Advanced decision modelling in the context of Health Technology Assessment

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2021-11-15

Contents

Introduction

Bringing a new health technology to market and into the hands of a patient is a long process. Most of the times patients, who have a medical need, ask themselves why does it take so long to make the health technology available to everyone. When a health technology is in the market, it usually took between 5 to 10 years to make it available.

Depending on the country, governments usually are involved in the reimbursement process. They usually ask the next questions when a new health technology is available:

- How much does it cost?
- Will it save lives and/or improve quality of life?
- Do we have enough budget to fund it?
- If we have a pool of interventions for a specific disease, which one/ones should we reimburse?

Moreover, physicians, patients, insurance plans, and advocacy groups play an important role when new technologies are available in the market (why?). Even though a new technology see the light (i.e. it has proved to be safe and effective), insurance providers or the government will not necessarily cover it. Usually they argue that the new technology is "Not cost-effective" or "Not have good value for money". *These notes aim to provide all the necessary tools to decide if a new intervention has a good value-for-money.* It is important to stress that value-for-money decision is only one of many questions that are asked by one of the users of a **health technology assessment (HTA)**: patients, healthcare workers, government, and others.

Why reimbursment submissions fail?

According to Goeree (2015), the reasons for rejection are:

1. Inappropriate comparator. Lack of proper statistical analysis.

2. Inappropriate outcome. Use of surrogates.
3. Inappropriate analysis. Lack of robust evidence for costs and quality of life.
4. High cost to the government.

Topics of the course

1. What is HTA?
2. Introduction to decision-analytic models
3. Good practices in decision modelling
4. Evidence-based medicine
5. Decision tree-models
6. State-transition models with the Markov assumption
7. Partitioned survival models
8. Microsimulation
9. Discrete-event simulation
10. Uncertainty and decision-making
11. Presentation of results

Statistical computing

The use of open-source programming languages, such as `R`, in health decision sciences is growing and has the potential to facilitate model transparency, reproducibility, and shareability. However, realizing this potential can be challenging. Models are complex and primarily built to answer a research question, with model sharing and transparency relegated to being secondary goals. Moreover, many decision modelers are not formally trained in computer programming and may lack good coding practices, further compounding the problem of model transparency. **Therefore, throughout this course, the programming language `R` will be used to show its potential for advanced modelling in the context of HTA.**

For this course, we will be using the book "R for Data Science". To install `R` and `Rstudio`, instructions are provided in Chapter 1 of this book. We will also use Excel throughout this course.

Evaluation

Item	Percentage	Due date
Assignment 1	15%	Nov 27, 2021

Item	Percentage	Due date
Assignment 2	15%	Dec 23, 2021
Take-home exam	30%	Jan 7, 2022
Project proposal	5%	Nov 22, 2021
Project presentation	5%	Jan 14, 2022
Final project	30%	Jan 17, 2022

The intent is to allow the students to demonstrate their mastery of this class through the following way. **Project proposal, presentation and final project will be done in pairs**.

Asssignments

The assignments are handed out approximately two weeks prior to the due date. Late work will not be marked, with the exception of an advance permission from the instructor.

Project proposal

(1 page)

The final deliverable for this course is a mini-HTA on a medical technology (preferably something topical), with a focus on the quantitative aspect of it. Given that the translation of a health policy question into a relevant research question is an essential first step in the conduct of HTA, students are required to formulate a research question and submit for grading purposes. This should include at leas some of the following: an overview of the technology being assessed; a clear specification of the policy problem; and the research question(s) (including PICO) with objectives.

Project presentation

(20 minutes with extra 5 minutes for questions)

Students will be expected to present their final course paper and answer questions. Student will be graded on their presentations.

Final project

(20 pages double-spaced)

The main assignment will require students to produce a scaled down HTA, with a focus on the quantitative aspect of it. The objective of the final project is for the

student to show that they have obtained a clear understanding of the advanced methods in decision modelling in the context of HTA. More information will be provided throughout the course, but the paper should contain the following:

a) Background and technology overview
b) Formulation of the question you are trying to answer through your mini-HTA
c) Review of the clinical literature
d) Description of the structure of the model
e) Description of the function of the model
f) Results
g) Conclusions

Bibliography

Briggs, A., Sculpher, M., & Claxton, K. (2006). Decision modelling for health economic evaluation. Oxford University Press.

Gray, A. M., Clarke, P. M., Wolstenholme, J. L., & Wordsworth, S. (2011). Applied methods of cost-effectiveness analysis in healthcare (Vol. 3). Oxford University Press.

Edlin, R., McCabe, C., Hulme, C., Hall, P., & Wright, J. (2015). Cost effectiveness modelling for health technology assessment: a practical course. Springer.

Chapter 1

What is HTA?

1.1 Pre-session readings

Goodman, C. S. (2004). Introduction to health technology assessment. The Lewin Group. virginia, USA. link. Chapters 1, 2, and 5.

Briggs, A., Sculpher, M., & Claxton, K. (2006). Decision modelling for health economic evaluation. Oxford University Press. Chapter 1.

Chapters 1 and 2 of *R for data science*.

1.2 Definition and rationale

The first thing that we need to know is the definition of a **health technology**. A health technology is any intervention that may be used to promote health, to prevent, diagnose or treat disease or for rehabilitation or long-term care.

Questions

1. List some examples of health technologies.

Depending on the agency, health technology assessment has a broad spectrum of definitions:

"HTA is a multidisciplinary process that uses explicit methods to determine the value of a health technology at different points in its lifecycle. The purpose is to inform decision-making in order to promote an equitable, efficient, and high-quality health system." INAHTA

"Health technology assessment is a multidisciplinary process that uses explicit methods to determine the value of a health technology at different points in its

lifecycle. The purpose is to inform decision-making in order to promote an equitable, efficient, and high-quality health system." EUnetHTA

"A comprehensive, objective, evidence-based analysis of the clinical effectiveness, cost-effectiveness and broader impact of drugs, medical technologies and health systems. HTA examines technologies at all stages of their life cycle, from development through to maturity and obsolescence." CADTH

The purpose of HTA is to support/help decision makers by identifying technologies that will improve health outcomes and deliver value for every dollar invested.

- Does a new health technology offer a clinical advantage over the alternatives/standard approaches?
- Is it worth the investment?
- Can I pay for it?
- Who would benefit from it?
- Any ethical, social or legal issues

But, what are the reasons for conducting HTAs?

- Increased demand for healthcare (why?)
- Soaring healthcare costs
- Increased rate of diffusion of new technologies and associated evidence

Once we have seen the definition and rationale for conducting HTAs, it is important to talk about the potential users.

- Government
- Managers in hospitals
- Healthcare workers
- Researchers

1.3 HTA process

1. Identification and prioritization of technologies
2. Clear specification of the problem
3. Technology assessment and review
    - Evidence and systematic literature review
    - Aggregation and appraisal of evidence
    - Synthesize and consolidate
    - Collect primary data (if necessary)
    - Economic evaluation, budget and health system impact

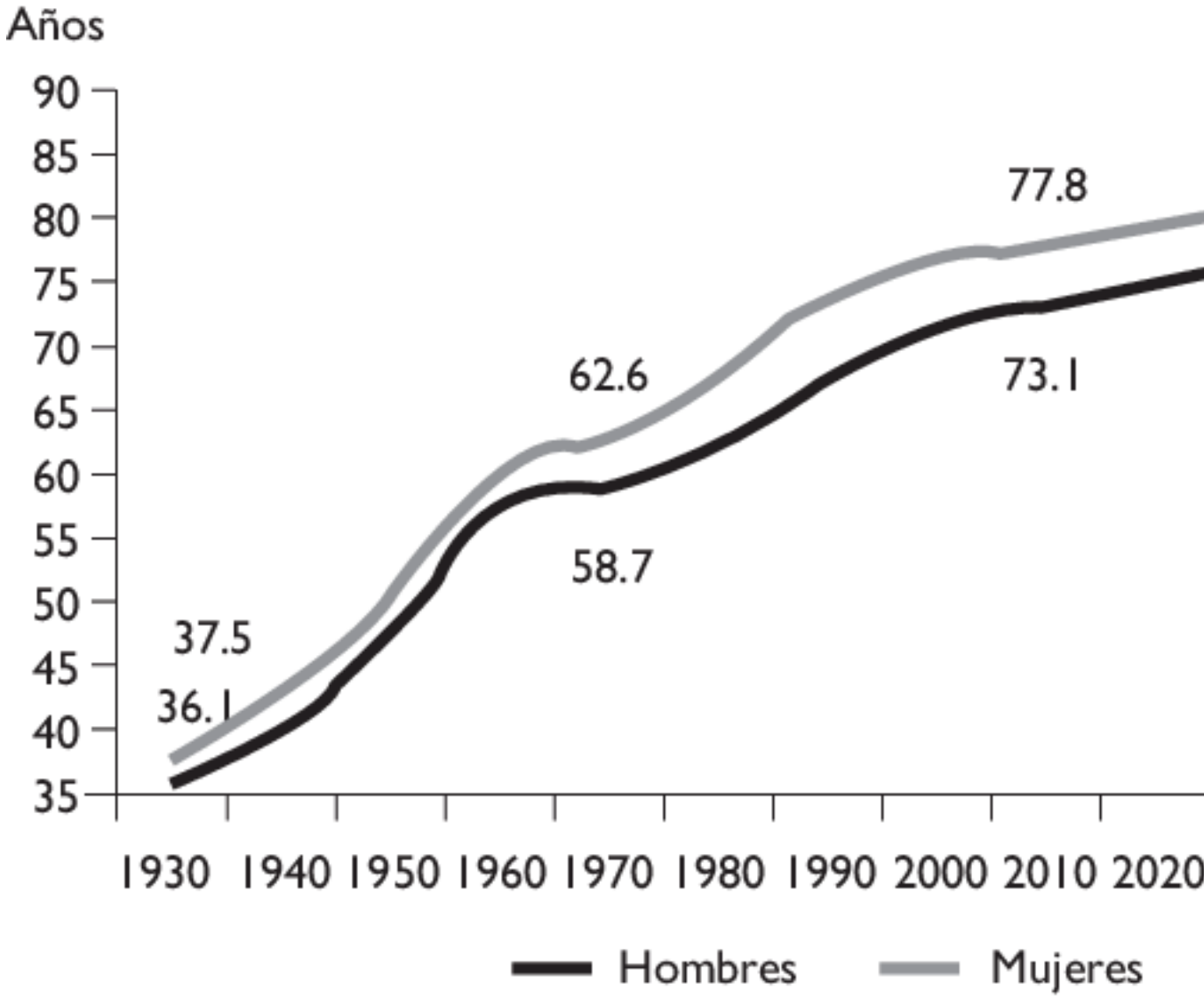

Figure 1.1: Life expectancy in Mexico. Source: CONAPO

    - Assessment of social, legal, and ethical consideration
    - Formulation of finding
4. Dissemination and implementation of recommendations
5. Monitor the impact of assessment reports

1.3.1 Identification and prioritization of technologies

- Drugs seeking public or private reimbursement
- Variable for non-drug technologies. However candidates:
    - High potential to improve health outcomes, reduce harm or decrease costs with similar efficacy
    - Large numbers of individuals affected
    - Political pressure
    - Unmet needs—no current treatment

1.3.2 Clear specification of the problem

- Problem statements need to consider:
    - Patient population affected (indication; epidemiology)
    - Intervention being considered (drug, device, new/old)
    - Comparators
    - Outcome(s) or interest
    - Setting (e.g. hospital, community)
- Well formulated question

1.3.3 Technology assessment and review

1.3.3.1 Evidence and systematic literature review

- A comprehensive search of the literature based on systematic methods is essential
- 2 main types of resources relevant to HTA:
    - Published literature
    - Grey literature

1.3.3.2 Identification, aggregation & appraisal of evidence

- Objective, systematic process for screening and determine studies to be included in the synthesis
- Classify the studies

  - Randomised, non-randomised and economic
- Critical appraisal of the quality of the evidence

1.3.3.3 Synthesize & consolidate

- Findings from multiple studies often combined to respond to the HTA question
- Techniques commonly used to synthesize data in HTA are:
  - Meta-analysis, meta-regression
  - Network meta-analysis

1.3.3.4 Economic evaluation

- Measures the incremental costs and benefits of the technology under review compared to one or more relevant technologies
- CEA, CUA and CBA
- Budget impact

1.3.3.5 Assessment of social, legal & ethical considerations

- Example: genetic information (why?)
- Any access or equity issues following the dissemination and implementation of technologies?

1.3.3.6 Formulation of findings

- Explicitly link quality of the evidence to the strength of findings and recommendations as well as any limitations
- Recommendations based on the findings that reflect the original question(s)

1.3.4 Dissemination of recommendations

- Findings translated into relevant and understandable information
- Knowledge translation

1.3.5 Monitoring the impact of reports

- Some recommendations are translated into policies with clear and quantifiable impacts (e.g. adoption of new technology, change in reimbursement)
- Others go ignored and are not readily adopted into general practice

1.4 Excercises

Read the following HTA published by NICE in the UK. Do the following:

- What is the population?
- What is the intervention and comparators?
- Is there a reproducible search strategy for the clinical evidence in the HTA?
- Was the clinical evidence critically appraised? How?
- Describe the evidence synthesis process
- What type of economic evaluation they used?
- What type of model was used in the economic evaluation?
- How was the uncertainty handled in the economic evaluation?
- Is there a budget impact in the HTA?
- What is the recommendation?

Chapter 2

Introduction to decision-analytic models

2.1 Pre-session readings

Chapter 3 of *R for data science*.

Economic evaluation

Gray, A. M., Clarke, P. M., Wolstenholme, J. L., & Wordsworth, S. (2011). Applied methods of cost-effectiveness analysis in healthcare (Vol. 3). Oxford University Press. Chapter 2.

Birch, S., & Gafni, A. (1992). Cost effectiveness/utility analyses: do current decision rules lead us to where we want to be?. Journal of health economics, 11(3), 279-296. Doubilet, P., Weinstein, M. C., & McNeil, B. J. (1986). Use and misuse of the term "cost effective" in medicine.

Decision modelling

Briggs, A., Sculpher, M., & Claxton, K. (2006). Decision modelling for health economic evaluation. Oxford University Press. Chapter 2. Sections 2.1 and 2.2

Gray, A. M., Clarke, P. M., Wolstenholme, J. L., & Wordsworth, S. (2011). Applied methods of cost-effectiveness analysis in healthcare (Vol. 3). Oxford University Press. Chapter 8. Sections 8.1 to 8.4

Buxton, M. J., Drummond, M. F., Van Hout, B. A., Prince, R. L., Sheldon, T. A., Szucs, T., & Vray, M. (1997). Modelling in ecomomic evaluation: an unavoidable fact of life. Health economics, 6(3), 217-227.

2.2 Economic evaluation

Cost-effectiveness analysis (CEA) and cost-utility analysis (CUA) have been proposed as methods for comparing alternative uses of scarce health-care resources. The difference between CEA and CUA lies in the way outputs are measured.

We can find different objectives of CEA across the literature:

"The underlying premise of cost-effectiveness analysis in health problems is that for any given level of resources available, society (or the decision making jurisdiction involved) wishes to maximize the total aggregate health benefits conferred" Weinstein and Stason (1977).

"For any given rate of output [the combination of inputs] . that costs the decision maker least" Culyer (1980)

"A method of determining the most efficient way of dealing with a specified health problem" Green and Barker (1988)

The goal of CEA is to maximize health benefits produced from a given level of resources. Therefore, it is consistent with welfare economics concept of Pareto efficiency (Birch and Gafni, 1992) (Figure 2.1).

In practice, CEA **relaxes the constraint on available resources**. Because the focus of the evaluation is not a fixed resource pool, but a specific programme making demands on resources, the comparison of the programme under evaluation with an existing programme (e.g., services aimed at improving FS) must consider not only the inter-programme differences in outputs (incremental benefits), but also the inter-programme differences in resources used (incremental costs).

Weinstein and Stason (1977) state that: *"the criterion for cost-effectiveness is the ratio of the net increase of health-care costs to the net effectiveness. The lower the value of this ratio, the higher the priority in terms of maximizing benefits derived from a given health expenditure"*. Issue is that applying a ratio does nod lead to the maximization of benefits from a fixed resource pool (movement from A to C in Figure). **The real problem of the application of CEA is the failure to adhere strictly to the notion of opportunity cost in the measurement of the (incremental) cost of a programme.** The existing programme represents a true opportunity cost for the entire resource requirements of the new programme, even though it does not absorb this level of resources.

2.2.1 Cost-effectiveness in practice

As mentioned before, CEA include both costs and effects, which are represented graphically in a plane:

Questions

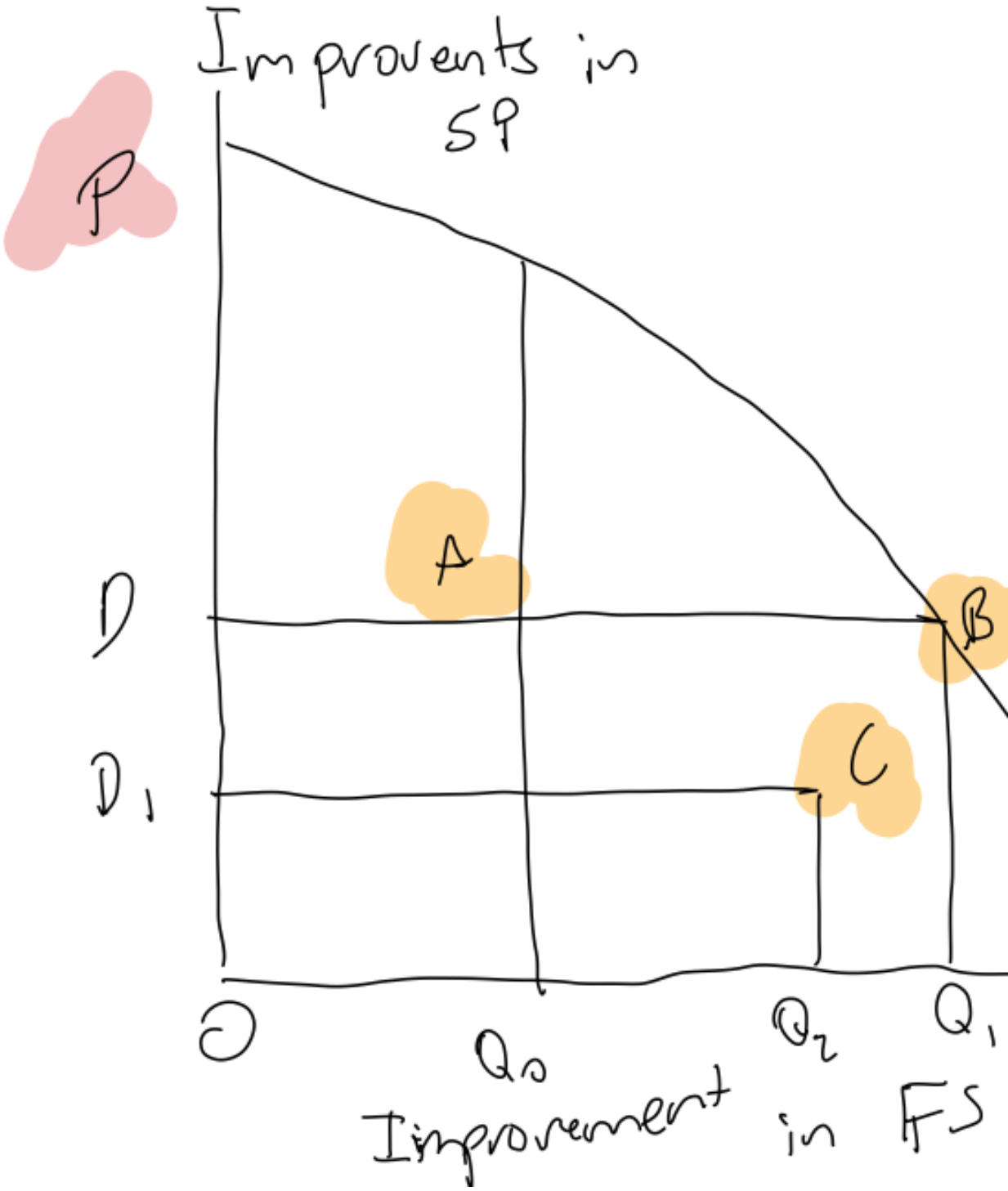

Figure 2.1: Production possibilities frontier

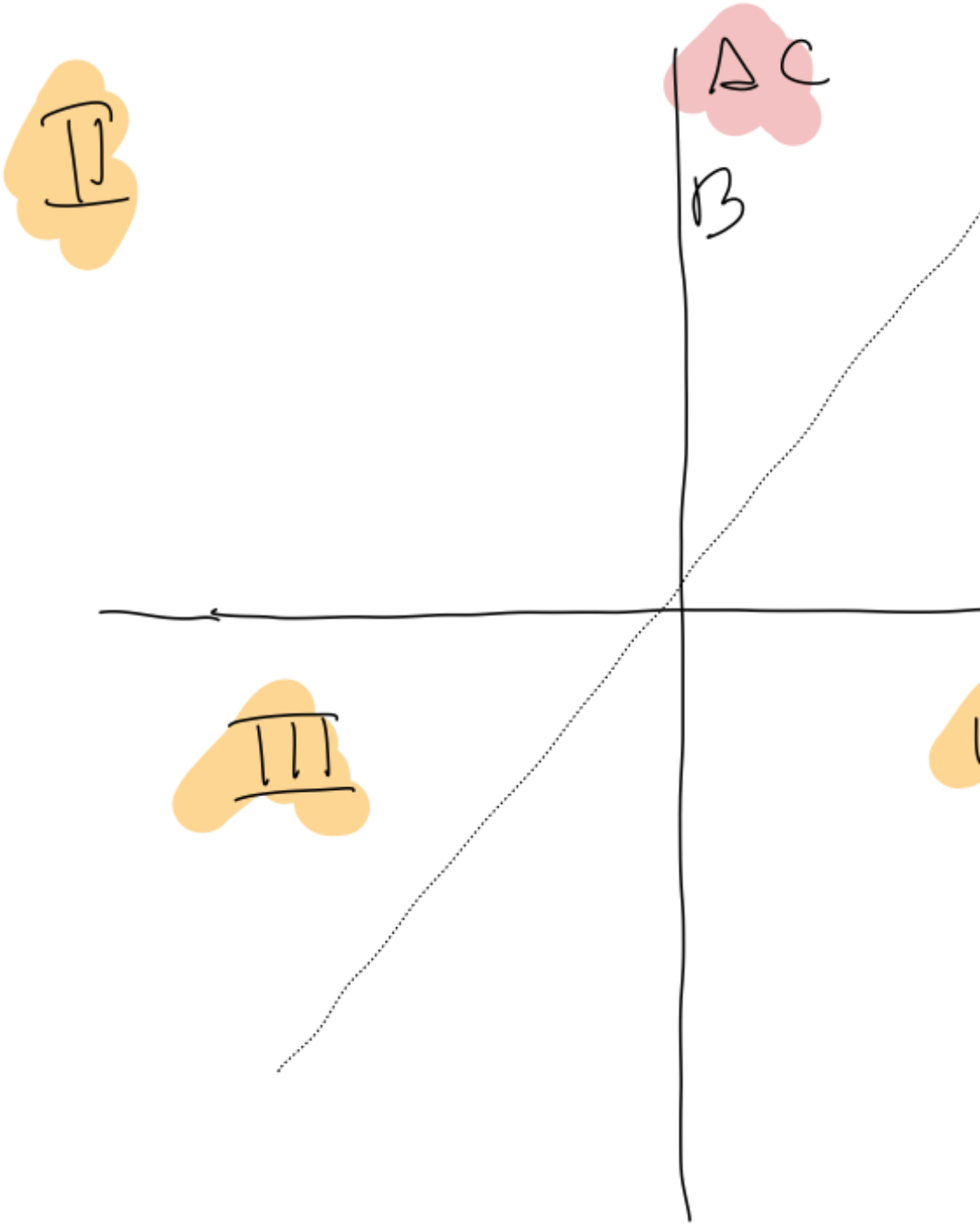

Figure 2.2: Incremental CE plane

Table 2.1: Calculating incremental cost-effectiveness

Option	Cost	QALYs	Incremental cost	Incremental QALY	ICER
A	0				
B	10,000	0.40	10,000	0.40	25,000
C	22,000	0.55	12,000	0.15	80,000
D	25,000	0.50	3,000	-0.05	-60,000
E	40,000	1.00	15,000	0.50	30,000

1. Describe the plane.
2. What is the willingness-to-pay in this plane?
3. What type of uncertainties are encountered in this plane?

Why incremental? We can see it using the example from Gray et al. (2011) applied to mutually exclusive options (see Figure 2.3):

- Diet and excercise (C): Reference
- Metformin (A): \$500k/250 life-years
- New drug (B): \$2500k/300 life-years

Clearly, as this example shows, it is quite misleading to calculate average cost-effectiveness ratios, as they ignore the alternatives available.

Questions

1. What is the difference between average cost-effectiveness ratios vs incremental?

The idea of CEA is to maximize health benefits with the available resources, which in terms of the CE plane represents pushing as far to the right as possible while moving up the vertical axis as little as possible. The next example from Gray et al. (2011) shows the ideas behind **cost-effectivness frontier, dominance, extended dominance** (Table 2.1).

Once we have the ICERs for different independent programmes. How can we maximize health gains with this information? Note that now we are comparing different programmes as opposed to mutually exclusive options. Let's work in the next example:

Finally, we can ask ourselves. What is the maximum value of the incremental cost-effectivess ratio (λ)?

- Rule-based approaches - Adopting arbitrary thresholds. For example, Laupacis et al. (1992) adopted identical cut-off points of CAN\$20,000 per

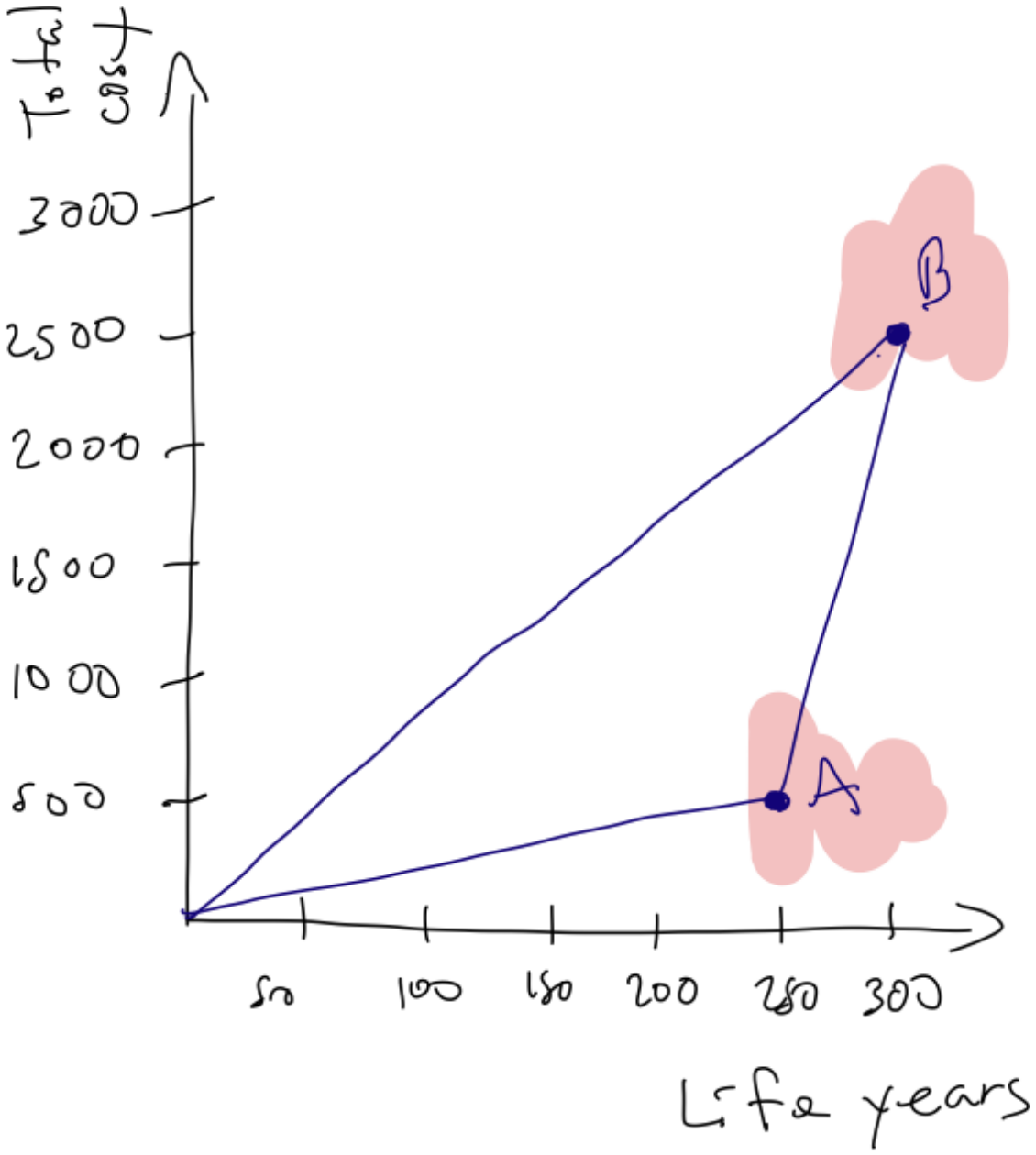

Figure 2.3: Average and incremental cost-effectivenessr

Table 2.2: Using cost-effectiveness to maximize health gain

Intervention	Incremental cost (per k)	Incremental QALYs	ICER
1	1,300	165	7,879
2	600	28	21,429
3	750	110	6,818
4	750	13	57,692
5	2,200	75	29,333
6	400	85	4,706
Total	6,000	476	

QALY gained, up to which level they considered that there would be strong grounds for adoption, and CAN$100,000 per QALY gained, above which they considered that evidence for adoption was weak. An alternative approach is to use the country's gross domestic product (GDP) per capita. Williams et al. (2004) advanced one line of reasoning in support of this, arguing that each person has an entitlement to a 'fair share' of the country's wealth.

- League table approach - If we had full information on the ICERs of all available interventions, it would be possible to rank them by ICER. See the example in Table 2.1.

What are the issues with these approaches?

1. λ is a function of the budget. Therefore it is constantly changing
2. The dynamic nature of λ. As new programs are funded and others replaced, the identification of the last program funded changes.

2.2.2 Conclusions

- Irrespective of whether the problem face by decision-makers is simple (maximizing health gains from available resources) or complex (subject to considerations of equity, accessibility, etc.), if it is not to be considered in the context of a resource constraint there is little use for economics in the way the problem is considered.
- Other approaches have been considered, such as methods in linear programming, which is consistent with the objective of CEA.

$$\max_{x_i,\ldots,x_n} \sum_{i=1}^{n} x_i E_i \text{s.t.} \qquad \sum_{i=1}^{n} x_i c_i \leq C$$

where x_i is the health intervention presented as a binary outcome (1 or 0), E_i is the present value of the health benefits (measured using QALYs) generated by programme over the planning period, and c_i is the present value of the cost of providing programme i over the planning period.

2.3 Decision modelling

HTA is undertaken in order to inform decision-making regarding the appropriate use of particular healthcare programs and interventions, and involves the synthesis of a range of evidence. Broadly speaking, this implies two important components of this process:

1. Gathering evidence for the disease and technology of concern from a range of primary studies. This includes effectiveness, costs, epidemiology, natural history of the disease, quality of life, etc.
2. Synthesizing the evidence found in the first component in order to inform policy and decision-making.

Because of the nature of these two components, decision-analytic modelling has played an important role in HTA. This is because it represents an explicit approach to synthesizing currently available evidence regarding the effectiveness and costs of alternative (mutually exclusive) healthcare strategies (Philips et al., 2006). Therefore one of the main objectives of decision-analytic modelling is to address the relationship between the effectiveness and costs of alternative healthcare strategies in order to assess relative cost-effectiveness (CE) and to determine which options should be adopted given existing information (Philips et al., 2006). Consequently, modelling in the context of HTA is a typical problem of decision-making under uncertainty.

Traditionally randomised controlled trials (RCTs) have been a key component of many HTA process. This is because randomsation protects against selection bias and confounding. Nevertheless, the information produced by RCTs can be limited with respect to evaluating health care as delivered in the real world. This can be because:

1. Not all interventions to be compared are included in the trial.
2. Not enough follow-up.
3. Not enough flexibility (controlled trial).
4. Small sample sizes.
5. Patients in trial are not representative to the target population.

Consequently, it is advised that HTA submissions incorporate information from as many sources as possible to address some of these problems (Sculpher et al.,

2006). As mentioned before, decision analytical models allow for the synthesis of information across multiple sources and for the comparison of multiple options that might not have been included as part of an RCT.

Briefly, Dahabreh et al. (2016) consider some potential goals of modelling in a health-care context:

- To structure investigators' thinking and to facilitate the communication of data, assumptions, and results.
- To synthesize data from disparate sources.
- To make predictions.
- To support causal explanations.
- To inform decision making.

Moreover, they also distinguish different stages for the development of a decision analytic model

1. Define a question
2. Decide on the type of decision model most appropriate
3. Conceptualize the model (and its mathematical structure).
4. Gather all the evidence required for the model and synthesize it.
5. Implement and run the model.
6. Assess the model.

The development of models, especially those trying to explain complex phenoma and informing difficult decisions, is a demanding task. Choosing between alternative modeling approaches can be difficult because the correct choice would not be obvious at early stages in developing a decision analytical model. In general, modelling is most useful when data have limitations (e.g. non-randomised evidence, sparse evidence, etc.), when the research question is complex and when choices are preference laden (Dahabreh et al., 2016). Another important aspect when choosing between modelling approaches is whether the model in question is likely to show results that the intended audience will consider credible and useful. Multiple iterations are typically needed between the key activities outlined previously because at each activity the need for changes at earlier stages may become evident.

2.3.1 Importance of decision-analytic models in HTA

When doing a cost-effectiveness analysis in the context of HTA, one usually starts conceptualizing the model that will help answer the research question. But what is a model? A model a simplified representation of reality (Roberts et al., 2012), where inputs from different sources inform it and its purpose, in the context of HTA, is to inform medical decisions and health-related resource allocation questions (Roberts et al., 2012).

Methods for the conduct of decision-analytic modelling have continued evolving to address the ever-increasing information needs of decision makers. The complexity and continued advances of the relevant methods have spurred the publication of recommendation statements on "best practices" for modeling in the context of HTA (Roberts et al., 2012; Briggs et al., 2012). Some of these modelling techniques (Caro et al., 2012) include:

- Decision-tree models.
- State-transition models.
- Micro-simulation models.
- Discrete event simulation (DES) models.
- Dynamic transmission models.

2.4 Excercises

1. Question 1 and 2 from Chapter 2 in *Applied methods of cost-effectiveness analysis in healthcare* .
2. Read the articles in our google classroom.

Chapter 3

Good practices in decision modelling and decion-tree models

3.1 Pre-session readings

Good practices

Roberts, M., Russell, L. B., Paltiel, A. D., Chambers, M., McEwan, P., & Krahn, M. (2012). Conceptualizing a model: a report of the ISPOR-SMDM modeling good research practices task force–2. Medical Decision Making, 32(5), 678-689.

Decision-tree models

Tarride, J. E., Blackhouse, G., Bischof, M., McCarron, E. C., Lim, M., Ferrusi, I. L., … & Goeree, R. (2009). Approaches for economic evaluations of health care technologies. Journal of the American College of Radiology, 6(5), 307-316.

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Roberts, M., Russell, L. B., Paltiel, A. D., Chambers, M., McEwan, P., and Krahn, M. (2012). Conceptualizing a model: a report of the ispor-smdm modeling good research practices task force–2. *Medical Decision Making*, 32(5):678–689.

Sculpher, M. J., Claxton, K., Drummond, M., and McCabe, C. (2006). Whither trial-based economic evaluation for health care decision making? *Health economics*, 15(7):677–687.

Weinstein, M. C. and Stason, W. B. (1977). Foundations of cost-effectiveness analysis for health and medical practices. *New England journal of medicine*, 296(13):716–721.

Williams, A. et al. (2004). What could be nicer than nice? *Monographs*.