Exam in Heval4200, 25 March 2022:

Suggested/outlined solution

Version intended for candidates

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Introduction

The exam was arranged digitally on the Inspera platform and consisted of 5 questions.

Question 5 was an application of a checklist from the course's main textbook, Drummond et al. (2015), on the "exam article" by Nayagam et al. (2016). The exam article was made available to the students 6 weeks before the exam, so the candidates were expected to be well prepared.

The maximum total score was 180 points. The following relation between grades (A–F) and points [0–180] was used: A: [145–180], B: [120–144], C: [95–119], D: [80–94], E: [60–79], F: [0–59].

Explanation of grades. The candidates will receive a note with their individual scores on each question and the present suggested solution. Combined, these two documents explain the general principles for how scores and grades were awarded and constitute the formal explanation of grades.

Appeal against grades. Appeals against grades must be submitted following the procedure described on the course webpage (that is, not submitted to the course coordinator).

Informal feedback. Candidates who wish to receive additional feedback may ask the course coordinator for an informal talk (phone call or Zoom meeting). The candidates must then email the course coordinator 2-3 suggested times. These suggested times should be within normal office hours (0900h-1700h), with at least two workdays notice, and within the period 2-6 May 2022.

Suggested solution

Question 1 (35 points)

The key points below should be discussed and linked to the specific application. Detailed knowledge about hepatitis C and liver transplant is not required, but the candidates should still be able to employ their general knowledge about these topics.

- The relevant health states (say, mild or asymptomatic liver disease, severe liver disease, post-transplant, dead) and their frequencies are likely to differ between patients who are included in the intervention and patients who receive the current standard of care.
- An explanation of how the health effects is defined and measured in QALYs.
    - QALY weights/health related quality of life for different health states, and the average duration in each health state.

- The time horizon (preferably lifelong but including at least some time before a transplant becomes relevant and some years afterwards).

- Avoided liver transplants for this patient group could imply health benefits for other patients who are on a waiting list to receive a donated liver.

Question 2 (30 points)

a) (10 points)

Patient group 1				Patient group 2			
Treatment	ΔC	ΔE	ΔC/ΔE	**Treatment**	ΔC	ΔE	ΔC/ΔE
A	100	9	11.1	**F**	200	10	20.0
B	100	4	25.0	**G**	300	9	33.3
C	100	1	100.0	**H**	300	6	50.0
D	100	6	16.7				
E	100	1	100.0				

b) (10 points)

We exclude alternative C, because it is extendedly dominated by alternative D, and recalculate the ICER for alternative D.

Patient group 1				Patient group 2			
Treatment	ΔC	ΔE	ΔC/ΔE	**Treatment**	ΔC	ΔE	ΔC/ΔE
A	100	9	11.1	**F**	200	10	20.0
B	100	4	25.0	**G**	300	9	33.3
C	-	-	-	**H**	300	6	50.0
D	200	7	28.6				
E	100	1	100.0				

When the decision makers' willingness to pay threshold is EUR 31,000 per QALY gained, the optimal pair of treatments are alternative D for patient group 1 and alternative F for patient group 2.

c) (10 points)

If the willingness to pay threshold falls below EUR 28,600, then alternative D should be replaced with alternative B for patient group 1 (the optimal pair will then be B and F). If the willingness to pay threshold is increased to EUR 33,300, then alternative G should replace alternative F (the optimal pair will then be D and G).

Question 3 (40 points)

A full economic evaluation should consider both costs and health effects for at least two alternatives. Initially, a time horizon (for instance two years) and the perspective (preferably societal) should be chosen. Given the substantial implications for the society at large, a cost benefit analysis should at least be considered.

The decision tree should show the three mentioned strategies. Health endpoints could include dead due to COVID-19, dead due to other causes, long COVID-19, vaccinated, uninfected, or recovered after COVID-19 infection. The population proportions of people in various risk groups (e.g., elderly, chronically ill, or obese) could be a relevant issue. For the vaccination alternative, information on

uptake and efficacy will influence the distribution of individuals across endpoints. Possible health outcome includes deaths, life years, QALYs, or using monetary terms. A main difference between "do nothing" and "social distancing" is the difference in timing on infections; the total number of people infected could be similar but the number of infected at a given point in time could be reduced with social distancing and hence reducing the strain on the health care sector.

The costs should include resources spent/saved in treating or preventing COVID-19, and resources spent/saved in the health care sector for non-COVID-19 patients (provider perspective). Societal costs due to social distancing, which could be imposed by the government or result from the population's behavioral response to spikes in infection rates, could be difficult to assign to specific endpoints in the decision tree but should be mentioned because it has been universally important during the pandemic.

It could be mentioned that the decision tree framework (and Markov models) has limitations and that mathematical modelling of infectious disease (e.g., an SIR model) could be used as a supplement. However, such models are beyond the scope of this course.

Question 4 (30 points)

a) (5 points)

The probability of going from Stage 1 to Stage 3 is 0, the probability of going from Stage 2 to Stage 1 is 0, and the probabilities of going from Stage 3 to Stage 1 or Stage 2 are both 0.

The probability of staying in Stage 1 is 0.96, and the probability of staying in Stage 3 is 0.67.

The probability of going from Dead to either of the Stages 1-3 are 0, and the probability of staying in Dead is 1.

b) (10 points)

Several answers are possible. If we assume that the severity of Stage 2 is somewhere between Stage 1 and Stage 3, we can assume that the probability of going from Stage 2 to Dead is between 0.01 (the probability of going from Stage 1 to Dead) and 0.33 (the probability of going from Stage 3 to Dead). If a patient is in Stage 2, it is perhaps less likely that the patient dies than that the patient progresses to Stage 3. If so, the probability of going from Stage 2 to Dead is less than 0.07. We can for instance assume that this probability is 0.04. The probability of staying in Stage 2 will then be 0.89, and the transition matrix becomes:

	Stage 1	**Stage 2**	**Stage 3**	**Dead**
Stage 1	0.96	0.03	0	0.01
Stage 2	0	0.89	0.07	0.04
Stage 3	0	0	0.67	0.33
Dead	0	0	0	1

c) (15 points)

Given the transition matrix from b) and the initial distribution of patients, the distribution of patients after one cycle is as follows:

Stage 1	**Stage 2**	**Stage 3**	**Dead**
960	646	183	111

Question 5 (45 points)

a) (30 points)

Nayagam et al. assessed cost from a health provider perspective (p. e572, l. 53, cf. checklist point 1.3).

Checklist point 6: Yes, the costs and consequences were valued credibly. The study by Nayagam et al appears to be based on the PROLIFICA study, which was a feasibility study of a screen and treat HBV intervention program in The Gambia (p. e569, l. 48-81). It is not fully clear whether market values have been applied.

6.1: Yes, detailed cost values were presented in Table 1 (p. e570) and in the main text (p. e572, l. 90-96). Most cost items (measured in US$) were obtained from the PROLIFICA study budget and references 8 and 9. Three average annual costs were obtained by multiplying costs per hospital admission with the assumed number of hospital admissions (three last items under the heading "cost of hospital admission" in Table 1). The values used for the consequences are discussed under point 6.4 below.

6.2: Market values are not explicitly mentioned in the main article. The price of tenofovir has a strong influence on the ICER (p. e574, l. 23-30) and the current pharmaceutical price in sub-Saharan Africa (US$ 207 per year) is about four times higher than the price in HIV programs in The Gambia (48 US$ per year).

6.3: The study did not mention absent market values, such as volunteer labor or donated clinic space. However, the authors stated that their costs are likely to be overestimated "because of field teams dedicated entirely to HBV screening as it formed part of a research programme" (p. e575, l. 89-94).

6.4: The study was a cost-effectiveness and cost-utility analysis, in Drummond et al.'s terminology, using life-years, DALYs and QALYs as outcome measures (Table 2). The two latter measures seem appropriate, given that the relevant health states have substantially different health related quality of life, or disability weights (for DALY calculations), that must be weighted together (Table 1, under the heading "Disability weights"). The corresponding QALY weights are not presented, but the authors referred to health utilities obtained from a multi-country study (p. e572 l. 112 – p. e573, l. 1). They also presented a range of ICERs where the lower and upper values were obtained based on health utilities from China and Singapore, respectively.

Checklist point 10: Yes, the presentation and discussion included all issues of concern to users.

10.1: Yes, the conclusion was based on ICERs, US$ per DALY and US$ per QALY (p. e575, l. 38-50). The index was interpreted intelligently by comparing the ICER estimates to established, yet controversial, willingness to pay thresholds.

10.2: The authors claim that their study is the first to assess "the cost-effectiveness of active population-level screening and treatment for HBV in a low-income or middle-income setting" (p. e575, l. 65-76). The authors mentioned that their costs were relatively low compared to HIV screening studies in similar settings (p. e575, l. 81-89). The authors did not consider potential differences in study methodology between their study and the HIV screening studies.

10.3: Yes, the authors mentioned that their results were robust and could be relevant for other sub-Saharan regions (p. e576, l. 50-59). They mention that it could be possible to integrate HBV and HIV screening in the future, which could make the interventions even more cost-effective (p. e576, l. 85-90).

10.4: The authors mentioned that, in this setting, most people die at home and related costs are borne by family members. This could imply that the quality of care in the terminal phase depends on household income. Liver cancers occur when people are relatively young, often in working age, (median 40 years). This suggests that from a societal perspective, the intervention could be more cost effective than the results presented by the authors. These issues could also be linked to checklist point 4.2, that is, it could have been relevant to include the patients' perspective and a societal perspective.

10.5: Yes, the authors mentioned that cost-effectiveness is not the only criterion, and that also affordability and funding should be considered (e.576, p. 67-76).

10.6: Yes, the authors pointed out the most important factors in the cost-effectiveness of the intervention (p. e575, l 50-59) and uncertainty in these factors will have the strongest implication in decision making (confer point 6.2 above). The authors mentioned recent trials with finite treatment courses, as opposed to the lifelong treatment they studied themselves (p. e575, l. 50-62). They also mention the possibility of adding HBV vaccination to the screening and treatment intervention (p. e576, l. 90-93).

b) (15 points)

Checklist point 7: Yes.

7.1: Costs and health outcomes were both discounted at 3% (Table 1; p. e572, l. 99-101).

7.2: Two references were presented as authoritative sources for the chosen discount rate (p. e572, l. 100-101).

Nayagam et al. took inflation into account by expressing costs in 2013 US$ (p. e572, l. 98-99), and both costs and consequences were discounted. In the deterministic sensitivity analysis, the discount rate varied between 0% and 6%. When costs were discounted at 6% and the health outcome were undiscounted, the ICER was $221 per DALY averted (p. e574, 85-88), that is, much lower than the $540 baseline point estimate (Table 2) in which both costs and health outcomes were discounted at 3%. When this is compared to the bars in the tornado diagram (Figure 1), the discounting appears to have a large influence on the ICER.