Using early health economic models to support drug development decisions

Richard Nixon

Economic Modeling, Advanced Quantitative Sciences, Novartis

Joint BBS and EFSPI Seminar on Health Technology Assessment

2013 June 4

NOVARTIS

Health Economic Models can support drug development decisions

- Health economics models are used for demonstrating the value of a drug to payers post-registration
- **Health economic models can be used to support drug development decisions**
  - Development decisions and Phase III trials should also focus on HTA considerations as well as drug registration
- **Decisions and concerns during drug development are different from those for reimbursement**
  - Leading to different models and metrics

Burman and Wiklund framework for modeling

Powerful generic guidelines that can be used to think about HE models

- **Framing**
  - (1) Good modeling is about making better decisions and (2) is driven by the underlying question
- **Data integration**
  - (3) Good modeling is based on applied sciences and (4) uses a diversity of information sources
- **Continuous parsimony**
  - (5) Good modeling is not made unnecessarily complicated and (6) is a continuous process
- **Communication**
  - (7) Good modeling facilitates communication

Case study

Support development decisions of a new drug

- A pharmaceutical company has a new drug in development
  - A dose range finding study is currently underway
  - Confirmatory registration studies are being planned
- This drug is a treatment for a recurrent event disease
  - Events are acute and life threatening
- Development plan should consider reimbursement in addition to registration

NOVARTIS

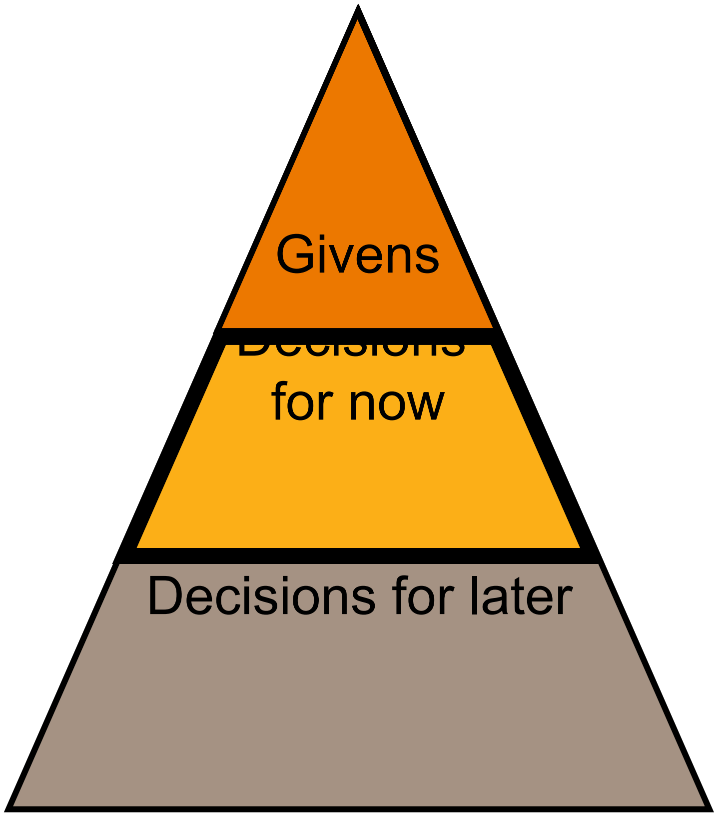
Framing

"A problem well put is half solved" – John Dewey

Good modeling is about making better decisions and is driven by the underlying question

- Don't model unless you see which decision could be improved by your model
- Failure to do so can lead to work that is unfocused leaving the decision maker with the question "so what?"

A decision hierarchy identifies issues to be decided and issues already decided or that can be deferred



- Policy
- Environment
- Decisions already made

- Near- and long-term strategic direction
- Near-term significant resource commitments
- Issues that must be resolved today

- Later significant resource commitments
- Decisions for specialists
- Operational or tactical decisions

Decisions for reimbursement are different from decisions during drug development

	Reimbursement	Development
Decision perspective	Payer	Sponsor
Decision	• Do I reimburse this drug? • In which patients? • Which other treatments should have already been tried?	• Should development be continued? • What level of efficacy is required to demonstrate cost-effectiveness? • Which patient population should be targeted? • What price should be charged for the drug? • What information do I need to collect during Phase III development?
Metrics	• ICER • CEAC • Budget impact	• Value of information • Drug price • Sensitivity analysis

NOVARTIS

Model should not try to answer everything, but be tailored to the specific problem

- Should development be continued?
  - What price could be justified for the drug to be cost-effective?
  - Is there a cost-effective sub-population?
- What do we need to measure in the development program if we continue?
  - What are the key value drivers of the drug?

Data integration

Aim to be a "one stop" modeling shop

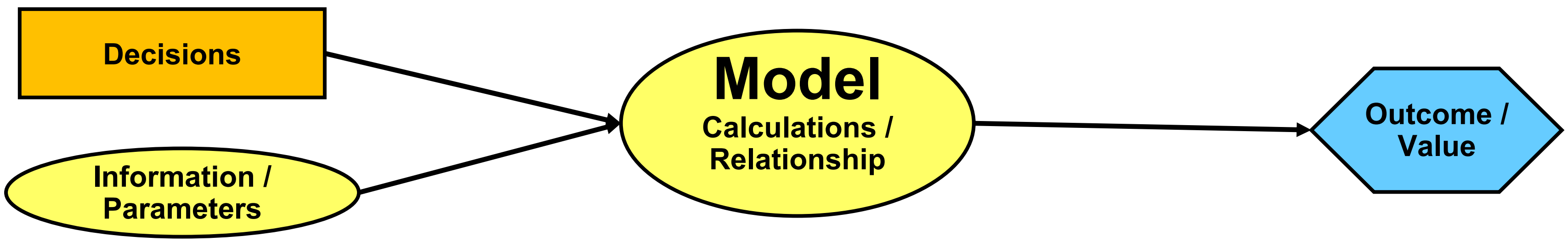
Good modeling is based on applied sciences and uses a diversity of information sources

- Aim for a portfolio of inter-related skills and rather than fragmentation of role into ever smaller pieces
- A good modeler is a translational scientist capable of understanding the problem, translating it to a model, and communicating back the results

NOVARTIS

What is a model?

A way to simplify reality, synthesis information, and communicate decisions



- *"A model is a **mathematical construct to mimic reality**, built based on data, ... and the current scientific understanding of the process involved."*
  - A model is always a simplification

Think Tank Report 2007

- Find the best model for the purpose, considering the available data and the decision to be made

NOVARTIS

Divide and conquer

Break it down, understand it, and put it back together

"The spirit of decision analysis is divide and conquer:

decompose a complex problem into simpler problems,

get one's thinking straight on these **simpler problems**,

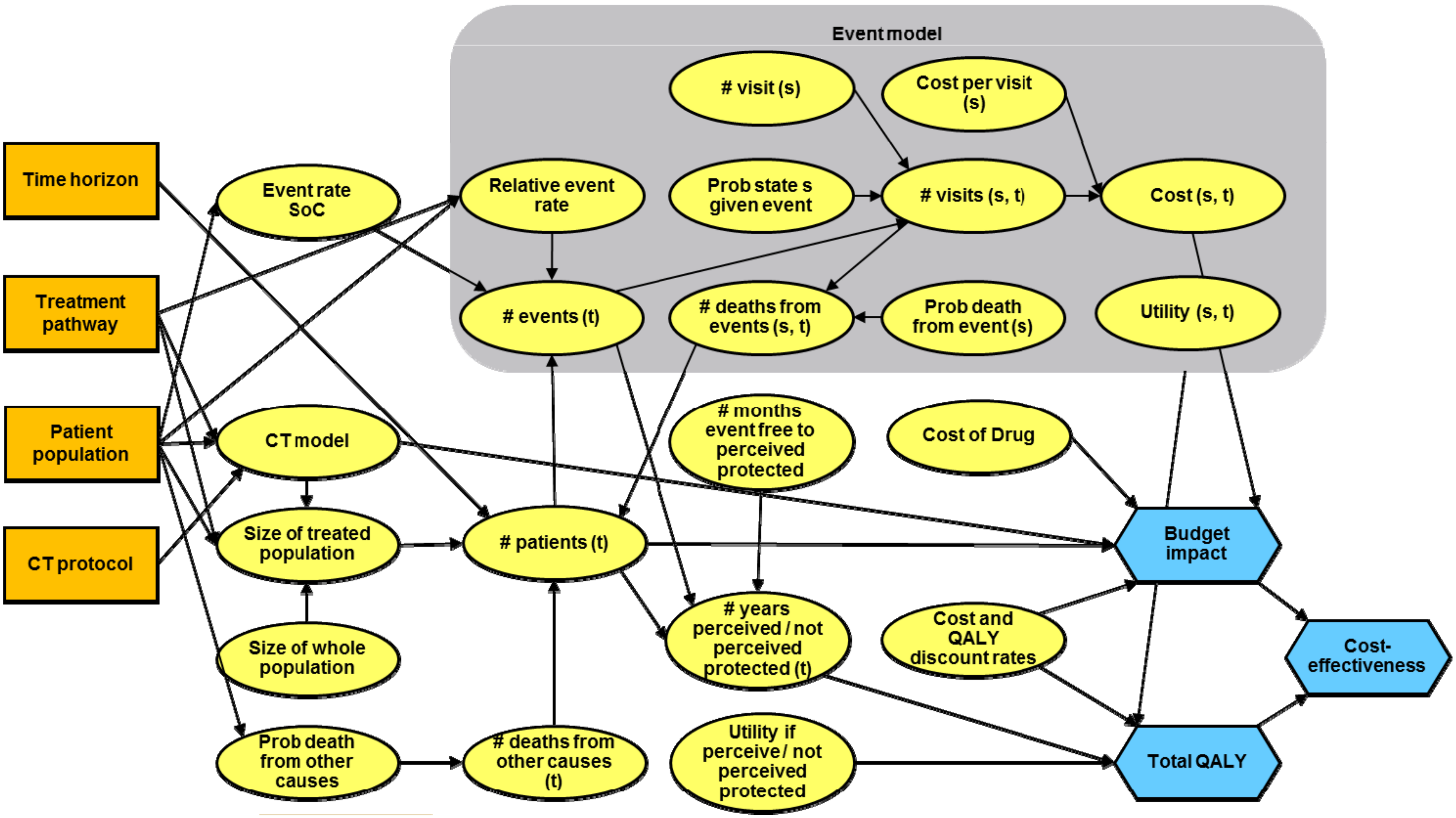
paste these analyses together with **logical glue**, and

come out with a **program of action** for the complex problem"

-- Howard Raiffa

Influence diagrams are a useful tool for model building

t = time
s = state



Influence diagrams also show what data you need

- The information nodes with no parents show what data you need to populate the model
- Data come from a variety of sources
  - In house clinical trial data
  - External databases
  - Literature
  - Expert knowledge
  - Other modeling activities
  - ...
- To get these data you need a strong network of experts, who can identify relevant data sources and can give their opinions

Continuous parsimony

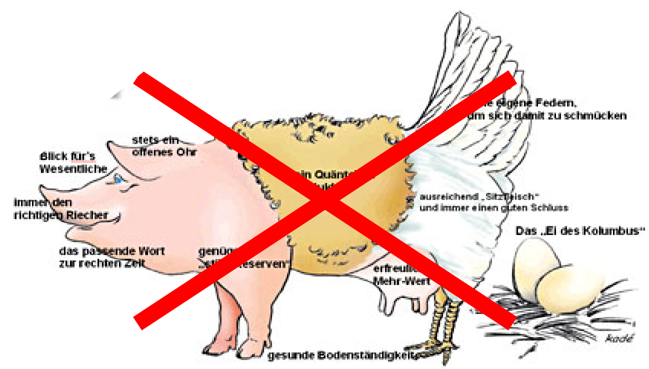
A simple model can be an underlying framework for drug development

Good modeling is not made unnecessarily complicated and is a continuous process

- “Everything should be as simple as it can be but not simpler” -- Albert Einstein
- “Any fool can make something complicated. It takes a genius to make it simple” -- Woody Guthrie

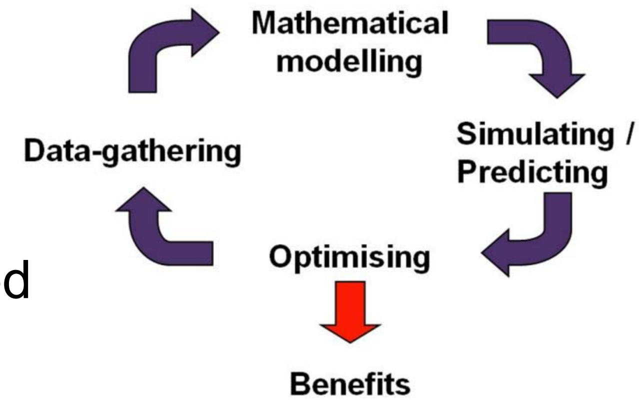
Work hard to make your model easy

- Building a simple model is difficult
  - Models tend to get overly complicated
  - A simple elegant model require a lot of thought
  - Large part of it is tacit knowledge that you learn by doing
- Tips for keeping it simple
  - Always remember the decision context and keep focused on it
  - Don’t try to make a Eierlegende Wollmilchsau ("Egg-Laying Wool-Milk-Sow“)
  - Resist the temptation for “scope creep”



A simple model is easier to maintain and explain

- The decision process can be iterative
  - The process of framing, and structuring the model, and exploring data can lead to insights that require the model to be adapted



- The model structure can be used through out the development process
  - A simple model is easier to build on later and is easier to communicate

- The model can form the basis of the model used for reimbursement
  - Used for early interaction with HA and HTA organizations

Communication

"People decide, not models" -- Larry Phillips

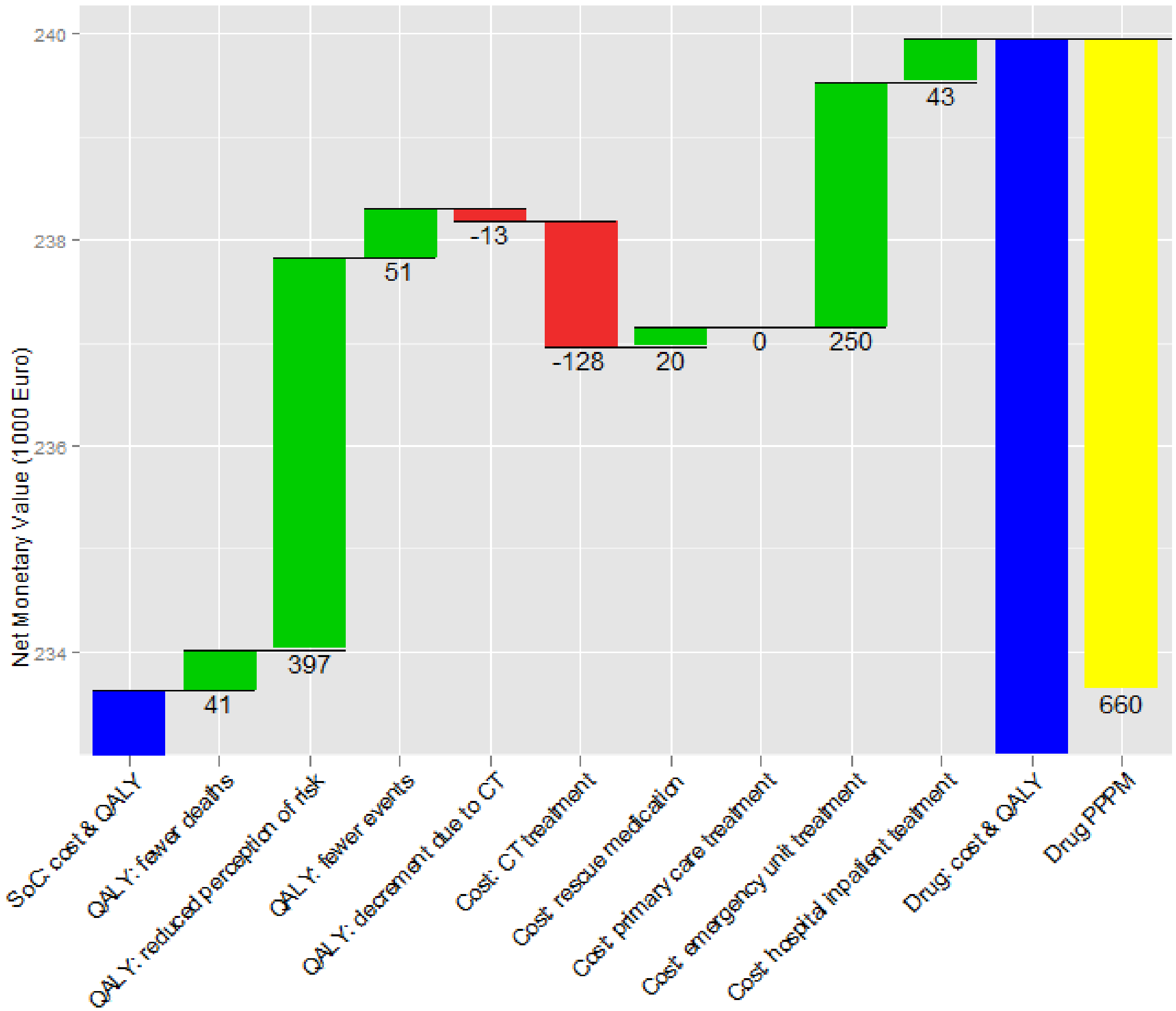
Good modeling facilitates communication

- Modeling is about bringing clarity to decisions and supporting decision makers, not replacing them
- Sensitivity analysis is especially important in early health economic models as there is a lot of uncertainty
  - Perhaps less need for probabilistic sensitivity analysis at this stage

NOVARTIS

Waterfall plot shows the main value drivers

Assume a Willingness–to-pay of 35K Euro



- The Net Monetary Value of each treatment is shown by the blue bars
- Net Monetary Value is converted to a price of Drug PPPM and is shown under each bar
- The yellow bar shows that the drug is adds value worth 6300 Euro more than SoC
  - This gives a drug price of 660 Euro PPPM
- The biggest value components are:
  - QALY gains from reduced perception of risk
  - Less spent on emergency unit treatment
- Utility gains from fewer events themselves has little effect on value

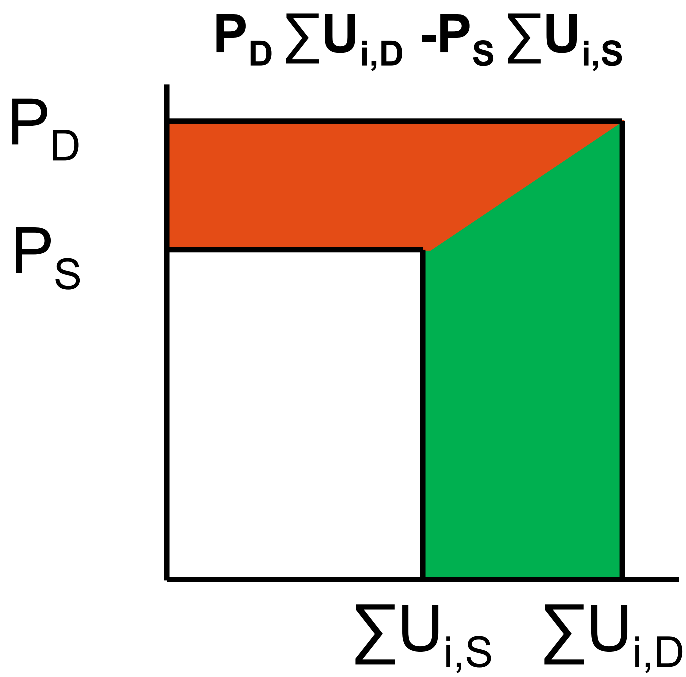
A note on how to partition costs and utilities (1/2)

- At a given time we have
  - $\mathbf{C_{i,D}}$ and $\mathbf{C_{i,S}}$ for the cost from component *i* given Drug or SoC
  - $\mathbf{U_{i,D}}$ and $\mathbf{U_{i,S}}$ for the utility from component *i* given Drug or SoC, given that the patient is alive
  - $\mathbf{P_D}$ and $\mathbf{P_S}$ for the probability of being alive given Drug or SoC
- The model has been structured in such a way that the total utility can be writen as
  - $U_{TOT,D} = \Sigma U_{i,D}$
  - The incremental cost for a **component** is $C_{i,D} - C_{i,S}$
  - The incremental utility (accounting for death) **overall** is $P_D \Sigma U_{i,D} - P_S \Sigma U_{i,S}$
  - **How is the contribution of each utility component to the over all incremental utility obtained?**

NOVARTIS

A note on how to partition costs and utilities (2/2)

- Graphical representation of incremental overall utility

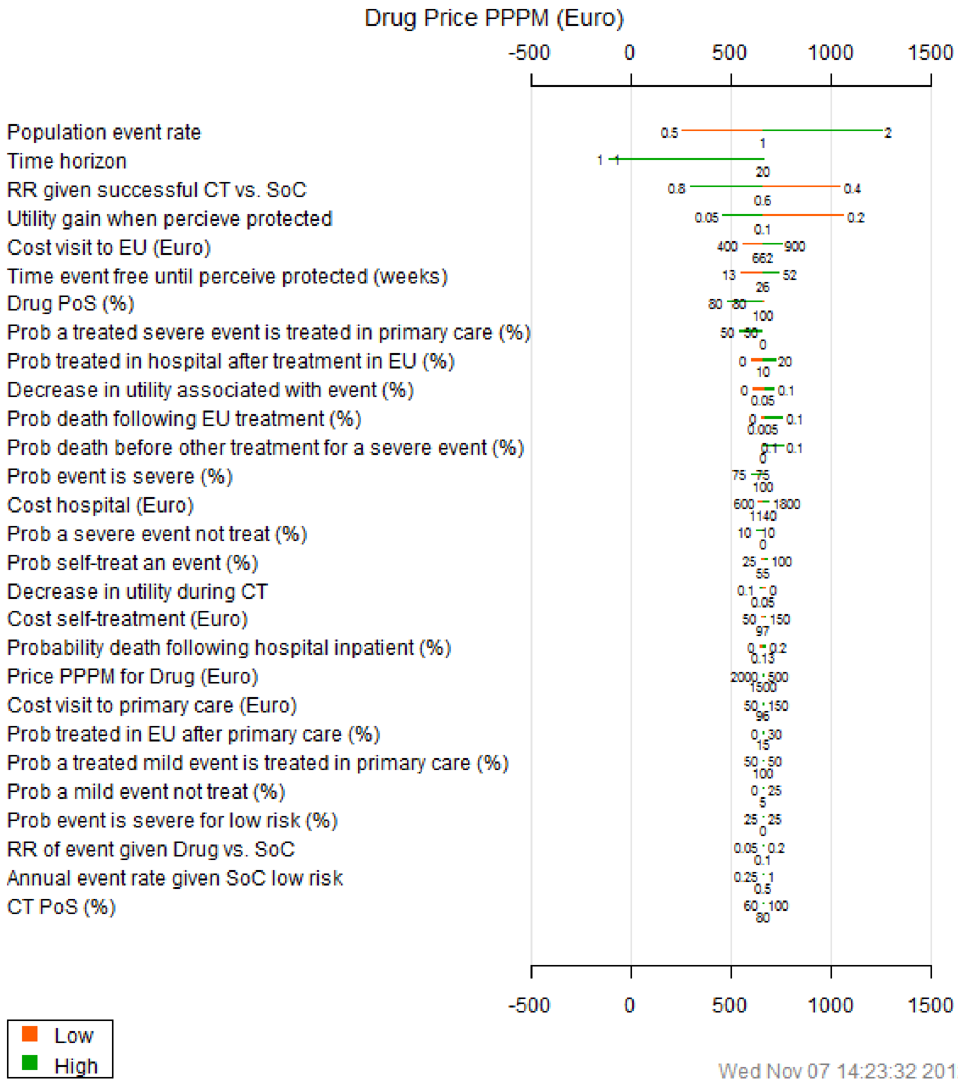


Death: $\frac{1}{2}(P_D - P_S)(\sum U_{i,D} + \sum U_{i,S})$

Total Utility: $\frac{1}{2}(P_D + P_S)(\sum U_{i,D} - \sum U_{i,S})$

Utility from comp *i*: $\frac{1}{2}(P_D + P_S)(U_{i,D} - U_{i,S})$

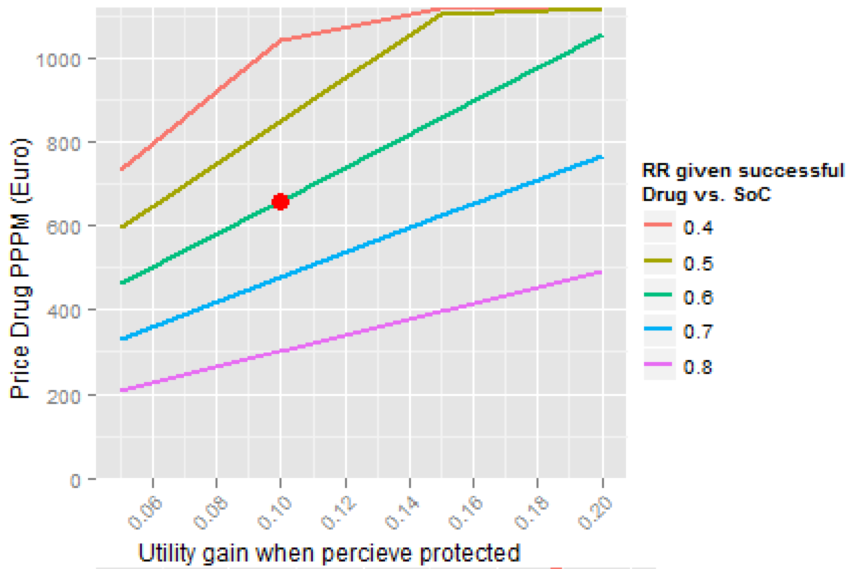
Tornado plots show a one-way sensitivity analysis



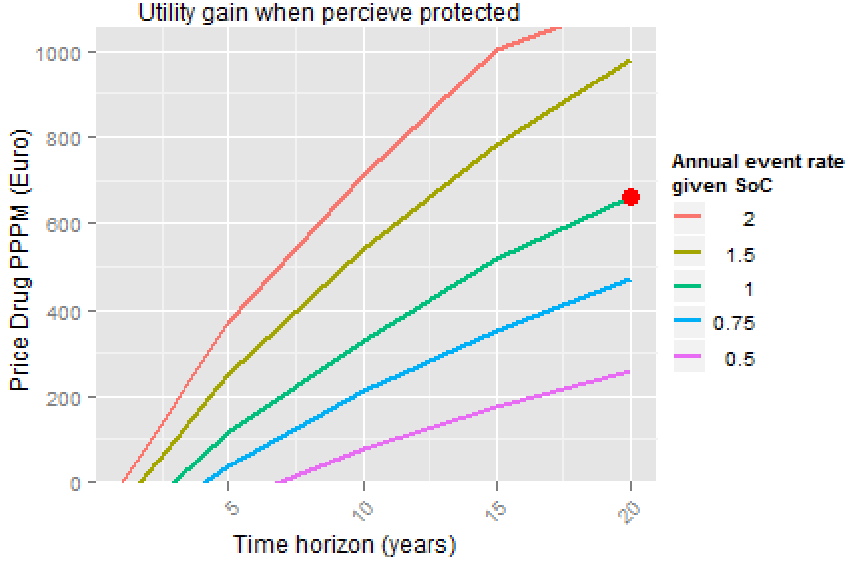
- The base case price is 660 Euro PPPM
  - Parameters values at base case are shown under each bar
- Sensitivity analysis: The parameter values are changed one at a time. The new values are shown at the ends of each bar
- The price increases most when
  - The event rate of the population is larger
  - The time horizon is longer
  - The relative risk of an event given Drug (compared to SoC) is smaller
  - Utility gain when perceive protected is larger

NOVARTIS

Two-way sensitivity analysis of most important uncertainties



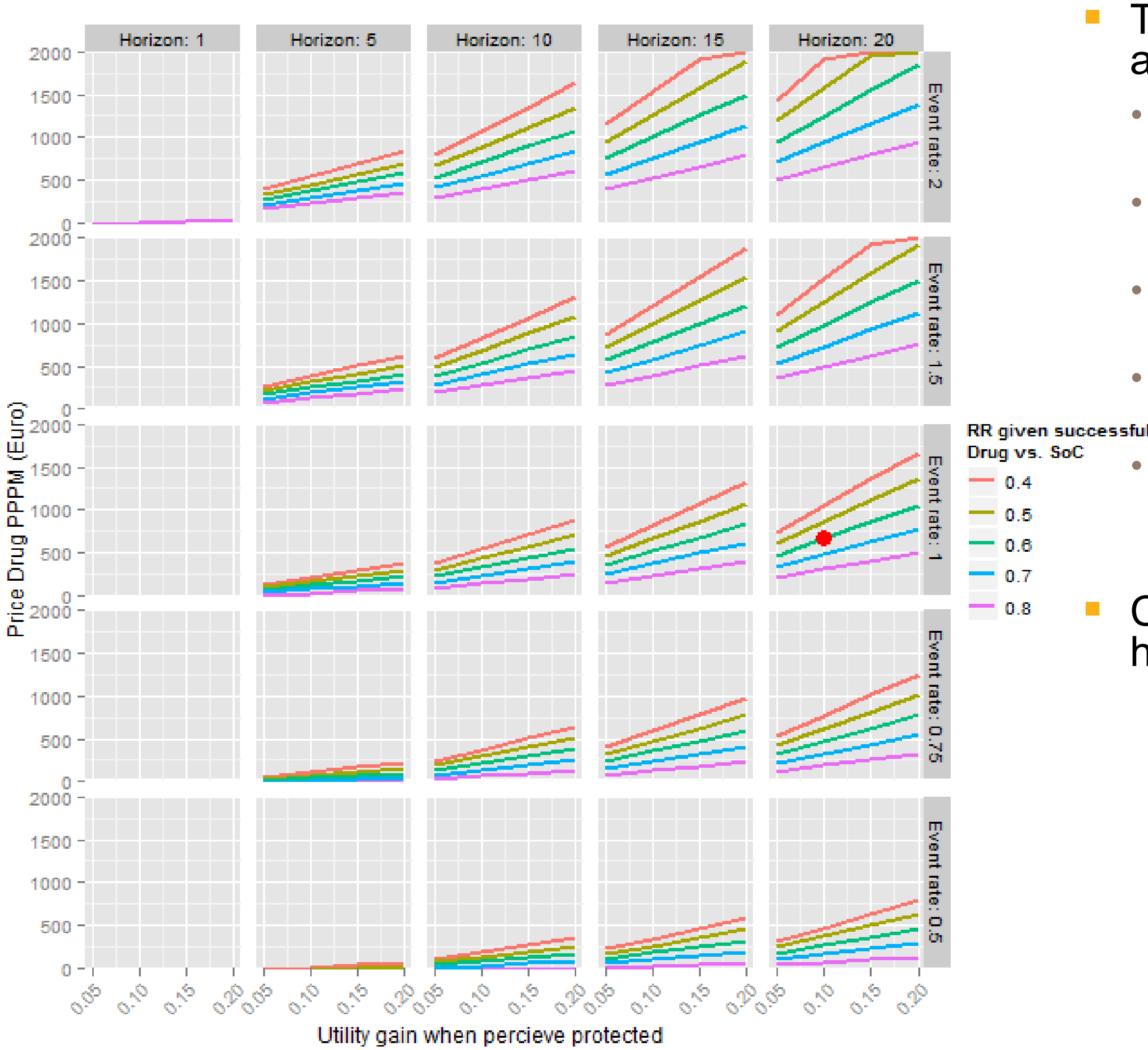
- Utility gain when perceive protected on the x-axis. Base case = 0.1
- Each line shows the RR of an event given successful Drug vs. SoC . Base case = 0.6
- Price PPM of Drug is 660 Euro
  - Price of 800 Euro is achievable if the RR of an event given successful treatment is decreased to 0.5, or utility gain increases to 0.14



- Time horizon is on the x-axis
- Each line shows the event rates. Base case = 1 per year
- Benefits are only realized in the long term because the costs are upfront
- In a population with an event rate of 0.5 per year, the supported price of the drug reduces to 280 Euro

NOVARTIS

Four-way sensitivity analysis of most important uncertainties



- The four most important parameters are all varied together.
  - Red dot is the base case with a drug price of 660 Euro PPPM.
  - Different time horizons are given in the columns.
  - Different population event rates are given in the rows.
  - The utility gain when perceive protected is on the x-axis.
  - Each line shows the time a patient is event free until they perceive they are protected.
- Can assess what would need to happed to justify a given drug price.

Revisit the original decisions to be made

Distill big difficult decisions down to smaller simpler decisions

- Should development be continued?
  - *What price could be justified for the drug to be cost-effective?*
  - *Is there a cost-effective sub-population?*
  - **The drug has an expected value of 660 Euro PPPM in a population with an event rate of 1 per year, increasing to 1100 Euro in a population with double this rate**
- What do we need to measure in the development program if we continue?
  - *What are the key value drivers of the drug?*
  - **To demonstrate the value of the drug it is crucial to measure the QALY gains from reduced perception of risk and the resource use in emergency units**

NOVARTIS

Skills in a statistician’s toolbox can be readily applied in this area

- Traditional (pharma) statistician role
  - Close regard for regulator guidelines is important for confirmatory trials
- Opportunity for expansion of statistician role
  - Model-based drug development needs a different mindset and different methodologies
- Statistical training is readily transferable
  - Clear logical structuring, comfortable with complexity, elegant mindset, quantitative skills, and understanding of uncertainty

Conclusions

- Need to demonstrate the value of a new drug to payers
- Health economic decision models can support decision making during the drug development process
  - Supporting go – no-go decisions
  - Population section
  - Identifying what information needs to be collected at Phase III
  - Assessing the price that can be justified for the drug
- The decisions and decision makers during drug development are different from reimbursement
- Statisticians are well placed to support this process

NOVARTIS