Appendix.

Here we assume a series of successive interventions each achieving the same relative risk (*RR*) reduction for mortality over the preceding intervention. In other words, the *RR* is constant across generations of interventions. We denote as p the proportion of patients who experience the event of interest with the "standard" intervention in the general population.

In each generation, we denote as r and r' the event rates (proportions) in the control and experimental arms of hypothetical pragmatic randomized trials. The control arm receives the current "standard" intervention, and the experimental arm receives the intervention that will become the "standard treatment" in the next generation.

The table helps to fix notation.

Generation	**Rate with current treatment (*r*)**	**Rate in the experimental arm (*r'*)**
0 (baseline)	$r_0 = p_0$	$r'_0 = p_0 RR$
1	$r_1 = p_0 RR$	$r'_1 = p_0 RR^2$
2	$r_2 = p_0 RR^2$	$r'_2 = p_0 RR^3$
i	$r_i = p_0 RR^i$	$r'_i = p_0 RR^{i+1}$

Benefit

In the paper, the benefit *B* conferred by the "experimental treatment in the i-th generation is defined as the absolute risk reduction (risk difference) conferred by the experimental treatment. At baseline (generation 0) this would be:

$$B_0 = r - r' = p_0 - p_0 RR = p_0 \underbrace{(1 - RR)}_{E} = p_0 E$$

At the i-th generation, the benefit would be described by a declining exponential function:

$$B_i = r_i - r'_i = p_0 RR^i - p_0 RR^{i+1} = p_0 \underbrace{RR^i}_{(1-E)^i} \underbrace{(1 - RR)}_{E} = \underbrace{p_0 E}_{B_0} (1 - E)^i = B_0 (1 - E)^i$$

Sample size determinations:

One can calculate the required sample size that the aforementioned hypothetical trials should attain to have power β to detect a difference in the event rates from r to r' at level of significance α, assuming equal number of patients in the compared arms. However, when we assume arms of equal size, the following formula gives the approximate total sample size for a trial that compares the standard treatment at generation i against the experimental treatment at generation $i+1$. *Z* denotes a standard normal deviant.

$$S_i = \overbrace{2\left(Z_{1-\alpha/2} + Z_{1-\beta}\right)^2}^{f(\alpha,\beta)} \frac{(1 - r_i) r_i + \left(1 - r'_i\right) r'_i}{\left(r_i - r'_i\right)^2}$$

We can show empirically that, for up to 5 generations, the following approximation is reasonable:

$S_i \sim S_0/(1-E)^i$

Because the power and the significance level are factored out, we fix them at 90% and 0.05, respectively.

Assuming α=0.05, β=0.90 and allocation ratio 1

p_0	**RR**	**Generation**	**Actual calculated sample size**	**Approximated sample size $S_i \sim S_0/(1-E)^i$**	**Difference (%)**
0.08	0.75	0	7036	7076	0.6
0.08	0.75	1	9554	9537	0.2
0.08	0.75	2	12910	12853	0.4
0.08	0.75	3	17388	17322	0.4
0.08	0.75	4	23356	23346	<0.1
0.08	0.75	5	31314	31463	0.5
0.04	0.75	0	14590	14630	.3
0.04	0.75	1	19626	19609	.1
0.04	0.75	2	26340	26283	.2
0.04	0.75	3	35292	35229	.2
0.04	0.75	4	47230	47219	<0.1
0.04	0.75	5	63146	63290	.2
0.12	0.75	0	4518	4558	.9
0.12	0.75	1	6196	6179	.3
0.12	0.75	2	8434	8375	.7
0.12	0.75	3	11418	11352	.6
0.12	0.75	4	15398	15388	.1
0.12	0.75	5	20704	20857	.7

Unit cost

We defined unit cost as

$$U_i = \frac{B_i}{S_i} \approx \frac{S_0}{B_0(1-E)^{2i}} = \frac{U_0}{(1-E)^{2i}}$$