Potential bias associated with modeling the effectiveness of treatment using an overall hazard ratio

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Treatment's efficacy in clinical trials

- Clinical trials often report treatment efficacy in terms of the reduction of all-cause mortality rate between the treatment and control arms, i.e., an **overall hazard ratio (OHR)**

$$\text{OHR}_{\text{Clinical Trial}} = \frac{\hat{\mu}^{\text{Treatment}}}{\hat{\mu}^{\text{Control}}}$$

  instead of the specific reduction over the excess hazard from the disease, i.e., the **disease-specific hazard ratio (DSHR)**
- OHR from clinical trials is usually reported over a relatively short period compared to a life span.

Modeling treatment's effectiveness

- Decision-analytic models are used to evaluate the treatment's effectiveness beyond the trial's time horizon.
- If we assume the relationship between disease-specific mortality rate μ_{Dis} and age-,sex-, and race- specific mortality rate μ_{ASR} is additive (i.e., $\mu_{\text{ASR}} + \mu_{\text{Dis}}$) and that μ_{ASR} doesn't vary by treatment arm, OHR is defined as

$$\text{OHR} = \frac{\hat{\mu}_{\text{ASR}} + \hat{\mu}^{*}_{\text{Dis}}}{\hat{\mu}_{\text{ASR}} + \hat{\mu}_{\text{Dis}}} \quad (1)$$

  where $\hat{\mu}_{\text{ASR}} = \frac{\sum_{t=1}^{T} \mu_{\text{ASR}}(t)}{T}$ and $\hat{\mu}_{\text{Dis}} = \frac{\sum_{t=1}^{T} \mu_{\text{Dis}}(t)}{T}$, i.e., the mean rates over the number of periods of the trial T. $\hat{\mu}^{*}_{\text{Dis}}$ is the mean specific mortality rate after the effectiveness of treatment

$$\hat{\mu}^{*}_{\text{Dis}} = \hat{\mu}_{\text{Dis}} \cdot \text{DSHR} \quad (2)$$

Objective

To quantify the bias associated with using OHR as a treatment's efficacy beyond the time horizon of the clinical trial.

Model

- We simulated a hypothetical cohort of patients with a generic disease that increases μ_{ASR} by a constant μ_{Dis}.
- We compared the effectiveness of treatment under two approaches
  - **OHR:**

$$(\mu_{\text{ASR}} + \mu_{\text{Dis}}) \cdot \text{OHR}$$

  - **DSHR:**

$$\mu_{\text{ASR}} + \mu_{\text{Dis}} \cdot \text{DSHR}$$

Parameters

Parameter		Base case scenario	Interval
Age of cohort (yrs.)		50	40-70
μ_{ASR}	(Annual)	2009 US life tables	-
μ_{Dis}	(Annual)	0.05	0.01-0.09
DSHR	(Annual)	0.5	0.3-0.9

Quantification of bias

We quantified the bias as the percentage change in the life expectancy (LE) gains (ΔLE with treatment vs. no treatment) under an OHR approach compared to a DSHR approach

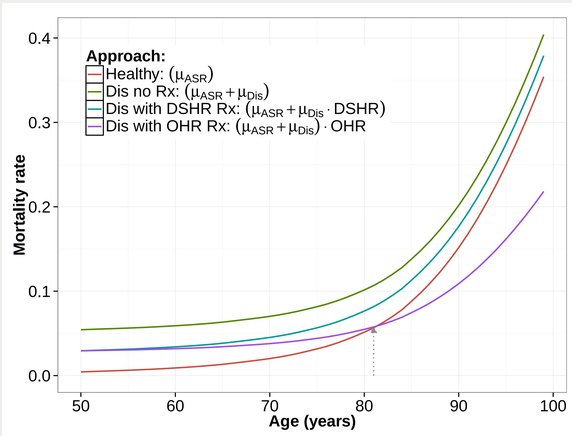
$$\text{Bias} = \frac{\Delta\text{LE}_{\text{OHR}} - \Delta\text{LE}_{\text{DSHR}}}{\Delta\text{LE}_{\text{DSHR}}}$$

Base Case

For the base-case scenario we assumed a DSHR of 0.5, a 50 year old cohort and calculated an OHR of 0.54.

Base Case: Mortality rates over time

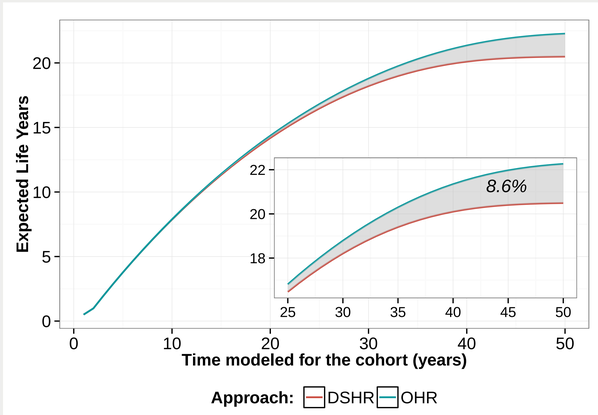
Mortality rates for base-case scenario



Under OHR approach, at age 81 the mortality rate of individuals with disease is lower than it would be if they were healthy.

Base Case: Bias

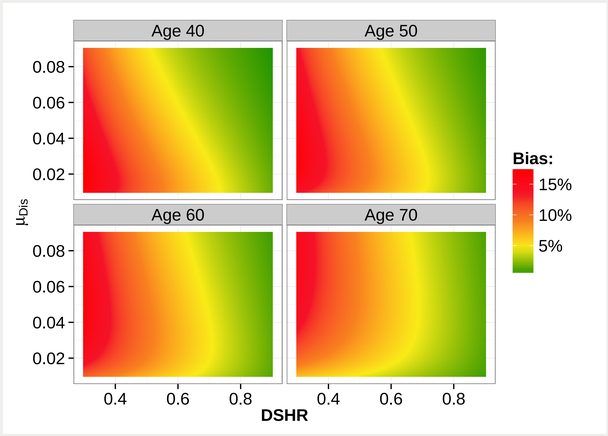
Bias for base-case scenario



The bias for the base case scenario is a 8.6% increase in the life expectancy gain.

Bias as a function of DSHR, μ_{Dis} and age

Bias



The OHR bias ranges between 0.4%-17.5% increase in the life expectancy gains.

OHR derived from DSHR, μ_{Dis} and age

OHR

μ_{Dis}	DSHR 0.3	0.5	0.7	0.9
0.01	0.41	0.58	0.75	0.92
0.03	0.34	0.53	0.72	0.91
0.05	0.32	0.52	0.71	0.90
0.07	0.32	0.51	0.71	0.90
0.09	0.31	0.51	0.71	0.90

(a) Age 40

μ_{Dis}	DSHR 0.3	0.5	0.7	0.9
0.01	0.51	0.65	0.79	0.93
0.03	0.39	0.56	0.74	0.91
0.05	0.36	0.54	0.72	0.91
0.07	0.34	0.53	0.72	0.91
0.09	0.33	0.52	0.71	0.90

(b) Age 50

μ_{Dis}	DSHR 0.3	0.5	0.7	0.9
0.01	0.63	0.74	0.84	0.95
0.03	0.46	0.62	0.77	0.92
0.05	0.41	0.58	0.75	0.92
0.07	0.38	0.56	0.73	0.91
0.09	0.36	0.55	0.73	0.91

(c) Age 60

μ_{Dis}	DSHR 0.3	0.5	0.7	0.9
0.01	0.77	0.83	0.90	0.97
0.03	0.58	0.70	0.82	0.94
0.05	0.50	0.64	0.79	0.93
0.07	0.46	0.61	0.77	0.92
0.09	0.43	0.59	0.75	0.92

(d) Age 70

Alternative solutions

- Using the trial's information and life tables for the study population, calculate DSHR substituting Equation (**2**) into Equation (**1**) and solving for DSHR.

$$\text{DSHR} = \frac{(\text{OHR})[\hat{\mu}_{\text{ASR}} + \hat{\mu}_{\text{Dis}}] - \hat{\mu}_{\text{ASR}}}{\hat{\mu}_{\text{Dis}}}$$

- Use the OHR as an estimate of DSHR, as the latter is not often reported. The treatment effecitvenes would then be

$$\mu_{\text{ASR}} + (\mu_{\text{Dis}}) \cdot \text{OHR}$$

  This results in a slight shift in the mortality rate compared to the DSHR approach, yielding an underestimation of the LE gain. For our base-case scenario this approach yields a bias of -2.8%.

Conclusions

- The use of an OHR approach to model treatment effectiveness beyond the time horizon of the trial overestimates treatment's benefit.
- Under an OHR approach it is possible that sick individuals at some point will face a lower mortality rate compared with healthy individuals.

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