Hello and welcome
In this presentation I will introduce a study that my and my co-authors Karin Groothuis, Brett Hauber and Maarten IJzerman are working on.
Before I introduce our model and show you some results from an illustrative case study, I will shortly describe the background
Consider a decision,

- Where we have a goal, which is
  - operationalized by multiple criteria, on which
  - we are assessing one or more treatments

- Take for example market access or reimbursement decisions for new medical treatments. Attributes can then be beneficial effects, adverse (side) effects, costs, etc… and treatments can be applicant drugs, or a newly proposed drug and the current standard of care.

- To reach a decision in line with our objectives, we must know
  1. How the treatments perform on the attributes. Consider e.g. an adverse event, then performance can be how probable it is that a patient experiences that adverse event.
  2. There is a long history of gathering, reporting and assessing such evidence about performance; e.g. RCT’s & systematic reviews, but!
  3. We cannot decide solely on such data. To make a sensible decision we must also include the relative importance of the various attributes into our decision, e.g. benefits-risks, or when multiple risks exist, what is the most severe?
So how do we assess the relative importance of attributes?

1. Nowadays mostly experts who try to take a patient or societal perspective
2. The patient perspective is esp. Important when assessing the importance of clinical attributes
   a) But since they are not patients, they cannot always know that’s best for patients, esp. When the benefit/risk balance is not immediately clear.
3. That is why increasingly patient representatives or “professional” patients are involved to obtain more insight into the patient perspective.
   a) But questions about representativeness
4. More representative could be quantitative patient preferences, i.e. structured surveys sent to large group of patients and analyzed with statistical methods to elicit the patients’ relative preferences for outcomes.
The aims of this study are twofold.

First, we aim to explicitly combine patient preferences with data from clinical trials, to enable insight into the patient-weighted utility of treatments.

Secondly, we aim to take uncertainty in both preferences and performance into account simultaneously.

Why?

- Be able to assess confidence in decision, and $P$(wrong choice), because reversal is costly (in hrqol and time/money)
- Are there gaps in the evidence base?

We do this by …
(To do this) we adopt a probabilistic framework, i.e. we represent uncertainty in preferences and clinical performances with probability distributions.

The quantitative patient preferences are elicited with …
discrete choice experiments, where patient-respondents are presented with a choice between two treatments that are described on a set of attributes. The relative importance of the attributes is estimated with logistic regression based on the idea that a treatment with preferable attributes levels is more likely to be chosen. The parameters for the probability distributions around preferences can be found using a mixed (or random parameters) logit analysis approach.
• Similarly, parameters for the performance PDs can be estimated from clinical trials. Ideally from patient-level data, but it is also possible to estimate it based on published (aggregate) data.

• By combining the PDs around preferences and clinical performance, we can obtain a PD around the patient-weighted utility of treatments.

• from this obtain two useful outcomes measures, namely:
A probability that the utility is more than zero. This might be useful for market access decisions, where benefits (positive utility) are compared with risks (negative utility) and drugs are only accepted onto the market when the benefits are perceived to outweigh the risks. The latter can be made concrete with the patient-weighted utility, and because we have not only the mean patient-weighted utility but also the PD, we also have a sense of how confident we can be that the B/R balance is indeed positive.
Secondly, the patient-weighted utilities can be used to rank treatments. The overlap between the utility distributions is then a measure of uncertainty in that ranking. From the distributions follow ranking probabilities, e.g. $p(\text{rank}=1)$, $p(\text{rank}=2)$, etc.
The distribution around the patient-weighted utility is thus a function of the distributions around preferences and performances. The precise structure depends on the decision structure, but most often linearly additive combination is used. In any case, analytically obtaining PD(U) can be difficult, and a more straightforward approach is to use Monte Carlo simulations where many draws from the prior preference and performance distributions are performed to estimate PD(U).

In our model, we

- first sample from the preference distribution,
- Then draw from the performance distribution
- And then interpolate to estimate the (part-worth) utility in this simulation run.
- Repeat to estimate PD(U)
ILLUSTRATIVE CASE STUDY
PREFERENCES

- Case on preferences for antiretroviral treatments of patients
  - 147 adult HIV-positive african americans
  - Treatment-naive
- Five attributes:
  1. P(virological failure)
  2. P(allergic reaction)
  3. P(bone damage)
  4. P(kidney damage)
  5. Treatability bone/kidney damage (can treat, cannot treat, do not know)
- Mixed logit, to estimate multivariate normal distribution


We will illustrate the model with a case on antiretroviral treatments. The patient preferences come from a study done in 2009 that looked at the preferences of (…)

African-americans are a subgroup that are disproportionally likely to delay or forego antiretroviral treatment.

The attributes were (…)

Preferences-> multivariate normal
ILLUSTRATIVE CASE STUDY
PERFORMANCES + MODELING PROCESS

- Included treatments: Recommended initial regimens from NIH guideline
  - DTG+ABC/3TC
  - EFV+TDF/FTC
  - RAL+TDF/FTC
  - ATV/r+TDF/FTC
  - EVG/COBI+TDF/FTC
  - DRV/r+TDF/FTC
- Also two treatments part of other treatments
  - ABC/3TC
  - TDF/FTC
- Performance data gathered from RCT’s cited by NIH guideline
- Beta distributions used

As treatment alternatives we included the recommended regimens (irrespective of initial viral load or CD4 count) as recommended in the most recent (May 2014) national institute of health guideline on the use of antiretroviral agents in hiv-1 infected adults and adolescents. Most recommended regimens consist of one active antiretroviral drug in combination with two nucleoside reverse transcriptase inhibitors (or NRTIs). For completeness data on just these NRTI’s was also included. The data for all the performances were obtained from randomized clinical trials on which the guidelines are based.

TDF/FTC=tenofovir/emtricitabine; EFV=efavirenz; ATV/r=atazanavir/ritonavir; DRV/r=darunavir/ritonavir; DTG=dolutegravir; RAL=raltegravir, ABC/3TC=abacavir/lamivudine

The monte carlo simulations were programmed in R, and 10,000 simulations were run. The results are as follows...
Notice:
Means of abc/3tc and tdf/ftc alone, are low, this intuitively makes sense
Much overlap
Negative utility; might makes sense considering the population the preferences were elicited from.

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How to deal with structural uncertainty. DCE can practically only deal with a small number of attributes (or present respondents with subset of attributes; but then larger $n$ is needed.)
Ways to incorporate other elicitation methods. We have done AHP.

Heterogeneity in both preferences and expected clinical outcomes. Maybe we can identify subgroups for who

The balance is very bad and certain: lose indication, or oblige shared decision making processes if the balance is mostly bad due to preferences

Very good and certain: early acces; since uncertainty is very unlikely to shift the B-R balance below zero

Very uncertain → postpone decision, gather more evidence (for this we need value of information)

Ethical questions
THANK YOU