How to prepare a drug file for the HTA committee?

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What is pharmacoeconomical analysis and why?

- An attempt to foresee how widespread use of new drug will affect spending and earning within the healthcare system
- Therefore we need a mathematical model to foresee costs and gains (effects) with certain probability
- The aim is to persuade the PAYER that there will be benefit of paying for new drug

Drummond MF. Economic evaluation of pharmaceuticals: science or marketing? Pharmacoeconomics. 1992;1(1):8–13.

Two main pillars of a pharmacoeconomical analysis

- To foresee whether new drug performs better than old ones (already paid for), i.e. whether its cost/effectiveness ratio is better than that of old drugs: **COST/EFFECTIVENESS ANALYSIS**
- To foresee how new drug will affect the available budget of the healthcare payer (will the payer need more or less money than before, and how much): **BUDGET IMPACT ANALYSIS**

Buxton MJ, Drummond MF, Van Hout BA, Prince RL, Sheldon TA, Szucs T, Vray M. Modelling in ecomomic evaluation: an unavoidable fact of life. Health economics. 1997;6(3):217-27.

First to be decided:

- What do we want to achieve?
  - Of course drug company wants to maximize the profit, but it has to be accepted by the payer, who is limited by available budget and other health needs in a population
- Therefore:
  - Check roughly whether the payer has to give more money for new drug if it replaces an old one
  - If so, the payer will accept new drug only if the budget is somehow increased or there is high pressure from patient organizations and health professionals: consider decreasing the price or ask for partial reimbursement, and later on apply for full reimbursement
- A pharmacoeconomic model can inform us **both before and later on** (in relaton to our initial decision about price) how far exactly we can go with price or reimbursement conditions

Janković SM. Basics of Pharmacoeconomics. In: Basics of Clinical Pharmacy, University of Kragujevac, 2008.

Then undertake basic steps we have to do in building any kind of pharmacoeconomical model for applying at a Health Insurance Fund:

- Precisely define **THERAPEUTIC ALTERNATIVES** to your product and choose a **COMPARATOR**
- Define all possible **OUTCOMES** of each of the alternatives
- Decide about **PERSPECTIVE** (Who makes decisions about financing?)
- Determine **POPULATION** of patients to whom the analysis relates
- Decide about **TIME HORIZON** of the model
- Choose **TYPE** of the **MODEL**

Sonnenberg FA, Beck JR. Markov models in medical decision making: a practical guide. Medical decision making. 1993;13(4):322-38.

More of basic steps:

- Decide about **DEGREE OF DETAILING** in the model
- Calculate total **COSTS and EFFECTS** of each therapeutic alternative
- Express **EFFECTS** in Qality Adjusted Life Years (QALY)
- Calculate **IMPACT ON THE BUDGET** of a healthcare payer
- Include 1st and 2nd order **UNCERTAINTY** in the models
- Perform **SENSITIVITY ANALYSIS**

Sonnenberg FA, Beck JR. Markov models in medical decision making: a practical guide. Medical decision making. 1993;13(4):322-38.

Finding a COMPARATOR and defining OUTCOMES

- Comparator to your product should be:
  - **VERIFIED AS THERAPEUTIC ALTERNATIVE IN GUIDELINES**
  - **ALREADY REIMBURSED**
- Take into account all **OUTCOMES** of a treatment, both positive (decrease of mortality, cure rate, improvement of quality of life, etc.) and negative (adverse effects) that could be **TRANSFORMED** to **COSTS and GAINED LIFE, adjusted for quality**
    - **Sometimes problematic: example of antidiabetic drugs**

PERSPECTIVE, POPULATION AND TIME HORIZON

- **PERSPECTIVE** is always that of the payer
  - Key issue is to find out **what costs is payer covering** (usually only DIRECT costs)
- **POPULATION** is defined by approved indication(s) of the drug
  - It could be further decreased by: adherence issues, resistance to therapy issues, severity of the disease, etc.
- **TIME HORIZON** depends on natural course of the disease and the peak patients' age of occurence

CHOOSE TYPE OF THE MODEL

- There are many different options, but the most frequently used are:
- **DECISION TREE** – for short-term health conditions (acute diseases)
- **MARKOV MODEL** – for long-term health conditions (chronic diseases)

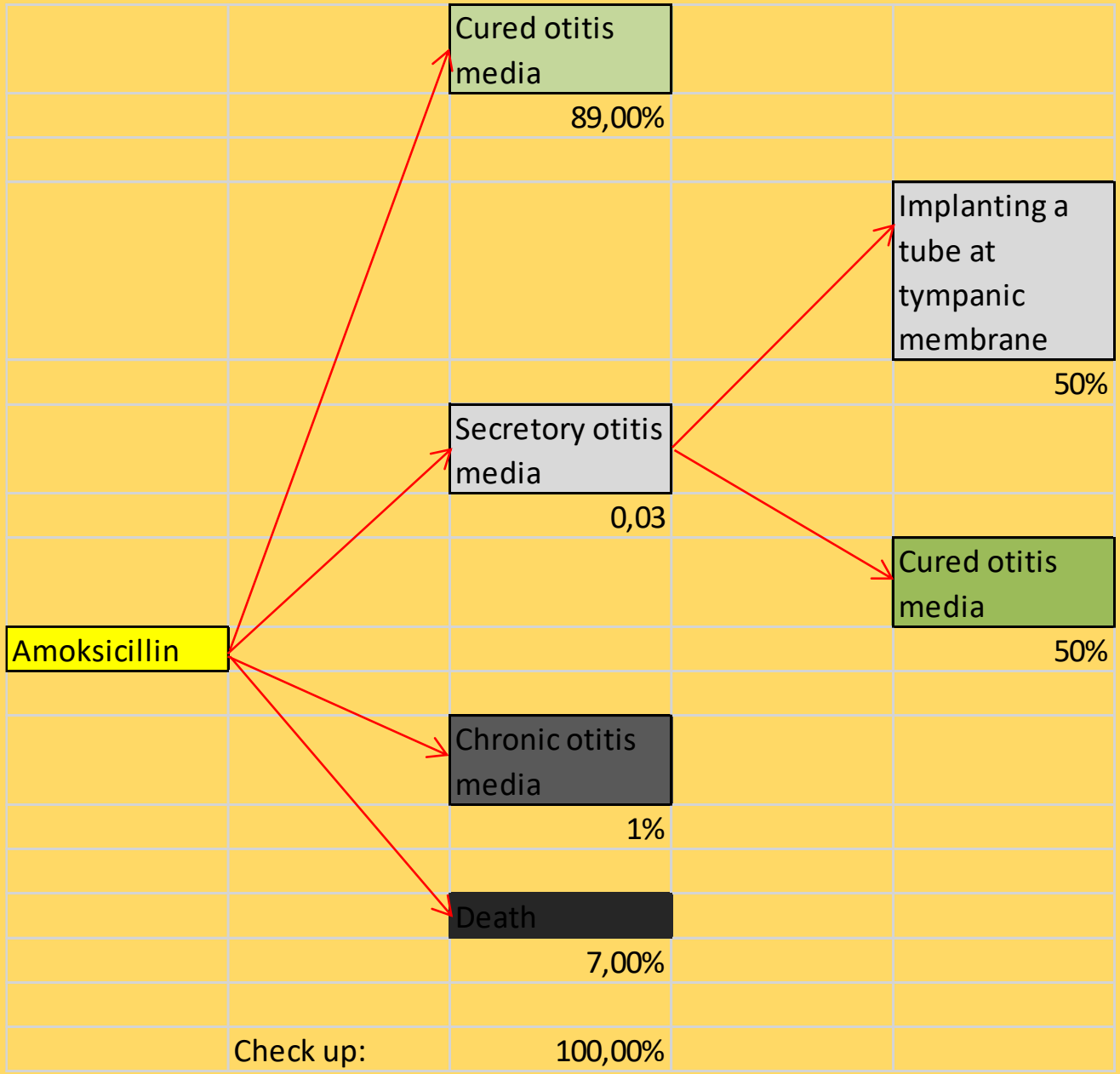
Deterministic and stochastic models

- **Deterministic models** link input parameters with model outputs by mathematical equations
- **Stochastic models** have an element of uncertainty, i.e. randomness
- Pharmacoeconomical analyses are based on stochastic models

Weinstein MC, O'Brien B, Hornberger J, Jackson J, Johannesson M, McCabe C, Luce BR. Principles of good practice for decision analytic modeling in health-care evaluation: report of the ISPOR Task Force on Good Research Practices—Modeling Studies. Value in health. 2003 Jan;6(1):9-17.

DECISION TREE

- It is used for comparison of therapeutic alternatives in short-term disorders where outcomes are not repeatable, e.g. antibiotics for treatment of pneumonia
- The options chosen within the decision tree have to be mutually exclusive

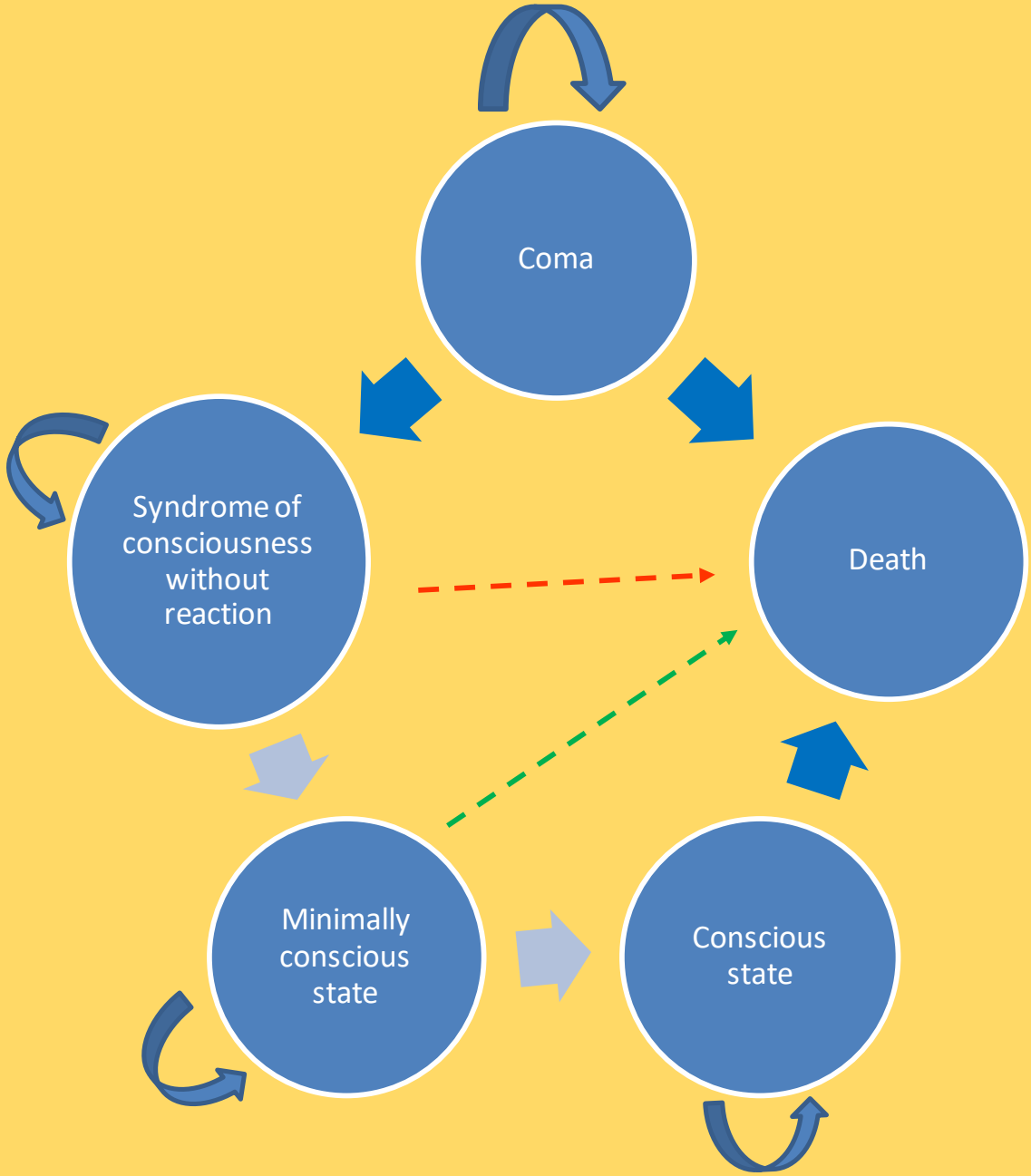

Cured otitis media
89,00%
Implanting a tube at tympanic membrane
50%
Secretory otitis media
0,03
Cured otitis media
50%
Amoksicillin
Chronic otitis media
1%
Death
7,00%
Check up:
100,00%

Decision tree

- Each possible outcome is assigned with relevant costs and effects (quality of life, cure or else)
- Probabilities along a pathway towards certain outcome are multiplied to get the probability of this outcome
- All costs and all outcome values for certain therapeutic option are summed

Markov model

- It is used for comparison of therapeutic option in long-term (chronic) diseases, where a patient could be in various states which could be repeated
- The basics were set by Andrej Andrejevič Markov, Russian matematician, in the first decade of XX century
- Principle: probability that a patient will be in some of the states in future depends only on the state where the patient currently is, and NOT on his previous history

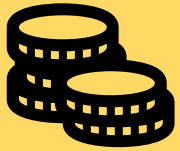

Coma
Syndrome of consciousness without reaction
Death
Minimally conscious state
Conscious state

TRANSITIONAL MATRIX is basis for further calculations in Markov models

			To	
	Initial matrix	Stabile disease or improvement	Progression	Death
	Stabile disease or improvement	64,00%	34,60%	1,40%
From	Progression	0,00%	94,08%	5,92%
	Death	0,00%	0,00%	100,00%
		Stabile disease or improvement	Progression	Death
	Initial distribution	1	0	0
Cycle No:	1	0,64	0,346	0,014
	2	0,4096	0,54696718	0,04343282
	3	0,262144	0,656324732	0,081531268
	4	0,16777216	0,708191822	0,124036018

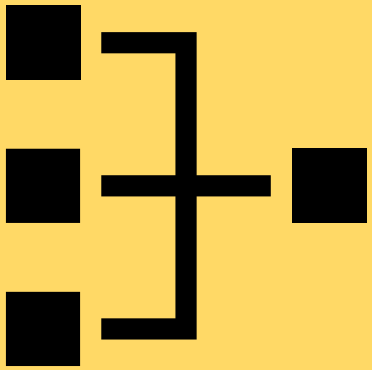
INPUTS TO THE MODEL REGARDLESS OF THE TYPE

Costs – drug + services (visits, hospitalizations, diagnostics, treatment of adverse effects)

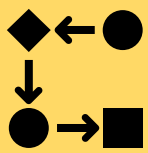


Quality of life, expressed in utility index from 0 to 1

Syndrome of consciousness without reaction (three months)



Probabilities of outcomes in Decision tree models, from 0 to 1



Transitional Probabilities in Markov models, from 0 to 1

Minimally conscious state (three months)

KEY ISSUE: QUALITY OF DATA SOURCES USED TO CREATE THE MODEL INPUTS

- Intentional manipulation with data inputs to the model will bias the model results
- The same model may give opposite results if studies with extreme results are used as source of data interchangeably
- Therefore, QUALITY OF DATA SOURCES MUST BE GUARANTEED by:
  - TRANSPARENCY OF THE DATA SOURCES IN THE MODEL
  - ASSESSMENT OF METHODOLOGICAL QUALITY AND ABSENCE OF BIAS IN STUDIES USED TO CREATE INPUT TO THE MODEL

Bowrin K, Briere JB, Levy P, Millier A, Clay E, Toumi M. Cost-effectiveness analyses using real-world data: an overview of the literature. Journal of medical economics. 2019 Jun 3;22(6):545-53.
Walton SM, Graves PE, Mueser PR, Dow JK. The bias against new innovations in health care: value uncertainty and willingness to pay. Value Health. 2002 Apr;5(2):67–70.

PRINCIPLES OF GOOD METHODOLOGICAL QUALITY AND ABSENCE OF BIAS IN STUDIES USED TO ESTIMATE **COST AND EFFECT** INPUTS TO A MODEL

- Randomization and adequate control in clinical trials
- Removing key confounders from clinical trials, and taking them into account in observational studies when processing the data
- Intention-to-treat analysis in clinical trials
- Measuring a study outcomes independently from the investigators and only by validated methods with tested error potential
- Sufficient sample size to achieve statistical power > 80%
- Using particular statistical test only if essential assumptions are satisfied
- Testing normality of data distribution prior applying parametric statistical tests
- Frankly discussing weaknesses and limitations of the study

Janković SM, Mašić I. EVALUATION OF PRECLINICAL AND CLINICAL STUDIES PUBLISHED IN MEDICAL JOURNALS OF BOSNIA & HERZEGOVINA: METHODOLOGY ISSUES. Acta Informatica Medica 2020; 28(1): 4-10.

PRINCIPLES OF GOOD METHODOLOGICAL QUALITY AND ABSENCE OF BIAS IN STUDIES USED TO ESTIMATE **PHARMACOEPIDEMIOLOGICAL** INPUTS TO A MODEL

- Pharmacoepidemiological inputs are necessary for Budget Impact analysis
- Key quality indicators:
  - Precise definition of target population with inclusion and exclusion criteria
  - Sufficient sample size to achieve statistical power > 80%
  - Random sampling:
    - Simple
    - Stratified
    - Cluster sampling
  - Managing missing data, losses, withdrawals, non-response
  - Testing completeness of the records in databases used as sources
  - Retrieving data from the databases independently from the investigators
  - Taking into account confounders

Delgado-Rodríguez M, Llorca J. Bias. Journal of Epidemiology & Community Health [Internet]. 2004 Aug 1 [cited 2020 Feb 9];58(8):635–41. Available from: https://jech.bmj.com/content/58/8/635

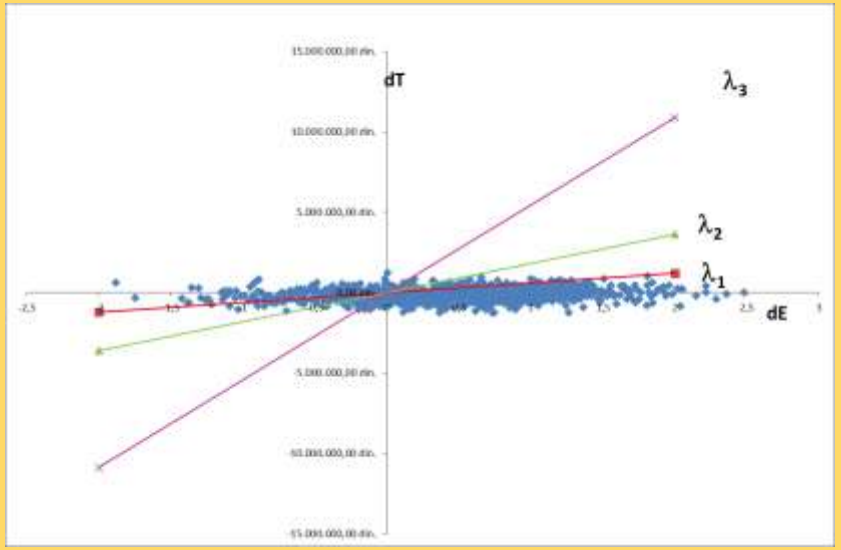
BASE CASE ANALYSIS

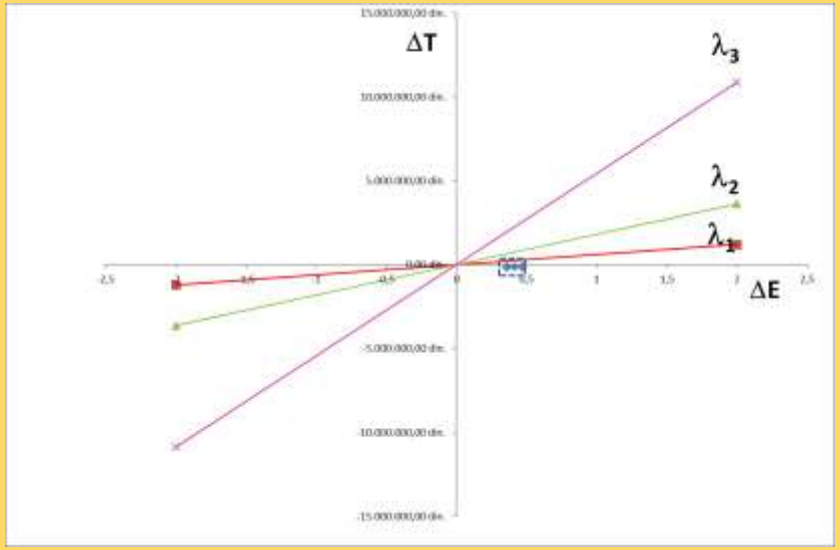
- Input parameters are set to the most probable values
- The model outcomes are without variability („point estimate“)
- Cohort analysis: virtual cohort of 1000 patients passes through the model, and each state has its costs and quality of life („utility“)
- Monte Carlo simulation: each patient starts from certain state, then in next cycles randomly gets to the same or to other states, based on the transitional probabilities
    - Invented by Stanislaw Ulam, a Polish born mathematician who worked on the United States Manhattan Project during World War II.
- All costs and utilities (effects) are summed

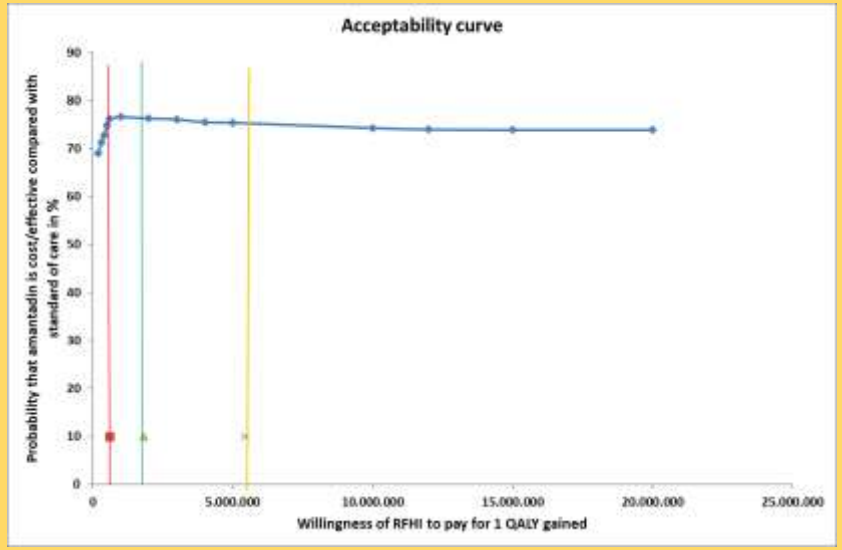
Hay JW, Smeeding J, Carroll NV, Drummond M, Garrison LP, Mansley EC, Mullins CD, Mycka JM, Seal B, Shi L. Good research practices for measuring drug costs in cost effectiveness analyses: issues and recommendations: the ISPOR Drug Cost Task Force Report—Part I. Value in Health. 2010;13(1):3-7..

Outputs of the models – cost/effectiveness (utility) part

	Costs per patient with Amantadine	Costs per patient without therapy	Gained QALYs with Amantadine	Gained QALYs without therapy	ΔE	ΔT	ICER	NET MONETARY BENEFIT
Average	730.882,99 din.	847.051,74 din.	2,655099268	2,240675712	0,414423556	-116.168,75 din.	2.304.130,88 din.	366.404,32 din.
SD	253.727,27 din.	285.270,97 din.	0,492719943	0,477959784	0,685510864	392.136,39 din.	64.825.291,62 din.	525.169,90 din.
CI (96%)	20.667,32 din.	23.236,71 din.	0,04	0,04	0,06	31.941,42 din.	5.280.336,00 din.	42.777,65 din.







Sensitivity analysis – what it is?

- Is analysis of changes in model outcomes after variation of input parameters
- Types:
  - **One-way sensitivity analysis** (each parameter is varied independently and separately of others, ± 20-50%
  - Two-way sensitivity analysis - two parameters are varied simultaneously
  - Multi-way sensitivity analysis – a number of parameters are varied simultaneously
  - Analysis of the best case – all parameters get the most beneficial values
  - Analysis of the worst case – all parameters get the most un-beneficial values
  - **Probabilistic sensitivity analysis** – all key parameters are entered to the model in form of distributions, simultaneously

Aims of **SENSITIVITY ANALYSIS** of a model

- To test whether the model was built properly, i.e. whether it gives the results that could be expected according to our previous knowledge about the disorder that is subject of the analysis
- To establish which variables of the model have the most profound influence on the model outcomes, and how
- All types of sensitivity analysis except the probabilistic one are called „deterministic sensitivity analysis“

Jain R, Grabner M, Onukwugha E. Sensitivity analysis in cost-effectiveness studies. Pharmacoeconomics. 2011 Apr 1;29(4):297-314.

Probabilistic sensitivity analysis (stochastic)

- Some model parameters are assigned with values according to probability distributions
- The distribution are chosen:
  - **Normal distribution** for variables which are known to be normally distributed in real life
  - **Uniform or triangular** distribution when reliable information is missing
  - **Beta distributions** for probabilities
  - **Gamma distributions** for costs

Baio G, Dawid AP. Probabilistic sensitivity analysis in health economics. Statistical methods in medical research. 2015 Dec;24(6):615-34.

Presenting results of probabilistic sensitivity analysis

- Incremental cost/effectiveness graph with results for 1000 virtual patients
- Acceptability curve
- Confidence intervals of ICER and net benefit

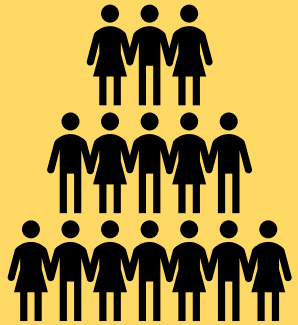
Budget impact analysis

- Testing consequences of using new drug in whole population of eligible patients
- The best estimate of financial consequences (within the defined time period) for healthcare payer if new drug is reimbursed

Mauskopf JA, Sullivan SD, Annemans L, Caro J, Mullins CD, Nuijten M, Orlewska E, Watkins J, Trueman P. Principles of good practice for budget impact analysis: report of the ISPOR Task Force on good research practices—budget impact analysis. Value in health. 2007 Sep;10(5):336-47.

Obligatory elements of Budget impact analysis

- To define a **PERSPECTIVE**
- To define **SIZE OF THE DRUG BUDGET**
- To define **REIMBURSEMENT ASSUMPTIONS** (**limitations** to subpopulations and percent of patient **participation** in costs)
- To define **SIZE OF TARGET POPULATION**



Obligatory elements of Budget impact analysis

- To define **MARKET SHARE** (using equations)
- To consider possible out of label drug use
- To describe clearly advantages of new drug in comparison to old ones in regard to efficacy, safety, ease of administration, etc.
- To define time horizon, but budget impact should be calculated for **EACH YEAR SEPARATELY**, usally for the first **THREE YEARS** after acceptance for reimbursement

Sullivan SD, Mauskopf JA, Augustovski F, Caro JJ, Lee KM, Minchin M, Orlewska E, Penna P, Barrios JM, Shau WY. Budget impact analysis—principles of good practice: report of the ISPOR 2012 Budget Impact Analysis Good Practice II Task Force. Value in health. 2014;17(1):5-14.

Calculation of market share

- *peak_share = 0.23 + 0.46 promotional_share - 0.18 third - 0.23 fourth - 0.009 time + 0.007 time*third + 0.01 time*fourth - 0.06 new_competitor*

  - promotional share assumptions: 53% for a second entrant, 29% for a third entrant and 24% for a fourth entrant
  - Time – delay of entrance of new drug to the market relative to the first drug, expressed in number of quarters of a year
  - new competitor – equal to 1, if our drug was second sentrant, and there was also a third entrant to the market after our drug

Regnier SA, Ridley DB. Market watch: Forecasting market share in the US pharmaceutical market. Nat Rev Drug Discov. 2015 Sep;14(9):594-5.

Obligatory elements of Budget impact analysis

- To define comparators and influence of new drug to their utilization
- MODEL
  - Should be connected with cost/utility model
  - Should be transparent
  - It should be based on open cohort principle, i.e. the patients could be leaving and entering the model
  - It should be validated:
    - Validation of structure – does it corresponds to real world situation
    - Validation of content (an independent expert should check data, sources, calculation)
    - Validation of outcomes – could be checked for drugs that are already on the list

Obligatory elements of Budget impact analysis

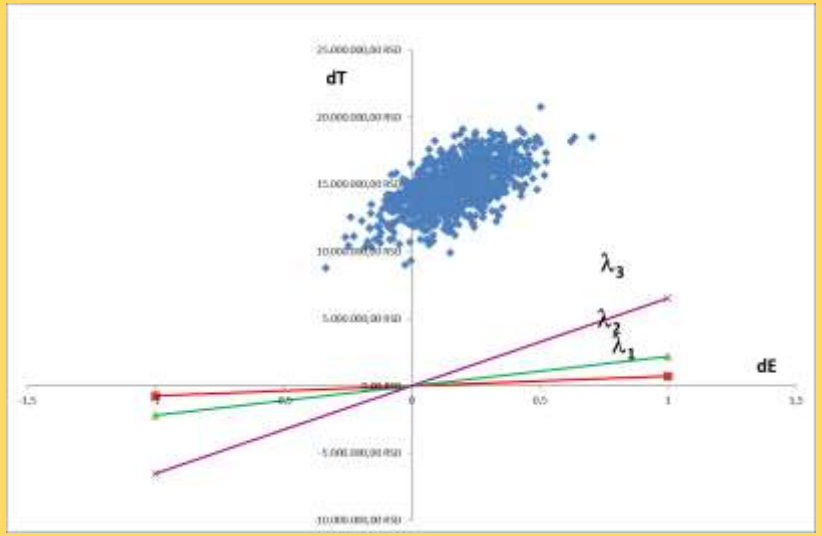
- Each model input should be supported by a reference and given in the form of range of values
- No discounting of costs is neccessary
- Adherence should be taken into account
- Presentation of results:
    - Base case
    - The best case
    - The worst case
    - Probabilistic sensitivity analysis

What software to use to build pharmacoeconomic models?

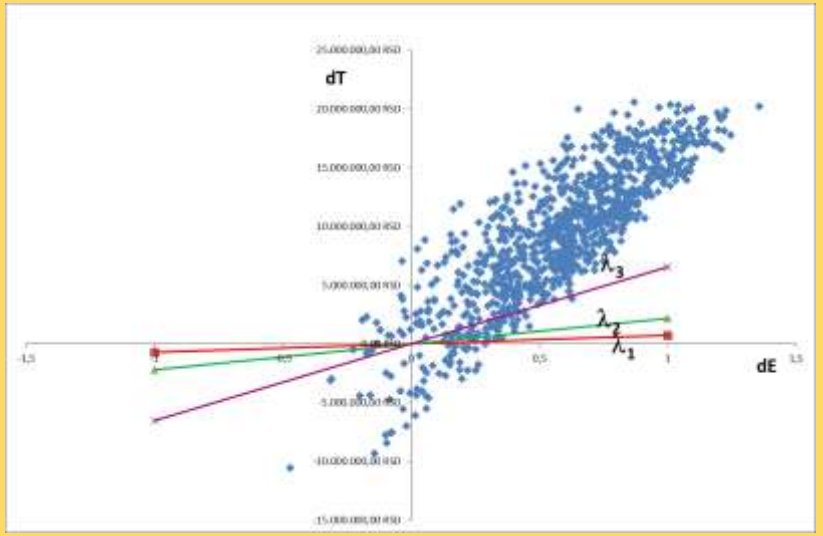
- „a recent systematic review of modeling approaches for the cost effectiveness of hepatitis C treatment with direct-acting antivirals found 15 **(42%) out of 36 studies used Excel** as the primary modeling software, while 9 **(25%) used TreeAge**, 5 (14%) did not report the modeling software, 4 (**11%) primarily used R**, only 1 (3%) used Microsoft Visual Studio, only 1 (3%) used C++ programming language, and only 1 (3%) used Arena.“

Dasbach EJ, Elbasha EH. Verification of decision-analytic models for health economic evaluations: an overview. Pharmacoeconomics. 2017 Jul 1;35(7):673-83.

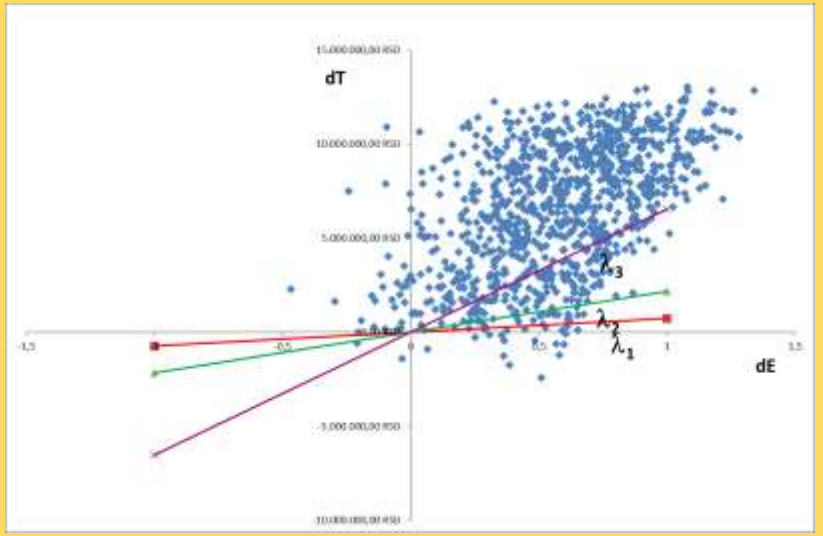
What to do with extremely expensive, but also effective innovative drugs in low-budget economy? ADJUST YOUR APPROACH!
Example of pembrolizumab in NSCLC, Serbian economy milieu



Comparison with chemotherapy, 1st line



Comparison 1st line/2nd line, 2 years of therapy with pembrolizumab



Comparison 1st line/2nd line, 1 year of theapy with pembrolizumab