S1 Supporting Information

Methodological details

Approach 1: Area between the two pooled survival curves

- **Stewart-Parmar:**

Stewart and Parmar methodology allows one to estimate the pooled survival curve for the experimental arm $S_{Exp,pooled}(t)$ using the pooled hazard ratio (inverse variance weighted average) and the naive Kaplan-Meier survival curve in the control group $S_{Control,KM}(t)$. The pooled survival curve for the control arm $S_{Control,pooled}(t)$ is simply set equal to $S_{Control,KM}(t)$:

$$S_{Control,pooled}(t) = S_{Control,KM}(t) \qquad (S1)$$

$$S_{Exp,pooled}(t) = S_{Control,KM}(t)^{HR_{pooled}} \qquad (S2)$$

- **Peto:**

In the Peto method, survival probabilities are estimated at predetermined time intervals i (actuarial method) based on survival probability p_i of the whole population and a pooled hazard ratio $HR_{pooled,i}$ which can vary between time periods.

$$p_i = \exp(-\frac{D_i}{PP_i}) \qquad (S3)$$

Where D_i is the number of deaths during period i and PP_i the total number of person-periods at period i. One person-period is equivalent to one person-year when the time interval chosen is one year.

$$\ln(HR_{pooled,i}) = \frac{\sum_{j=1}^{N} \frac{\ln(HR_{i,j})}{Var[\ln(HR_{i,j})]}}{\sum_{j=1}^{N} \frac{1}{Var[\ln(HR_{i,j})]}} \qquad (S4)$$

Where $HR_{i,j}$ are the hazard ratios estimated at time i in trial j through the use of the log-rank observed minus expected number of deaths and its variance.

Survival probabilities at each period i in the control arm ($p_{Control,i}$) and in the experimental arm ($p_{Exp,i}$) are estimated as follow:

$$p_{Control,i} = p_i - [0,5 \times p_i \times (p_i - 1) \times \ln(HR_{pooled,i})] \qquad (S5)$$

$$p_{Exp} = p_i + [0,5 \times p_i \times (p_i - 1) \times \ln(HR_{pooled,i})] \qquad (S6)$$

The survival probability at time t in each arm is the product of the probabilities across periods: $\mathrm{S}_{\mathrm{Control pooled}}(\mathrm{t}) = \prod_{\mathrm{i}=1}^{n_i} \mathrm{p}_{\mathrm{Control i}}$ and $\mathrm{S}_{\mathrm{Exp,pooled}}(\mathrm{t}) = \prod_{\mathrm{i}=1}^{n_i} \mathrm{p}_{\mathrm{Exp,i}}$ (S7)

Approach 2: Pooling differences in restricted mean survival time

The method to estimate the overall difference in restricted mean survival time (rmstD) aggregating the $\mathrm{rmstD_j}$ estimated in each of the N trials is developed below with a fixed-effect model:

$$rmstD = \frac{\sum_{j=1}^{N} \frac{rmstD_j}{Var(rmstD_j)}}{\sum_{j=1}^{N} \frac{1}{Var(rmstD_j)}} \quad \text{and} \quad Var[rmstD] = \left[\sum_{j=1}^{N} \frac{1}{Var[rmstD_j]} \right]^{-1} \qquad \text{(S8)}$$

With difference in restricted mean survival time in each trial:

$$rmstD_j = \int_0^{t^*} \mathrm{S}_{\mathrm{Exp,j}}(\mathrm{t}).\mathrm{dt} - \int_0^{t^*} \mathrm{S}_{\mathrm{Control,j}}(\mathrm{t}).\mathrm{dt} = \hat{\mu}_{Exp,t^*,j} - \hat{\mu}_{Control,t^*,j} \qquad \text{(S9)}$$

$\hat{\mu}_{Exp,t^*,j}$ and $\hat{\mu}_{Control,t^*,j}$ are the restricted mean survival times estimated in trial j, respectively for the experimental (Exp) and for the control arm.

Var[$rmstD_j$] in each trial j can be estimated based on the following formula (Karrison T. *Control Clin Trials* 1997;18:151-67):

$$rmstD_j = \hat{\mu}_{Exp,t^*,j} - \hat{\mu}_{Control,t^*,j} \Rightarrow Var[rmstD_j] = Var[\hat{\mu}_{Exp,t^*,j}] + Var[\hat{\mu}_{Control,t^*,j}] \qquad \text{(S10)}$$

Where the variances of mean survival time are estimated (Klein JP, Moeschberger ML. 1997. Survival Analysis: techniques for censored and truncated data, 1st ed. New York: Springer-Verlag):

$$Var[\hat{\mu}_{arm,T,j}] = \sum_{i=1}^{D_j} \left[\int_{t_{i,j}}^{t^*} \mathrm{S}_{\mathrm{arm,j}}(\mathrm{t}).\mathrm{dt} \right]^2 \frac{d_{i,j}}{Y_{i,j}(Y_{i,j} - d_{i,j})} \quad \text{where arm = Exp or Control} \qquad \text{(S11)}$$

In each trial j: D_j is the number of distinct event times ($t_{1,j} < t_{2,j} < \ldots < t_{D,j}$), $Y_{i,j}$ is the number of individuals who are at risk at time $t_{i,j}$ and $d_{i,j}$ is the number of events at time $t_{i,j}$.

To calculate the overall rmstD (equation (S8)), $S_{arm,j}(t)$ has then to be replaced by its estimator depending on the survival analysis method chosen (Kaplan-Meier and exponential in our empirical application) in the equations (S9) and (S11)

- **Pooled Kaplan-Meier:**

Replacing $S_{arm,j}(t)$ by the Kaplan-Meier estimator $\hat{S}_{arm,j}(t)$, it leads to:

$$rmstD_j = \hat{\mu}_{Exp,t^*,j} - \hat{\mu}_{Control,t^*,j} = \sum_{i=1}^{D_j} \hat{S}_{Exp,j}(t_{i,j}) \times (t_{i+1,j} - t_{i,j}) - \sum_{i=1}^{D_j} \hat{S}_{Control,j}(t_{i,j}) \times (t_{i+1,j} - t_{i,j}) \quad \text{(S9-bis)}$$

$$Var\left[\hat{\mu}_{arm,T,j}\right] = \frac{m_j}{m_j - 1} \sum_{i=1}^{D_j - 1} \frac{{a_{i,j}}^2}{Y_{i,j}(Y_{i,j} - d_{i,j})} \quad \text{(S11-bis)}$$

where $a_{i,j} = \sum_{l=i}^{D_j - 1} \hat{S}_{arm,j}(t_{l,j}) \times (t_{l+1,j} - t_{l,j})$ and $m_j = \sum_{l=1}^{D} d_{l,j}$

- **Pooled Exponential**

Replacing $S_{arm,j}(t)$ by the exponential estimator $\hat{S}_{arm,j}(t) = e^{-\lambda_{arm,j}.t}$, it leads to:

$$rmstD_j = \int_0^{t^*} e^{-\lambda_{Exp,j}.t}.\text{dt} - \int_0^{t^*} e^{-\lambda_{Control,j}.t}.\text{dt} = \frac{1 - e^{-\lambda_{Exp,j}.t^*}}{\lambda_{Exp,j}} - \frac{1 - e^{-\lambda_{Control,j}.t^*}}{\lambda_{Control,j}} \quad \text{(S9-ter)}$$

and $$Var\left[\hat{\mu}_{arm,T,j}\right] = \sum_{i=1}^{D} \left[\frac{e^{-\lambda_{arm,j}.t_i} - e^{-\lambda_{arm,j}.t^*}}{\lambda_{arm,j}}\right]^2 \frac{d_{i,j}}{Y_{i,j}(Y_{i,j} - d_{i,j})} \quad \text{(S11-ter)}$$