Appendix

Manuscript: Effect modification in settings with “truncation by death”

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Relationship between w', w''_m, and w'''

As mentioned in the main text, recall that the SACE is expressed as follows:

$$\begin{aligned}\text{SACE} &= E[Y^1 - Y^0|S^1 = 1, S^0 = 1] \\ &= \sum\nolimits_u E[Y^1 - Y^0|S^1 = 1, S^0 = 1, U = u]\Pr(U = u|S^1 = 1, S^0 = 1) \\ &= \sum\nolimits_u \text{SACE}_u \cdot \Pr(U = u|S^1 = 1, S^0 = 1).\end{aligned}$$

Alternatively, the SACE is expressed as follows:

$$\begin{aligned}\text{SACE} &= E[Y^1 - Y^0|S^1 = 1, S^0 = 1] \\ &= \sum\nolimits_{u,m} E[Y^1 - Y^0|S^1 = 1, S^0 = 1, U = u, M = m]\Pr(U = u, M = m|S^1 = 1, S^0 = 1) \\ &= \sum\nolimits_{u,m} E[Y^1 - Y^0|S^1 = 1, S^0 = 1, U = u]\Pr(U = u, M = m|S^1 = 1, S^0 = 1) \ \left(\because Y^T \perp\!\!\!\perp M|(S^T, U)\right) \\ &= \sum\nolimits_u E[Y^1 - Y^0|S^1 = 1, S^0 = 1, U = u]\sum\nolimits_m \Pr(U = u, M = m|S^1 = 1, S^0 = 1) \\ &= \sum\nolimits_u \text{SACE}_u \sum\nolimits_m \Pr(U = u|S^1 = 1, S^0 = 1, M = m)\Pr(M = m|S^1 = 1, S^0 = 1).\end{aligned}$$

Note that the following equation holds from the law of total probability:

$$\Pr(U = u|S^1 = 1, S^0 = 1) = \sum\nolimits_m \Pr(U = u|S^1 = 1, S^0 = 1, M = m)\Pr(M = m|S^1 = 1, S^0 = 1).$$

This means that the following relationship holds between w', w''_m, and w''':

$$w' = w''_{m=0}w''' + w''_{m=1}(1 - w''').$$

On the other hand, SACE is also expressed as follows:

$$\begin{aligned}\text{SACE} &= \sum\nolimits_{u,m} E[Y^1 - Y^0|S^1 = 1, S^0 = 1, U = u]\Pr(U = u, M = m|S^1 = 1, S^0 = 1) \\ &= \sum\nolimits_m \sum\nolimits_u E[Y^1 - Y^0|S^1 = 1, S^0 = 1, U = u]\Pr(U = u|S^1 = 1, S^0 = 1, M = m)\Pr(M = m|S^1 = 1, S^0 = 1) \\ &= \sum\nolimits_m \Pr(M = m|S^1 = 1, S^0 = 1)\sum\nolimits_u \text{SACE}_u \cdot \Pr(U = u|S^1 = 1, S^0 = 1, M = m).\end{aligned}$$

This means that the following equation holds:

$$\mathrm{SACE}_m = \sum_u \mathrm{SACE}_u \cdot \Pr(U = u | S^1 = 1, S^0 = 1, M = m).$$

Derivation of weights when the SACE is defined as a risk ratio

First, we present the derivation of the SACE in the total "always-survivors" stratum in terms of U level-specific SACE*:*

$$\text{SACE}_{RR} = \frac{\Pr[Y^1 = 1|S^1 = 1, S^0 = 1]}{\Pr[Y^0 = 1|S^1 = 1, S^0 = 1]}$$

$$= \frac{\sum_u \Pr[Y^1 = 1|(S^1 = 1, S^0 = 1), U = u] \Pr(U = u|S^1 = 1, S^0 = 1)}{\Pr[Y^0 = 1|S^1 = 1, S^0 = 1]}$$

$$= \frac{\sum_u \frac{\Pr[Y^1 = 1|(S^1 = 1, S^0 = 1), U = u]}{\Pr[Y^0 = 1|(S^1 = 1, S^0 = 1), U = u]} \Pr(U = u|S^1 = 1, S^0 = 1) \Pr[Y^0 = 1|(S^1 = 1, S^0 = 1), U = u]}{\Pr[Y^0 = 1|S^1 = 1, S^0 = 1]}$$

$$= \sum_u \text{SACE}_{RR,u} \frac{\Pr[Y^0 = 1,\ U = u|(S^1 = 1, S^0 = 1)]}{\Pr[Y^0 = 1|S^1 = 1, S^0 = 1]}$$

$$= \sum_u \text{SACE}_{RR,u} \Pr[U = u|(S^1 = 1, S^0 = 1), Y^0 = 1]$$

Note that, unlike the results in the main text, the weights above, $\Pr[U = u|(S^1 = 1, S^0 = 1), Y^0 = 1]$, involve potential outcomes of both the survival variable and the outcome of interest.

Below, we present the M level-specific SACE in terms of U level-specific SACEs:

$$\text{SACE}_{RR,m} = \frac{\Pr[Y^1 = 1|(S^1 = 1, S^0 = 1), M = m]}{\Pr[Y^0 = 1|(S^1 = 1, S^0 = 1), M = m]}$$

$$= \frac{\sum_u \Pr[Y^1 = 1|(S^1 = 1, S^0 = 1), M = m, U = u] \Pr(U = u|(S^1 = 1, S^0 = 1), M = m)}{\Pr[Y^0 = 1|(S^1 = 1, S^0 = 1), M = m]}$$

$$= \frac{\sum_u \frac{\Pr[Y^1 = 1|(S^1 = 1, S^0 = 1), M = m, U = u]}{\Pr[Y^0 = 1|(S^1 = 1, S^0 = 1), M = m, U = u]} \Pr(U = u|(S^1 = 1, S^0 = 1),\ M = m) \Pr[Y^0 = 1|(S^1 = 1, S^0 = 1), M = m, U = u]}{\Pr[Y^0 = 1|(S^1 = 1, S^0 = 1), M = m]}$$

$$= \frac{\sum_u \frac{\Pr[Y^1 = 1|(S^1 = 1, S^0 = 1), U = u]}{\Pr[Y^0 = 1|(S^1 = 1, S^0 = 1), U = u]} \Pr(U = u|(S^1 = 1, S^0 = 1),\ M = m) \Pr[Y^0 = 1|(S^1 = 1, S^0 = 1), M = m, U = u]}{\Pr[Y^0 = 1|(S^1 = 1, S^0 = 1), M = m]}$$

(under $Y^T \perp\!\!\!\perp M|(S^T, U)$)

$$= \sum_u \text{SACE}_{RR,u} \frac{\Pr[Y^0 = 1,\ U = u|(S^1 = 1, S^0 = 1), M = m]}{\Pr[Y^0 = 1|(S^1 = 1, S^0 = 1), M = m]}$$

$$= \sum_u \text{SACE}_{RR,u} \Pr[U = u|(S^1 = 1, S^0 = 1), M = m, Y^0 = 1]$$

Note that for effect modification of the $SACE_{RR}$ by the variable M to be present, the weights $\Pr[U = u|(S^1 = 1, S^0 = 1), M = m, Y^0 = 1]$ need to vary by levels m.

Data generation for the numerical example

To generate the data for the numerical example in **Tables 1** and **2**, we used the following approach. Firstly, individuals were randomly assigned to treatment A, and randomly allocated to different levels of U and M:

$$Pr(A = 1) = Pr(U = 1) = Pr(M = 1) = 0.5$$

We modelled the relation between S-defined principal strata membership and the variables U and M using a multinomial model. To simplify the notation, G_S is used to denote principal strata membership with respect to S, and can take four values: *'ss'* $(S^1 = 1, S^0 = 1)$, *'sd'* $(S^1 = 1, S^0 = 0)$, *'ds'* $(S^1 = 0, S^0 = 1)$, *'dd'* $(S^1 = 0, S^0 = 0)$. Membership to the *'dd'* stratum is modelled as:

$$Pr(G_S = dd) = \frac{1}{1 + \sum_{g_S \in (ss,sd,ds)} e^{\alpha_0^{g_S} + \alpha_1^{g_S} u + \alpha_2^{g_S} m}}$$

where $\alpha_0^{g_S}$ is an intercept and $\alpha_1^{g_S}$ and $\alpha_2^{g_S}$ are parameters for the variables U and M with respect to the stratum g_S. Probabilities of principal strata $p \in \{'ss', 'sd', 'ds'\}$ are:

$$Pr(G_S = p) = \frac{e^{\alpha_0^p + \alpha_1^p u + \alpha_2^p m}}{1 + \sum_{g_S \in (ss,sd,ds)} e^{\alpha_0^{g_S} + \alpha_1^{g_S} u + \alpha_2^{g_S} m}}$$

Analogously, probabilities of principal strata defined with respect to Y were modelled using a multinomial model for individuals in the "always-survivors" stratum. We use the variable G_y to denote the principal strata for Y; in particular, G_y can take four values *'hh'* $(Y^1 = 1, Y^0 = 1)$, *'hl'* $(Y^1 = 1, Y^0 = 0)$, *'lh'* $(Y^1 = 0, Y^0 = 1)$, *'ll'* $(Y^1 = 0, Y^0 = 0)$. Note that M is assumed not to influence these probabilities. For the *'ll'* stratum, we have:

$$Pr(G_y = ll) = \frac{1}{1 + \sum_{g_y \in (hh,hl,lh)} e^{\beta_0^{g_y} + \beta_1^{g_y} u}}$$

where $\beta_0^{g_y}$ is an intercept term, and $\beta_1^{g_y}$ is the parameter for U with reference to stratum g_y. Probabilities for principal strata $p \in \{'hh', hl', 'lh'\}$ can be calculated as:

$$Pr(G_y = p) = \frac{e^{\beta_0^p + \beta_1^p u}}{1 + \sum_{g_y \in (hh,hl,lh)} e^{\beta_0^{g_y} + \beta_1^{g_y} u}}$$

The values assumed for parameters α and β are shown in **Table S1**, and in **Table S3**, SACEs in examples that assume other parameter values are presented.

A possible approach to identify SACE weights under monotonicity

In this section, we illustrate how monotonicity, together with randomization of the exposure, might identify the weights derived in the main text. In particular, if we assume $S^1 \geq S^0$ for all individuals, $A \perp\!\!\!\perp (S^0, S^1, U, M)$ as well as consistency, then

$$
\begin{aligned}
w' &= \Pr(U = 0 | S^1 = 1, S^0 = 1) \\
&= \Pr(U = 0 | S^0 = 1) \ \text{(monotonicity)} \\
&= \Pr(U = 0 | A = 0, S^0 = 1) \ \text{(exchangeability)} \\
&= \Pr(U = 0 | A = 0, S = 1) \ \text{(consistency)}
\end{aligned}
$$

Analogously,

$$
\begin{aligned}
w''_m &= \Pr(U = 0 | (S^1 = 1, S^0 = 1), M = m) \\
&= \Pr(U = 0 | S^0 = 1, M = m) \ \text{(monotonicity)} \\
&= \Pr(U = 0 | A = 0, S^0 = 1, M = m) \ \text{(exchangeability)} \\
&= \Pr(U = 0 | A = 0, S = 1, M = m) \ \text{(consistency)}
\end{aligned}
$$

And finally,

$$
\begin{aligned}
w''' &= \Pr(M = 0 | S^1 = 1, S^0 = 1) \\
&= \Pr(M = 0 | S^0 = 1) \ \text{(monotonicity)} \\
&= \Pr(M = 0 | A = 0, S^0 = 1) \ \text{(exchangeability)} \\
&= \Pr(M = 0 | A = 0, S = 1) \ \text{(consistency)}
\end{aligned}
$$

To apply the exchangeability condition, the weak union property of conditional independences is used [1].

Supplementary Tables

Table S1. Assumed parameter values for the numerical example.

Parameters	***Assumed values***
Alphas	
α_0^{ss}	0
α_0^{sd}	-0.2
α_0^{ds}	-0.4
α_1^{ss}	1.5
α_1^{sd}	0.5
α_1^{ds}	0
α_2^{ss}	2
α_2^{sd}	0.5
α_2^{ds}	0
Betas	
β_0^{hh}	0
β_0^{hl}	-0.2
β_0^{lh}	-0.4
β_1^{hh}	0
β_1^{hl}	1.5
β_1^{lh}	0

Footnote: *See definition of parameters in the section Data generation for the numerical example. These values imply the following proportions of S-defined principal strata for individuals with* $M = 0$ *and* $U = 0$*: 0.29, 0.23, 0.19 and 0.29 for strata* $(S^1 = 1, S^0 = 1)$*,* $(S^1 = 1, S^0 = 0)$*,* $(S^1 = 0, S^0 = 1)$*,* $(S^1 = 0, S^0 = 0)$*, respectively. Both M and U were assumed to increase the probability of membership to the "always-survivors" stratum: the proportion of individuals in the "always-survivors" stratum was 0.60 for participants with* $M = 1$ *and* $U = 0$*, and 0.71 for those with* $M = 0$ *and* $U = 1$*. As expected (but not shown), the distributions of S-defined and Y-defined principal strata did not differ for those individuals who had* $A = 1$ *or those with* $A = 0$*.*

Table S2. Dependence between Y^T and M in the "always-survivors" stratum, and $Y^T \perp\!\!\!\perp M|(S^T, U)$. As these concern the "always-survivors" stratum, cells with information on this principal stratum are highlighted in orange. Further, to facilitate demonstration that these conditions hold, in each table cell for the "always-survivors" stratum, we included proportions in parentheses that refer to the groups defined by U and M levels. Note that this table differs from **Table 1** in that four columns, corresponding to quality of life potential outcomes for levels of U (M) without conditioning on M (U), were included. The dependence between Y^T and M in the "always-survivors" stratum can be seen in the two rightmost columns, where distributions of the response types Y^T are presented by levels of M without conditioning on U. Further, it can be seen that $Y^T \perp\!\!\!\perp M|(S^T, U)$ holds, as proportions of quality of life response types for the two levels of M are approximately equal when conditioning on a particular U level. Finally, note that the SACE$_m$ can be directly obtained from the two rightmost columns.

	Survival outcome (S)								Quality of life (Y)									
		S^a			U = 1		U = 0		Y^a		U = 1			U = 0			M = 1	M = 0
SY type	Response type of S	S^1	S^0	Total population	M = 1	M = 0	M = 1	M = 0	Y^1	Y^0	M = 1 or 0	M = 1	M = 0	M = 1 or 0	M = 1	M = 0	U = 1 or 0	U = 1 or 0
1	"Always-survivors"	1	1	0.62	0.226	0.148	0.177	0.071	1	1	0.059 (0.159)	0.036 (0.159)	0.023 (0.158)	0.071 (0.286)	0.051 (0.288)	0.020 (0.282)	0.087 (0.216)	0.043 (0.198)
2	"Always-survivors"	1	1						1	0	0.216 (0.581)	0.130 (0.580)	0.086 (0.589)	0.058 (0.234)	0.041 (0.232)	0.017 (0.239)	0.171 (0.424)	0.103 (0.475)
3	"Always-survivors"	1	1						0	1	0.039 (0.105)	0.024 (0.106)	0.015 (0.103)	0.048 (0.194)	0.034 (0.192)	0.014 (0.197)	0.058 (0.144)	0.029 (0.133)
4	"Always-survivors"	1	1						0	0	0.058 (0.156)	0.036 (0.159)	0.022 (0.151)	0.071 (0.286)	0.051 (0.288)	0.020 (0.282)	0.087 (0.216)	0.042 (0.193)
5	"Protectable"	1	0	0.15	0.016	0.045	0.032	0.058	1	Undefined	NS	NS	NS	NS	NS	NS	NS	NS
6	"Protectable"	1	0						0	Undefined	NS	NS	NS	NS	NS	NS	NS	NS
7	"Defiers"	0	1	0.09	0.004	0.021	0.016	0.049	Undefined	1	NS	NS	NS	NS	NS	NS	NS	NS
8	"Defiers"	0	1						Undefined	0	NS	NS	NS	NS	NS	NS	NS	NS
9	"Never-survivors"	0	0	0.14	0.007	0.034	0.024	0.072	Undefined	Undefined	NS	NS	NS	NS	NS	NS	NS	NS
Total				1	0.25	0.25	0.25	0.25										

Table S3. SACE by levels of M under different parameter assumptions. Data in each row are based on 50,000 simulated patients. Note that in the table below, except for the parameter value presented in each row, the other parameter values used were those presented in **Table S1**.

Parameters	***Assumed values***	***SACE$_{m=0}$***	***SACE$_{m=1}$***	***Difference***
Alphas				
α_1^{ss}	0	0.24	0.24	0.00
α_1^{ss}	0.5	0.29	0.27	0.02
α_1^{ss}	1	0.32	0.29	0.03
α_1^{ss}	1.5	0.34	0.28	0.05
α_2^{ss}	0	0.33	0.35	-0.01
α_2^{ss}	1	0.34	0.31	0.03
α_2^{ss}	1.5	0.34	0.29	0.04
α_2^{ss}	2	0.34	0.28	0.06
Betas				
β_1^{hl}	0	0.03	0.04	0.00
β_1^{hl}	0.5	0.12	0.12	0.01
β_1^{hl}	1	0.22	0.20	0.03
β_1^{hl}	1.5	0.35	0.29	0.06

Reference

1. Pearl, J., *Causality: Models, Reasoning and Inference*. 2nd edition ed. 2009: Cambridge University Press.