Informing a decision framework for when NICE should recommend the use of health technologies only in the context of an appropriately designed programme of evidence development

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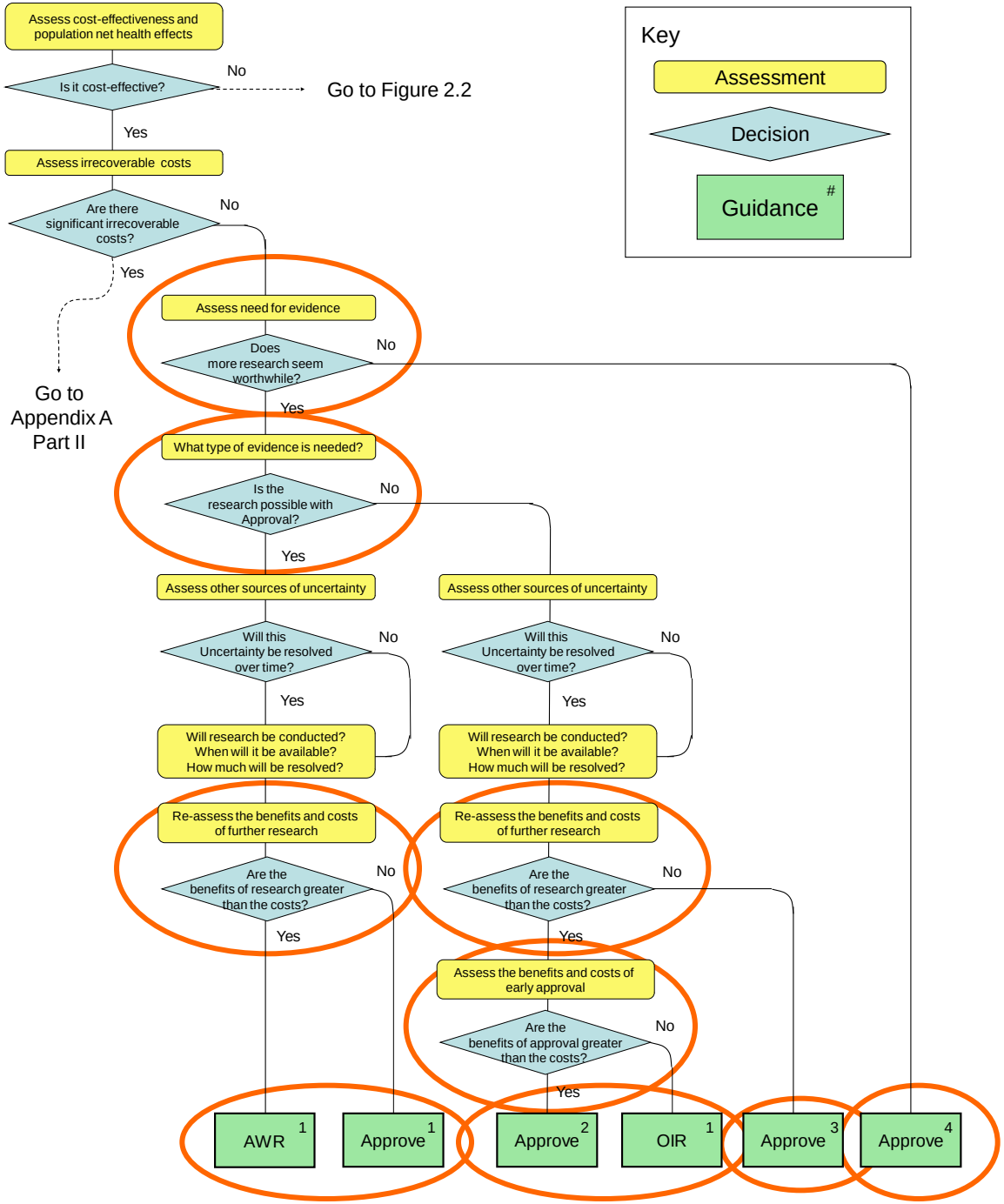
What assessments are needed

- Is it expected to be cost-effective?
  - What impact on overall population health
- Are there significant investment or reversal costs?
  - Capital costs and initially negative net health effects (NHE)
- Is additional evidence needed
  - Does further research seem worthwhile
- What type of evidence is needed
  - Type of research required, is it possible with approval
- Will other sources of uncertainty resolve over time?
  - Changes in prices, technologies and evidence
- Do the benefits of research exceed the costs
  - Will it be conducted, when will it be available, how much will be resolved
- Are the benefits of approval greater than the costs

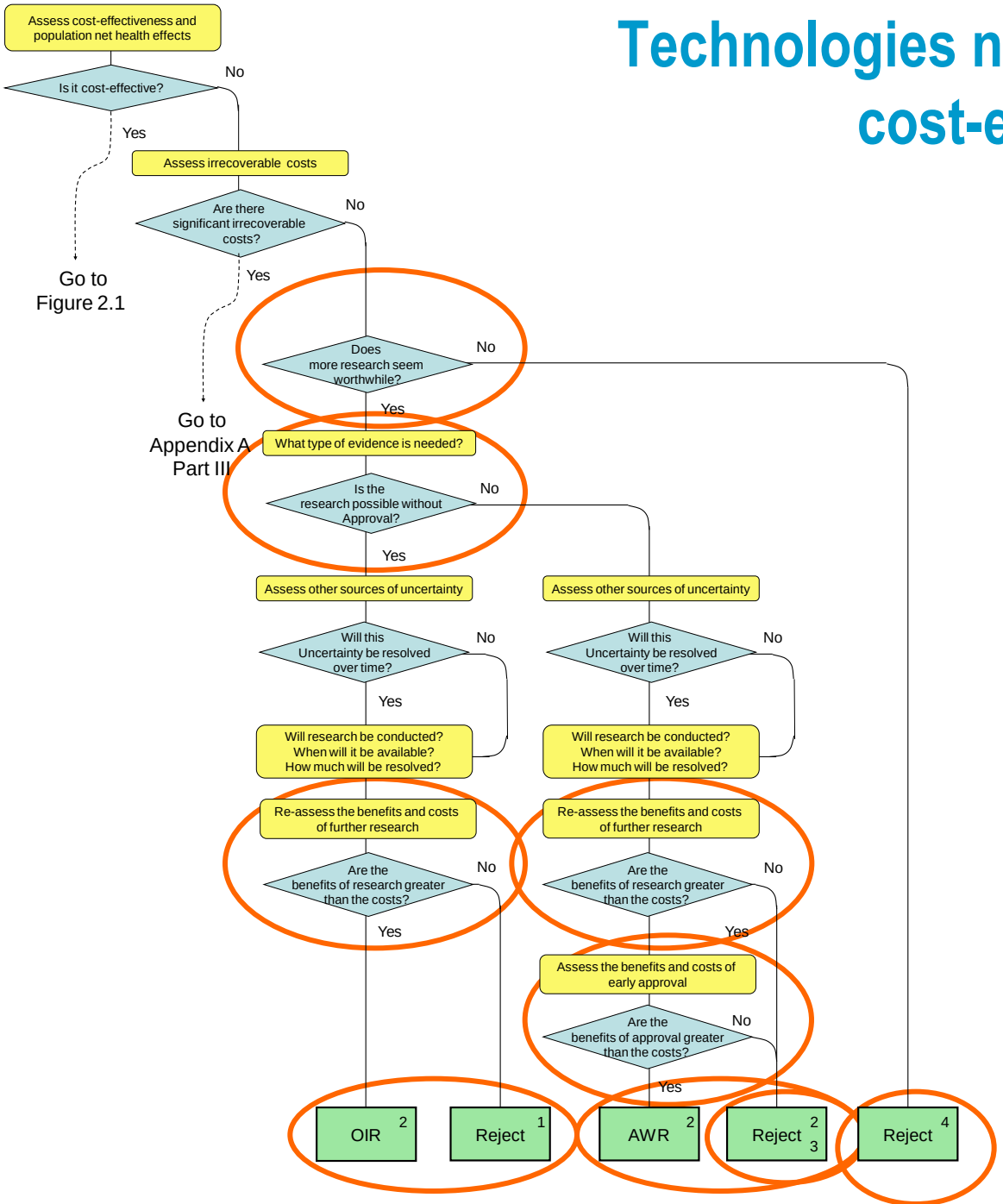
Sequence of assessment and decision (judgements)

- Start where NICE appraisal stops
  - Assessment of expected cost-effectiveness is not sufficient
  - Categories of guidance
    - Approve and Reject
    - OIR = approval restricted to use only in research
    - AWR = approval but only with research, i.e., those not participating in the research can also have access
  - Different types of OIR, AWR (different considerations)
- Represented as an algorithm
  - How different categories of guidance might be arrived at
  - Different consideration lead to the same category of guidance
  - Order of the assessments required
  - How guidance might change (price, evidence and technologies

Technologies expected to be cost-effective



Technologies not expected to be cost-effective



Technologies with investment and reversal costs

- Costs which are irrecoverable
  - Capital costs of long lived equipment (training and learning)
  - Initial losses (negative NHE) offset by later gains
- Guidance might change
  - Research reports
  - Prices change, new technologies, other evidence
- Expected to be cost-effective
  - OIR rather than AWR even if research is possible
  - OIR rather than Approve more likely to be appropriate
  - Reject rather than Approve is possible
- Not expected to be cost-effective
  - Reject rather than OIR is more likely

Different types of guidance

	No significant irrecoverable costs					Significant irrecoverable costs				
Research	Not needed	Possible with approval		Not possible with approval		Not needed	Possible with approval		Not possible with approval	
		Benefits > costs	Benefits < costs	Benefits > costs	Benefits < costs		Benefits > costs	Benefits < costs	Benefits > costs	Benefits < costs
Approve (12)	4		1	2	3	11, 12		5,6	7, 9	8, 10
AWR (3)		1					3,4			
OIR (5)				1			3,4		5,6	
Reject (3)						7		5		6

	No significant irrecoverable costs					Significant irrecoverable costs				
Research	Not needed	Possible without approval		Not possible without approval		Not needed	Possible without approval		Not possible without approval	
		Benefits > costs	Benefits < costs	Benefits > costs	Benefits < costs		Benefits > costs	Benefits < costs	Benefits > costs	Benefits < costs
Approve (0)										
AWR (2)				2					5	
OIR (2)		2					7			
Reject (8)	4		1	2	3	11		8	9	10

Change in effective prices (PAS VBP) and evidence

- Price influences the benefits of early approval and the benefits of research
  - Threshold price (p*) for Reject to Approve (no uncertainty)
    - Reject to OIR > p* > OIR to Approve
    - Reject to OIR > OIR to AWR > AWR to Approve
- Incentives for evaluative research
- Prospects of research
  - Type of research needed
  - Will it be feasible and regarded as ethical
  - When likely to report
  - Priority for public funding or for manufacturers to undertake

A checklist of assessments

Technologies expected to be cost-effective

Point	Assessment	Judgement	
		Yes	No
1	Is it cost-effective?	Yes	
2	Are there significant irrecoverable costs?		
3	Does more research seem worthwhile?		
4	Is the research possible with approval?		
5	Will other sources of uncertainty resolve over time?		
6	Are the benefits of research greater than the costs?		
7	Are the benefits of approval greater than the costs?		

A checklist of assessments

Technologies not expected to be cost-effective

Point	Assessment	Judgement	
		Yes	No
1	Is it cost-effective?		No
2	Are there significant irrecoverable costs?		
3	Does more research seem worthwhile?		
4	Is the research possible without approval?		
5	Will other sources of uncertainty resolve over time?		
6	Are the benefits of research greater than the costs?		
7	Are the benefits of approval greater than the costs?		

Possible pathways

Assessment	1	2	3	4	5	6	7	Guidance
1	Yes	No	Yes	Yes	Yes/No	Yes	-	AWR 1
2	Yes	No	Yes	Yes	Yes/No	No	-	Approve 1
3	Yes	No	Yes	No	Yes/No	Yes	Yes	Approve 2
4	Yes	No	Yes	No	Yes/No	Yes	No	OIR 1
5	Yes	No	Yes	No	Yes/No	No	-	Approve3
6	Yes	No	No	-	-	-	-	Approve 4
7	No	No	Yes	Yes	Yes/No	Yes	-	OIR 2
8	No	No	Yes	Yes	Yes/No	No	-	Reject 1
9	No	No	Yes	No	Yes/No	Yes	Yes	AWR 2
10	No	No	Yes	No	Yes/No	Yes	No	Reject 2
11	No	No	Yes	No	Yes/No	No	-	Reject 3
12	No	No	No	-	-	-	-	Reject 4
13	Yes	Yes	Yes	Yes	Yes	Yes	Yes	AWR 3
14	Yes	Yes	Yes	Yes	Yes	Yes	No	OIR 3
15	Yes	Yes	Yes	Yes	Yes	No	Yes	Approve 5
16	Yes	Yes	Yes	Yes	Yes	No	No	Reject 5
17	Yes	Yes	Yes	Yes	No	Yes	Yes	AWR 4
18	Yes	Yes	Yes	Yes	No	Yes	No	OIR 4
19	Yes	Yes	Yes	Yes	No	No	-	Approve 6
20	Yes	Yes	Yes	No	Yes	Yes	Yes	Approve 7
21	Yes	Yes	Yes	No	Yes	Yes	No	OIR 5
22	Yes	Yes	Yes	No	Yes	No	Yes	Approve 8
23	Yes	Yes	Yes	No	Yes	No	No	Reject 6
24	Yes	Yes	Yes	No	No	Yes	Yes	Approve 9
25	Yes	Yes	Yes	No	No	Yes	No	OIR 6
26	Yes	Yes	Yes	No	No	No	-	Approve 10
27	Yes	Yes	No	n/a	Yes	n/a	Yes	Approve 11
28	Yes	Yes	No	n/a	Yes	n/a	No	Reject 7
29	Yes	Yes	No	n/a	No	-	-	Approve 12
30	No	Yes	Yes	Yes	Yes/No	Yes	-	OIR 7
31	No	Yes	Yes	Yes	Yes/No	No	-	Reject 8
32	No	Yes	Yes	No	Yes/No	Yes	Yes	AWR 5
33	No	Yes	Yes	No	Yes/No	Yes	No	Reject 9
34	No	Yes	Yes	No	Yes/No	No	-	Reject 10
35	No	Yes	No	-	-	-	-	Reject 11

Part I of the algorithm

Part II of the algorithm

Part III of the algorithm

Selection of case studies

- Challenging circumstances
- Interesting characteristics
- Feasibility of full range of analysis given constraints
  i. Clopidogrel for the management of patients with non-ST-segment elevation acute coronary syndromes (CLOP)
  ii. Enhanced External Counterpulsation for chronic stable angina (EECP)
  iii. Omalizumab for the treatment of severe persistent allergic asthma in children aged 6 to 11 years (OMAL)
  iv. Etanercept, infliximab and adalimumab for the treatment of active and progressive psoriatic arthritis (PsA)

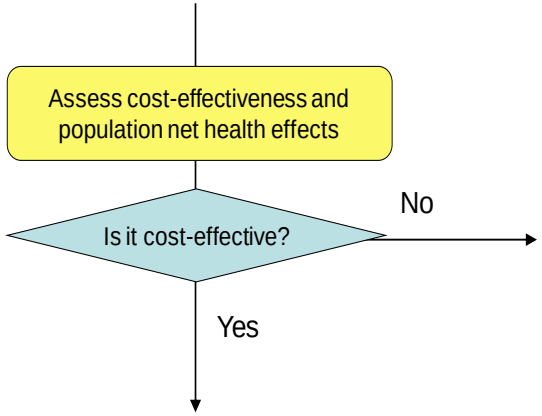
Questions

- Is the distinction between assessment and decision (judgement) useful
- Is the sequence of assessment and decision described in the algorithm and summarised as a checklist likely to be helpful
- Is useful to identify the combinations of considerations which might lead to different categories and types of guidance
- Are the social values and ethical principles associated with OIR and AWR acceptable?

3.3 Is it cost effective and what are the risks?

- Assessment and judgement at points 1 and 2 of the checklist
  - Does not lead directly to guidance
  - Determines subsequent pathway

3.3.1 Point 1 - Is it expected to be cost effective?



- Starting where current NICE appraisal finishes
  - i.e., after an assessment of effectiveness, potential for harms and costs over a patient time horizon

i) Cost-effectiveness at the patient level

Table 3.2a Expected cost-effectiveness of EECP per patient treated

				Cost-effectiveness threshold at:			
				£20,000 per QALY		£30,000 per QALY	
Treatment	**Costs**	**QALYs**	**ICER**	**NHE,** QALY (£)	**Incr NHE,** QALY (£)	**NHE,** QALY (£)	**Incr NHE,** QALY (£)
EECP	£4,744	7.6045	£19,391	7.3673 (147,346)	0.0074 (£149)	7.4464 (£223,391)	0.0865 (£2,595)
Std	-	7.3598	-	7.3598 (147,197)	-	7.3598 (£220,795)	-

Net Health Effects (NHE) =

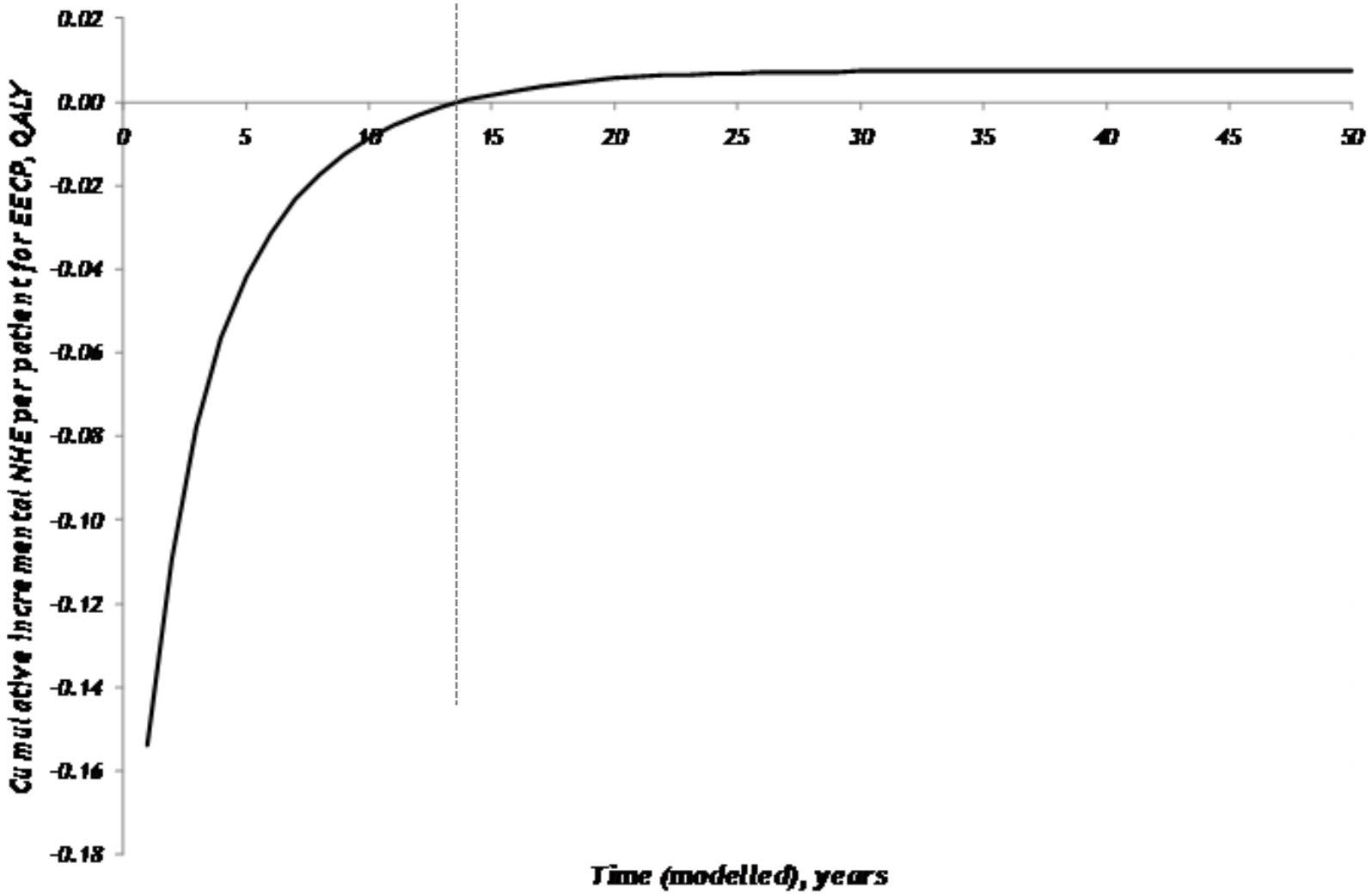
health expected to be gained (effectiveness and potential for harms) net of health expected to be forgone elsewhere (costs/threshold)

NHE > 0 is the same as ICER < threshold

Express NHE in £ (NHS resources required to achieve the same NHE)

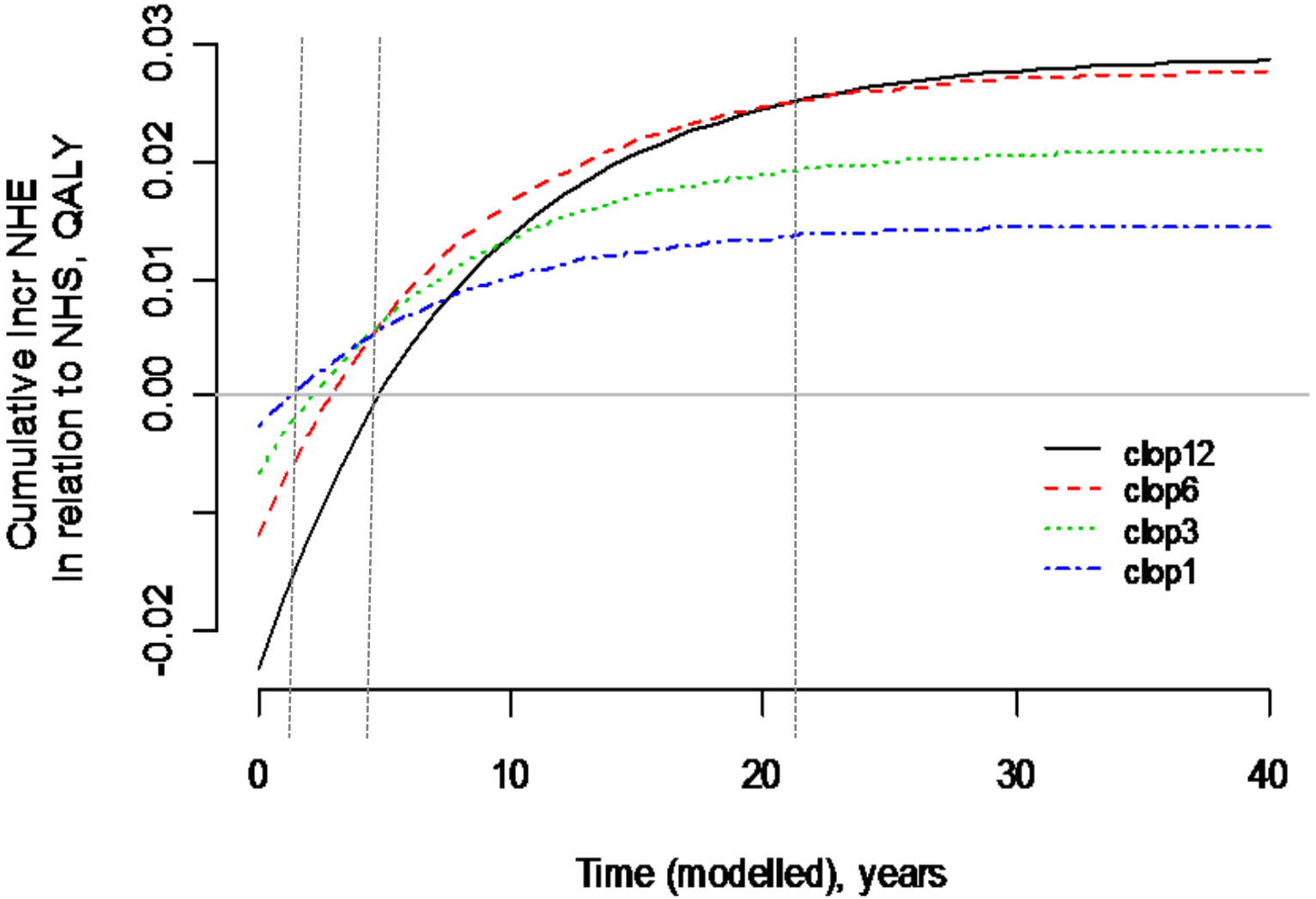
i) Cost-effectiveness at the patient level

Figure 3.1a Cumulative incremental NHE of EECP over the patient time horizon



i) Cost-effectiveness at the patient level

Figure 3.1b Cumulative incremental NHE of CLOP over the patient time horizon



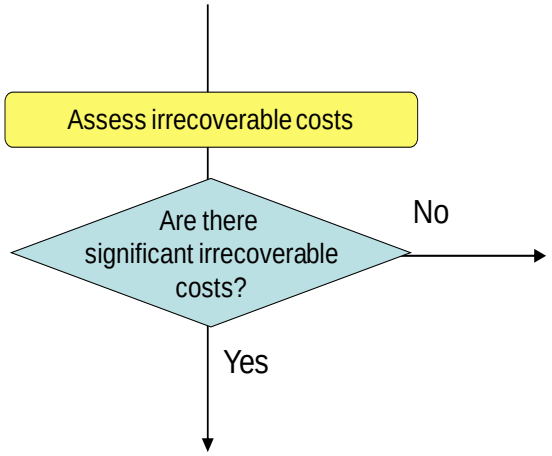
ii) Cost-effectiveness at the population level

Table 3.3b Expected cost-effectiveness of CLOP for the population

			Breakeven points (years)		
Technology time horizon	**Treatment**	**Incr NHE,** QALYs (£m)	**12 months vs 6 months**	**12 months vs NHS**	**1 month vs NHS**
5 years	1: clop12 2: clop6 3: clop3 4: clop1 5: NHS	269 (5.4) 1,881 (37.6) 1,804 (36.1) 4,073 (81.5) -	24	8	4
10 years	1: clop12 2: clop6 3: clop3 4: clop1 5: NHS	495 (9.9) 3,465 (69.3) 3,324 (66.5) 7,502 (150) -	27	11	4
15 years	1: clop12 2: clop6 3: clop3 4: clop1 5: NHS	686 (13.7) 4,799 (96) 4,603 (92.1) 10,389 (207.8) -	30	12	4
20 years	1: clop12 2: clop6 3: clop3 4: clop1 5: NHS	846 (16.9) 5,921 (118.4) 5,680 (113.6) 12,820 (256.4) -	33	12	4

3.3.2 Point 2 - Are there significant irrecoverable costs?

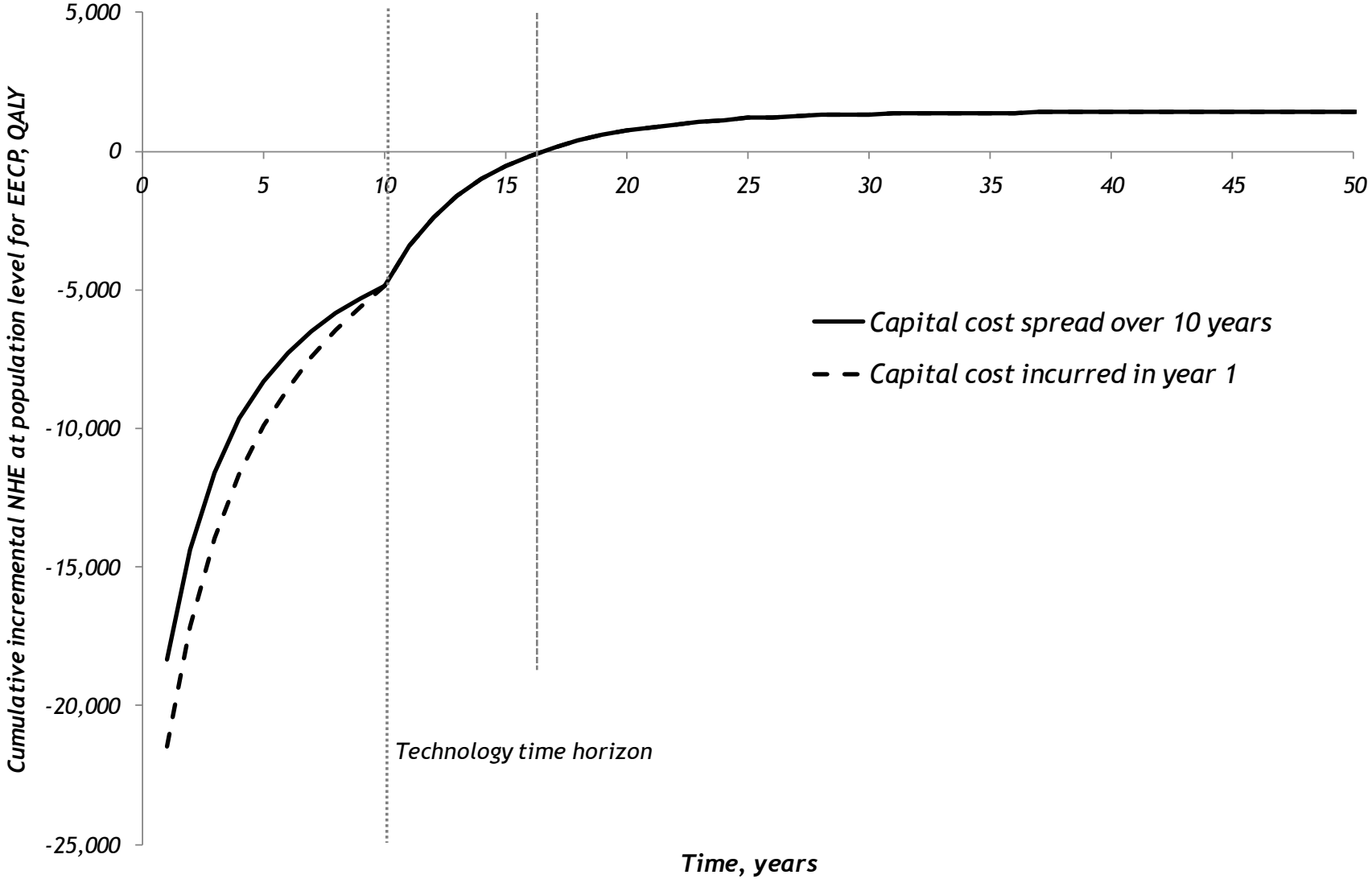
i. Are there irrecoverable costs
ii. A judgement of their potential significance



- No significant irrecoverable costs
  - 4 out of the 12 possible pathways require all 7 assessments
- Significant irrecoverable costs
  - 25 out of the 33 possible pathways require all 7 assessments

i) Irrecoverable capital costs and NHE profile

Figure 3.2 Cumulative incremental NHE of EECP for the population



ii) Are they significant

- Ultimately depends on subsequent events
  - Research reporting (Point 3,4, and 6)
  - Other sources of uncerinty (Point 5 and 6)
- Capital costs
  - Scale of capital costs (% of total)
  - Time to breakeven
- Initially negative NHE (irrecoverable opportunity costs)
  - Is the decision to treat irreversible – not significant
    - CLOP for acute condition – not significant
    - EECP and PsA chronic – maybe significant
    - OMAL – chronic but effect while on treatment, i.e., a poor rather than risky investment

Questions

- Is presenting cost-effectiveness in terms of expected population NHE (as well as over patient and technology time horizons) helpful?
- Is the assessment of irrecoverable costs (capital costs and initially negative NHE) useful?

3.4 Is further research required?

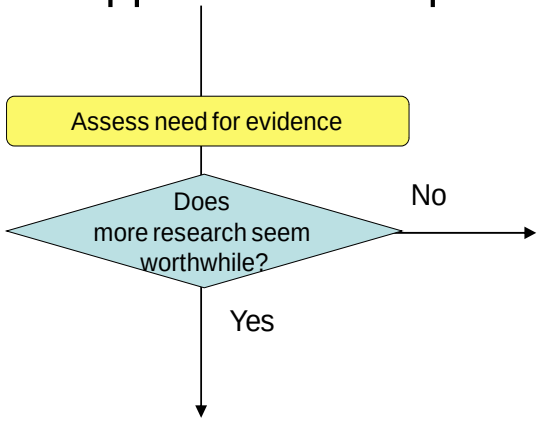
- Assessment and judgement at points 3 and 4 of the checklist
  - Sometimes leads directly to guidance
  - Determines whether OIR or AWR are possibilities

3.4.1 Point 3 – Does more research seem worthwhile?

i. How uncertain is a decision to approve or reject

ii. Do the likely consequences of uncertainty justify further research.

- NHE that could be gained if it could be resolved immediately
- Upper bound on potential benefits of more



'No' sometimes leads directly to guidance e.g., OMAL, pathway 12, Reject 4

Pathway number

Assessment	1	2	3	4	5	6	7	Guidance
6	Yes	No	No	-	-	-	-	Approve 4
12	No	No	No	-	-	-	-	Reject 4
35	No	Yes	No	-	-	-	-	Reject 11

i) Assessing the consequences of uncertainty

i. How uncertain is a decision based on expected cost-effectiveness

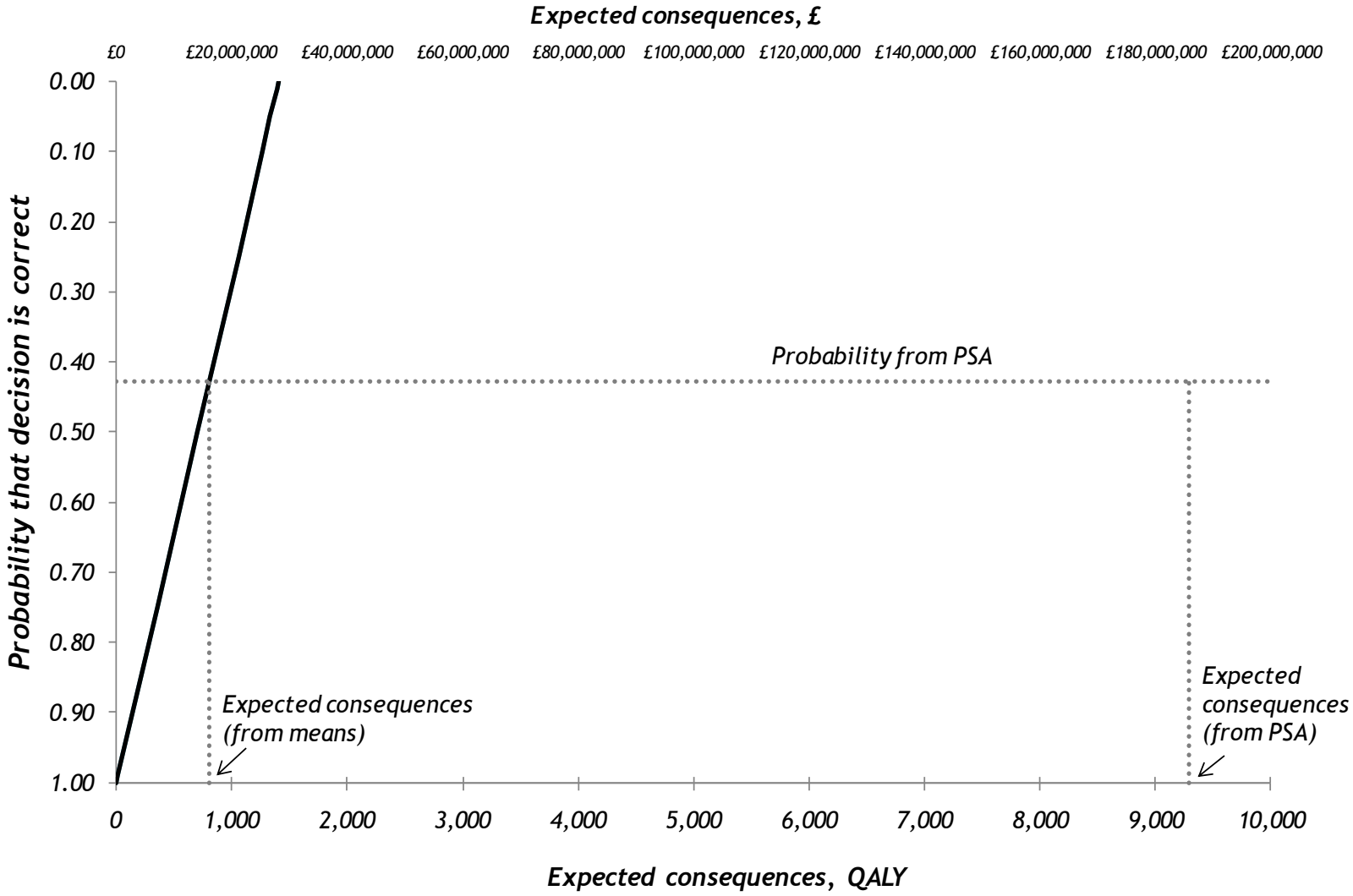
ii. What consequences, in terms of population NHE, are there likely to be if an incorrect decision is made.

Table 3.5a Expected consequences of uncertainty for EECP

		Cost-effectiveness threshold at: £20,000 per QALY			£30,000 per QALY		
Treatment	**ICER**	**Incr NHE** QALY (£m)	**Probability cost-effective**	**Expected consequences,** QALY (£m)	**Incr NHE,** QALY (£m)	**Probability cost-effective**	**Expected consequences,** QALY (£)
EECP	£19,391	1,405 (28.1)	0.428	9,287 (185.7)	1,405,930 (490)	0.7	2,774 (83.2)
Std		-	0.572		-	0.3	

i) Assessing the consequences of uncertainty

Table 3.5a Expected consequences of uncertainty for EECP



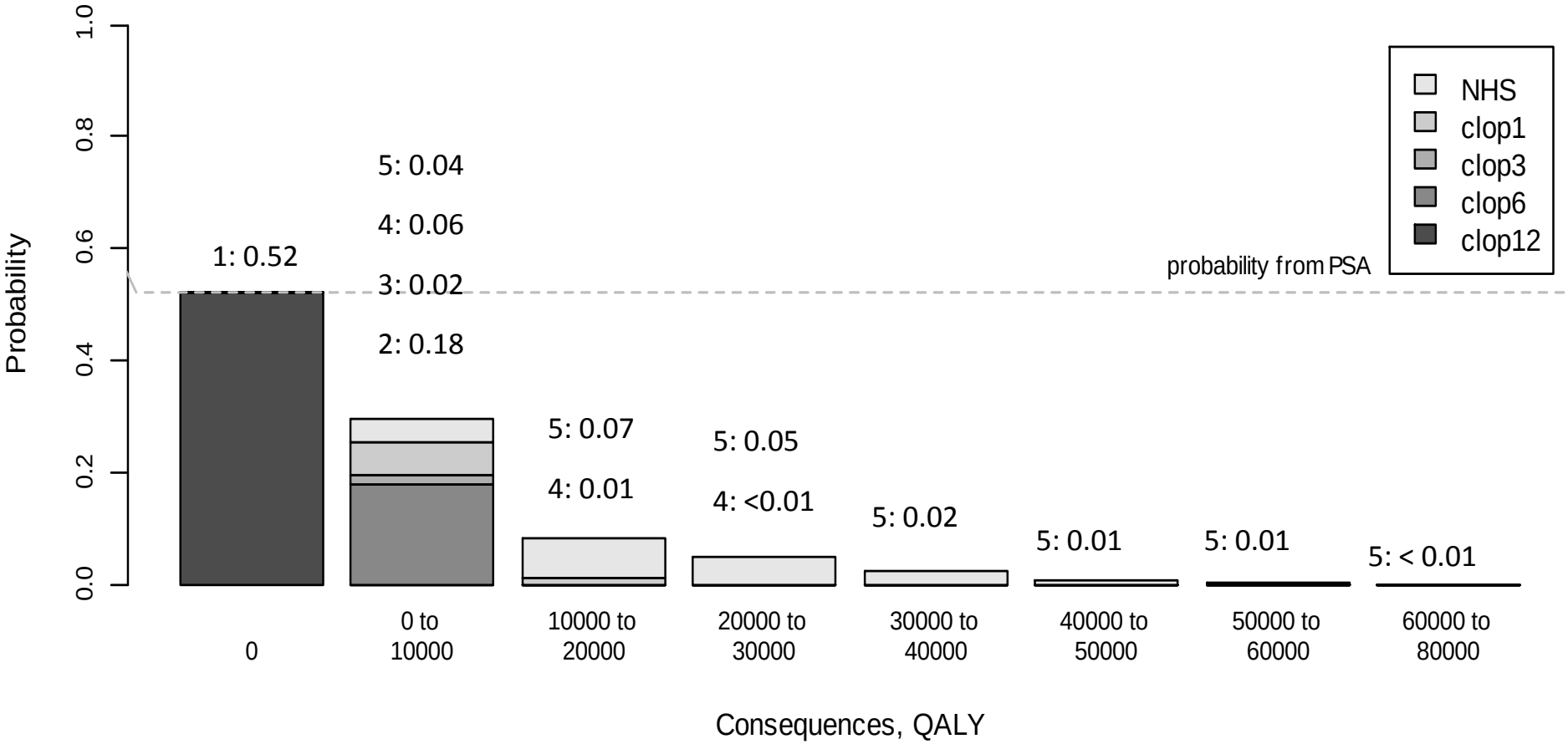
i) Assessing the consequences of uncertainty

Table 3.5b Expected consequences of uncertainty for CLOP

		Cost-effectiveness threshold at:					
		£20,000 per QALY			£30,000 per QALY		
Treatment	**ICER,**	**Incr NHE *** QALY (£m)	**Probability cost-effective**	**Expected consequences** QALY (£m)	**Incr NHE *** QALY (£m)	**Probability cost-effective**	**Expected consequences** QALY (£m)
1: clop12	£18,663	495 (9.9m)	0.524	5,194 (103.9)	2,798 (56.0m)	0.677	3,657 (109.7)
2: clop6	£10,477	3,465 (69.3m)	0.180		4,736 (94.7m)	0.092	
3: clop3	£9,396	3,324 (66.5m)	0.018		4,305 (86.1m)	0.009	
4: clop1	£4,961	7,502 (150.0m)	0.075		8,327 (166.5m)	0.052	
5: NHS	-	-	0.202		-	0.170	

i) Assessing the consequences of uncertainty

Figure 3.4b Distribution of the consequences of uncertainty for CLOP



ii) Analysis of subgroups

Table 3.5c Expected consequences of uncertainty for OMAL

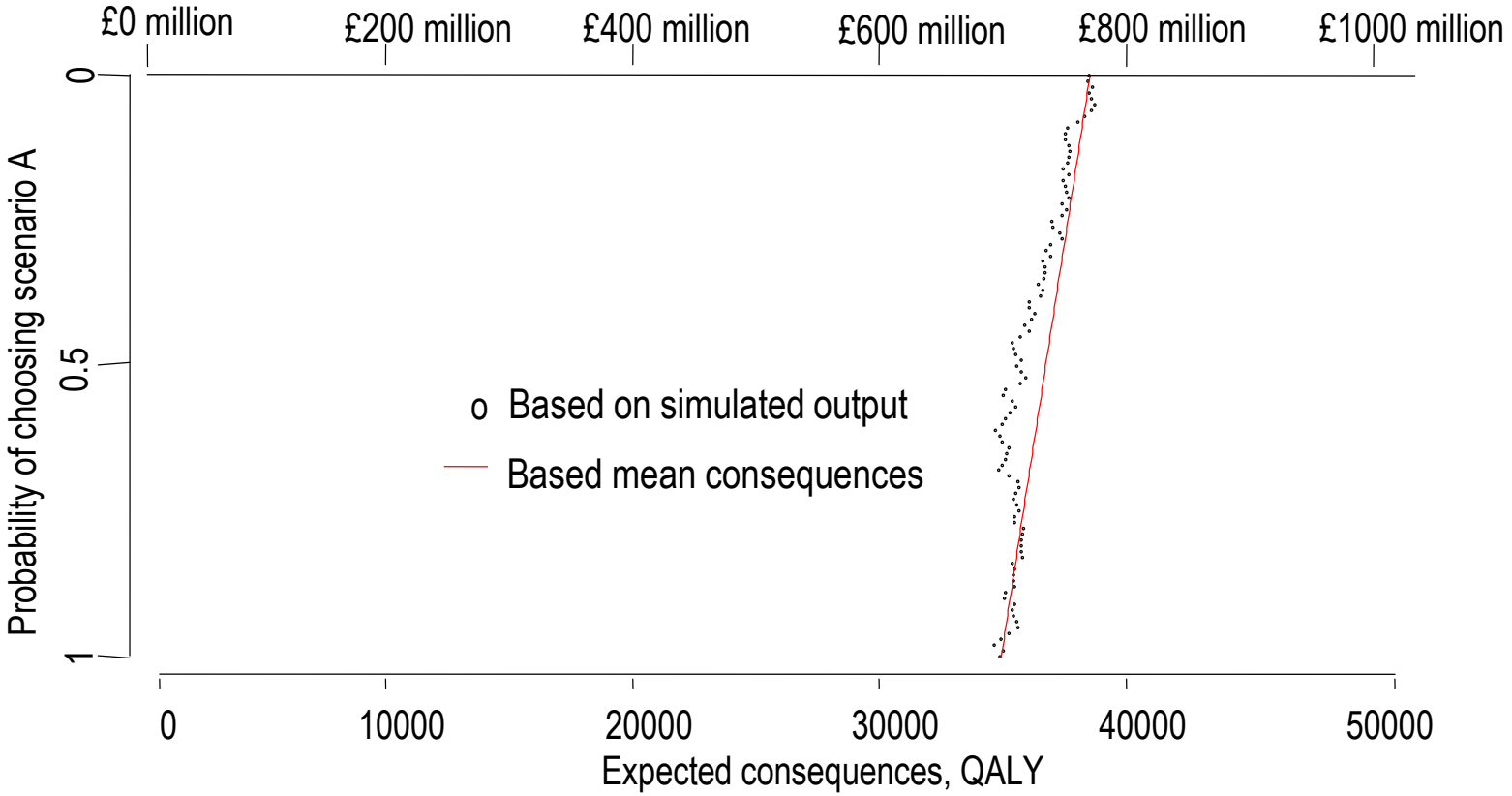
Severe population		**Cost-effectiveness threshold at:**					
		£20,000 per QALY			**£30,000 per QALY**		
Treatment	**ICER**	**Incr NHE** QALY (£m)	**Probability cost-effective**	**Expected consequences** QALY (£)	**Incr NHE** QALY (£m)	**Probability cost-effective**	**Expected consequences** QALY (£)
Omal + Std	£93,844	-5,789 (-116)	0.0	0	-3,337 (-100)	0.0	0.0
Std		-	1.0		-	1.0	
High risk subgroup		**Cost-effectiveness threshold at:**					
		£20,000 per QALY			**£30,000 per QALY**		
Treatment	**ICER**	**Incr NHE** QALY (£m)	**Probability cost-effective**	**Expected consequences,** QALY (£)	**Incr NHE** QALY (£m)	**Probability cost-effective**	**Expected consequences,** QALY (£m)
Omal + Std	£69,463	-3,851 (-77)	0.0	0	-2,048 (-61)	0.013	10.61 (0.32)
Std		-	1.0		-	0.987	

iii) Alternative scenarios

i. Implicit or explicit weights (probability) for scenarios (judgement following deliberation at the AC)

i. Uncerinty both between and within each scenario

Figure 3.5b Expected consequences of uncertainty with alternative scenarios (PsA)



iii) Alternative scenarios (elicitation)

- Uncertain parameters instead of assumptions (e.g., EECP)
- Equivalent to 3 scenarios with probabilities
  - Simple weighted average = 1,442 QALYs
  - Weighting the simulated output = 9,287 QALYs
  - All the information from elicitation = 13,081 QALYs

i. Simple weighted average maybe misleading
   - Under or over estimate

ii. Elicitation provide a richer characterisation of uncertainty
   - Implies the probabilities for alternative assumptions

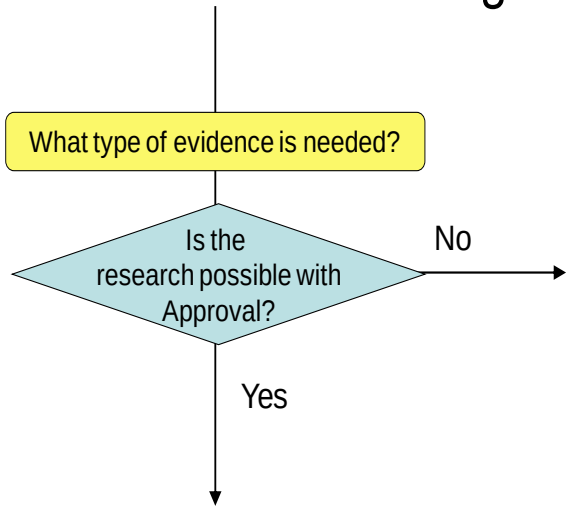
iii. Prior to AC deliberation
   - based on judgement of experts
   - In real time (e.g., TIDY)?

3.4.2 Point 4 - Is research possible with approval?

i. Type of evidence needed?

ii. Research required be conducted while approved?

- Importance of parameters (values that change the decision)
- Uncertainty in possible values (how likely to change)
- NHE that are to be gained (expected consequences)



- Assessment and judgement at point 4
  - Does not lead directly to guidance
  - Determines whether AWR is a possibility

i) Importance: how values related to NHE (CLOP)

	Parameter		Elasticity over the NHE (QALY) of clop12	clop6	clop3	clop1	NHS	Elasticity over the INHE (QALY) of clop12 vs. NHS	clop12 vs. clop6	clop12 vs. all
Natural history	1	P_die_0.1	-0.208	-0.207	-0.207	-0.207	-0.222	0.014	-	0.003
	2	P_NFMI_0.1	-0.012	-0.012	-0.011	-0.011	-0.015	0.004	-	-
	3	P_die_1.3	-0.137	-0.137	-0.137	-0.147	-0.145	0.008	-	0.004
	4	P_NFMI_1.3	-0.002	-0.002	-0.002	-0.002	-0.002	0.001	-	-
	5	P_die_3.6	-0.146	-0.146	-0.157	-0.157	-0.154	0.008	-	0.007
	6	P_NFMI_3.6	-0.005	-0.005	-0.007	-0.007	-0.007	0.002	-	0.001
	7	P_die_6.12	-0.148	-0.159	-0.158	-0.157	-0.155	0.007	0.011	0.010
	8	P_NFMI_6.12	-0.005	-0.007	-0.007	-0.007	-0.007	0.002	0.002	0.002
	9	TP_AC	-0.121	-0.120	-0.120	-0.120	-0.118	-0.003	-0.001	-0.002
	10	TP_AD	-3.637	-3.622	-3.604	-3.594	-3.541	-0.096	-0.016	-0.047
	11	TP_CD	-0.233	-0.235	-0.239	-0.240	-0.253	0.020	0.002	0.009
	12	TP_BD	-0.586	-0.593	-0.602	-0.605	-0.641	0.055	0.007	0.024
Utilities	13	U_Well	0.746	0.745	0.743	0.742	0.737	0.009	0.001	0.004
	14	U_Well1	6.090	6.064	6.034	6.017	5.929	0.160	0.026	0.079
	15	U_NFMI	0.133	0.134	0.136	0.136	0.144	-0.011	-0.001	-0.005
	16	U_POSTMI	1.138	1.150	1.165	1.171	1.236	-0.099	-0.012	-0.043
RE	17	RR_death	-0.639	-0.491	-0.344	-0.207		-0.641	-0.150	-0.380
	18	RR_NFMI	-0.024	-0.018	-0.013	-0.011		-0.025	-0.006	-0.014
Costs	19	C_Well	-0.740	-0.737	-0.733	-0.731	-0.720	-0.019	-0.003	-0.009
	20	C_MI_LT	-0.051	-0.052	-0.053	-0.053	-0.056	0.004	0.001	0.002
	21	C_PostMI	-0.142	-0.143	-0.145	-0.146	-0.154	0.012	0.002	0.005
	22	TC_Well_Dead	-0.027	-0.027	-0.027	-0.027	-0.027	-	-	-
	23	C_t1	-0.045	-	-	-	-	-0.045	-0.045	-0.045
	24	C_t2	-	-0.033	-	-	-	-	0.033	0.008
	25	C_t3	-	-	-0.026	-	-	-	-	0.007
	26	C_t4	-	-	-	-0.022	-	-	-	0.005
	27	C_t5	-	-	-	-	-0.016	0.016	-	0.004

i) Importance: what values change decisions (CLOP)

	Parameter		Mean value	Clop12	Clop6	Clop3	Clop1	NHS
Natural history	1	P_die_0.1	0.032	0 to 0.10	0.11 to 0.54	0.54 to 0.63	0.63 to 1	-
	2	P_NFMI_0.1	0.040	0 to 0.14	0.14 to 0.71	0.71 to 0.82	0.82 to 1	-
	3	P_die_1.3	0.022	0 to 0.10	0.10 to 0.55	0.55 to 1	-	-
	4	P_NFMI_1.3	0.004	0 to 0.10	0.10 to 0.7	0.7 to 1	-	-
	5	P_die_3.6	0.023	0.01 to 0.10	0.10 to 1	0 to 0.01	-	-
	6	P_NFMI_3.6	0.011	0 to 0.11	0.11 to 1	-	-	-
	7	P_die_6.12	0.024	0.02 to 1	0 to 0.02	-	-	-
	8	P_NFMI_6.12	0.009	0.005 to 1	0 to 0.005	-	-	-
	9	TP_AC	0.018	0 to 0.06	0.06 to 1	-	-	-
	10	TP_AD	0.072	0 to 0.08	0.08 to 0.10	-	-	0.10 to 1
	11	TP_CD	0.188	0.12 to 1	0 to 0.12	-	-	-
	12	TP_BD	0.070	0.06 to 1	0.04 to 0.06	-	-	0 to 0.04
Utilities	13	U_Well	0.798	0.29 to 1	0 to 0.29	-	-	-
	14	U_Well1	0.930	0.90 to 1	0.74 to 0.90	-	-	0 to 0.74
	15	U_NFMI	0.801	0 to 1	-	-	-	-
	16	U_POSTMI	0.931	0 to 1	-	-	-	-
RE	17	RR_death	0.931	0 to 0.93	0.94 to 0.97	0.97 to 0.98	0.98 to 0.99	1.00 to max*
	18	RR_NFMI	0.710	0 to 0.82	0.83 to 1.55	1.56 to 1.83	-	1.84 to max*
Costs	19	C_Well	2061.5	0 to 2690	2690 to 5611	-	-	5611 to max*
	20	C_MI_LT	6050.0	0 to max*	-	-	-	-
	21	C_PostMI	2309.7	870 to max*	0 to 870	-	-	-
	22	TC_Well_Dead	871.5	0 to 20474	20474 to max*	-	-	-
	23	C_t1	895.1	0 to 910	910 to max*	-	-	-
	24	C_t2	651.6	630 to max*	0 to 630	-	-	-
	25	C_t3	524.2	370 to max*	-	0 to 370	-	-
	26	C_t4	434.8	150 to max*	-	-	0 to 150	-
	27	C_t5	329.8	0 to max	-	-	-	-

ii) How likely to change decisions (CLOP)

Table 3.6a Probabilities associated with parameter values (CLOP)

	Parameter	Clop12	Clop6	Clop3	Clop1	NHS
Natural history	1 P_die_0.1	1	-	-	-	-
	2 P_NFMI_0.1	1	-	-	-	-
	3 P_die_1.3	1	-	-	-	-
	4 P_NFMI_1.3	1	-	-	-	-
	5 P_die_3.6	1	-	-	-	-
	6 P_NFMI_3.6	1	-	-	-	-
	7 P_die_6.12	0.65	0.35	-	-	-
	8 P_NFMI_6.12	0.91	0.09	-	-	-
	9 TP_AC	1	-	-	-	-
	10 TP_AD	0.83	0.17	-	-	-
	11 TP_CD	1	-	-	-	-
	12 TP_BD	0.85	0.15	-	-	-
Utilities	13 U_Well	1	-	-	-	-
	14 U_Well1	0.94	0.06	-	-	-
	15 U_NFMI	1	-	-	-	-
	16 U_POSTMI	1	-	-	-	-
RE	17 RR_death	0.55	0.18	0.01	0.10	0.16
	18 RR_NFMI	0.97	0.03	-	-	-
Costs	19 C_Well	0.78	0.19	-	-	0.03
	20 C_MI_LT	1	-	-	-	-
	21 C_PostMI	0.89	0.11	-	-	-
	22 TC_Well_Dead	1	-	-	-	-
	23 C_t1	0.95	0.05	-	-	-
	24 C_t2	0.99	0.01	-	-	-
	25 C_t3	1	-	-	-	-
	26 C_t4	1	-	-	-	-
	27 C_t5	1	-	-	-	-

iii) Expected consequences (importance and uncerinty)

Table 3.6b Consequences of uncertainty associated with parameter values (CLOP)

		Decomposed by treatment choice					
Parameter		clop12	clop6	clop3	clop1	NHS	Overall
Natural history*	1 P_die_0.1	0	-	-	-	-	-
	2 P_NFMI_0.1	0	-	-	-	-	-
	3 P_die_1.3	0	-	-	-	-	-
	4 P_NFMI_1.3	0	-	-	-	-	-
	5 P_die_3.6	0	-	-	-	-	-
	6 P_NFMI_3.6	0	-	-	-	-	-
	7 P_die_6.12	0	250	-	-	-	250
	8 P_NFMI_6.12	0	9	-	-	-	9
	9 TP_AC	0	-	-	-	-	-
	10 TP_AD	0	47	-	-	-	47
	11 TP_CD	0	-	-	-	-	-
	12 TP_BD	0	35	-	-	-	35
Utilities*	13 U_Well	0	-	-	-	-	-
	14 U_Well1	0	10	-	-	-	10
	15 U_NFMI	0	-	-	-	-	-
	16 U_POSTMI	0	-	-	-	-	-
RE	17 RR_death	0	284	16	518	3614	4433
	18 RR_NFMI	0	3	-	-	-	3
Costs*	19 C_Well	0	153	-	-	321	474
	20 C_MI_LT	0	-	-	-	-	-
	21 C_PostMI	0	8	-	-	-	8
	22 TC_Well_Dead	0	-	-	-	-	-
	23 C_t1	0	8	-	-	-	8
	24 C_t2	0	0	-	-	-	-
	25 C_t3	0	-	-	-	-	-
	26 C_t4	0	-	-	-	-	-
	27 C_t5	0	-	-	-	-	-

Implications for case studies?

- CLOP
  - Relative effect so probably 'No' (AWR not possible)
  - Sequence if OIR after AWR is feasible?
- EECP
  - Effect on QoI (12months and longer run)
  - 'No' (AWR not possible) but examine 'Yes' (AWR possible)
- OMAL
  - No research needed – Reject[4]
  - Subgroup? No research need – Reject[4]
- PsA
  - Natural history (HAQ progression) so 'Yes'
  - Relative effect (of alternatives to etanercept) so probably 'Yes'
  - AWR for etanercept (OIR for comparators) seems possible for PsA

Questions

- Is an assessment of the expected consequences of uncertainty helpful?
- Which ways of presenting the importance, uncertainty and consequences of different groups of parameters (i.e., types of evidence) help the assessment of what evidence might be needed?
- Is the analysis of uncertain assumptions (between scenarios, as well as within) important and might elicitation play a greater role?

3.5 Do the benefits of research exceed the costs?

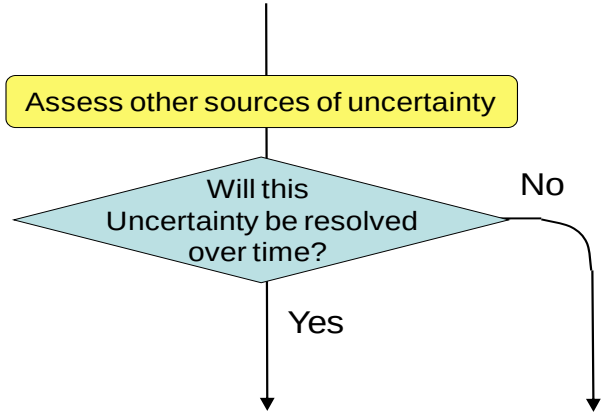
- Assessment and judgement at points 5 and 6 of the checklist
  - leads directly to guidance in many circumstances
- Other sources of uncerinty need to be assessed first
  - Will influence the potential benefits of research
  - Influence the category of guidance if significant irrecoverable costs
    - even when research is not needed

3.5.1 Point 5 - Will other sources of uncertainty resolve over time?

i. Other sources of uncertainty
   - Changes in price (technology and comparators)
   - New technologies entering
   - Other evidence becoming available

ii. Impact on benefits of research – Point 6

iii. Impact of benefits and costs of early approval – Point 7



Pathway number

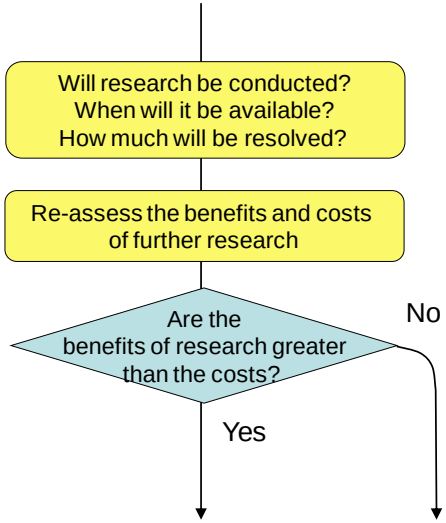
Assessment	1	2	3	4	5	6	7	Guidance
29	Yes	Yes	No	-	No	-	-	Approve 12

Implications for case studies?

- Change in price
  - Dates for patent expiry in UK (restricted access)
  - Extent of price reduction (generics) (limited)
- New technologies
  - Topic selection, NHS Horizon Scanning licence applications (restricted)
  - Phase I,II,III research, probability and time to launch
  - Scenarios: A = make obsolete; B = Similar to existing
- Other research
  - Trial and other research registries
- CLOP
  - Generic entry in 7 years (25% of brand)
  - Scenarios A and B for new technologies
- EECP
  - Scenarios A and B for new technologies

3.5.1 Point 6 – Are the benefits of research greater than the costs?

i. Will the research be conducted
ii. When will it be available
iii. How much will be resolved?
iv. Impact of other sources (point 5)

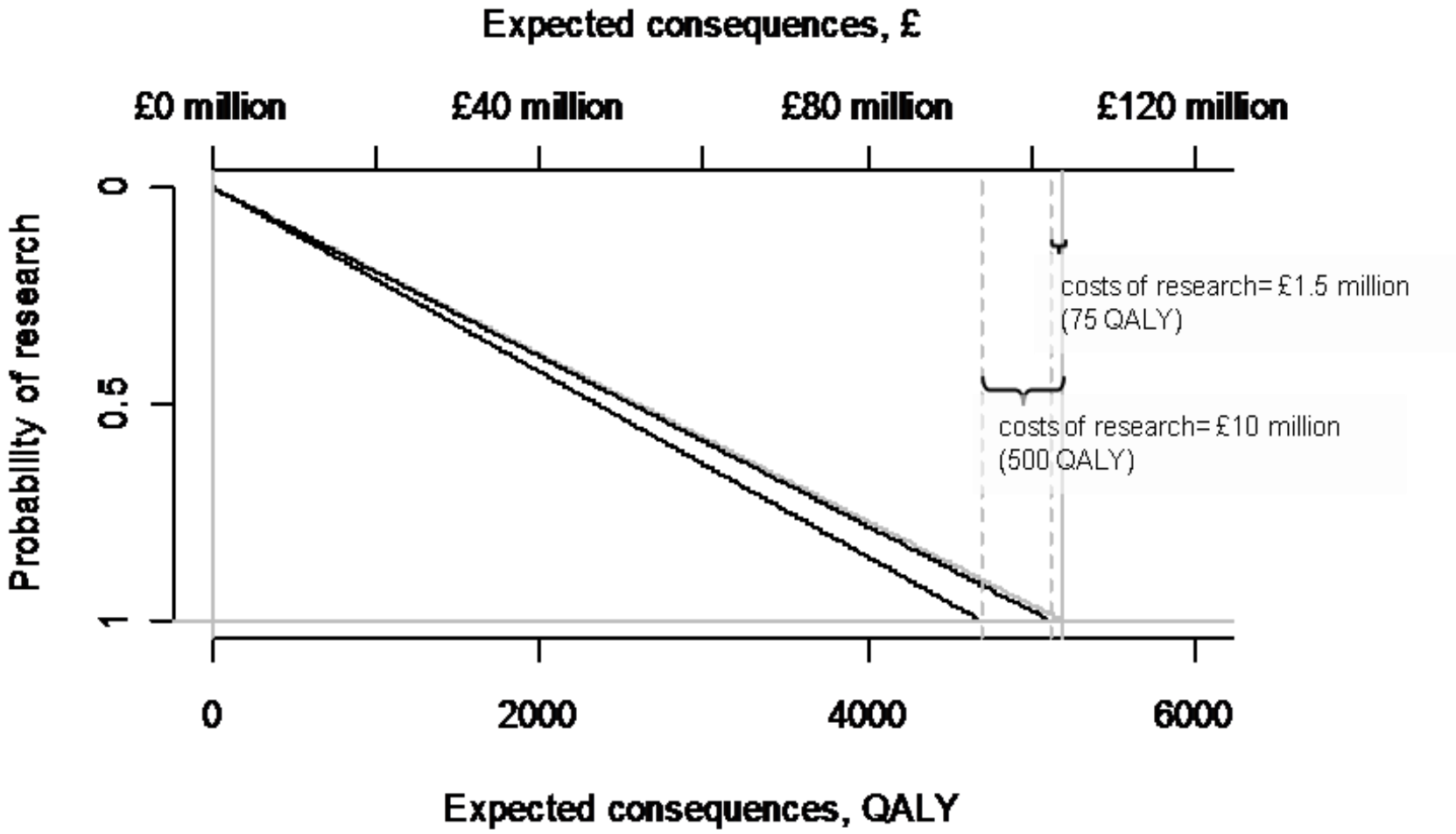


Pathway number

Assessment	1	2	3	4	5	6	7	Guidance
1	Yes	No	Yes	Yes	Yes/No	Yes	-	AWR 1
2	Yes	No	Yes	Yes	Yes/No	No	-	Approve 1
5	Yes	No	Yes	No	Yes/No	No	-	Approve3
7	No	No	Yes	Yes	Yes/No	Yes	-	OIR 2
8	No	No	Yes	Yes	Yes/No	No	-	Reject 1
11	No	No	Yes	No	Yes/No	No	-	Reject 3
19	Yes	Yes	Yes	Yes	No	No	-	Approve 6
26	Yes	Yes	Yes	No	No	No	-	Approve 10
30	No	Yes	Yes	Yes	Yes/No	Yes	-	OIR 7
31	No	Yes	Yes	Yes	Yes/No	No	-	Reject 8
34	No	Yes	Yes	No	Yes/No	No	-	Reject 10

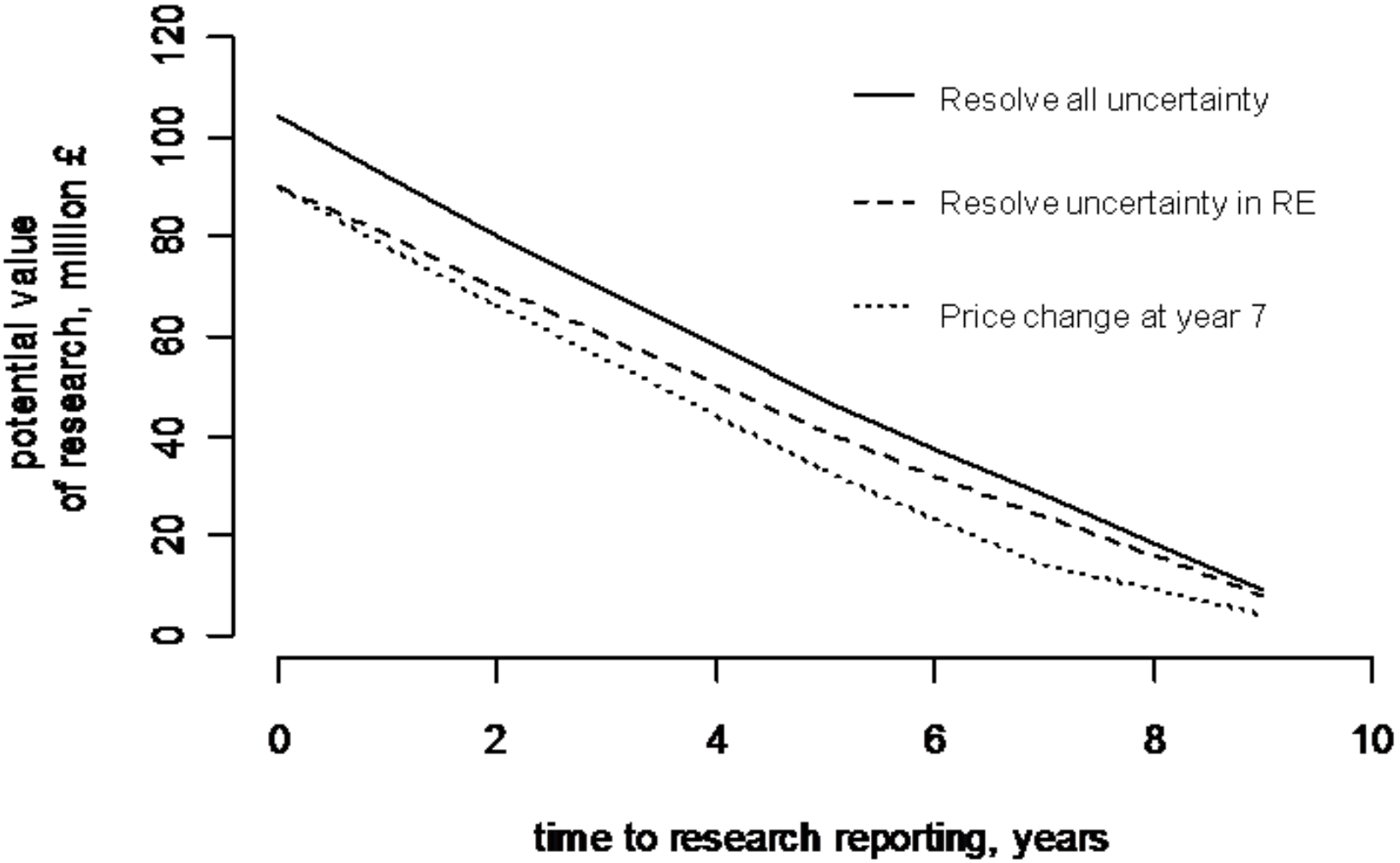
i) Will the research be conducted?

Figure 3.6a Expected potential benefits of research (CLOP)



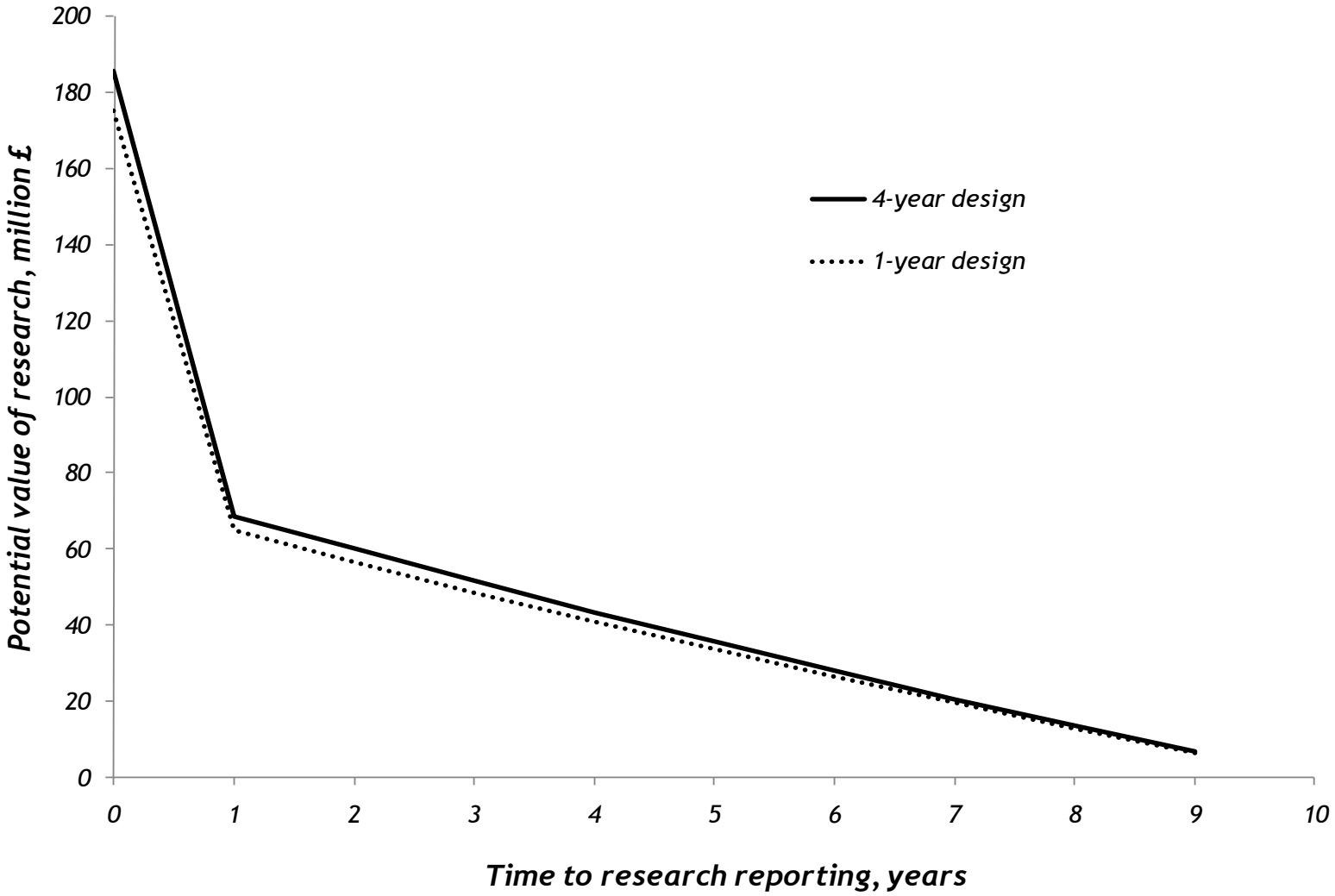
ii) When will it be available?

Figure 3.7a Potential value of research and time to report (CLOP)



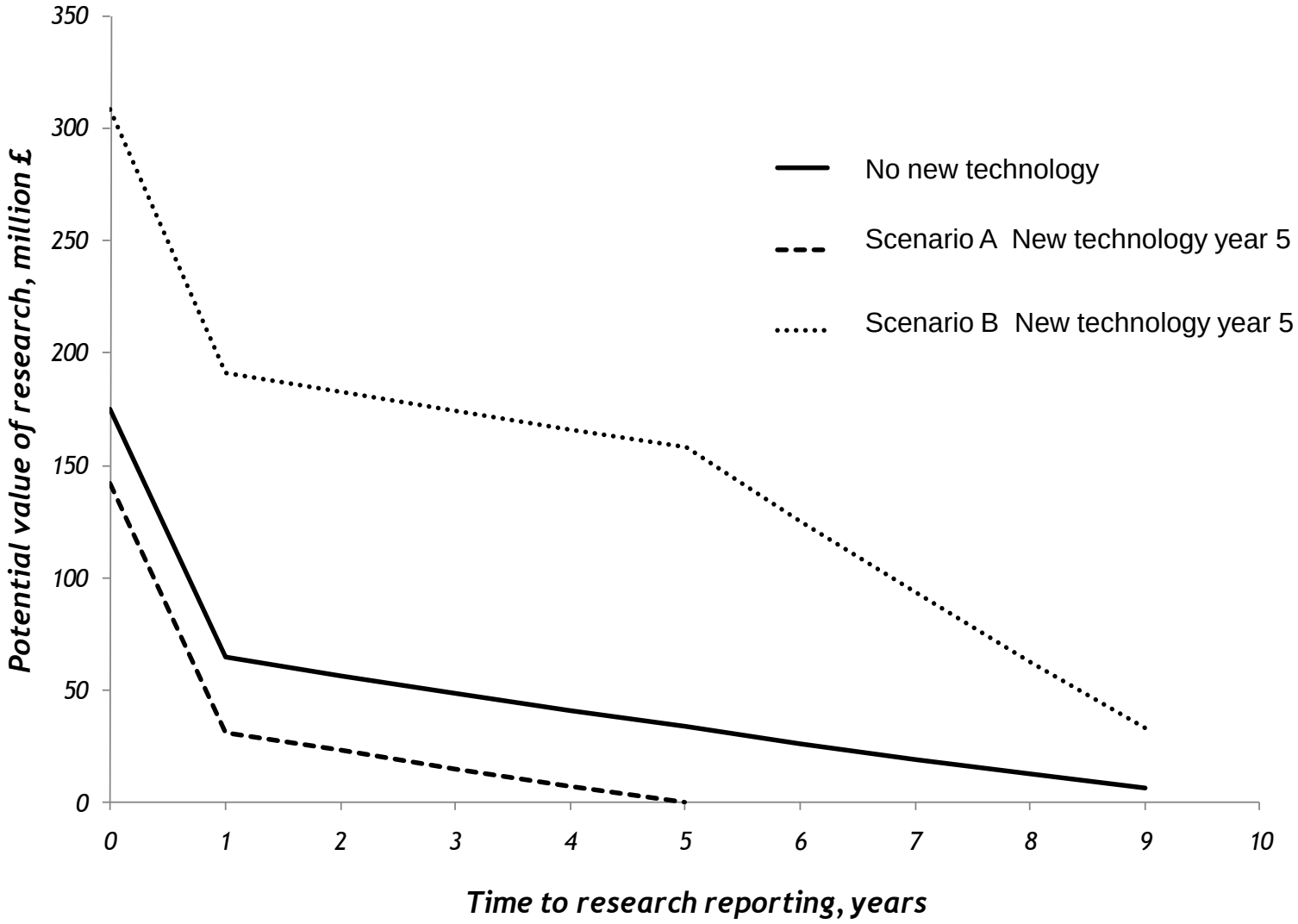
iii) How much will be resolved?

Figure 3.7b Potential benefits of research and time to report (EECP)



iv) Other sources of uncertainty?

Figure 3.7b Potential benefits of research and time to report (EECP)

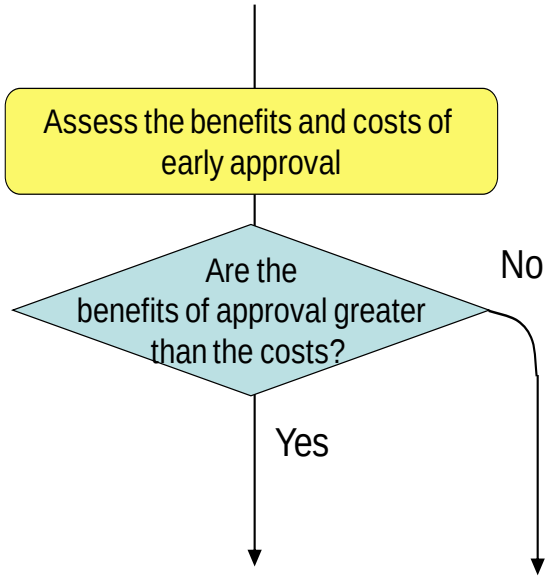


Questions

- How can access to the additional information required to assess other sources of uncertainty that might resolve over time be made more readily available to TAR teams, ERGs and manufacturers?
- Can the judgements required to assess the benefits of research be reasonably made by the AC alone
  - e.g., will research be conducted, when will it be available, how much will be resolved and what are the likely costs of the research?

3.6 Point 7 – Are the benefits of approval greater than the costs

- Benefits of approval
  - Expected additional NHE for the target population
- Costs of approval are opportunity costs
  - Potential value of research which maybe forgone
    - NHE for future patents
  - Irrecoverable costs committed by approval
    - Capital costs (equipment, facilities, training and learning)
    - Initially negative NHE (when treatment decisions can be changed)



Always leads directly to guidance

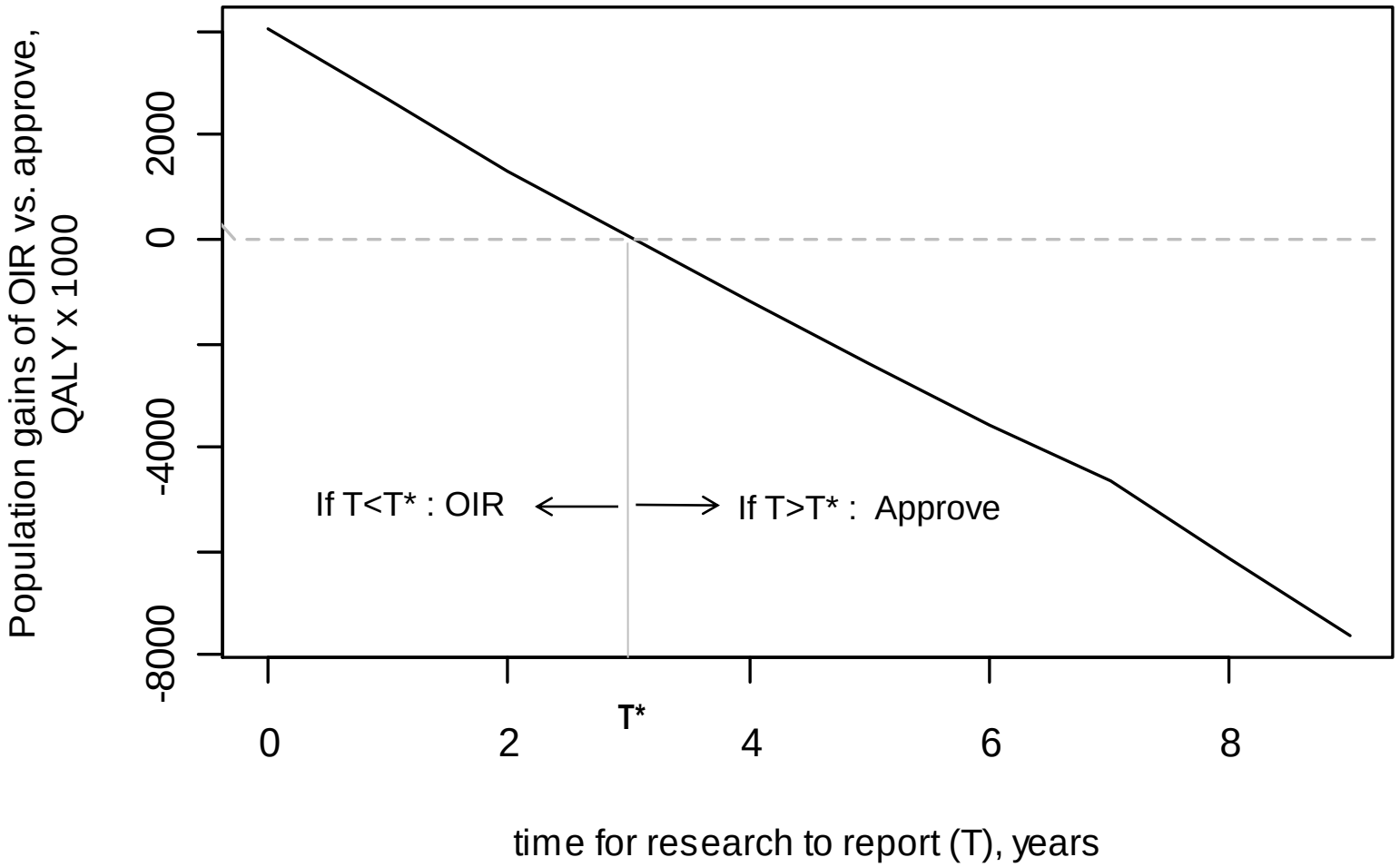
Pathway number

Assessment	1	2	3	4	5	6	7	Guidance
3	Yes	No	Yes	No	Yes/No	Yes	Yes	Approve 2
4	Yes	No	Yes	No	Yes/No	Yes	No	OIR 1
9	No	No	Yes	No	Yes/No	Yes	Yes	AWR 2
10	No	No	Yes	No	Yes/No	Yes	No	Reject 2
13	Yes	Yes	Yes	Yes	Yes	Yes	Yes	AWR 3
14	Yes	Yes	Yes	Yes	Yes	Yes	No	OIR 3
15	Yes	Yes	Yes	Yes	Yes	No	Yes	Approve 5
16	Yes	Yes	Yes	Yes	Yes	No	No	Reject 5
17	Yes	Yes	Yes	Yes	No	Yes	Yes	AWR 4
18	Yes	Yes	Yes	Yes	No	Yes	No	OIR 4
20	Yes	Yes	Yes	No	Yes	Yes	Yes	Approve 7
21	Yes	Yes	Yes	No	Yes	Yes	No	OIR 5
22	Yes	Yes	Yes	No	Yes	No	Yes	Approve 8
23	Yes	Yes	Yes	No	Yes	No	No	Reject 6
24	Yes	Yes	Yes	No	No	Yes	Yes	Approve 9
25	Yes	Yes	Yes	No	No	Yes	No	OIR 6
27	Yes	Yes	No	n/a	Yes	n/a	Yes	Approve 11
28	Yes	Yes	No	n/a	Yes	n/a	No	Reject 7
32	No	Yes	Yes	No	Yes/No	Yes	Yes	AWR 5
33	No	Yes	Yes	No	Yes/No	Yes	No	Reject 9

Significant irrecoverable costs

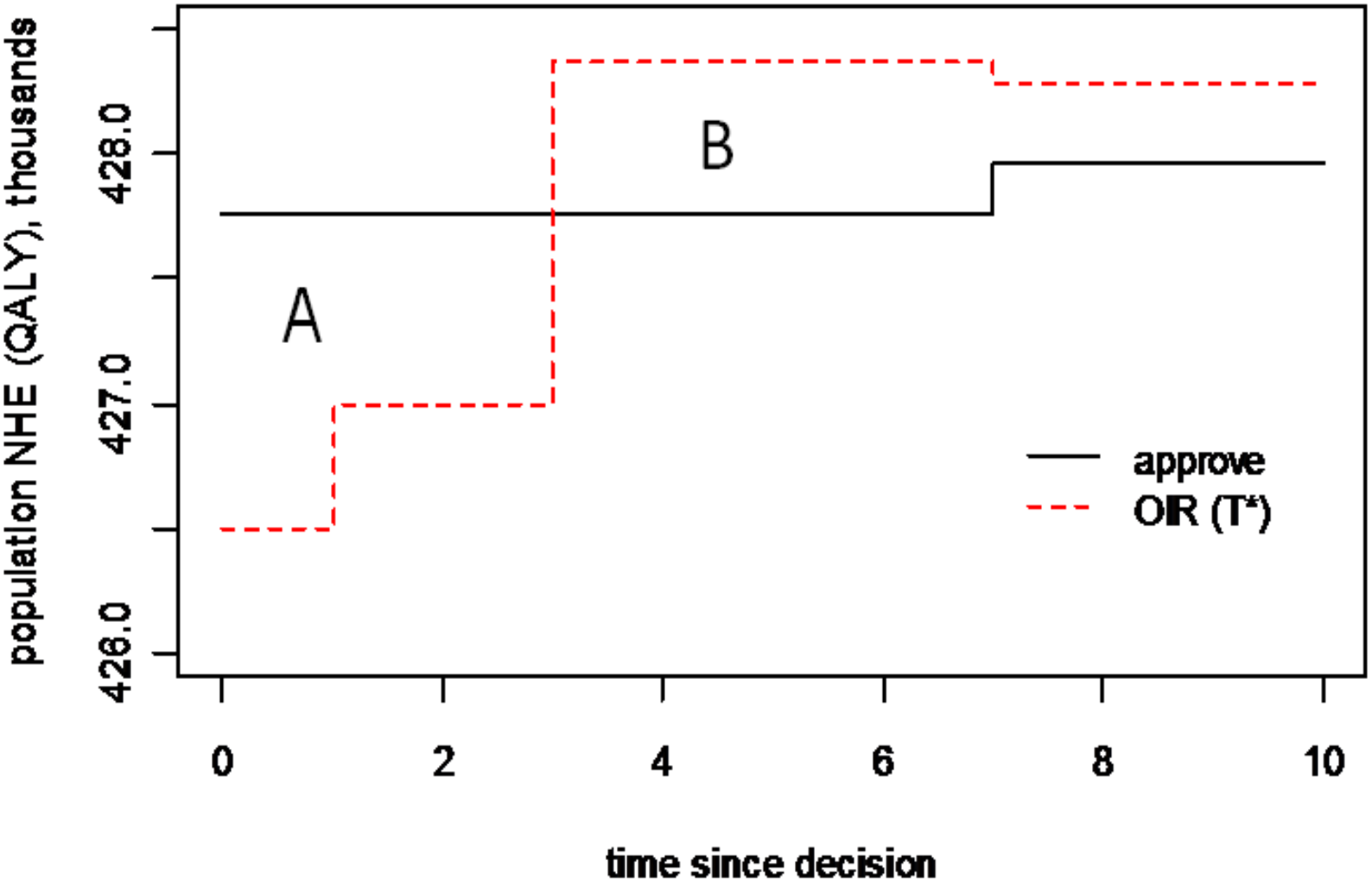
3.6.1 Technologies without significant irrecoverable costs

Figure 3.9a Population NHE of Approve and OIR for time to research reporting (CLOP)



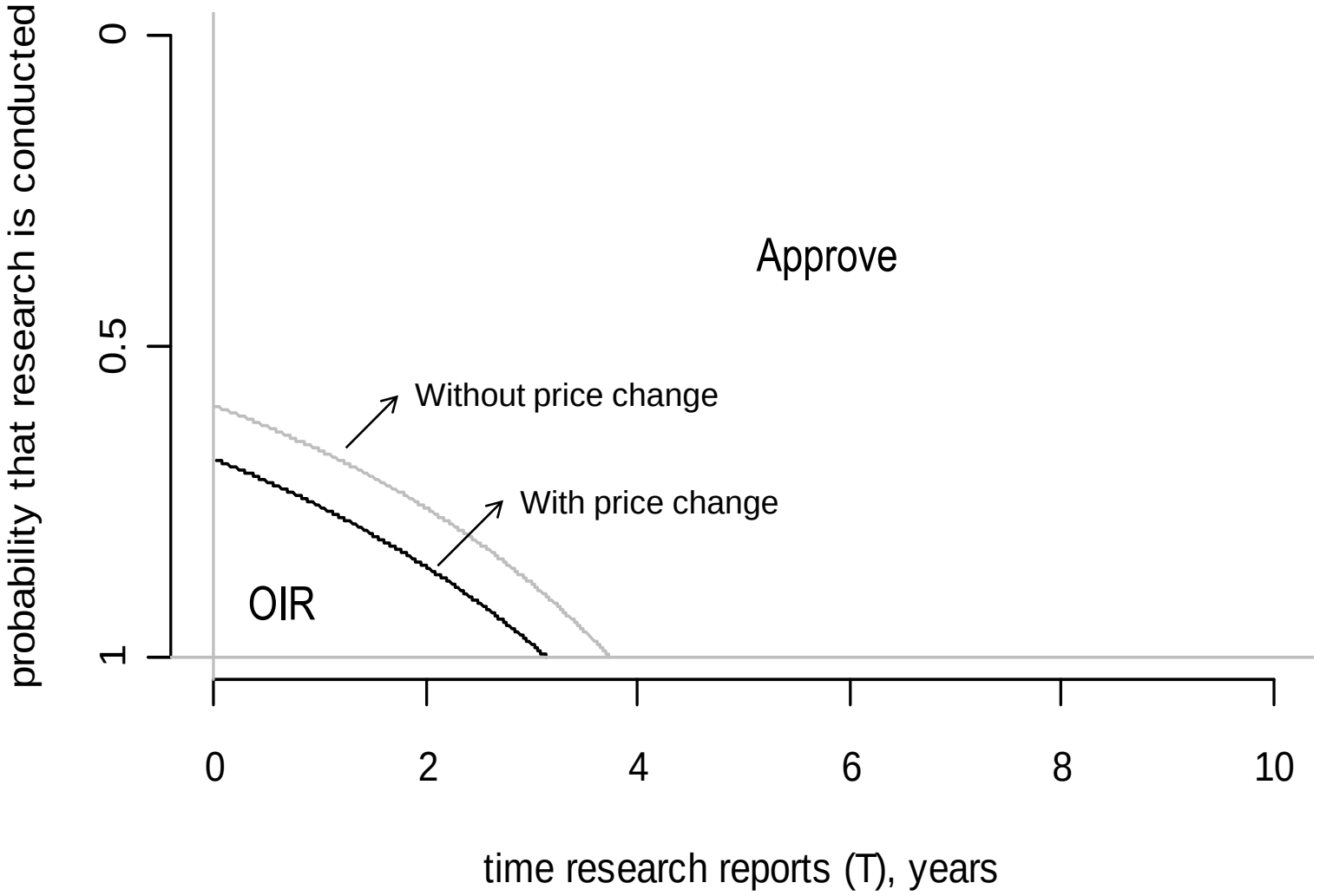
3.6.1 Technologies without significant irrecoverable costs

Figure 3.10 Population NHE of Approve and OIR at T* (CLOP)



3.6.1 Technologies without significant irrecoverable costs

Figure 3.11a An OIR or Approve boundary (CLOP)



3.6.1 Technologies without significant irrecoverable costs

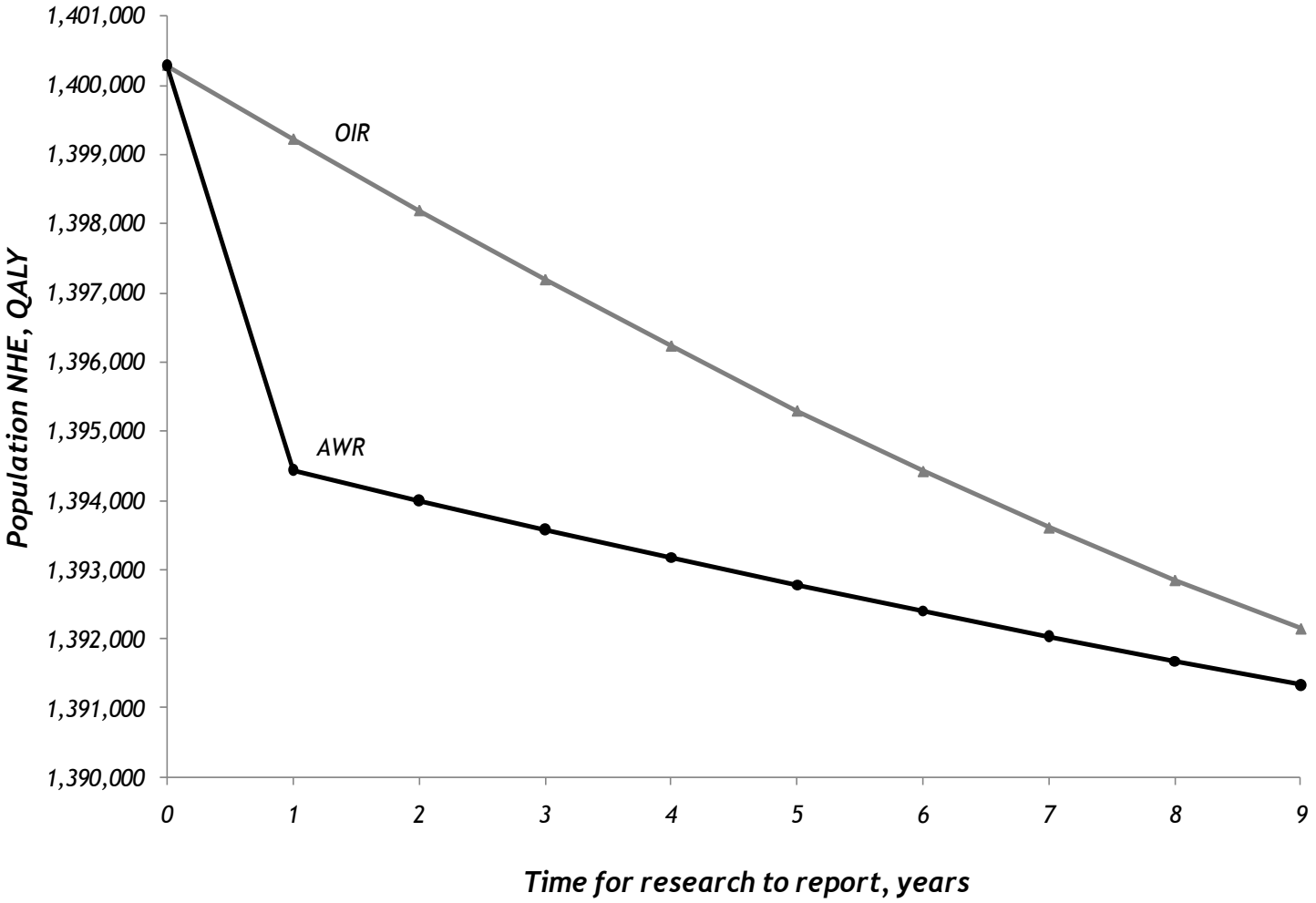
Table 3.7a Population NHE over the technology time horizon for different policies (CLOP)

	Approve	OIR	AWR*	Reject	Value of AWR	Uncertainty resolved at launch	Value of evidence at launch
Expressed in QALY							
T<T* (T=2)	3,680,187	3,681,480	3,682,995	3,671,660	1,515	3,684,181	2,701
T>T* (T=7)	3,680,187	3,675,487	3,680,362	3,671,660	175	3,684,181	3,994
NHE expressed in £m							
T<T* (T=2)	73,604	73,630	73,660	73,433	30	73,684	54
T>T* (T=7)	73,604	73,510	73,607	73,433	4	73,684	80

- Investments which might make AWR possible
- Value of having the evidence needed at Launch
  - Policies for better, more relevant an timely evidence
- Commercial value of AWR and early evidence
  - When should research be publically funded
  - How should value and costs be shared
  - Absolute and comparative advantage

3.6.2 Technologies with significant irrecoverable costs
i) Research is possible with approval

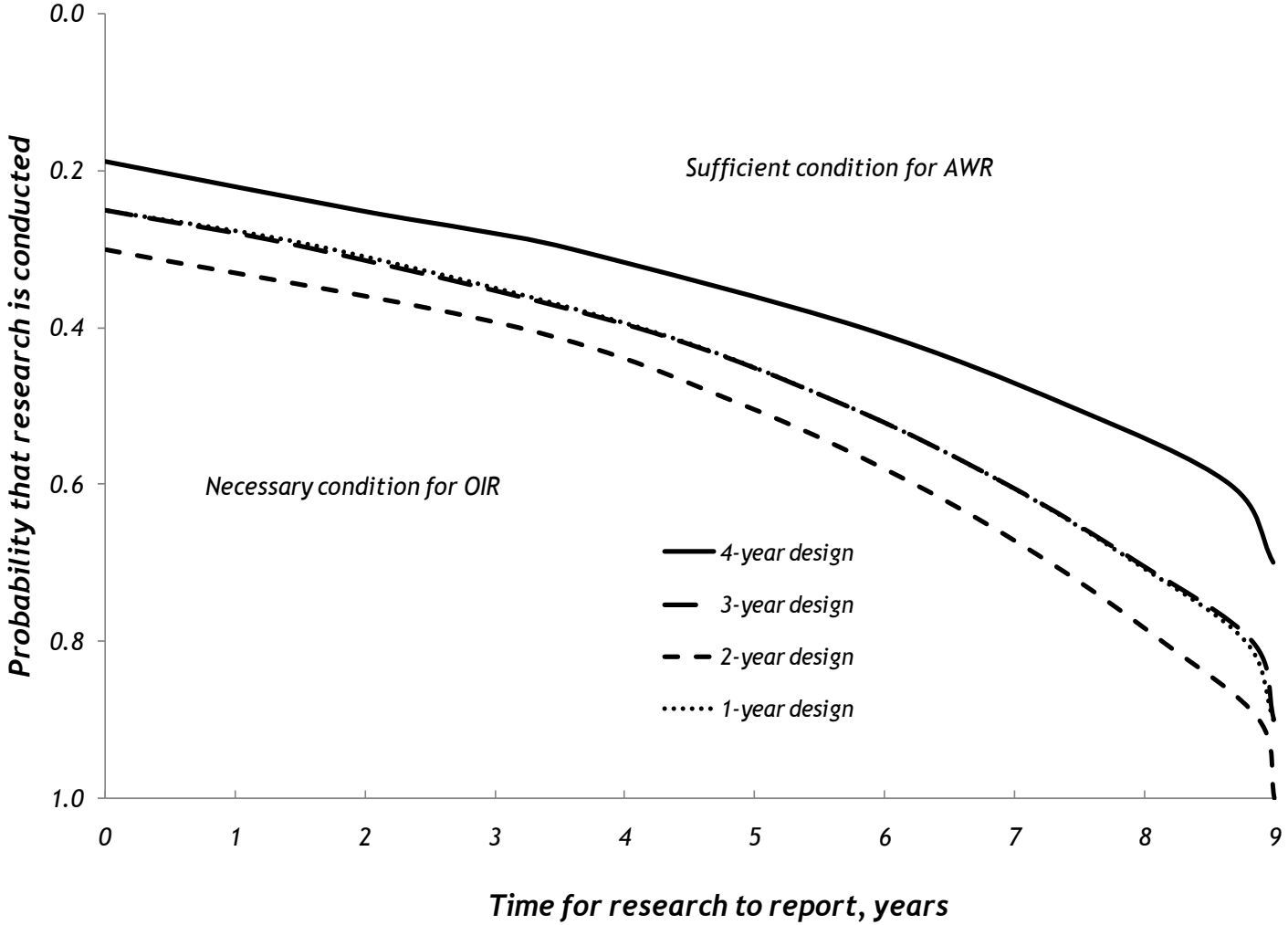
Figure 3.9b Population NHE of Approve and OIR for time to research reporting (EECP)



3.6.2 Technologies with significant irrecoverable costs

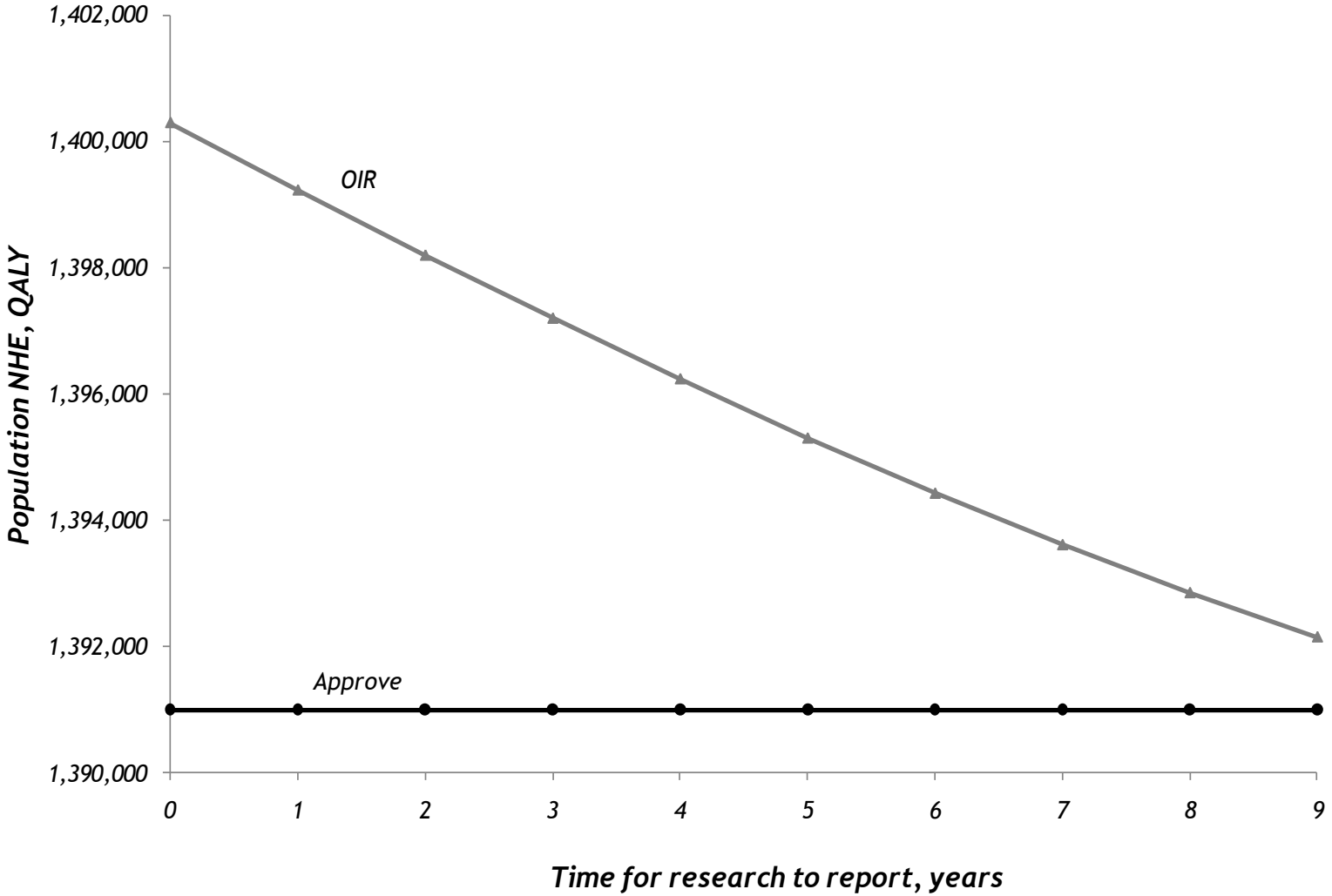
i) Research is possible with approval

Figure 3.11b An OIR or AWR boundary (EECP)



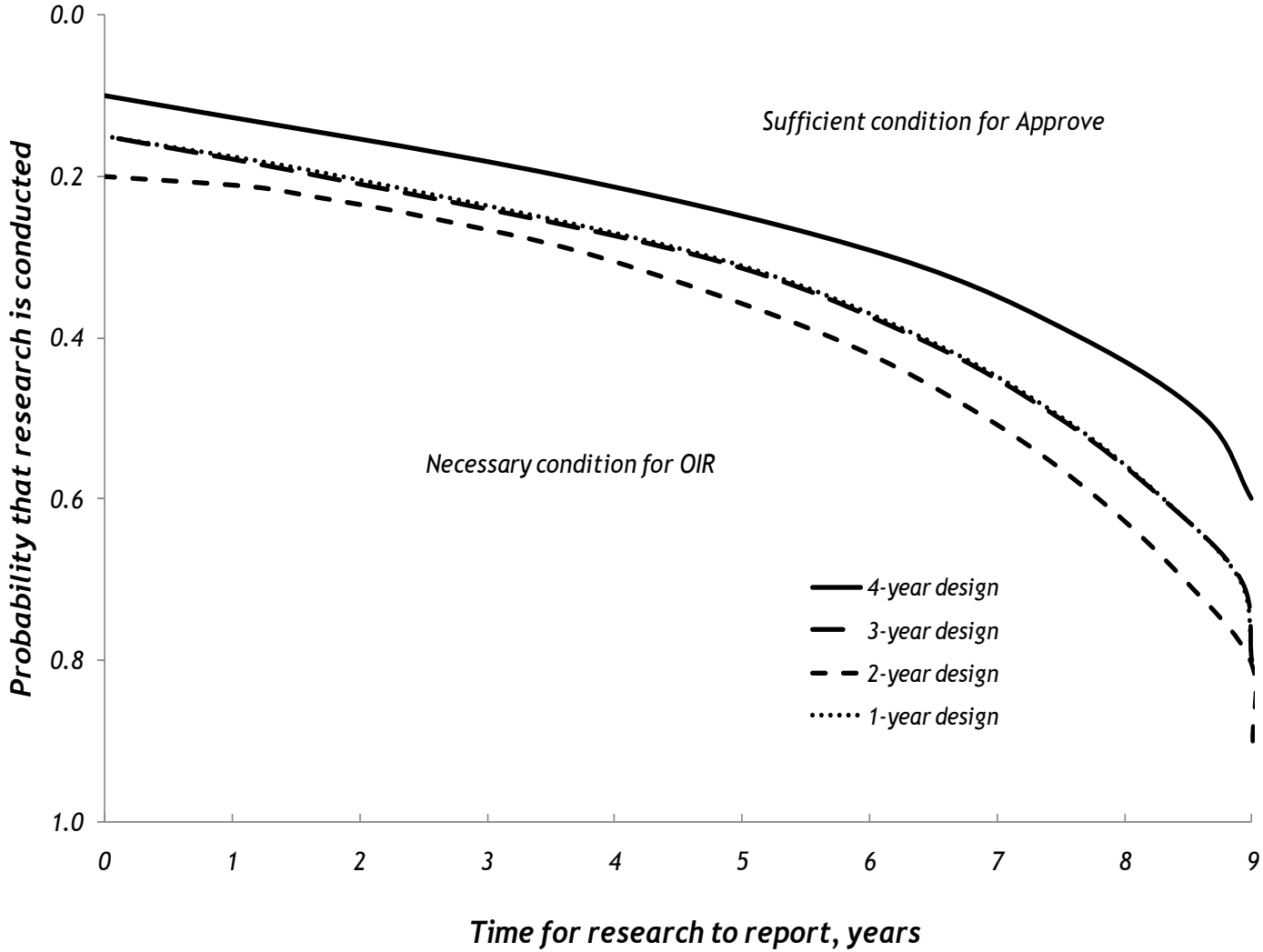
3.6.2 Technologies with significant irrecoverable costs
ii) Research is not possible with approval

Figure 3.9c Population NHE of Approve and OIR for time to research reporting (EECP)



3.6.2 Technologies with significant irrecoverable costs
ii) Research is not possible with approval

Figure 3.11c An OIR or Approve boundary (EECP)



3.6.2 Technologies with significant irrecoverable costs

Table 3.7a Population NHE over the technology time horizon for different policies (CLOP)

	Approve	OIR	AWR	Reject	Value of AWR	Uncertainty resolved at launch	Value of evidence at launch
Expressed in QALY							
T=3	1,391,001	**1,397,192**	1,393,578	1,389,596	-3,614	1,400,288	3,096
T=7	1,391,001	**1,393,608**	1,392,030	1,389,596	-1,578	1,400,288	6,680
Expressed in £m							
T=3	27,820	**27,944**	27,872	27,792	-72	28,006	62
T=7	27,820	**27,872**	27,841	27,792	-32	28,006	134

- No value in making AWR possible
- Value of having the evidence needed at Launch
  - Policies for better, more relevant an timely evidence
- Commercial value of early evidence
  - When should research be publically funded
  - How should value and costs be shared
  - Absolute and comparative advantage

Questions

- Are the critical times for research to report (T*), beyond which Approval would be more appropriate, useful?
- Are the OIR and AWR boundaries, which include an assessment of probability of research, as well as when it reports, likely to be helpful to the AC?
- Is using the analysis to consider the value of making AWR possible or having the evidence needed at launch likely to be useful for the AC, NICE or other bodies and stakeholders
- Should NICE or other bodies also assess the commercial value to manufacturers of early evidence, AWR and improving the time taken for research to report?

4 Implications for policy, process and methods

- Informed by discussion and feedback from workshop
  - Identify critical issues and potential challenges
  - Balance between deliberation based on informal assessment and more explicit analysis
  - Implications for NICE and broader policy issues
  - Possible recommendations for consideration by NICE and other relevant bodies
- Long list of questions reflect proposed report structure
  - Use as prompts for group discussion
  - Focus on main themes
  - Identify issues and questions not raised

4.1.1 Policy issues directly relevant to the NICE remit

- (i) Is there a wider role for OIR/AWR guidance/policy?
  - Does this pose particular challenges to the Institute?
  - Does the need for transparency, accountability and sustainability have implications for how the assessments should be informed?
  - Are the different types of OIR, AWR, Approve and Reject helpful in this respect?

- (ii) Is the sequence of assessments and judgements required also useful for other NICE programmes?
  - Are the principles and assessments similar? Would the checklist be helpful?
  - Are there additional considerations? What are the most important differences in how these assessments might be informed?

4.1.1 Policy issues directly relevant to the NICE remit (Continued)

- (iii) Is understanding the link between effective price and categories of guidance helpful?
  - Should these be considered in the evaluation of PAS?
  - Is it useful to identify effective price thresholds for which categories of guidance change?
  - Should these considerations be the responsibility of NICE and undertaken during appraisal once a VBP scheme is in a place?
- (iv) Would the assessments and judgments be better made with greater involvement of those responsible for research decisions?
  - How might this be achieved?
  - What are the main considerations in guiding whether the research should be publicly funded or not?
  - Are contractual arrangements necessary? How would these be monitored and enforced?

4.1.2 Other broader policy issues

- (i) Should the need for evidence and irrecoverable costs be included in the assessment of VPB?
  - Is NICE best placed to make these assessments?
  - Should OIR, AWR be retained even with a VBP scheme?
  - Are the incentives for earlier evaluative research appropriate?
- (ii) Is the analysis of the value of earlier research and AWR useful in informing:
  - The value of reducing the time taken for research to report?
  - Investment which would make AWR possible?
  - Investments or incentives for making evidence needed available at launch?
  - Who should pay/conduct research and how might this be contracted?

4.2 Implications for the process of appraisal

- (i) Is additional expertise required?
  - How could co-ordination between NICE and those responsible for research design and commissioning be improved?
  - Which judgements are most critical concerning the type of research required?
  - Who should make these judgements and should a separate research advisory committee be established?
- (ii) What are the implications of applying the framework during the appraisal process?
  - Which assessments could be undertaken before the committee meets?
  - Which assessments are most critical in requiring judgement from the committee?
  - Are the additional judgements feasible within the time constraints of AC meetings?
  - Is additional analysis inevitable or only in particular circumstances?
  - How could any delays be minimised and ensure that any delay is worthwhile?

4.3 Implications for the methods of appraisal

- (i) What additional information, evidence and analysis might help the AC based on the assessments and judgements required?
  - Will the balance between deliberation based on informal assessment and more explicit analysis differ for different points on the checklist?
  - At which point(s) on the checklist would additional information and analysis be most important?

- (ii) Implications arising from issues raised in individual sections