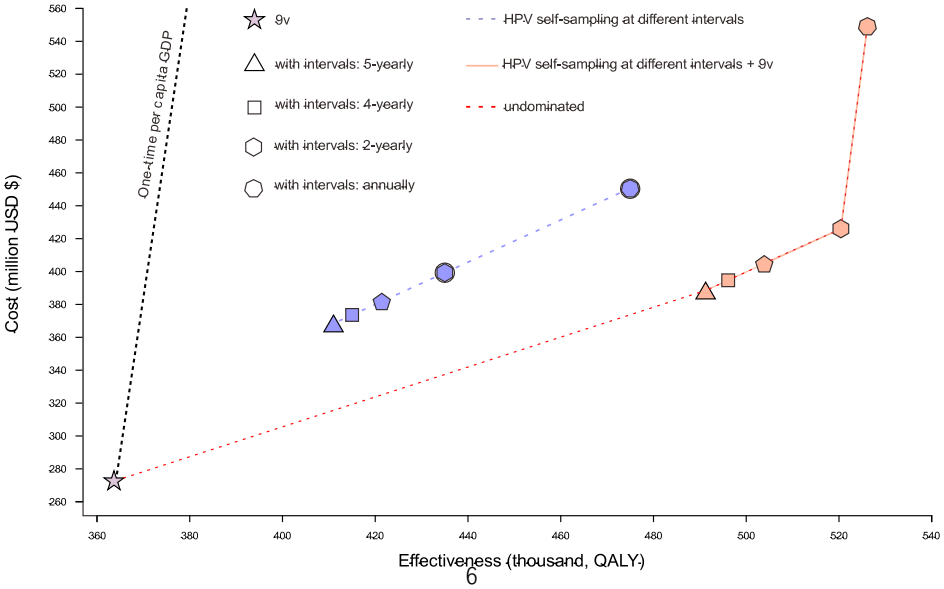
A HPV self-sampling at different intervals with bivalent vaccination vs. HPV self-sampling at different intervals
HPV self-sampling at different intervals with bivalent vaccination vs. bivalent vaccination



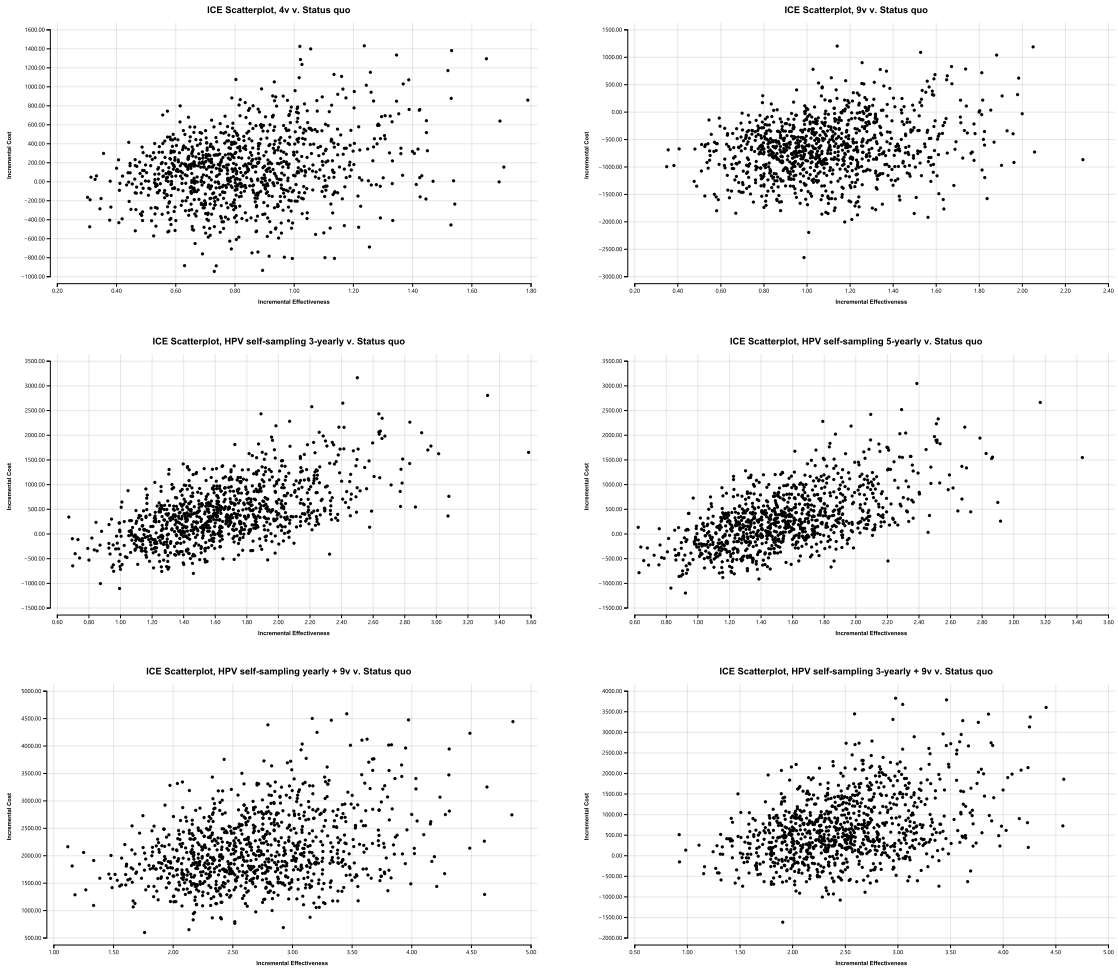
B HPV self-sampling at different intervals with quadrivalent vaccination vs. HPV self-sampling at different intervals
HPV self-sampling at different intervals with quadrivalent vaccination vs. quadrivalent vaccination



C HPV self-sampling at different intervals with nine-valent vaccination vs. HPV self-sampling at different intervals
HPV self-sampling at different intervals with nine-valent vaccination vs. nine-valent vaccination



Additional file 1: Fig. S3: Cost-effectiveness of the integration of HPV self-sampling (a cohort of 100,000 MSM).



Additional file 1: Fig. S4: Probabilistic sensitivity analysis of the incremental costs and incremental QALYs.

(A) The most two cost-effective scenarios of vaccination alone; (B) The most two cost-effective scenarios of HPV self-sampling at different intervals; (C) The most two cost-effective scenarios of HPV self-sampling at different intervals with vaccination. QALY=quality-adjusted life year; ICER=incremental cost-effectiveness ratio.

Additional file 1: Table S1: Model assumptions

	Assumption	Source
1.	The duration of protection from HPV vaccination was considered to be lifelong.	[37, 38]
2.	There was no protective effect against the corresponding uncovered subtypes of bivalent, quadrivalent, and nine-valent vaccines.	/
3.	100% efficacy of HPV-16/18 vaccine eliminates infections with these subtypes post-vaccination.	[39]
4.	The female-exclusive vaccination program has conferred 22% herd immunity in the male population.	[40]

5.	The prevalence of HPV-specific types across various cancer types is derived from a synthesis of existing literature.	[41-46]
6.	We assume that MSM will not remain in a low-risk HPV state and will return to a susceptible state due to the self-limited nature of low-risk HPV infection.	/
7.	There is only a cost parameter for rectal HPV self-sampling, we assume that the cost of HPV self-sampling in the three sites (oropharyngeal, rectal and urogenital) is the same, and obtain the total cost of HPV self-sampling in the three sites.	/

Additional file 1: Table S2: Model supplementary parameters

Transition probability	**Value**	**Source**	**Range for one-way sensitivity analysis**
Initiators → Susceptible	Age- / Cycle-dependent 12-15: 0.074 16-19: 0.18 20-24: 0.19 24-40: 0.13 40+: 0	Chance to become susceptible for infection, corrected for group size [47].	±10%∗value
Low-risk HPV → HPV-6, 11	0.759	[18, 19].	±10% (68.3%-83.5%)
HPV+ → HPV-16, 18	0.398	[19]	±10% (35.8%-43.8%)
HPV+ → HPV-31, 33, 45, 52, 58	0.332	[19]	±10% (29.9%-36.5%)
Vaccinated → Virgin Vaccinated → susceptible	0.0	Given the maintenance of high antibody titers, we assume a zero vaccine waning rate. [37, 38].	/
High-risk HPV → penile cancer	0.000025	Prevalence of penile cancer: 1/100,000.	0.00002-0.00003
High-risk HPV → oropharyngeal cancer	0.000083	Prevalence of penile cancer: 3.28/100,000.	0.00008-0.00009

Susceptible → Infected	Cycle- / Type-dependent (Min-Max) HPV-16: 0.00000046 – 0.0318 HPV-18: 0.00000045 – 0.00917 HPV-31: 0.00002 -0.016 HPV-33: 0.0000000033 – 0.0046 HPV-45: 0.000000004 – 0.0063 HPV-52: 0.000000001 – 0.0073 HPV-58: 0.000000004 – 0.0072	The chance to be infected by a specific type of HPV. All transmission probabilities are type-specific [48]. Also, shown in Fig. S4.	±10%∗value

1 Collection and transportation of specimens

1.1 HPV facility-sampling

The research subjects need to first complete HPV sampling at the site. In this study, place sampling includes the following three methods: sampling by medical personnel, self-sampling by medical places, and sampling by community workers. Among the four research sites, the sampling method in Shenyang was for medical staff, in Beijing it was for self-sampling in medical facilities, and in Tianjin and Harbin it was for staff from community organizations. The project team will provide technical training, regular competency testing, and on-site supervision and inspection for all sites involved in the project.

When sampling by medical staff and community workers, the sampler will require the subject to adopt a lateral bending position or a standing forward bending position with both hands supporting the table and chair. Then, the sampler will stand on the side of the subject, hold the sampling tube, slowly rotate and insert it forward in the direction of the anal canal, and ask the subject to relax. When the swab is inserted 3-5 centimeters, stop and rotate 180 ° clockwise and 180 ° counterclockwise, then slowly withdraw and observe for any bleeding in the study subject's anus. After confirming that there are no abnormal conditions in the subject being collected, immediately place the sampling swab into a transfer bottle containing cell preservation solution, and label the bottle with the subject's number, sampling time, location, and other information. The sampling process of self-sampling in medical institutions is to stand at a specific collection site, and under the

guidance of medical staff, step on a higher object with one leg, or adopt squatting or lateral lying positions. Then, gently insert a sterilized swab into the anus 3-5 centimeters, rotate clockwise 180 °, counterclockwise 180 °, and then gently rotate and pull it out, Place the swab into an outer spiral cap collection tube containing cell protective fluid, label the relevant information on the outside of the collection tube, and then hand it over to medical personnel. Any operational issues encountered by the subjects during the sampling process can be consulted with medical personnel. All samples collected from different locations must be stored in a -20 ℃ refrigerator within 6 hours after sampling, and then sent to the Shenyang laboratory via cold chain mail.

1.2 HPV self-sampling

After the completion of facility-sampling, relevant staff distributed HPV home self-sampling packages to each research subject. The home self-sampling package includes collection swabs, transfer bottles containing cell preservation solutions, self-sampling step diagrams, and mailing information. The research subjects need to complete home self-sampling within 24-36 hours after the completion of facility-sampling. The sampling requirement is for the subject to take out the sampling swab after washing their hands, and during this process, ensure that the swab does not come into contact with other parts and places to avoid contamination. Then the subject gently inserts the collection swab into the anus 3-5 centimeters away, and gently presses it with their fingers to rotate the swab clockwise 180 ° and then counterclockwise 180 °. After completing the sampling, place the swab vertically into the transfer bottle containing the cell preservation solution, break the head of the swab and cover it with a lid. Mark your own number and sampling time on the surface of the bottle. The research subjects need to immediately mail the self-sampled samples to the Shenyang laboratory at room temperature after sampling is completed. We assume that the type of HPV does not change within 24-36 hours in the study subjects.

2 Human papillomavirus detection

2.1 Testing reagents and principles

HPV detection was carried out using the human papillomavirus (23 types) nucleic acid typing detection kit (fluorescent polymerase chain reaction (PCR) method) produced by Guangdong Kaipu Biotechnology Co., Ltd. This kit is based on multiple fluorescence PCR technology and utilizes a real-time fluorescence PCR instrument for synchronous nucleic acid amplification and detection. Divided into 6 reaction tubes, four fluorescence detection channels are used in the instrument to achieve genotyping and detection of 23 types of human papillomavirus, as well as intracellular control β-Global DNA testing. Intracellular control DNA is used to evaluate sample quality and PCR inhibition factors. The 23 types of HPV detection include 14 high-risk HPV types (HPV16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, 68) and 9 low-risk HPV types (HPV6, 11, 42, 43, 44, 53, 81, 73, 82). The detection steps include HPV DNA extraction, PCR amplification, and flow hybridization.

3 Costs of HPV self-sampling and facility-sampling

3.1 Sources of economic variables

454 research subjects participated in both home and workplace sampling for HPV. Among the three workplace sampling methods, 26.9% (122/454) utilized self-sampling at medical facilities, 37.4%

(170/454) involved sampling from medical personnel, and 35.7% (162/454) engaged community workers for sampling. During the research process, we determined a HPV detection cost of 100 yuan per person and a printing cost of 1 yuan per person for the sampling diagram, based on actual expenses. Additionally, considering the practical aspects, we estimated various costs such as transportation costs for specimens, staff fees, venue rent, water and electricity expenses, sampling tools and freezer costs, transportation costs, and work loss costs for the research subjects (Table S3).

Table S3: Different sampling methods and sources of economic variables.

Economic variables	Sources
The cost of HPV testing	It comes from actual expenses. The cost of testing each specimen is 100 yuan.
The transportation cost of specimens	It is estimated based on the actual situation. The average transportation cost for each self-sampling specimen is 15 yuan, and the transportation cost for facility-sampling specimens is determined based on actual expenses.
The cost of printed sampling diagram	It is based on actual expenses. 1 yuan per person
Staff salaries	It is estimated based on actual circumstances. Shenyang medical staff costs 15000 yuan per month, which takes 3 months, while community workers pay 10000 yuan per month, which takes 2 months.
The venue rent, water and electricity	It is estimated based on the actual situation. Shenyang 1500/month, taking 3 months; Beijing 4000/month, taking 2 months; Tianjin and Harbin average 2000/month, taking 2 months.
Costs of sampling tools, freezers, etc.	It is estimated based on actual conditions. Each facility is equipped with one freezer, which costs about 1000 yuan, and the remaining consumables cost about 200 yuan.
Transportation costs	It is estimated based on actual conditions. Shenyang costs 5 yuan/person, Beijing costs 10 yuan/person, and Tianjin and Harbin average 5 yuan/person.
The cost of lost work	It is estimated based on the monthly income in the questionnaire. We assume that wages are paid on average every half day, and sampling at the research site takes half a day.

Note: 1. Among the four research sites, the sampling method in Shenyang is for medical personnel, Beijing is for self-sampling in medical facilities, and Tianjin and Harbin are for community workers; 2. Since both Harbin and Tianjin are sampled by community workers, the relevant costs in the table are the average of the two.

3.2 Analysis of cost composition of different HPV sampling methods

Table 5 shows the cost composition of different sampling methods, with 454 people included in the analysis. The total cost of household self-sampling was 52664 yuan, mainly for HPV testing, accounting for 86.21% of the total investment cost. The total cost of self-sampling in medical facilities is 33614 yuan, and the highest proportion of investment is also the cost of HPV testing, accounting for 36.29%. Medical staff spent a total of 78344 yuan on sampling, while community workers spent a total of 53907 yuan on sampling. Medical staff and community workers have the

highest proportion of labor costs for sampling, accounting for 57.44% and 37.10% of the total input costs, respectively (Table S4). Health economics parameters: cost of self-sampling and cost of facility-sampling are derived from here.

Table S4: Analysis of cost composition of different HPV sampling methods

Economic variables	Self-sampling (n=454)		Medical facility self-sampling (n=122)		Medical staff sampling (n=170)		Community staff sampling (n=162)		Facility-sampling (n=454)	
	Cost (yuan)	Proportion (%)	Cost (yuan)	Proportion (%)	Cost (yuan)	Proportion (%)	Cost (yuan)	Proportion (%)	Cost (yuan)	Proportion (%)
HPV testing fee	45400	86.21	12200	36.29	17000	21.70	16200	30.05	45400	27.37
Sample transportation cost	6810	12.93	100	0.30	80	0.10	100	0.19	280	0.17
Sampling diagram printing	454	0.86	-	-	-	-	-	-	-	-
Staff service fee	-	-	-	-	45000	57.44	20000	37.10	65000	39.19
Venue, Rent, Water and Electricity	-	-	8000	23.80	4500	5.74	4000	7.42	16500	9.95
Sampling tools, freezers, etc.	-	-	1200	3.57	1200	1.53	1200	2.23	3600	2.17
Transportation fee	-	-	1220	3.63	850	1.08	810	1.50	2880	1.74
Lost time expenses	-	-	10894	32.41	9714	12.40	11597	21.51	32205	19.42
Total	52664	100.00	33614	100.00	78344	100.00	53907	100.00	165865	100.00

HPV=human papillomavirus.

CHEERS 2022 checklist

Consolidated Health Economic Evaluation Reporting Standards 2022 (CHEERS 2022) checklist
The CHEERS 2022 statement is intended to be used for any form of health economic evaluation, the new CHEERS checklist contains 28 items with accompanying descriptions.
https://link.springer.com/article/10.1007/s40258-021-00704-x/tables/1

Section/topic	Item No	Guidance for reporting	Reported on page No
Title			
Title	1	Identify the study as an economic evaluation and specify the interventions being compared.	1
Abstract			
Abstract	2	Provide a structured summary that highlights context, key methods, results, and alternative analyses.	2
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.	4–5
Methods			
Health economic analysis plan	4	Indicate whether a health economic analysis plan was developed and where available.	7–8
Study population	5	Describe characteristics of the study population (such as age range, demographics, socioeconomic, or clinical characteristics).	6
Setting and location	6	Provide relevant contextual information that may influence findings.	6
Comparators	7	Describe the interventions or strategies being compared and why chosen.	6–7
Perspective	8	State the perspective(s) adopted by the study and why chosen.	–
Time horizon	9	State the time horizon for the study and why appropriate.	6
Discount rate	10	Report the discount rate(s) and reason chosen.	9
Selection of outcomes	11	Describe what outcomes were used as the measure(s) of benefit(s) and harm(s).	8–9
Measurement of outcomes	12	Describe how outcomes used to capture benefit(s) and harm(s) were measured.	8–9
Valuation of outcomes	13	Describe the population and methods used to measure and value outcomes.	8–9

Section/topic	Item No	Guidance for reporting	Reported on page No
Measurement and valuation of resources and costs	14	Describe how costs were valued.	Appendix 11-13
Currency, price date, and conversion	15	Report the dates of the estimated resource quantities and unit costs, plus the currency and year of conversion.	7-8
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.	6, Appendix 8-9
Analytics and assumptions	17	Describe any methods for analysing or statistically transforming data, any extrapolation methods, and approaches for validating any model used.	8-9 Appendix 3
Characterising heterogeneity	18	Describe any methods used for estimating how the results of the study vary for subgroups.	–
Characterising distributional effects	19	Describe how impacts are distributed across different individuals or adjustments made to reflect priority populations.	19-20
Characterising uncertainty	20	Describe methods to characterise any sources of uncertainty in the analysis.	Appendix 7
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 (such as clinicians or payers) in the design of the study.	Appendix 10
Results			
Study parameters	22	Report all analytic inputs (such as values, ranges, references) including uncertainty or distributional assumptions.	19-20
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.	9-10, 21-22
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.	11
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	Appendix 10-11
Discussion			

Section/topic	Item No	Guidance for reporting	Reported on page No
Study findings, limitations, generalisability, and current knowledge	26	Report key findings, limitations, ethical or equity considerations not captured, and how these could affect patients, policy, or practice.	11, 15
Other relevant information			
Source of funding	27	Describe how the study was funded and any role of the funder in the identification, design, conduct, and reporting of the analysis	16
Conflicts of interest	28	Report authors conflicts of interest according to journal or International Committee of Medical Journal Editors requirements.	16