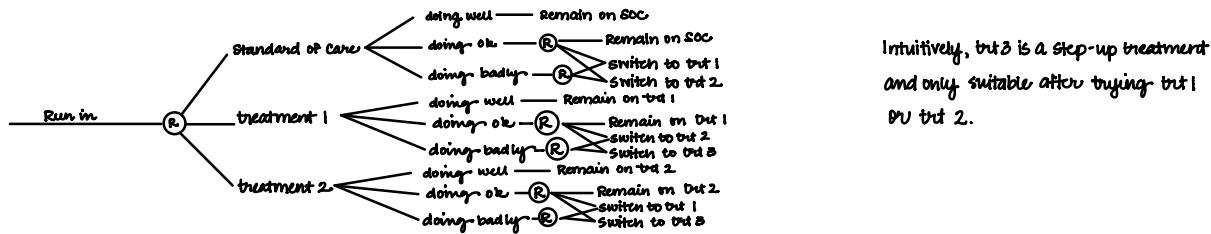


### Design 1

Firstline treatments : Standard of care (soc), treatment 1, treatment 2

Secondline treatments : treatment 1, treatment 2, treatment 3, soc (only for those w/ firstline soc)



### Simulation parameters

$$N = \text{seq}(\text{from} = 600, \text{to} = 1200, \text{by} = 100)$$

P(Responder status) cut-offs : \*use normal quantiles

$$\text{Tailoring var: } X_1 \in \{-1, 1\}$$

Additional covariates: {None}, {N(0,1)}, {N(0,1), Bern(0.5)}

$$X_2 \sim N(0,1) \text{ unless otherwise specified.}$$

$$\mathbb{E}(Y | H_2, A_2) = f(H_2, A_2)$$

$$= f_1(H_2) + A_2 f_2(H_2)$$

$$= f_1(X_1, A_1, X_2) + A_2 f_2(X_1, A_2, X_2)$$

$$= f_1(X_1, A_1, X_2) + \mathbb{1}(A_2 = \text{soc})(1, X_1, \mathbb{1}(A_1 = \text{soc}), X_2) \beta_{01} \quad * \text{By design, trt2 can be soc only if soc is 1st trt}$$

$$+ \mathbb{1}(A_2 = \text{trt 1})(1, X_1, \mathbb{1}(A_1 = \text{soc}), \mathbb{1}(A_1 = \text{trt 1}), \mathbb{1}(A_1 = \text{trt 2}), X_2) \beta_{12}$$

$$+ \mathbb{1}(A_2 = \text{trt 2})(1, X_1, \mathbb{1}(A_1 = \text{soc}), \mathbb{1}(A_1 = \text{trt 1}), \mathbb{1}(A_1 = \text{trt 2}), X_2) \beta_{13}$$

$$+ \mathbb{1}(A_2 = \text{trt 3})(1, X_1, \mathbb{1}(A_1 = \text{trt 1}), \mathbb{1}(A_1 = \text{trt 2}), X_2) \beta_{14} \quad * \text{By design, trt3 only available at stage 2 if trt1 or trt2 rec @ stage 2}$$

$$= (1, X_1, X_2) \beta_{00} + \mathbb{1}(A_1 = \text{soc})(1, X_1) \beta_{01}$$

$$+ \mathbb{1}(A_1 = \text{trt 1})(1, X_1) \beta_{02}$$

$$+ \mathbb{1}(A_1 = \text{trt 2})(1, X_1) \beta_{03}$$

$$+ \mathbb{1}(A_2 = \text{soc})(1, X_1, \mathbb{1}(A_1 = \text{soc}), X_2) \beta_{11}$$

$$+ \mathbb{1}(A_2 = \text{trt 1})(1, X_1, \mathbb{1}(A_1 = \text{soc}), \mathbb{1}(A_1 = \text{trt 1}), \mathbb{1}(A_1 = \text{trt 2}), X_2) \beta_{12}$$

$$+ \mathbb{1}(A_2 = \text{trt 2})(1, X_1, \mathbb{1}(A_1 = \text{soc}), \mathbb{1}(A_1 = \text{trt 1}), \mathbb{1}(A_1 = \text{trt 2}), X_2) \beta_{13}$$

$$+ \mathbb{1}(A_2 = \text{trt 3})(1, X_1, \mathbb{1}(A_1 = \text{trt 1}), \mathbb{1}(A_1 = \text{trt 2}), X_2) \beta_{14}$$

$$= \beta_{000} + X_1 \beta_{001} + X_2 \beta_{002} + \mathbb{1}(A_1 = \text{soc})(\beta_{010} + X_1 \beta_{011})$$

$$+ \mathbb{1}(A_1 = \text{trt 1})(\beta_{020} + X_1 \beta_{021})$$

$$+ \mathbb{1}(A_1 = \text{trt 2})(\beta_{030} + X_1 \beta_{031})$$

$$+ \mathbb{1}(A_2 = \text{soc})(\beta_{110} + X_1 \beta_{111} + \mathbb{1}(A_1 = \text{soc})\beta_{112} + X_2 \beta_{113})$$

$$+ \mathbb{1}(A_2 = \text{trt 1})(\beta_{120} + X_1 \beta_{121} + \mathbb{1}(A_1 = \text{soc})\beta_{122} + \mathbb{1}(A_1 = \text{trt 1})\beta_{123} + \mathbb{1}(A_1 = \text{trt 2})\beta_{124} + X_2 \beta_{125})$$

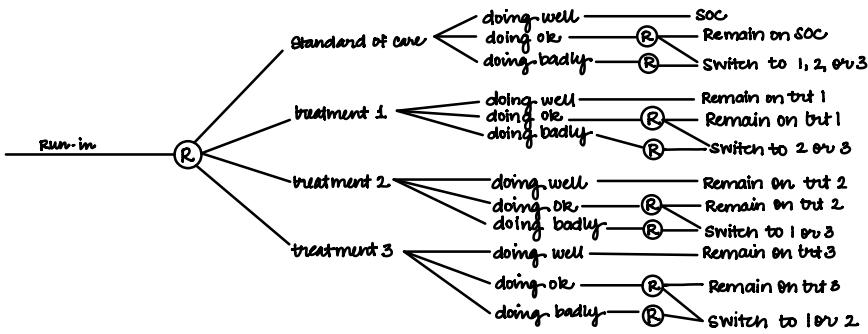
$$+ \mathbb{1}(A_2 = \text{trt 2})(\beta_{130} + X_1 \beta_{131} + \mathbb{1}(A_1 = \text{soc})\beta_{132} + \mathbb{1}(A_1 = \text{trt 1})\beta_{133} + \mathbb{1}(A_1 = \text{trt 2})\beta_{134} + X_2 \beta_{135})$$

$$+ \mathbb{1}(A_2 = \text{trt 3})(\beta_{140} + X_1 \beta_{141} + \mathbb{1}(A_1 = \text{trt 1})\beta_{142} + \mathbb{1}(A_1 = \text{trt 2})\beta_{143} + X_2 \beta_{144})$$

## Design 2

First line treatments: standard of care (soc), treatment 1, treatment 2, treatment 3

Second line treatments: treatment 1, treatment 2, treatment 3, soc (only if soc first line)



### Simulation parameters

$N = \text{seq}(\text{from}=600, \text{to}=1200, \text{by}=100)$

P(Responder status) cut offs: \*use normal quantiles

Tailoring var:  $X_i \in \{-1, 1\}$

Additional covariates: {None}, { $N(0,1)$ }, { $N(0,1)$ ,  $Bern(0.5)$ }

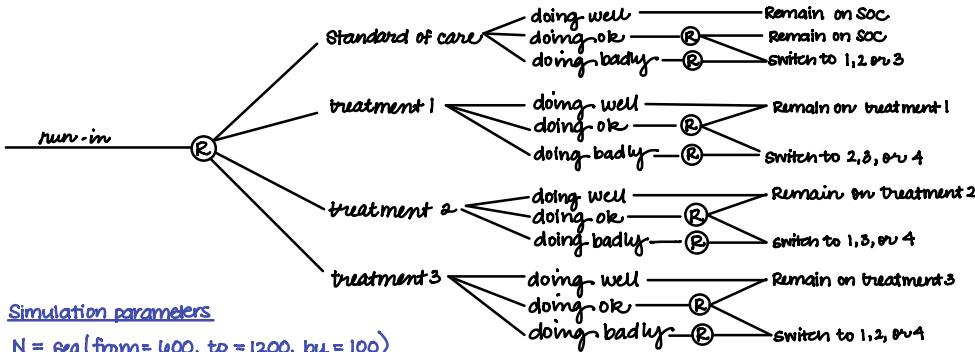
$X_2 \sim N(0,1)$  unless otherwise specified.

$$\begin{aligned}
 E(Y | H_1, A_2) &= f(H_1, A_2) \\
 &= f_1(H_1) + A_2 f_2(H_1) \\
 &= f_1(X_1, A_1, X_2) + A_2 f_2(X_1, A_1, X_2) \\
 &= f_1(X_1, A_1, X_2) + \mathbb{1}(A_2 = \text{soc})(1, X_1, \mathbb{1}(A_1 = \text{soc}), X_2) \vec{\beta}_{11} \\
 &\quad + \mathbb{1}(A_2 = \text{trt } 1)(1, X_1, \mathbb{1}(A_1 = \text{soc}), \mathbb{1}(A_1 = \text{trt } 1), \mathbb{1}(A_1 = \text{trt } 2), \mathbb{1}(A_1 = \text{trt } 3), X_2) \vec{\beta}_{12} \\
 &\quad + \mathbb{1}(A_2 = \text{trt } 2)(1, X_1, \mathbb{1}(A_1 = \text{soc}), \mathbb{1}(A_1 = \text{trt } 1), \mathbb{1}(A_1 = \text{trt } 2), \mathbb{1}(A_1 = \text{trt } 3), X_2) \vec{\beta}_{13} \\
 &\quad + \mathbb{1}(A_2 = \text{trt } 3)(1, X_1, \mathbb{1}(A_1 = \text{soc}), \mathbb{1}(A_1 = \text{trt } 1), \mathbb{1}(A_1 = \text{trt } 2), \mathbb{1}(A_1 = \text{trt } 3), X_2) \vec{\beta}_{14} \\
 &= (1, X_1, X_2) \beta_{00} + \mathbb{1}(A_1 = \text{soc})(1, X_1) \beta_{01} \\
 &\quad + \mathbb{1}(A_1 = \text{trt } 1)(1, X_1) \beta_{02} \\
 &\quad + \mathbb{1}(A_1 = \text{trt } 2)(1, X_1) \beta_{03} \\
 &\quad + \mathbb{1}(A_1 = \text{trt } 3)(1, X_1) \beta_{04} \\
 &\quad + \mathbb{1}(A_2 = \text{soc})(1, X_1, \mathbb{1}(A_1 = \text{soc}), X_2) \vec{\beta}_{11} \\
 &\quad + \mathbb{1}(A_2 = \text{trt } 1)(1, X_1, \mathbb{1}(A_1 = \text{soc}), \mathbb{1}(A_1 = \text{trt } 1), \mathbb{1}(A_1 = \text{trt } 2), \mathbb{1}(A_1 = \text{trt } 3), X_2) \vec{\beta}_{12} \\
 &\quad + \mathbb{1}(A_2 = \text{trt } 2)(1, X_1, \mathbb{1}(A_1 = \text{soc}), \mathbb{1}(A_1 = \text{trt } 1), \mathbb{1}(A_1 = \text{trt } 2), \mathbb{1}(A_1 = \text{trt } 3), X_2) \vec{\beta}_{13} \\
 &\quad + \mathbb{1}(A_2 = \text{trt } 3)(1, X_1, \mathbb{1}(A_1 = \text{soc}), \mathbb{1}(A_1 = \text{trt } 1), \mathbb{1}(A_1 = \text{trt } 2), \mathbb{1}(A_1 = \text{trt } 3), X_2) \vec{\beta}_{14} \\
 &= \beta_{000} + X_1 \beta_{001} + X_2 \beta_{002} + \mathbb{1}(A_1 = \text{soc})(\beta_{001} + X_1 \beta_{011}) \\
 &\quad + \mathbb{1}(A_1 = \text{trt } 1)(\beta_{002} + X_1 \beta_{021}) \\
 &\quad + \mathbb{1}(A_1 = \text{trt } 2)(\beta_{003} + X_1 \beta_{031}) \\
 &\quad + \mathbb{1}(A_1 = \text{trt } 3)(\beta_{004} + X_1 \beta_{041}) \\
 &\quad + \mathbb{1}(A_2 = \text{soc})(\beta_{110} + X_1 \beta_{111} + \mathbb{1}(A_1 = \text{soc})\beta_{112} + X_2 \beta_{113}) \\
 &\quad + \mathbb{1}(A_2 = \text{trt } 1)(\beta_{120} + X_1 \beta_{121} + \mathbb{1}(A_1 = \text{soc})\beta_{122} + \mathbb{1}(A_1 = \text{trt } 1)\beta_{123} + \mathbb{1}(A_1 = \text{trt } 2)\beta_{124} + \mathbb{1}(A_1 = \text{trt } 3)\beta_{125} + X_2 \beta_{126}) \\
 &\quad + \mathbb{1}(A_2 = \text{trt } 2)(\beta_{130} + X_1 \beta_{131} + \mathbb{1}(A_1 = \text{soc})\beta_{132} + \mathbb{1}(A_1 = \text{trt } 1)\beta_{133} + \mathbb{1}(A_1 = \text{trt } 2)\beta_{134} + \mathbb{1}(A_1 = \text{trt } 3)\beta_{135} + X_2 \beta_{136}) \\
 &\quad + \mathbb{1}(A_2 = \text{trt } 3)(\beta_{140} + X_1 \beta_{141} + \mathbb{1}(A_1 = \text{soc})\beta_{142} + \mathbb{1}(A_1 = \text{trt } 1)\beta_{143} + \mathbb{1}(A_1 = \text{trt } 2)\beta_{144} + \mathbb{1}(A_1 = \text{trt } 3)\beta_{145} + X_2 \beta_{146})
 \end{aligned}$$

### Design 3

firstline treatments: standard of care (soc), treatment 1, treatment 2, treatment 3

secondline treatments: treatment 1, treatment 2, treatment 3, treatment 4, soc\*  
(step up trt)



### Simulation parameters

$$N = \text{seq}(\text{from}=600, \text{to}=1200, \text{by}=100)$$

P(Responder status) cut offs: \*use normal quantiles

Tailoring var:  $X_i \in \{-1, 1\}$

Additional covariates: {None}, { $N(0,1)$ }, { $N(0,1)$ ,  $Bern(0.5)$ }

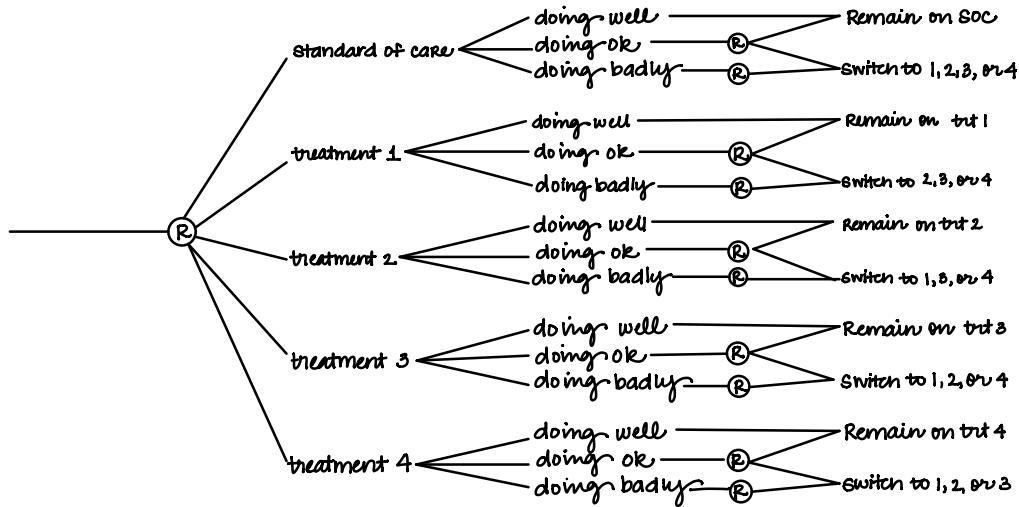
$X_2 \sim N(0,1)$  unless otherwise specified.

$$\begin{aligned}
 E(Y|H_2, A_2) &= f(H_2, A_2) \\
 &= f_1(H_2) + A_2 f_2(H_2) \\
 &= f_1(X_1, A_1, X_2) + A_2 f_2(X_1, A_2, X_2) \\
 &= f_1(X_1, A_1, X_2) + \mathbb{1}(A_2=soc)(1, X_1, \mathbb{1}(A_1=soc), X_2) \vec{\beta}_{11} \\
 &\quad + \mathbb{1}(A_2=treat1)(1, X_1, \mathbb{1}(A_1=soc), \mathbb{1}(A_1=treat1), \mathbb{1}(A_1=treat2), \mathbb{1}(A_1=treat3), X_2) \vec{\beta}_{12} \\
 &\quad + \mathbb{1}(A_2=treat2)(1, X_1, \mathbb{1}(A_1=soc), \mathbb{1}(A_1=treat1), \mathbb{1}(A_1=treat2), \mathbb{1}(A_1=treat3), X_2) \vec{\beta}_{13} \\
 &\quad + \mathbb{1}(A_2=treat3)(1, X_1, \mathbb{1}(A_1=soc), \mathbb{1}(A_1=treat1), \mathbb{1}(A_1=treat2), \mathbb{1}(A_1=treat3), X_2) \vec{\beta}_{14} \\
 &\quad + \mathbb{1}(A_2=treat4)(1, X_1, \mathbb{1}(A_1=treat1), \mathbb{1}(A_1=treat2), \mathbb{1}(A_1=treat3), X_2) \vec{\beta}_{15} \\
 &= (1, X_1, X_2) \vec{\beta}_{00} + \mathbb{1}(A_1=soc)(1, X_1) \beta_{01} \\
 &\quad + \mathbb{1}(A_1=treat1)(1, X_1) \beta_{02} \\
 &\quad + \mathbb{1}(A_1=treat2)(1, X_1) \beta_{03} \\
 &\quad + \mathbb{1}(A_1=treat3)(1, X_1) \beta_{04} \\
 &\quad + \mathbb{1}(A_1=treat4)(1, X_1) \beta_{05} \\
 &\quad + \mathbb{1}(A_2=soc)(1, X_1, \mathbb{1}(A_1=soc), X_2) \vec{\beta}_{11} \\
 &\quad + \mathbb{1}(A_2=treat1)(1, X_1, \mathbb{1}(A_1=soc), \mathbb{1}(A_1=treat1), \mathbb{1}(A_1=treat2), \mathbb{1}(A_1=treat3), X_2) \vec{\beta}_{12} \\
 &\quad + \mathbb{1}(A_2=treat2)(1, X_1, \mathbb{1}(A_1=soc), \mathbb{1}(A_1=treat1), \mathbb{1}(A_1=treat2), \mathbb{1}(A_1=treat3), X_2) \vec{\beta}_{13} \\
 &\quad + \mathbb{1}(A_2=treat3)(1, X_1, \mathbb{1}(A_1=soc), \mathbb{1}(A_1=treat1), \mathbb{1}(A_1=treat2), \mathbb{1}(A_1=treat3), X_2) \vec{\beta}_{14} \\
 &\quad + \mathbb{1}(A_2=treat4)(1, X_1, \mathbb{1}(A_1=treat1), \mathbb{1}(A_1=treat2), \mathbb{1}(A_1=treat3), X_2) \vec{\beta}_{15} \\
 &= \beta_{000} + X_1 \beta_{001} + X_2 \beta_{002} + \mathbb{1}(A_1=soc)(\beta_{001} + X_1 \beta_{011}) \\
 &\quad + \mathbb{1}(A_1=treat1)(\beta_{002} + X_1 \beta_{021}) \\
 &\quad + \mathbb{1}(A_1=treat2)(\beta_{003} + X_1 \beta_{031}) \\
 &\quad + \mathbb{1}(A_1=treat3)(\beta_{004} + X_1 \beta_{041}) \\
 &\quad + \mathbb{1}(A_2=soc)(\beta_{110} + X_1 \beta_{111} + \mathbb{1}(A_1=soc)\beta_{112} + X_2 \beta_{113}) \\
 &\quad + \mathbb{1}(A_2=treat1)(\beta_{120} + X_1 \beta_{121} + \mathbb{1}(A_1=soc)\beta_{122} + \mathbb{1}(A_1=treat1)\beta_{123} + \mathbb{1}(A_1=treat2)\beta_{124} + \mathbb{1}(A_1=treat3)\beta_{125} + X_2 \beta_{126}) \\
 &\quad + \mathbb{1}(A_2=treat2)(\beta_{130} + X_1 \beta_{131} + \mathbb{1}(A_1=soc)\beta_{132} + \mathbb{1}(A_1=treat1)\beta_{133} + \mathbb{1}(A_1=treat2)\beta_{134} + \mathbb{1}(A_1=treat3)\beta_{135} + X_2 \beta_{136}) \\
 &\quad + \mathbb{1}(A_2=treat3)(\beta_{140} + X_1 \beta_{141} + \mathbb{1}(A_1=soc)\beta_{142} + \mathbb{1}(A_1=treat1)\beta_{143} + \mathbb{1}(A_1=treat2)\beta_{144} + \mathbb{1}(A_1=treat3)\beta_{145} + X_2 \beta_{146}) \\
 &\quad + \mathbb{1}(A_2=treat4)(\beta_{150} + X_1 \beta_{151} + \mathbb{1}(A_1=treat1)\beta_{152} + \mathbb{1}(A_1=treat2)\beta_{153} + \mathbb{1}(A_1=treat3)\beta_{154} + X_2 \beta_{155})
 \end{aligned}$$

#### Design 4

Firstline treatments: Standard of care (soc), treatment 1, treatment 2, treatment 3, treatment 4

Secondline treatments: treatment 1, treatment 2, treatment 3, treatment 4, NCC<sup>#</sup>



#### Simulation parameters

N = seq(from=600, to=1200, by=100)

P(Responder status) cut offs : \*use normal quantiles

Tailoring var:  $X_i \in \{-1, 1\}$

Additional covariates: {None}, {N(0,1)}, {N(0,1), Bern(0.5)}

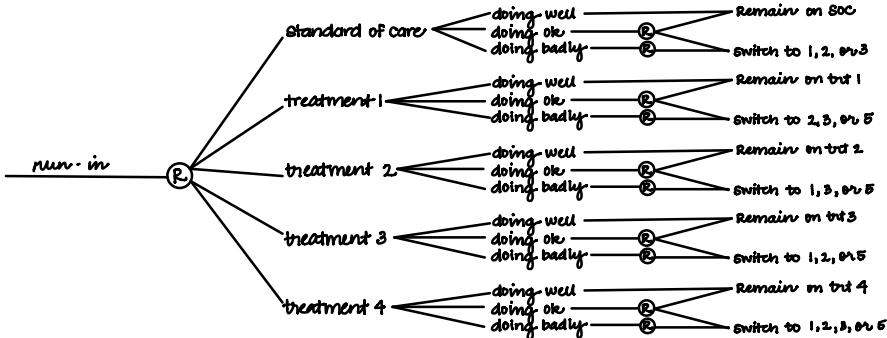
$X_2 \sim N(0,1)$  unless otherwise specified.

$$\begin{aligned}
 E(Y|H_2, A_2) &= f(H_2, A_2) \\
 &= f_1(H_2) + A_2 f_2(H_2) \\
 &= f_1(X_1, A_1, X_2) + A_2 f_2(X_1, A_2, X_2) \\
 &= f_1(X_1, A_1, X_2) + \mathbb{1}(A_2 = \text{soc})(1, X_1, \mathbb{1}(A_1 = \text{soc}), X_2) \vec{\beta}_{11} \\
 &\quad + \mathbb{1}(A_2 = \text{trt } 1)(1, X_1, \mathbb{1}(A_1 = \text{soc}), \mathbb{1}(A_1 = \text{trt } 1), \mathbb{1}(A_1 = \text{trt } 2), \mathbb{1}(A_1 = \text{trt } 3), \mathbb{1}(A_1 = \text{trt } 4), X_2) \vec{\beta}_{12} \\
 &\quad + \mathbb{1}(A_2 = \text{trt } 2)(1, X_1, \mathbb{1}(A_1 = \text{soc}), \mathbb{1}(A_1 = \text{trt } 1), \mathbb{1}(A_1 = \text{trt } 2), \mathbb{1}(A_1 = \text{trt } 3), \mathbb{1}(A_1 = \text{trt } 4), X_2) \vec{\beta}_{13} \\
 &\quad + \mathbb{1}(A_2 = \text{trt } 3)(1, X_1, \mathbb{1}(A_1 = \text{soc}), \mathbb{1}(A_1 = \text{trt } 1), \mathbb{1}(A_1 = \text{trt } 2), \mathbb{1}(A_1 = \text{trt } 3), \mathbb{1}(A_1 = \text{trt } 4), X_2) \vec{\beta}_{14} \\
 &\quad + \mathbb{1}(A_2 = \text{trt } 4)(1, X_1, \mathbb{1}(A_1 = \text{soc}), \mathbb{1}(A_1 = \text{trt } 1), \mathbb{1}(A_1 = \text{trt } 2), \mathbb{1}(A_1 = \text{trt } 3), \mathbb{1}(A_1 = \text{trt } 4), X_2) \vec{\beta}_{15} \\
 &= (1, X_1, X_2) \vec{\beta}_{00} + \mathbb{1}(A_1 = \text{soc})(1, X_1) \vec{\beta}_{01} \\
 &\quad + \mathbb{1}(A_1 = \text{trt } 1)(1, X_1) \vec{\beta}_{02} \\
 &\quad + \mathbb{1}(A_1 = \text{trt } 2)(1, X_1) \vec{\beta}_{03} \\
 &\quad + \mathbb{1}(A_1 = \text{trt } 3)(1, X_1) \vec{\beta}_{04} \\
 &\quad + \mathbb{1}(A_1 = \text{trt } 4)(1, X_1) \vec{\beta}_{05} \\
 &\quad + \mathbb{1}(A_2 = \text{soc})(1, X_1, \mathbb{1}(A_1 = \text{soc}), X_2) \vec{\beta}_{11} \\
 &\quad + \mathbb{1}(A_2 = \text{trt } 1)(1, X_1, \mathbb{1}(A_1 = \text{soc}), \mathbb{1}(A_1 = \text{trt } 1), \mathbb{1}(A_1 = \text{trt } 2), \mathbb{1}(A_1 = \text{trt } 3), \mathbb{1}(A_1 = \text{trt } 4), X_2) \vec{\beta}_{12} \\
 &\quad + \mathbb{1}(A_2 = \text{trt } 2)(1, X_1, \mathbb{1}(A_1 = \text{soc}), \mathbb{1}(A_1 = \text{trt } 1), \mathbb{1}(A_1 = \text{trt } 2), \mathbb{1}(A_1 = \text{trt } 3), \mathbb{1}(A_1 = \text{trt } 4), X_2) \vec{\beta}_{13} \\
 &\quad + \mathbb{1}(A_2 = \text{trt } 3)(1, X_1, \mathbb{1}(A_1 = \text{soc}), \mathbb{1}(A_1 = \text{trt } 1), \mathbb{1}(A_1 = \text{trt } 2), \mathbb{1}(A_1 = \text{trt } 3), \mathbb{1}(A_1 = \text{trt } 4), X_2) \vec{\beta}_{14} \\
 &\quad + \mathbb{1}(A_2 = \text{trt } 4)(1, X_1, \mathbb{1}(A_1 = \text{soc}), \mathbb{1}(A_1 = \text{trt } 1), \mathbb{1}(A_1 = \text{trt } 2), \mathbb{1}(A_1 = \text{trt } 3), \mathbb{1}(A_1 = \text{trt } 4), X_2) \vec{\beta}_{15} \\
 &= \beta_{000} + X_1 \beta_{001} + X_2 \beta_{002} + \mathbb{1}(A_1 = \text{soc})(\beta_{010} + X_1 \beta_{011}) + \mathbb{1}(A_1 = \text{trt } 1)(\beta_{020} + X_1 \beta_{021}) + \mathbb{1}(A_1 = \text{trt } 2)(\beta_{030} + X_1 \beta_{031}) + \mathbb{1}(A_1 = \text{trt } 3)(\beta_{040} + X_1 \beta_{041}) + \mathbb{1}(A_1 = \text{trt } 4)(\beta_{050} + X_1 \beta_{051}) \\
 &\quad + \mathbb{1}(A_2 = \text{soc})(\beta_{110} + \beta_{111} X_1 + \beta_{112} \mathbb{1}(A_1 = \text{soc}) + \beta_{113} X_2) \\
 &\quad + \mathbb{1}(A_2 = \text{trt } 1)(\beta_{120} + X_1 \beta_{121} + \mathbb{1}(A_1 = \text{soc}) \beta_{122} + \mathbb{1}(A_1 = \text{trt } 1) \beta_{123} + \mathbb{1}(A_1 = \text{trt } 2) \beta_{124} + \mathbb{1}(A_1 = \text{trt } 3) \beta_{125} + \mathbb{1}(A_1 = \text{trt } 4) \beta_{126} + X_2 \beta_{127}) \\
 &\quad + \mathbb{1}(A_2 = \text{trt } 2)(\beta_{130} + X_1 \beta_{131} + \mathbb{1}(A_1 = \text{soc}) \beta_{132} + \mathbb{1}(A_1 = \text{trt } 1) \beta_{133} + \mathbb{1}(A_1 = \text{trt } 2) \beta_{134} + \mathbb{1}(A_1 = \text{trt } 3) \beta_{135} + \mathbb{1}(A_1 = \text{trt } 4) \beta_{136} + X_2 \beta_{137}) \\
 &\quad + \mathbb{1}(A_2 = \text{trt } 3)(\beta_{140} + X_1 \beta_{141} + \mathbb{1}(A_1 = \text{soc}) \beta_{142} + \mathbb{1}(A_1 = \text{trt } 1) \beta_{143} + \mathbb{1}(A_1 = \text{trt } 2) \beta_{144} + \mathbb{1}(A_1 = \text{trt } 3) \beta_{145} + \mathbb{1}(A_1 = \text{trt } 4) \beta_{146} + X_2 \beta_{147}) \\
 &\quad + \mathbb{1}(A_2 = \text{trt } 4)(\beta_{150} + X_1 \beta_{151} + \mathbb{1}(A_1 = \text{soc}) \beta_{152} + \mathbb{1}(A_1 = \text{trt } 1) \beta_{153} + \mathbb{1}(A_1 = \text{trt } 2) \beta_{154} + \mathbb{1}(A_1 = \text{trt } 3) \beta_{155} + \mathbb{1}(A_1 = \text{trt } 4) \beta_{156} + X_2 \beta_{157})
 \end{aligned}$$

### Design 5

Frontline treatments: standard of care (soc), treatment 1, treatment 2, treatment 3, treatment 4

Secondline treatments: treatment 1, treatment 2, treatment 3, treatment 5, treatment 4 if frontline (step up)



### Simulation parameters

$$N = \text{seq}(\text{from}=600, \text{to}=1200, \text{by}=100)$$

P(Responder status) cut offs: \*use normal quantiles

Tailoring var:  $X_i \in \{-1, 1\}$

Additional covariates: {None}, { $N(0,1)$ }, { $N(0,1)$ ,  $Bern(0.5)$ }

$X_2 \sim N(0,1)$  unless otherwise specified.

$$\begin{aligned}
 E(Y | A_2, H_2) &= f(A_2, H_2) \\
 &= f_1(H_2) + A_2 f_2(H_2) \\
 &= f_1(X_1, A_1, X_2) + A_2 f_2(X_1, A_2, X_2) \\
 &= f_1(X_1, A_1, X_2) + \mathbb{1}(A_2 = \text{soc})(1, X_1, \mathbb{1}(A_1 = \text{soc}), X_2) \vec{\beta}_{11} \\
 &\quad + \mathbb{1}(A_2 = \text{trt 1})(1, X_1, \mathbb{1}(A_1 = \text{soc}), \mathbb{1}(A_1 = \text{trt 1}), \mathbb{1}(A_1 = \text{trt 2}), \mathbb{1}(A_1 = \text{trt 3}), \mathbb{1}(A_1 = \text{trt 4}), X_2) \vec{\beta}_{12} \\
 &\quad + \mathbb{1}(A_2 = \text{trt 2})(1, X_1, \mathbb{1}(A_1 = \text{soc}), \mathbb{1}(A_1 = \text{trt 1}), \mathbb{1}(A_1 = \text{trt 2}), \mathbb{1}(A_1 = \text{trt 3}), \mathbb{1}(A_1 = \text{trt 4}), X_2) \vec{\beta}_{13} \\
 &\quad + \mathbb{1}(A_2 = \text{trt 3})(1, X_1, \mathbb{1}(A_1 = \text{soc}), \mathbb{1}(A_1 = \text{trt 1}), \mathbb{1}(A_1 = \text{trt 2}), \mathbb{1}(A_1 = \text{trt 3}), \mathbb{1}(A_1 = \text{trt 4}), X_2) \vec{\beta}_{14} \\
 &\quad + \mathbb{1}(A_2 = \text{trt 4})(1, X_1, \mathbb{1}(A_1 = \text{trt 4}), X_2) \vec{\beta}_{15} \\
 &\quad + \mathbb{1}(A_2 = \text{trt 5})(1, X_1, \mathbb{1}(A_1 = \text{trt 1}), \mathbb{1}(A_1 = \text{trt 2}), \mathbb{1}(A_1 = \text{trt 3}), \mathbb{1}(A_1 = \text{trt 4}), X_2) \vec{\beta}_{16} \\
 &= (1, X_1, X_2) \beta_{000} + \mathbb{1}(A_1 = \text{soc})(1, X_1) \vec{\beta}_{01} \\
 &\quad + \mathbb{1}(A_1 = \text{trt 1})(1, X_1) \vec{\beta}_{02} \\
 &\quad + \mathbb{1}(A_1 = \text{trt 2})(1, X_1) \vec{\beta}_{03} \\
 &\quad + \mathbb{1}(A_1 = \text{trt 3})(1, X_1) \vec{\beta}_{04} \\
 &\quad + \mathbb{1}(A_1 = \text{trt 4})(1, X_1) \vec{\beta}_{05} \\
 &\quad + \mathbb{1}(A_2 = \text{soc})(1, X_1, \mathbb{1}(A_1 = \text{soc}), X_2) \vec{\beta}_{11} \\
 &\quad + \mathbb{1}(A_2 = \text{trt 1})(1, X_1, \mathbb{1}(A_1 = \text{soc}), \mathbb{1}(A_1 = \text{trt 1}), \mathbb{1}(A_1 = \text{trt 2}), \mathbb{1}(A_1 = \text{trt 3}), \mathbb{1}(A_1 = \text{trt 4}), X_2) \vec{\beta}_{12} \\
 &\quad + \mathbb{1}(A_2 = \text{trt 2})(1, X_1, \mathbb{1}(A_1 = \text{soc}), \mathbb{1}(A_1 = \text{trt 1}), \mathbb{1}(A_1 = \text{trt 2}), \mathbb{1}(A_1 = \text{trt 3}), \mathbb{1}(A_1 = \text{trt 4}), X_2) \vec{\beta}_{13} \\
 &\quad + \mathbb{1}(A_2 = \text{trt 3})(1, X_1, \mathbb{1}(A_1 = \text{soc}), \mathbb{1}(A_1 = \text{trt 1}), \mathbb{1}(A_1 = \text{trt 2}), \mathbb{1}(A_1 = \text{trt 3}), \mathbb{1}(A_1 = \text{trt 4}), X_2) \vec{\beta}_{14} \\
 &\quad + \mathbb{1}(A_2 = \text{trt 4})(1, X_1, \mathbb{1}(A_1 = \text{trt 4}), X_2) \vec{\beta}_{15} \\
 &\quad + \mathbb{1}(A_2 = \text{trt 5})(1, X_1, \mathbb{1}(A_1 = \text{trt 1}), \mathbb{1}(A_1 = \text{trt 2}), \mathbb{1}(A_1 = \text{trt 3}), \mathbb{1}(A_1 = \text{trt 4}), X_2) \vec{\beta}_{16} \\
 &= \beta_{000} X_1 \beta_{001} + X_2 \beta_{002} + \mathbb{1}(A_1 = \text{soc})(\beta_{010} + X_1 \beta_{011}) + \mathbb{1}(A_1 = \text{trt 1})(\beta_{020} + X_1 \beta_{021}) + \mathbb{1}(A_1 = \text{trt 2})(\beta_{030} + X_1 \beta_{032}) + \mathbb{1}(A_1 = \text{trt 3})(\beta_{040} + X_1 \beta_{041}) + \mathbb{1}(A_1 = \text{trt 4})(\beta_{050} + X_1 \beta_{051}) \\
 &\quad + \mathbb{1}(A_2 = \text{soc})(\beta_{110} + \beta_{111} X_1 + \beta_{112} \mathbb{1}(A_1 = \text{soc}) + \beta_{113} X_2) \\
 &\quad + \mathbb{1}(A_2 = \text{trt 1})(\beta_{120} + X_1 \beta_{121} + \mathbb{1}(A_1 = \text{soc}) \beta_{122} + \mathbb{1}(A_1 = \text{trt 1}) \beta_{123} + \mathbb{1}(A_1 = \text{trt 2}) \beta_{124} + \mathbb{1}(A_1 = \text{trt 3}) \beta_{125} + \mathbb{1}(A_1 = \text{trt 4}) \beta_{126} + X_2 \beta_{127}) \\
 &\quad + \mathbb{1}(A_2 = \text{trt 2})(\beta_{130} + X_1 \beta_{131} + \mathbb{1}(A_1 = \text{soc}) \beta_{132} + \mathbb{1}(A_1 = \text{trt 1}) \beta_{133} + \mathbb{1}(A_1 = \text{trt 2}) \beta_{134} + \mathbb{1}(A_1 = \text{trt 3}) \beta_{135} + \mathbb{1}(A_1 = \text{trt 4}) \beta_{136} + X_2 \beta_{137}) \\
 &\quad + \mathbb{1}(A_2 = \text{trt 3})(\beta_{140} + X_1 \beta_{141} + \mathbb{1}(A_1 = \text{soc}) \beta_{142} + \mathbb{1}(A_1 = \text{trt 1}) \beta_{143} + \mathbb{1}(A_1 = \text{trt 2}) \beta_{144} + \mathbb{1}(A_1 = \text{trt 3}) \beta_{145} + \mathbb{1}(A_1 = \text{trt 4}) \beta_{146} + X_2 \beta_{147}) \\
 &\quad + \mathbb{1}(A_2 = \text{trt 4})(\beta_{150} + X_1 \beta_{151} + \mathbb{1}(A_1 = \text{soc}) \beta_{152} + \mathbb{1}(A_1 = \text{trt 1}) \beta_{153}) \\
 &\quad + \mathbb{1}(A_2 = \text{trt 5})(\beta_{160} + X_1 \beta_{161} + \mathbb{1}(A_1 = \text{soc}) \beta_{162} + \mathbb{1}(A_1 = \text{trt 1}) \beta_{163} + \mathbb{1}(A_1 = \text{trt 2}) \beta_{164} + \mathbb{1}(A_1 = \text{trt 3}) \beta_{165} + \mathbb{1}(A_1 = \text{trt 4}) \beta_{166} + X_2 \beta_{167})
 \end{aligned}$$

Design 6

Frontline treatments : Standard of care, Treatment 1, Treatment 2, Treatment 3

Secondline treatments: Treatment 1, Treatment 2, Treatment 3, SOC\*

