Decision curve analysis for personalized treatment choice between multiple options

K. Chalkou, A. Manca, G. Salanti
Several strategies to decide upon treatments

**Default-average strategies:**
- Treat all patients with Treatment 1
- Treat all patients with Treatment 2
- Treat nobody

**Individualized treatment choices:**
- Treat patients according to an individualized prediction model
- Several prediction models available
Background

Decision curve analysis methods (DCA)

• The main methodological vehicle to evaluate the clinical relevance of each strategy

• Evaluate which strategy leads to better clinical decisions
Measure of performance in DCA – Net Benefit

Net benefit (NB)

The NB can be estimated for each strategy $s$: $NB_s$

The strategy with the highest NB leads to better clinical decisions
Background

DCA methods well established into an RCT framework where two treatment options are compared.

Nowadays, several treatment options exist for the same condition, evaluated in several RCTs for the same outcome.
Objectives

We aim to extend the DCA methodology, into a network meta-analysis framework (NMA), where several treatment options are compared coming from several studies, to compare default average strategies with individualized strategies.
Case study

Individualized treatment recommendation for patients with relapsing-remitting multiple sclerosis (RRMS)

Stage 1 – Baseline risk score
SMSC study

Stage 2 – IPD Network Meta-regression (Bayesian using MCMC)
https://cinema.ispm.unibe.ch/shinies/koms/
3 RCTs
Reaching treatment recommendations when we have multiple options via a model

**Threshold value** $T_j$

Even if a treatment $j$ is efficient, the treatment’s side-effects, inconvenience and risks need to be taken under consideration.

\[
RD_{i,N} = 3\% \quad \text{🤔} \quad RD_{i,N} = 35\% \quad \text{👍}
\]

“Which is the minimum risk difference compared to control that renders treatment $j$ worthwhile taking?”

For instance, a $T_j$ of 20% means that we would be willing to treat no more than 5 patients to prevent one relapse.
Reaching treatment recommendations when we have multiple options via a model

Let us assume: $T_{DF} = T_{GA} = 19\%$, $T_{N} = 28\%$

**Decision rule**

For a patient $i$, the recommended treatment $j$ under the prediction model is the one that satisfies $\max \{RD_{i,j} - T_j\}$, between those treatments with $RD_{i,j} \geq T_j$. When all active treatments lead to $RD_{i,j} < T_j$, then the control treatment is recommended for patient $i$.
The graph shows the estimated probability of relapse within two years. The text indicates:

- \( T_{DF} = T_{GA} = 19\% \)
- \( T_N = 28\% \)

The graph compares different treatments with the placebo. For example, Glatiramer Acetate (GA) has a 19% relapse rate, and Natalizumab has a 28% relapse rate at a baseline risk score of 0.75.
Reaching treatment recommendations when we have multiple options via a model

| Treatment                  | Placebo | Glatiramer Acetate | Dimethyl Fumarate | Natalizumab |
|----------------------------|---------|--------------------|-------------------|-------------|
| Predicted risk to relapse  |         |                    |                   |             |
| within two years ($R_{i,j}$) | 75%     | 60%                | 52%               | 43%         |
| Predicted risk difference vs placebo ($RD_{i,j}$) | - | 15% | 23% | 31% |
| Threshold value for treatment $j$ ($T_j$) | | 19% | 19% | 28% |
| $RD_{i,j} - T_j$ | -4% | 4% | 3% |   |

Recommended treatment via the prediction model: **Dimethyl Fumarate**
Measure of performance in DCA – Net Benefit

\[ NB_S = \varepsilon_0 - \varepsilon_s - \sum_j \pi_{s,j} \times T_j \]

\(\varepsilon_0\) denotes the event rate under no treatment,
\(\varepsilon_s\) the event rate under strategy \(s\), and
\(\pi_{s,j}\) the proportion of patients treated with treatment \(j\) under strategy \(s\)

\(T_j\) the threshold values chosen for treatment \(j\)

Reduction in a harmful event outcome

Associated with the treatment: side-effects, risks, costs
Estimation of $\varepsilon_0$, depends on the framework

A) One RCT available

**Observed proportion of events** in the placebo arm,

$\hat{\varepsilon}_0 = e_0^{Data}$, where $Data$ the available dataset

B) Several RCTs

**Pooled event rate estimation**, via a meta-analysis of all placebo events, in the dataset of all available RCTs $Data$

Patients randomized within trials but not across them

$NB_s = \varepsilon_0 - \varepsilon_s - \sum_j \pi_{s,j} \times T_j$
Measure of performance in DCA – Net Benefit

Estimation of $\pi_{s,j}$

We need the **congruent dataset** for strategy $s$, $Data_s$ – the subset of $Data$ including those patients where:
recommended treatment = actual given treatment

Using $Data_s$, we estimate all $\pi_{s,j}$ as the observed proportion of people under each treatment $j$, $\hat{\pi}_{s,j} = p_{s,j}^{Data_s}$

$$NB_s = \varepsilon_0 - \varepsilon_s - \sum_j \pi_{s,j} \times T_j$$
Measure of performance in DCA – Net Benefit

Estimation of $\varepsilon_s$

The weighted average event rate under strategy $s$:

$$\hat{\varepsilon}_s = \sum_{j=0}^{J} p_{s,j}^{Data_s} \times \hat{\varepsilon}_{s,j}$$

$p_{s,j}^{Data_s}$ is the observed proportion of patients treated with treatment $j$ in the congruent dataset, $Data_s$

$\hat{\varepsilon}_{s,j}$ is the event rate under treatment $j$ using strategy $s$

$$NB_s = \varepsilon_0 - \varepsilon_s - \sum_j \pi_{s,j} \times T_j$$
Measure of performance in DCA – Net Benefit

Estimation of $\varepsilon_s$, depends on the framework

1. One RCT

$$\hat{\varepsilon}_{s,j} = e^{-\text{Data}_s}_{j}$$ i.e., $\varepsilon_{s,j}$ the observed proportion of events under arm $j$ in $\text{Data}_s$

2. Several RCTs

Step 1: Pooled placebo event rate $\hat{\varepsilon}_{s,0}$

Step 2: Risk ratio of each treatment versus the control $RR^\text{Data}_s_j$

Step 3: The treatment-specific event rates are $\hat{\varepsilon}_{s,j} = \hat{\varepsilon}_{s,0} \times RR^\text{Data}_s_j$

$$\hat{\varepsilon}_s = \sum_{j=0}^{J} p^\text{Data}_s_{s,j} \times \hat{\varepsilon}_{s,j}$$

$$NB_s = \varepsilon_0 - \varepsilon_s - \sum_j \pi_{s,j} \times T_j$$
## Exemplifying the methodology deciding for treatment in patients with RRMS

| Approach                                            | $T_{DF} = T_{GA} = 19\%$, $T_N = 28\%$ | Net Benefit |
|-----------------------------------------------------|--------------------------------------|-------------|
| Treat nobody                                        |                                      | 0.000       |
| Treat all patients with Natalizumab                 |                                      | 0.025       |
| Treat all patients with Dimethyl Fumarate           |                                      | 0.030       |
| Treat all patients with Glatiramer Acetate          |                                      | 0.019       |
| Treat patients according to the prediction model    |                                      | 0.050       |

The strategy “treat patients according to the prediction model” leads to 5 fewer patients that will relapse per 100 participants compared to “treat nobody” strategy, and 2 fewer patients compared to strategy “treat all patients with Dimethyl Fumarate”
Different patients might weight differently the risk to relapse and the risks associated with each treatment

\[ T_{DF} = T_{GA} = 19\%, \]
\[ T_N = 20 - 35\% \]
Exemplifying the methodology deciding for treatment in patients with RRMS
Conclusions

- We extended the DCA methodology, a vehicle for evaluating which strategy leads to better clinical treatment decisions into a NMA framework.

- The methodology can be applied to compare any group-level strategy with individualized-level strategies, when IPD RCTs are available.

- The methodology can be applied to compare the clinical relevance of several personalized prediction models to identify which one leads to better clinical treatment decisions.

- The individualized prediction model for deciding upon treatments for patients with relapsing-remitting multiple sclerosis seems to lead to better clinical treatment decisions into a wide range of threshold values compared to default strategies.
References

- Vickers AJ, Elkin EB. Decision Curve Analysis: A Novel Method for Evaluating Prediction Models. *Med Decis Making*. 2006;26(6):565-574. doi:10.1177/0272989X06295361

- Chalkou K, Steyerberg E, Egger M, Manca A, Pellegrini F, Salanti G. A two-stage prediction model for heterogeneous effects of many treatment options: application to drugs for Multiple Sclerosis. *Stat Med* 2021 Sep 10;40(20):4362-4375.

- Chalkou K, Steyerberg E, Bossuyt P, Subramanian S, Benkert P, Kuhle J, Disanto G, Kappos L, Egger M. Development, validation and clinical usefulness of a prognostic model for relapse in relapsing-remitting multiple sclerosis. arXiv:2105.06941v1 [stat.AP]. https://arxiv.org/abs/2105.06941
Thank you for your attention!