

Exam in Heval4200, 6 April 2020: Suggested solution

Introduction

The exam was arranged digitally on the Inspira platform and consisted of 10 questions.

Questions 7–10 were applications of a check-list from the course's main textbook, Drummond et al. (2015), on the "exam article" by Zuluaga-Sanchez et al. (2019). The exam article was made available to the students approximately 7 weeks before the exam, so the candidates were expected to be well prepared. Different solutions are possible, but in general each point on the check-list should have a clear answer with an appropriate reference to the text (e.g., page and line numbers).

Question 1 (21 points)

The programs sorted by increasing C/E ratio:

Program	Cost (Million NOK)	Effect (QALY)	C/E (Mill. NOK/QALY)
B	65	748	0.087
D	193	722	0.267
C	37	67	0.552
A	296	501	0.591

a) If the available budget is 500 million NOK and the aim is to maximize the number of QALYs gained, the programs B, D, and C should be chosen. The total costs for these three programs are 295 million NOK.

The remainder of the budget, $500 - 295 = 205$ million NOK, can be spent on a part of Program A if that program is divisible.

b) If the WTP threshold is $\lambda = 0.500$ million NOK/QALY (500 000 NOK/QALY), programs B and D should be chosen because their C/E ratio is below the threshold.

c) $NMB = 0.500 \text{ million NOK/QALY} \cdot 501 \text{ QALY} - 296 \text{ million NOK} = -45.5 \text{ million NOK}$

Question 2 (20 points)

Table 1. The treatments sorted by increasing cost, including the current standard of care (SoC).

Treatment	Cost	Effect	ΔC	ΔE	ICER
Current SoC	0	0			
D	400 000	1.0	400 000	1.0	400 000
B	600 000	0.5	200 000	-0.5	-400 000
C	900 000	1.5	300 000	1.0	300 000
A	1 000 000	2.0	100 000	0.5	200 000

Table 2: The treatments sorted by increasing costs. A dominated strategy is excluded.

Treatment	Cost	Effect	ΔC	ΔE	ICER
Current SoC	0	0			
D	400 000	1.0	400 000	1.0	400 000
C	900 000	1.5	500 000	0.5	1 000 000
A	1 000 000	2.0	100 000	0.5	200 000

Table 3: The treatments sorted by increasing costs. Dominated and extendedly dominated strategies are excluded.

Treatment	Cost	Effect	ΔC	ΔE	ICER
Current SoC	0	0			
D	400 000	1.0	400 000	1.0	400 000
A	1 000 000	2.0	100 000	1.0	600 000

- a) Yes, Treatment B is dominated by Treatment D, because B has a higher cost and a lower effect (Table 1).
- b) Yes, Treatment C is extendedly dominated by treatments D and A, because the ICER is lower for A than for C (Table 2).
- c) The total available budget is 19 million. Divided by 20 patients this means $19\,000\,000/20 = 950\,000$ NOK per patient. Assuming the treatments are not divisible, treatment C should be chosen because it has the highest effect among the alternatives within the budget (Table 2).¹
- d) Treatment D should be chosen because it is the only alternative with ICER below the 500 000 NOK/QALY threshold (Table 3).

Question 3 (20 points)

Sensitivity: $P(T+ \mid D+) = 0.33$

Specificity: $P(T- \mid D-) = 0.93$

1) The prevalence is 1%, $P(D+) = 0.01$

Share of false positive: $P(D- \cap T+) = P(T+ \mid D-) \cdot P(D-) = (1 - 0.93)(1 - 0.01) = 0.0693$.

Share of false negative: $P(D+ \cap T-) = P(T- \mid D+) \cdot P(D+) = (1 - 0.33) \cdot 0.01 = 0.0067$.

¹ It is sufficient to mention only the solution based on the assumption that treatments are not divisible. If this assumption is relaxed, the problem becomes more complicated. To start, note that if 20 patients get treatment C, the total effect is $20 \cdot 1.5 = 30$ QALYs and that the total cost is $20 \cdot 900\,000 = 18$ million NOK which is below the available budget. If the treatments are divisible, it is possible to increase the total effect. One candidate solution is to let 10 patients get treatment C and 10 patients get treatment A, yielding a total effect of $10 \cdot 1.5 + 10 \cdot 2.0 = 35$ QALYs (total cost $10 \cdot 900\,000 + 10 \cdot 1\,000\,000 = 19$ million NOK). However, the optimal solution is to let 18 patients get treatment A and 2 patients get treatment D, with the total effect of $18 \cdot 2.0 + 2 \cdot 1.0 = 38$ QALYs (the total cost is $18 \cdot 1\,000\,000 + 2 \cdot 400\,000 = 18.8$ million NOK). Note that treatments A and D are on the efficiency frontier, while treatment C is not (Table 3).

	Infected (D+)	Not infected (D-)	Sum
Test positive (T+)	0.0033	<u>0.0693</u>	0.0726
Test negative (T-)	<u>0.0067</u>	0.9207	0.9274
Sum	<u>0.0100</u>	0.9900	1.0000

2) The prevalence is 10%, $P(D+) = 0.10$

Share of false positive: $P(D- \cap T+) = P(T+ | D-) \cdot P(D-) = (1 - 0.93)(1 - 0.10) = 0.0630$.

Share of false negative: $P(D+ \cap T-) = P(T- | D+) \cdot P(D+) = (1 - 0.33) \cdot 0.10 = 0.0670$.

	Infected (D+)	Not infected (D-)	Sum
Test positive (T+)	0.0330	<u>0.0630</u>	0.0960
Test negative (T-)	<u>0.0670</u>	0.8370	0.9040
Sum	<u>0.1000</u>	0.9000	1.0000

Question 4 (20 points)

A full answer should include the following points, with some elaboration:

- Contain a definition of QALYs, including QALY weights and length of life, preferably with the refinement that the QALY weights may vary over time.
- Mention specifically that QALY gains are used when comparing two or more alternatives.
- Mention direct methods for measuring QALY weights (visual analogue scale; standard gamble; time trade off).
- Mention indirect methods for measuring QALY weights (EQ-5D; SF-6D).

Question 5 (24 points)

A full answer could include the following points, with some elaboration:

a) Markov assumptions

- The health states are mutually exclusive and collectively exhaustive.
- Time is discrete and the time cycles has a fixed length.
- Movements between states are governed by transition probabilities. In a Markov chain, the transition probabilities are constant over time; in a Markov process, they can change over time.
- The transition probabilities depend only on the current health state (memory-less property).

b) Cohort simulation

- In the initial (first) period, a cohort of hypothetical individuals has a distribution over the health states, for instance 100% are in the state Mild symptoms.
- In the following (second) period, the distribution of individual has changed and some of the individuals have moved to the states Recovered, Severe disease, or Dead, while some remain in the state Mild symptoms.

- In the next (third), period, some of the individuals will reach the state Critical disease.
- The simulation continues until all individuals are distributed between the two absorbing states, Recovered or Dead, or until a limit on the number of cycles has been reached.
- The Markov trace can be used to predict how large share of the cohort is in, say, the state Critical disease at any given time, and how large share ends up in the state Dead.

c) Transition probabilities (alternative solutions can be acceptable)

- The transition probabilities will depend on several factors, including the properties of COVID-19 infections and available treatment options.
- From a purely clinical point of view, the transition probabilities from the state Mild symptoms may be comparable across countries, in particular if factors such as demographics (age) and comorbidities are controlled for.
- The reported transition probabilities from the state Mild symptoms may depend on a country's test strategy. In some countries, few people with mild symptoms are tested, while some countries (e.g., South Korea) have performed extensive testing. This means that the transition probability from Mild symptoms to Severe disease is subject to a (statistical) sampling bias that may vary between countries.
- The transition probabilities from the state Critical disease will depend strongly on the available capacity for offering mechanical ventilation. Patients in need of mechanical ventilation will almost certainly die if they do not get such treatment. Thus, the transition probability from the state Critical disease to the state Dead is likely to differ substantially between countries that have spare capacity and countries that have insufficient capacity.

Question 6 (25 points)

The question is open-ended and can be answered in many different ways. The following points are considered important:

- A full economic evaluation should consider both costs and health consequences for at least two alternative strategies.
- The perspective of the analysis (provider; societal).
- The type of analysis (CEA; CUA; CBA).
- Costs and health consequences should be identified, quantified and valued.
- The choice of time horizon and discount rate.
- A main difference between COVID-19 and seasonal influenza is that the latter is routinely handled within the normal hospital capacity in most developed countries, while an uncontrolled surge in COVID-19 cases will overwhelm the treatment capacity in any country.

Good answers should mention that some strategy choices have major societal/macroeconomic consequences, for instance "Do nothing" versus "Flatten the curve, by imposing a lockdown". In addition, it should be mentioned that important aspects of COVID-19 are highly uncertain and that sensitivity analyses are needed.

Question 7 (8 points)

1: Yes, the objective was stated concisely (p. 847, 2-5).

1.1: Yes, both costs (ch. 2.8) and effects (ch. 2.9) were examined. The time horizon was 40 years for infantile-onset SMA (p. 849, line 54) and 80 years for later-onset SMA (p. 849, line 65), which seem appropriate.

1.2: Yes, nusinersen plus standard of care was compared to standard of care plus a sham procedure, the latter alternative is referred to as SoC (p. 846, lines 85-91; p. 849, lines 84-86).

1.3: Yes, the models were developed from the societal perspective in Sweden, and the payer perspective was considered in sensitivity analyses (p. 849, lines 47-52).

1.4: Yes, the patient population can be identified by specific genetic conditions (p. 845, lines 96-98). Yes, two relevant subgroups are defined based on age at onset: infantile-onset (≤ 6 months of age) and later-onset (> 6 months of age)(p. 849, lines 71-72).

Question 8 (14 points)

3: Yes, safety and efficacy has been established in clinical trials (p. 846, lines 70-75; p. 849, lines 55-66).

3.1: The study appears not to be have directly linked to a randomized trial, but the authors seem to have had access to data from such trials, see above.

3.2: Yes, clinical and economic systematic literature reviews have been performed (p. 847, lines 26-28; p. 862, lines 80-81). The search strategy and rules for inclusion/exclusion are not presented in the main article.

3.3: No, the model data seem to be based on trials, not observational studies. An observational study regarding the natural history for infantile-onset SMA is mentioned (p. 847, lines 59-62), but it seems to be used only to establish a context for the scale used to compare the clinical effects of the two treatment options under consideration, that is, nusinersen and SoC (p. 847, lines 41-59). Overall survival after the trial follow-up was guided by an observational study (p. 852, lines 42-43). Biases related to observational studies are not discussed.

Question 9 (14 points)

6: Yes, the costs and consequences seem to have been valued credibly.

6.1: Yes, the sources for all values are identified in the article (Tables 1 and 2). An electronic supplement may contain additional information (p. 847, lines 28-30).

6.2: This point does not seem relevant in this case. Unit costs were mainly collected from hospital price lists (p. 856, lines 52-53).

6.3: The models include informal care costs (p. 849, lines 47-50). Caregivers' productivity loss are valued based on assumptions on monthly salary (i.e., market wage) and lost time at work (p. 856, lines 46-52).

6.4: Yes, the study is a cost-effectiveness study measuring QALY gains (that is, a cost-utility analysis in Drummond et al's terminology) for patients and caregivers (p. 849, lines 77-80). This seems appropriate given point 1.3 above.

Question 10 (14 points)

10: Yes, it appears that most issues of concern for the user has been included.

10.1: Yes, the conclusion was based on ICERs (p. 862, lines 56-78). The ICERs were interpreted intelligently in the relevant context.

10.2: No, the authors claim that this is the first economic evaluation for the treatment of SMA (p. 861, lines 49-51). They authors mention that their model structure has been used in ten health technology assessments across the world (p. 859, lines 84-88).

10.3: Yes, the ICERs of the present study are compared to other rare diseases (paragraph starting at p. 859, line 96).

10.4: No, the distribution of costs and consequences are not considered. However, it is mentioned that the WTP threshold could be higher for severe or rare diseases (p. 860, lines 43-46 and 93-100), and that will influence priority setting.

10.5: The new treatment has already been implemented, even though the ICER is higher than the regular WTP threshold (p. 862, lines 72-77; p. 845, lines 34-37). The high costs for the new treatment is mainly due to the price of nusinersen, the (p. 857 lines 21-24), so other resource or capacity constraints were perhaps less relevant.

10.6: Yes, several uncertainties are mentioned (from p. 861, line 101 to p. 862, line 53).