Moving from the hazard ratio to the difference in restricted mean survival time in IPD meta-analyses

Béranger Lueza

Statistical Methods and Designs in Clinical Oncology Symposium
Context

✓ **Difference in restricted mean survival time (rmstD)**
  is a commonly used survival measure in cost-effectiveness analyses

✓ **Cost-effectiveness analyses** based on individual patient data meta-analyses (IPD MA) are scarce

✓ **IPD MA** of randomized trials has become the gold standard = best evidence for treatment effects

✓ For this type of hierarchical data, statistical analyses are **stratified by trial and treatment effect heterogeneity** between trials is studied
Objectives

1. Investigate if the choice of the method used to estimate the \( rmstD(t^*) \) impacts the results of a cost-effectiveness analysis in the context of an IPD meta-analysis
   ➔ Motivating case study

2. Study and compare methods to estimate the \( rmstD(t^*) \) from an IPD meta-analysis
   ➔ Simulation study

3. Illustrate the use of the \( rmstD(t^*) \) as a measure for the treatment effect in an IPD meta-analysis
   ➔ Application
Methods
HR = 0.63: experimental arm always more efficient than control arm

\[ \text{rmstD}(t^* = \text{5 years}) = 6.9 \text{ months} \]

\[ \text{rmstD}(t^* = \text{10 years}) = 16.4 \text{ months} \]
Meta-analyses methodology

✓ **Stratification by trial**: comparison of patients in the experimental arm from a trial to patients in control arm within the same trial (comparison of like with like)

⇒ respect the randomization

✓ Estimation of the **overall treatment effect** in 2 stages:

1. Treatment effect estimation \( \hat{\theta}_j \) in every trial \( j \)

2. Weighted average: \( \hat{\theta}_{overall} = \frac{\sum_{j=1}^{J} \hat{\theta}_j w_j}{\sum_{j=1}^{J} w_j} \)

\( \hat{\theta}_j = \log(HR_j) \) for survival data

\( w_j = \frac{1}{\text{Var}(\hat{\theta}_j)} \) fixed effects

\( w_j = \frac{1}{\text{Var}(\hat{\theta}_j) + \tau^2} \) random effects: \( \tau^2 \Leftrightarrow \text{heterogeneity} \)
Forest-plot example (MAR-LC)

<table>
<thead>
<tr>
<th>Trial</th>
<th>No. Deaths / No. Entered</th>
<th>O-E</th>
<th>Variance</th>
<th>Hazard Ratio</th>
<th>HR [95% CI]</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mod RT / Conv RT</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RTOG 8808</td>
<td>155/163 / 156/163</td>
<td>-6.4</td>
<td>76.9</td>
<td></td>
<td>0.92 [0.74;1.15]</td>
</tr>
<tr>
<td>PMCI 88C091</td>
<td>48/48 / 52/53</td>
<td>-0.8</td>
<td>24.3</td>
<td></td>
<td>0.97 [0.65;1.44]</td>
</tr>
<tr>
<td>PMCI 88C091 CT</td>
<td>51/51 / 56/56</td>
<td>6.0</td>
<td>25.6</td>
<td></td>
<td>1.26 [0.86;1.86]</td>
</tr>
<tr>
<td>CHART</td>
<td>316/338 / 217/225</td>
<td>-29.4</td>
<td>120.7</td>
<td></td>
<td>0.78 [0.66;0.94]</td>
</tr>
<tr>
<td>NCCTG 902451</td>
<td>34/39 / 35/35</td>
<td>-7.0</td>
<td>15.7</td>
<td></td>
<td>0.64 [0.39;1.05]</td>
</tr>
<tr>
<td>NCCTG 942452</td>
<td>111/125 / 108/121</td>
<td>-2.6</td>
<td>54.6</td>
<td></td>
<td>0.95 [0.73;1.24]</td>
</tr>
<tr>
<td>CHARTWEL</td>
<td>132/150 / 132/150</td>
<td>0.2</td>
<td>65.8</td>
<td></td>
<td>1.00 [0.79;1.28]</td>
</tr>
<tr>
<td>CHARTWELCT</td>
<td>40/53 / 47/53</td>
<td>-6.4</td>
<td>21.2</td>
<td></td>
<td>0.74 [0.48;1.13]</td>
</tr>
<tr>
<td>ECOG 2597</td>
<td>51/60 / 55/59</td>
<td>-7.4</td>
<td>25.8</td>
<td></td>
<td>0.75 [0.51;1.10]</td>
</tr>
<tr>
<td>Gliwice 2001</td>
<td>26/29 / 27/29</td>
<td>-1.4</td>
<td>13.2</td>
<td></td>
<td>0.90 [0.52;1.54]</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>964/1056 / 885/944</td>
<td>-55.2</td>
<td>443.7</td>
<td></td>
<td><strong>0.88 [0.80;0.97], p=0.009</strong></td>
</tr>
</tbody>
</table>

Test for heterogeneity: $\chi^2_{9} = 9.74, p=0.37, I^2 = 8\%$
Two approaches to estimating the overall $\text{rmstD}(t^*)$ from an IPD meta-analysis

- **Approach 1:** $\text{rmstD}(t^*)$ is estimated as the area between the two “pooled” survival curves summarizing the information from the $J$ trials.

- **Approach 2:**
  1. $\text{rmstD}_j(t^*)$ is estimated in each of the $J$ trials
  2. Weighted average of the $\text{rmstD}_j(t^*)$ using fixed or random effects:

\[
\hat{\text{rmstD}}(t^*) = \frac{\sum_{j=1}^{J} \text{rmstD}_j(t^*)w_j}{\sum_{j=1}^{J} w_j}
\]
1st approach: Naïve Kaplan-Meier

Trials of the meta-analysis are considered as one and only trial; the overall $rmst_D(t^*)$ is estimated as the area between the two KM survival curves, thus ignoring trial effect.
1st approach: Peto-quintile

Actuarial method developed by Richard Peto (EBCTCG, 1992) to take into account trial effect for representing survival curves in IPD meta-analysis.

Time interval estimation is based on the quintiles of number of deaths until $t^*$ ➔ each interval contains an equal number of events.
2nd approach: Pooled Kaplan-Meier - Pooled Exponential

1. For each trial $j$, $rmstD_j(t^*)$ is estimated as the area between survival curves Kaplan-Meier or exponential

2. Then the $rmstD_j(t^*)$ are pooled using a fixed or random effects model
Motivating case study

Julia Bonastre, Audrey Mauguen, Jean-Pierre Pignon (Gustave Roussy, Inserm)
Oliver Rivero-Arias (Oxford University)
Meta-Analysis of Radiotherapy in Lung Cancer (MAR-LC)

- IPD MA in non-small cell lung cancer (Mauguen 2012)
- N = 2,000 patients and 10 phase III trials comparing:
  - Conventional radiotherapy (RT)
  - Modified RT (hyperfractionated and/or accelerated)

- Modified RT improved overall survival:
  \( \text{HR}_{\text{overall}} = 0.88 \ [\text{IC 95\%}: 0.80-0.97; p = 0.009] \)

→ Is modified radiotherapy cost-effective?
**rmstD(t*) and Incremental Cost-Effectiveness Ratio**

\[
ICER = \frac{\bar{C}_{Mod\ RT} - \bar{C}_{Conv\ RT}}{\text{rmstD}(t^* = 5)}
\]

expressed as a cost per life year gained

- **Modified RT more expensive:** 4 328 € [1 830€ ; 6 804€]

<table>
<thead>
<tr>
<th>Method</th>
<th>rmstD(t*) (months) [95% CI]</th>
<th>ICER (k€) [95% CI]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peto-quintile</td>
<td>1.7 [0.4 – 3.1]</td>
<td>35 [13 – 98]</td>
</tr>
<tr>
<td>Naïve Kaplan-Meier</td>
<td>2.2 [0.6 – 3.7]</td>
<td>27 [11 – 68]</td>
</tr>
<tr>
<td>Pooled Kaplan-Meier</td>
<td>2.3 [0.7 – 3.8]</td>
<td>26 [10 – 66]</td>
</tr>
<tr>
<td>Pooled Exponential</td>
<td>2.5 [0.7 – 4.2]</td>
<td>24 [10 – 59]</td>
</tr>
</tbody>
</table>
The choice of a survival method to estimate overall $rmstD(t^*)$ impacts the cost-effectiveness results.

These results were obtained based on a case study using an IPD meta-analysis with proportional hazards, no heterogeneity and a small treatment effect size.

→ need to investigate on other scenarios with simulation study.

Simulation study

Julia Bonastre, Stefan Michiels, Jean-Pierre Pignon, Federico Rotolo (Gustave Roussy, Inserm)
Simulation of meta-analysis time-to-event data

- For a trial $j \in \{1, \ldots, J\}$, the hazard function is:
  \[
  \lambda_j(t) = \lambda_0(t) \exp\{a_j + (\beta + b_j)x\}
  \]

- $\lambda_0(t)$ = baseline hazard function (exponential distribut.)
- $\beta$ = overall treatment effect
- $x$ = treatment variable ($\pm 1/2 \Rightarrow$ heterogeneity = 2 arms)
- $\text{Var}(a_j) = \sigma^2 = $ baseline hazard heterogeneity
- $\text{Var}(b_j) = \tau^2 = $ treatment effect heterogeneity

1,000 simulated meta-analyses per scenario

✓ Baseline hazard and treatment effect heterogeneity:

<table>
<thead>
<tr>
<th>Var($b_j$) = $\tau^2$</th>
<th>Low (0.01)</th>
<th>High (0.10)</th>
</tr>
</thead>
<tbody>
<tr>
<td>heterog_{trt}</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Var($a_j$) = $\sigma^2$</th>
<th>Low (0.01)</th>
<th>High (0.10)</th>
</tr>
</thead>
<tbody>
<tr>
<td>heterog_{hazard}</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

✓ Treatment effect size: $\beta=0$ (HR=1) / -0.2 (0.8) / -0.7 (0.5)

✓ Time horizon:

- $t^* = 5$ years: follow-up long enough for all trials
- $t^* = 10$ ans: too short follow-up for some trials

✓ Proportional or non-proportional hazards (piecewise exponential)
Compared methods and evaluation criteria

- **4 methods (fixed/random effects):**
  - 1\textsuperscript{st} approach (area between 2 « pooled » curves):
    Naïve Kaplan-Meier, Peto-quintile
  - 2\textsuperscript{nd} approach (weighted average of areas):
    Pooled Kaplan-Meier, Pooled Exponential

- **Evaluation criteria:**
  - **Bias** = Average of the 1,000 estimated \( rmstD(t^*) \)
    - True \( rmstD(t^*) \)
  - **Empirical standard error** = Standard deviation of the \( rmstD(t^*) \) over the 1,000 replicates
  - **Average standard error** = Average of the 1,000 analytically estimated standard errors
Standard error well estimated with Pooled KM/Exp

Proportional Hazards, $t^* = 10$ years

$\beta = 0 \Rightarrow$ True rmstD = 0 year

1. $\text{heterog}_{\text{hazard}}$ $\text{heterog}_{\text{trt}}$
2. $\text{heterog}_{\text{hazard}}$ $\text{heterog}_{\text{trt}}$
3. $\text{heterog}_{\text{hazard}}$ $\text{heterog}_{\text{trt}}$
4. $\text{heterog}_{\text{hazard}}$ $\text{heterog}_{\text{trt}}$

Treatment effect heterog $\uparrow$:
- Empirical standard error $\uparrow$
- Std Err under-estimated (except for Pooled KM/Exp)

θ

Bias

Empirical 95% CI
Average 95% CI

NKM = Naïve Kaplan–Meier
PKM = Pooled Kaplan–Meier
PE = Pooled Exponential
PQ = Peto–quintile
Peto-quintile biased when $\beta$ increases

Proportional Hazards, $t^* = 10$ years
$\beta = -0.7 \Rightarrow$ True $\text{rmstD} = 2.0$ years

$\text{heterog}_{\text{hazard}}$ $\text{heterog}_{\text{trt}}$

$\text{rmstD}(t^*)$ under-estimated with Peto-quintile

NKM = Naive Kaplan-Meier
PKM = Pooled Kaplan-Meier
PE = Pooled Exponential
PQ = Peto-quintile
Similar results but smaller in magnitude ($t^* = 5$)
Non-proportional Hazards, $t^* = 5$ years

$\beta = -0.7 \Rightarrow \text{True } \text{rmstD} = -0.3$ year

rmstD($t^*$) over-estimated with Pooled Exponential

- NKM = Naïve Kaplan–Meier
- PKM = Pooled Kaplan–Meier
- PE = Pooled Exponential
- PQ = Peto–quintile
Pooled KM/Expo and Peto-quintile biased ($t^* = 10$)

Non-proportional Hazards, $t^* = 10$ years

$\beta = -0.7 \Rightarrow$ True rmstD = 0.3 year

1. $\text{heterog}_{\text{hazard}}$, $\text{heterog}_{\text{trt}}$
2. $\text{heterog}_{\text{hazard}}$, $\text{heterog}_{\text{trt}}$
3. $\text{heterog}_{\text{hazard}}$, $\text{heterog}_{\text{trt}}$
4. $\text{heterog}_{\text{hazard}}$, $\text{heterog}_{\text{trt}}$

NKM = Naïve Kaplan–Meier
PKM = Pooled Kaplan–Meier
PE = Pooled Exponential
PQ = Peto–quintile
No major impact for other investigated scenarios

✓ Negative correlation between random effects $a_j$ and $b_j$
✓ Deleterious treatment effect
✓ Number of trials and nb patients per trial fixed/random:
  ▪ 5 trials and 200 patients per trial ($N=1,000$)
  ▪ 5 trials and nb patients random ($N=1,000$)
  ▪ 20 trials and 100 patients ($N=2,000$)
Conclusion

- **Pooled Kaplan-Meier** with random effects formed the best compromise in terms of bias and variance

- **Treatment effect size:**
  - Bias for Peto-quintile which increases with effect size

- **High treatment effect heterogeneity:**
  - Empirical Std Err increases no matter the method
  - Std Err well estimated (empirical = average) only for Pooled Kaplan-Meier and Pooled Exponential

- **Non-proportional hazards:**
  - Strong bias for Pooled Exponential
Application to an IPD meta-analysis
Radio-Therapy Timing in Small Cell Lung Cancer

RTT-SCLC

✓ IPD meta-analysis in small cell lung cancer, using both hazard ratio (primary measure) and \( rmstD(t^*) \) (secondary measure)

✓ Control RT versus experimental RT: HR = 1.01; p = 0.87

✓ Strong treatment effect heterogeneity: p = 0.003; \( I^2 = 67\% \)

Interaction remains significant using rmstD

Same conclusions with either HR or \( rmstD(t^* = 5 \text{ years}) \)

<table>
<thead>
<tr>
<th>Essai</th>
<th>Nb Décès / Effectif total</th>
<th>O-A</th>
<th>Variance</th>
<th>Hazard Ratio</th>
<th>HR [IC 95 %]</th>
<th>Bénéfice de survie restreint</th>
<th>rmstD [IC 95 %]</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>RT Cont</td>
<td>RT Exp</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BR.6</td>
<td>149/164</td>
<td>146/168</td>
<td>20,6</td>
<td>72,1</td>
<td>1.33 [1,06;1,68]</td>
<td>5,4 [1,3, 9,4]</td>
<td></td>
</tr>
<tr>
<td>ECOG3588</td>
<td>194/206</td>
<td>190/211</td>
<td>17,5</td>
<td>94,8</td>
<td>1,20 [0,98;1,47]</td>
<td>3,0 [-0,8, 6,9]</td>
<td></td>
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<tr>
<td>JCOG9104</td>
<td>96/117</td>
<td>88/114</td>
<td>11,5</td>
<td>45,3</td>
<td>1,29 [0,96;1,73]</td>
<td>4,6 [-0,4, 9,6]</td>
<td></td>
</tr>
<tr>
<td>Sous-total (a)</td>
<td>439/487</td>
<td>424/493</td>
<td>49,6</td>
<td>212,2</td>
<td>1,26 [1,10;1,45]</td>
<td>4,2 [1,8, 6,7]</td>
<td></td>
</tr>
</tbody>
</table>

(b) Different CT compliance between arms

<table>
<thead>
<tr>
<th>Essai</th>
<th>Nb Décès / Effectif total</th>
<th>O-A</th>
<th>Variance</th>
<th>Hazard Ratio</th>
<th>HR [IC 95 %]</th>
<th>Bénéfice de survie restreint</th>
<th>rmstD [IC 95 %]</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>RT Cont</td>
<td>RT Exp</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CALGB8083</td>
<td>146/154</td>
<td>127/138</td>
<td>-12,1</td>
<td>66,0</td>
<td>0,83 [0,65;1,06]</td>
<td>-4,0 [-7,8, -0,2]</td>
<td></td>
</tr>
<tr>
<td>03PCL88</td>
<td>71/76</td>
<td>83/88</td>
<td>-10,1</td>
<td>37,9</td>
<td>0,77 [0,56;1,05]</td>
<td>-3,9 [-7,8, 0,0]</td>
<td></td>
</tr>
<tr>
<td>EORTC08877</td>
<td>161/174</td>
<td>166/175</td>
<td>-15,3</td>
<td>80,3</td>
<td>0,83 [0,66;1,03]</td>
<td>-2,9 [-6,1, 0,3]</td>
<td></td>
</tr>
<tr>
<td>LLCG93</td>
<td>136/166</td>
<td>135/159</td>
<td>-9,8</td>
<td>67,0</td>
<td>0,86 [0,68;1,10]</td>
<td>-3,0 [-7,2, 1,2]</td>
<td></td>
</tr>
<tr>
<td>HeCOG93</td>
<td>35/39</td>
<td>37/42</td>
<td>1,3</td>
<td>17,6</td>
<td>1,08 [0,68;1,72]</td>
<td>2,7 [-5,2, 10,5]</td>
<td></td>
</tr>
<tr>
<td>Sous-total (b)</td>
<td>549/609</td>
<td>548/602</td>
<td>-46,0</td>
<td>268,9</td>
<td>0,84 [0,75;0,95]</td>
<td>-3,1 [-4,9, -1,3]</td>
<td></td>
</tr>
<tr>
<td>Total (a)+(b)</td>
<td>988/1096</td>
<td>972/1095</td>
<td>3,6</td>
<td>481,0</td>
<td>1,01 [0,92;1,10]</td>
<td>0,0 [-2,9, 2,8]</td>
<td></td>
</tr>
</tbody>
</table>

Test d'hétérogénéité: \( \chi^2 = 21,4 \) \( p=0,003 \)  \( I^2 = 67\% \)

Test d'interaction: \( \chi^2 = 19,5 \) \( p<0,001 \)
Varying time horizon $t^*$

- $rmstD(t^*)$ estimated using Pooled Kaplan-Meier (random effects) varying $t^*$
- $rmstD(t^*)$ significantly $\neq 0$ and increases for $t^* \in [0;10 \text{ yrs}]$
Discussion
Conclusion

✓ **Case study** showed that the choice of a method to estimate \( rmstD(t^*) \) exerts an impact on cost-effectiveness results in the context of an IPD meta-analysis.

✓ **Simulation study**, through various scenarios, allowed us to recommend the Pooled Kaplan-Meier method with random effects which formed the best compromise bias / variance.

✓ We have highlighted the **pros of using** \( rmstD(t^*) \) versus **HR** (non-proportional hazards, more intuitive) and have noted that **clinical conclusions** were similar with these two measures using 3 different IPD meta-analyses.
Discussion

- PRISMA-IPD guidelines suggest to report both absolute and relatives measures (Stewart 2015)

- Royston and Parmar proposed to use the $rmstD(t^*)$ to analyze and design a clinical trial (2011, 2013, 2016) + 1st simulation study for $rmstD(t^*)$ in the context of meta-analysis using also flexible parametric model (Wei 2015)

- In a publication of a phase III RCT, for which Parmar was co-author, $rmstD(t^*)$ was the primary outcome measure with non-proportional hazards (Oza 2015)

- To report the $rmstD(t^*)$ in an article can also be usefull for future economic evaluation
Should RCT or IPD MA publications include?

- \( rmstD(t^*) \) should be a secondary measure **systematically** reported in addition of a hazard ratio

- **Proportional hazards test**
  - \( \text{Only one HR? Average HR? Time varying HR?} \)

- **Restricted mean survival times** in the 2 arms and \( rmstD(t^*) \) considering different time horizons \( t^* \)

- Graphic with \( rmstD(t^*) \) varying time horizon \( t^* \)

- **We now include** \( rmstD(t^*) \) in the protocols of the IPD meta-analyses performed at Gustave Roussy
Acknowledgements

MAR-LC, MAC-NPC and RTT-SCLC collaborative groups and trialists

Julia Bonastre, Stefan Michiels, Jean-Pierre Pignon and Federico Rotolo
(Gustave Roussy - Inserm, France)

Oliver Rivero-Arias (Oxford University, UK)

IReSP, Ligue Nationale Contre le Cancer, Programme Hospitalier de Recherche Clinique
References

Survival curves MAR-LC

PMCI 88C091

PMCI 88C091 CT

CHART

ECOG 2597

CHARTWEL

CHARTWEL CT

NCCTG 902451 - Gliwice 2011

NCCTG 942452

RTOG 8808
Acceptability curves: 1,000 replicates bootstrap

Probability Modified radiotherapy is cost-effective

Willingness to pay for one life-year (€)

0% 10% 20% 30% 40% 50% 60% 70% 80% 90% 100%

0 25000 50000 75000 100000

- Pooled Exponential
- Pooled Kaplan-Meier
- Peto-month
- Naive Kaplan-Meier
- Stewart-Parmar
- Peto-year
- Peto-quintiles

31%

68%
## Estimation des Coûts : perspective Assurance Maladie

<table>
<thead>
<tr>
<th>Poste de coût</th>
<th>Ressource MAR-LC</th>
<th>Coût unitaire</th>
<th>Source</th>
<th>Pourcentage coût total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Traitement par radiothérapie</td>
<td>Nombre total de fractions reçues</td>
<td>1 004€ dosimétrie + 138€/fraction d’irradiation</td>
<td>PMSI 2012</td>
<td>21%</td>
</tr>
<tr>
<td>Transports pour la radiothérapie</td>
<td>Nombre total de fractions reçues</td>
<td>40€/fraction d’irradiation</td>
<td>Martin, 2003</td>
<td>5%</td>
</tr>
<tr>
<td>Traitement de la rechute</td>
<td>Temps de survie après rechute</td>
<td>3 073€/mois</td>
<td>Braud, 2003</td>
<td>73%</td>
</tr>
<tr>
<td>Traitement de l’œsophagite</td>
<td>Toxicité oesophagienne aigüe sévère</td>
<td>1 745€ si présence de toxicité</td>
<td>PMSI 2012</td>
<td>1%</td>
</tr>
</tbody>
</table>

- **Conventionnelle** = **25 331 €** ; IC95% [23 630€ ; 27 115€]
- **Modifiée** = **29 659 €** ; IC95% [27 845€ ; 31 507€]
7 methods to estimate the rmstD(t*)

<table>
<thead>
<tr>
<th>Method</th>
<th>Stratification by trial</th>
<th>Heterogeneity</th>
<th>Non-proportional hazards</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Treatment effect</td>
<td>Baseline hazard</td>
</tr>
<tr>
<td>Naïve Kaplan-Meier</td>
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<td>No</td>
<td>No</td>
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<td>Stewart-Parmar</td>
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<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Peto-month</td>
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<tr>
<td>Peto-year</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Peto-quintile</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Pooled Kaplan-Meier</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Pooled Exponential</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
</tbody>
</table>

£ Non-proportionality of hazards can however be taken into account by using a time varying HR
μ HR_{i,overall} can vary between time intervals
Varying the heterogeneity

\[
\lambda_j(t) = \lambda_0(t) \exp\{a_j + (\beta + b_j)x\} \quad (\text{ici: } \beta = -0.7 \Rightarrow \text{HR} = 0.5)
\]

- Trial 1: \(a_j = -1\)
- Trial 2: \(a_j = 0\)
- Trial 3: \(a_j = 1\)

\(b_j = 0\)

\(\text{Var}(a_j) = \sigma^2:\) variation of baseline hazard heterogeneity

- Trial 1: \(b_j = -1\)
- Trial 2: \(b_j = 0\)
- Trial 3: \(b_j = 1\)

\(a_j = 0\)

\(\text{Var}(b_j) = \tau^2:\) variation of treatment effect heterogeneity
Similarly to the work by Trinquart et al (2016) : comparison of treatment effect measured by

- Hazard ratio (Peto estimator)
- $\text{rmstD}(t^*)$ (Kaplan-Meier + Brown)

42 trials included in 3 meta-analyses

$t^* = 5$ years (MAR-LC, RTT-SCLC) or 10 years (MAC-NPC2)

Test for hazards proportionality: Grambsh and Therneau test (1994) threshold = 5%
HR vs $rmstD(t^*)$ (MAR-LC, MAC-NPC 2 and RTT-SCLC)

**3 trials (7%) with non-proportional hazards**
HR vs $rmstD(t^*)$ (MAR-LC, MAC-NPC 2 and RTT-SCLC)

4 trials (10%) same direction of treatment effect but different significativity (2 HRs NS and 2 $rmstD(t^*)$ NS)
HR vs \( rmstD(t^*) \) (MAR-LC, MAC-NPC 2 and RTT-SCLC)

- **2 trials** with different direction of treatment effect but both HR and \( rmstD(t^*) \) non significant

- **Trial with largest difference**: non-proportional hazards
  \[ rmstD(t^*) = -0.7 \text{ months} \ [ -7.9; 6.5] \text{ and } HR = 1.1 \ [ 0.8; 1.6] \]
**Formules**

- **Cochran test for heterogeneity:**
  
  \[ Q = \sum_{j=1}^{J} w_j (\hat{\theta}_j - \hat{\theta}_{overall, fixed})^2 \sim \chi^2_{J-1} \]

- **Random effects model:**
  
  \[ \hat{\theta}_{overall} = \frac{\sum_{j=1}^{J} \hat{\theta}_j w_j}{\sum_{j=1}^{J} w_j} \]

  with:

  \[ w_j = \frac{1}{\sqrt{\text{Var}(\hat{\theta}_j)} + \hat{\tau}^2} \]

  \[ \hat{\tau}^2 = \frac{Q - (J - 1)}{\sum_{j=1}^{J} w_j - \frac{\sum_{j=1}^{J} w_j^2}{\sum_{j=1}^{J} w_j}} \]

- \( \hat{\tau}^2 \) is estimated by the method of moments from DerSimonian and Laird

- \( I^2 \) Higgins: \( I^2 = \frac{Q - (J - 1)}{Q} \times 100 \) with \( J \) the number of trials