# Decision-theoretic design for a series of phase II trials with correlated treatment effects

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Innovative methodology for small populations research

# Setting

▶ Small population, $N$, is known

▶ $> 2$ treatments available for trial

▶ Only one of them can proceed to a phase III trial

▶ A series of single-arm phase II trials and one two-arm phase III trial

▶ Treatments for the same population may be related

▶ Extends Hee and Stallard (2012)

# Decision-theoretic design

▶ Start with experimental treatment, $E_1$

▶ Recruit $m$ patients

▶ Observe their responses and decide to:

- Action P: Stop and proceed to phase III

- Action A: Stop and abandon the programme

- Action T: Stop and start a new one with $E_2$

- Action R: Continue with another group of $m$ patients

▶ At each decision time point choose an optimal action based on utility

# Action P: Proceed to phase III

▶ At stage $i$ of trial $k$

▶ Remaining $N - \sum_{j=1}^{k-1} n_{j\cdot} - n_{ki}$ patients are randomized to a 2-arm phase III trial

$$\theta_k = \log\left\{\frac{p_k(1-p_C)}{p_C(1-p_k)}\right\}, V_k \approx \frac{1}{4}\left(N - \sum n_{j\cdot} - n_{ki}\right)\bar{p}(1-\bar{p})$$

▶ Test the null hypothesis: $H_0: \theta_k = 0$

$$1 - \Phi\left(z_{1-\alpha/2} - \theta_k\sqrt{V_k}\right)$$

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▶ Test the null hypothesis: $H_0: \theta_k = 0$

$$U\left(1 - \Phi\left(z_{1-\alpha/2} - \theta_k\sqrt{V_k}\right)\right) - c_{2k}n_{ki}$$
$$- c_{3k}\left(N - \sum_{j=1}^{k-1} n_{k \cdot} - n_{ki}\right) - l_{3k}$$

# Action P: Proceed to phase III

▶ At stage $i$ of trial $k$

▶ Remaining $N - \sum_{j=1}^{k-1} n_{j.} - n_{ki}$ patients are randomized to a 2-arm phase III trial

$$\theta_k = \log\left\{\frac{p_k(1-p_C)}{p_C(1-p_k)}\right\}, V_k \approx \frac{1}{4}\left(N - \sum n_{j.} - n_{ki}\right)\bar{p}(1-\bar{p})$$

▶ Test the null hypothesis: $H_0: \theta_k = 0$

$$\mathcal{G}_P(k, \boldsymbol{s_{ki}}, \boldsymbol{n_{ki}}, N)$$

$$= \int \dots \int U\left(1 - \Phi\left(z_{1-\alpha/2} - \theta_k\sqrt{V_k}\right)\right) h(\boldsymbol{p}|\boldsymbol{S_{ki}})d\boldsymbol{p} - c_{2k}n_{ki}$$

$$- c_{3k}\left(N - \sum_{j=1}^{k-1} n_{k.} - n_{ki}\right) - l_{3k}$$

# Action A: Abandon the programme

▶ Less the cost of patients recruited to the current trial so far,

$$\mathcal{G}_A(k, \boldsymbol{s_{ki}}, \boldsymbol{n_{ki}}, N) = -c_{2k} n_{ki}$$

# Action T: Start a new phase II trial

► The expected utility depends on the expected utility of the new trial and its resulting actions

$$\mathcal{G}_T(k, \boldsymbol{s_{ki}}, \boldsymbol{n_{ki}}, N)$$
$$= \mathcal{G}_{Total}(k + 1, \boldsymbol{s_{k+1,0}}, \boldsymbol{n_{k+1,0}}, N) - c_{2k} n_{ki}$$

# Action R: Recruit more to the current trial

▶ Action R requires us to recruit an additional $m$ patients

▶ Subsequently, take an optimal action on these future observations

▶ The gain depends on the action taken based on the observations from subsequent stages and trials

$$\mathcal{G}_R(k, \boldsymbol{s_{ki}}, \boldsymbol{n_{ki}}, N)$$

$$= \sum_{y=0}^{m} \max_{a \in \{P,A,T,R\}} \{G_a(k, \boldsymbol{s_{ki}} + y, \boldsymbol{n_{ki}} + m, N)\} \times g(y | \boldsymbol{s_{ki}}, \boldsymbol{n_{ki}})$$

# Case study

▶ Total hip arthroplasty (standard) vs. resurfacing arthroplasty (experimental) trial for patients with arthritis of the hip joint (Costa *et al*., BMJ, 2012;344)

▶ For our illustration, assume 2 newer resurfacing arthroplasty procedures that differ in the technical aspects

▶ Only one of them can proceed to a phase III trial

# Assumptions

▶ Binary outcome

$$Y_{ki} \sim Bin(m, p_k), S_{ki} = \sum_{j=1}^{i} Y_{kj} \sim Bin(n_{ki}, p_k)$$

$$p_k \sim Beta(a_k, b_k), k = 1,2$$

▶ The Sarmanov bivariate beta distribution is

$$h(p_1, p_2) = f(p_1)f(p_2)\big(1 + \omega\phi(p_1)\phi(p_2)\big)$$

where $\phi(p_k) = p_k - \mu_k$ and $\rho = \omega\sigma_1\sigma_2$

# Illustration

- $p_C = 0.5$
- $Beta(1, 1)$, $Beta(3, 2)$ and $Beta(2, 3)$
- $U = £3$ million; $l_{2k} = £30,000$; $l_{3k} = £300,000$; $c_{2k} = c_{3k} = £750$
- Projected size, $N = 350$
- Patients are recruited in groups of $m = 5$
- Minimum phase III size, $n_{\min} = 300$
- Mixing parameter, $\omega = 0, 4$

# Optimal action for the first phase II trial, $Beta(1, 1)$
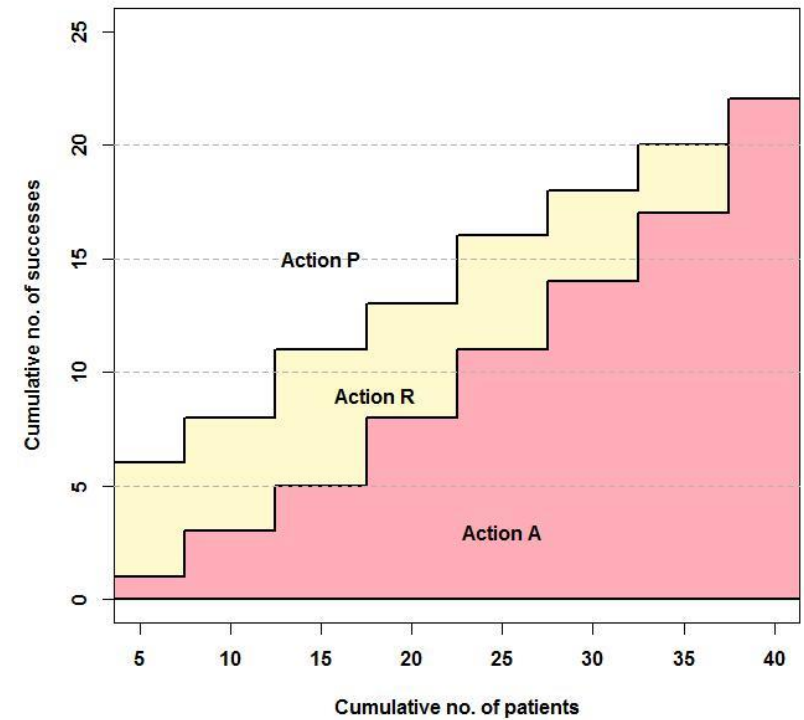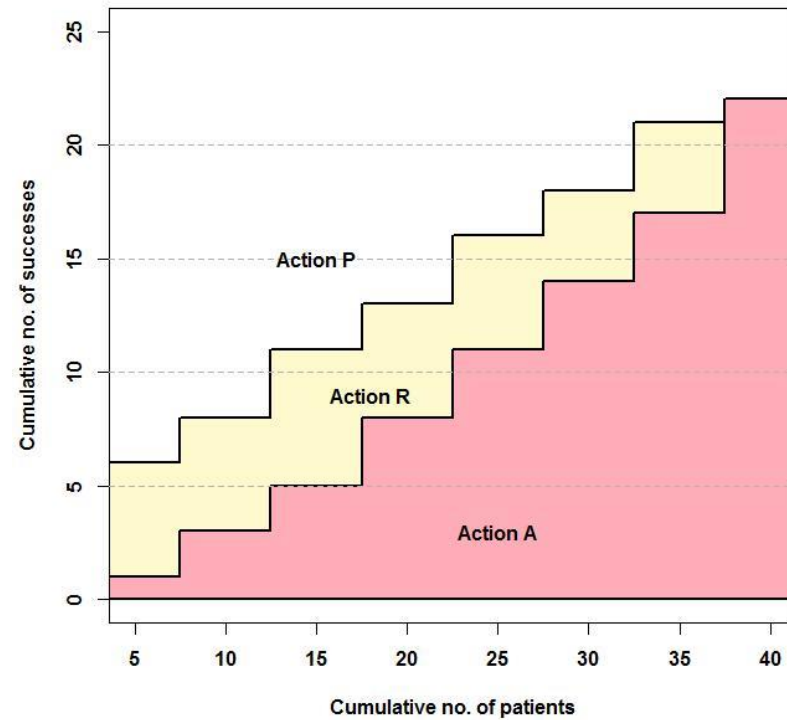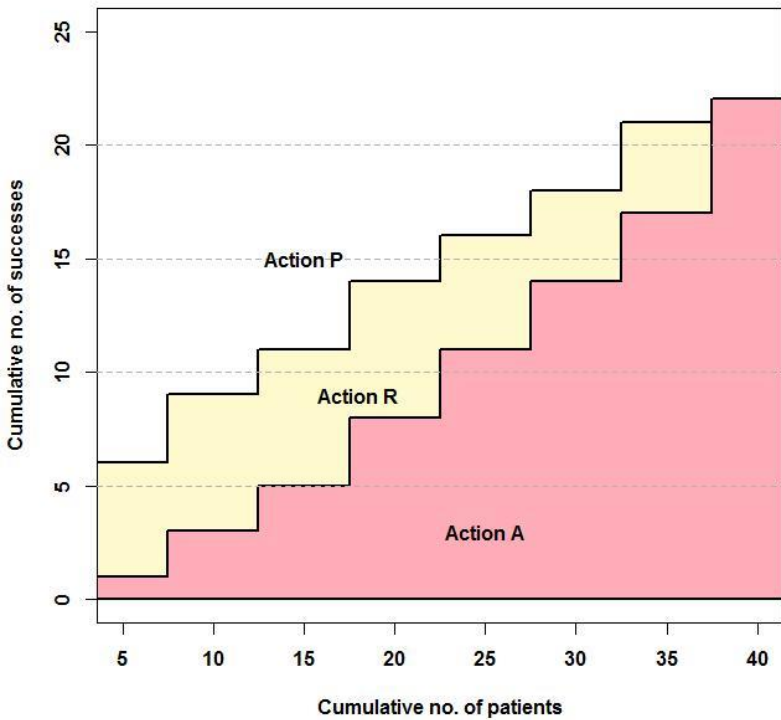
$\omega = 0, \rho = 0$
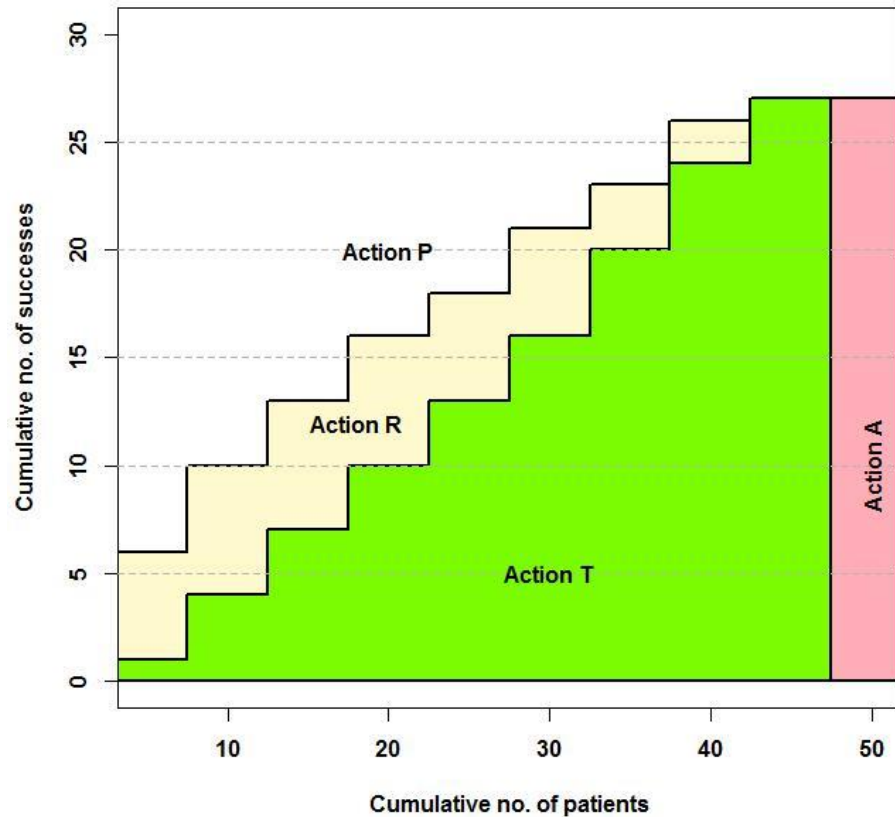
$\omega = 4, \rho = 0.33$
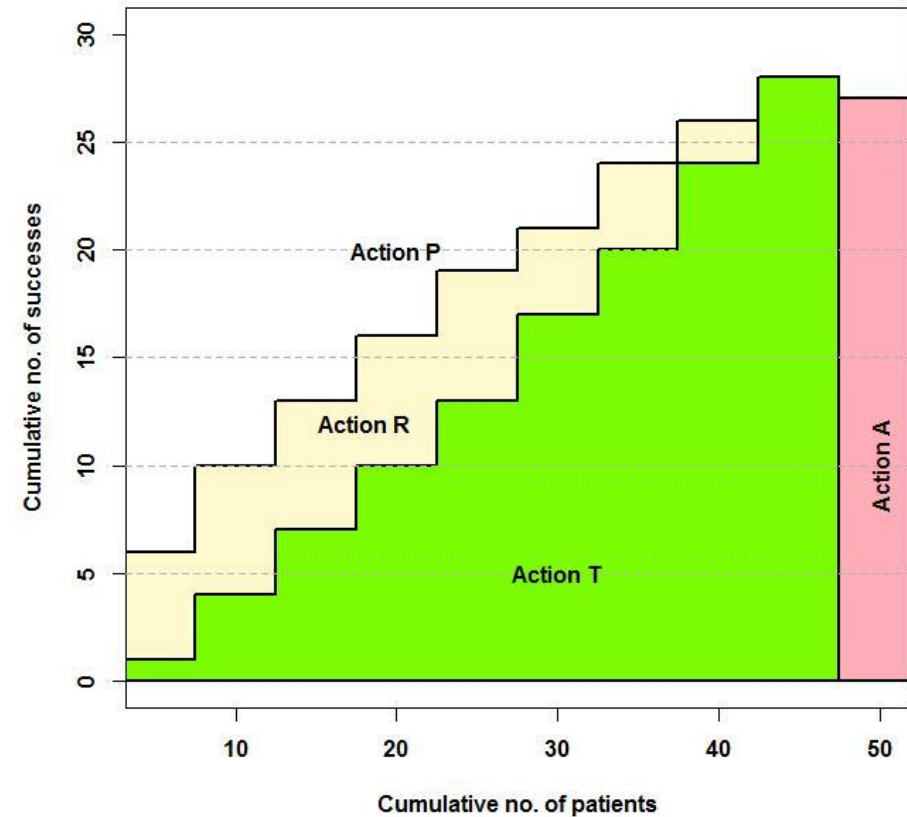
# Optimal action for the second phase II trial, $\rho = 0.33$

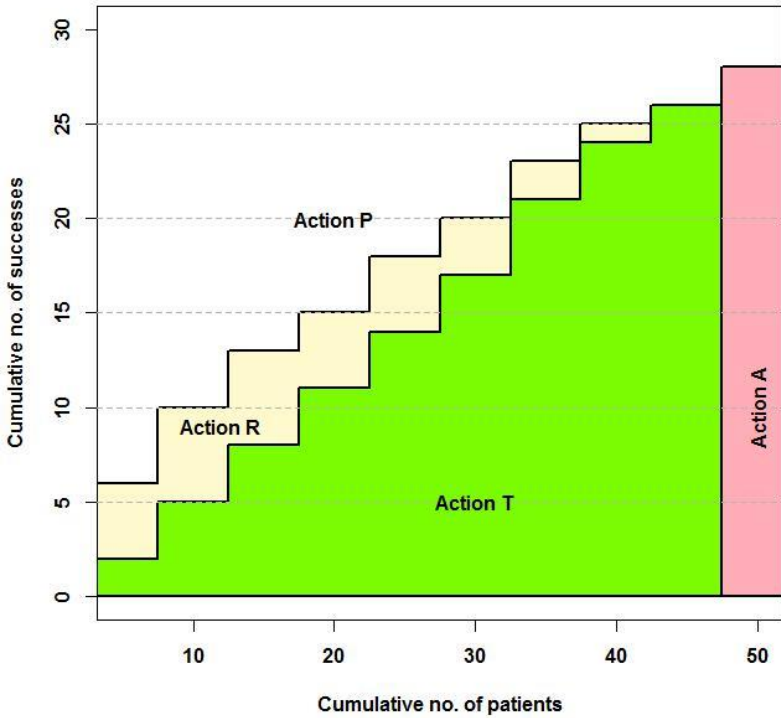$s_{1.} = 1, n_{1.} = 10$

$s_{1.} = 2, n_{1.} = 10$

$s_{1.} = 3, n_{1.} = 10$

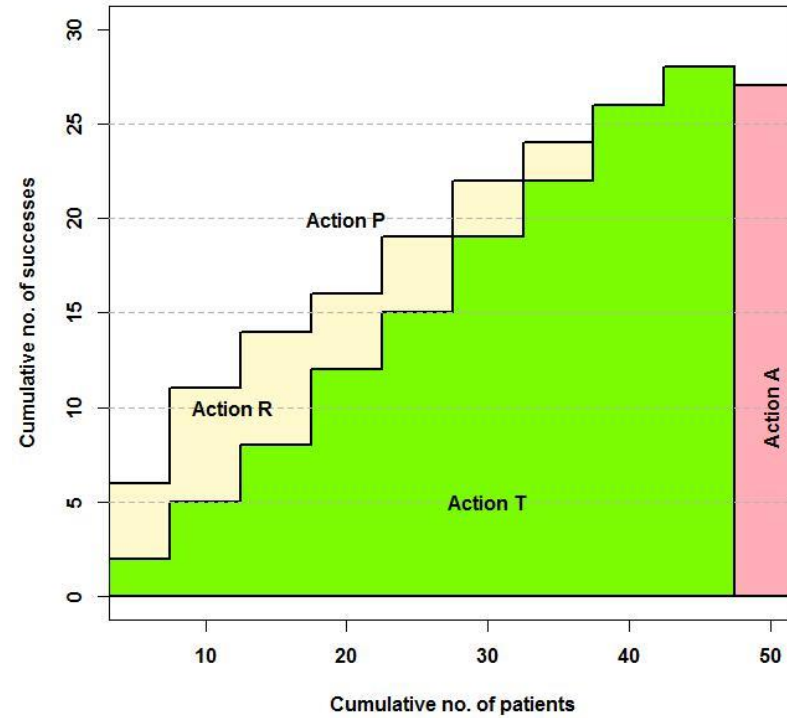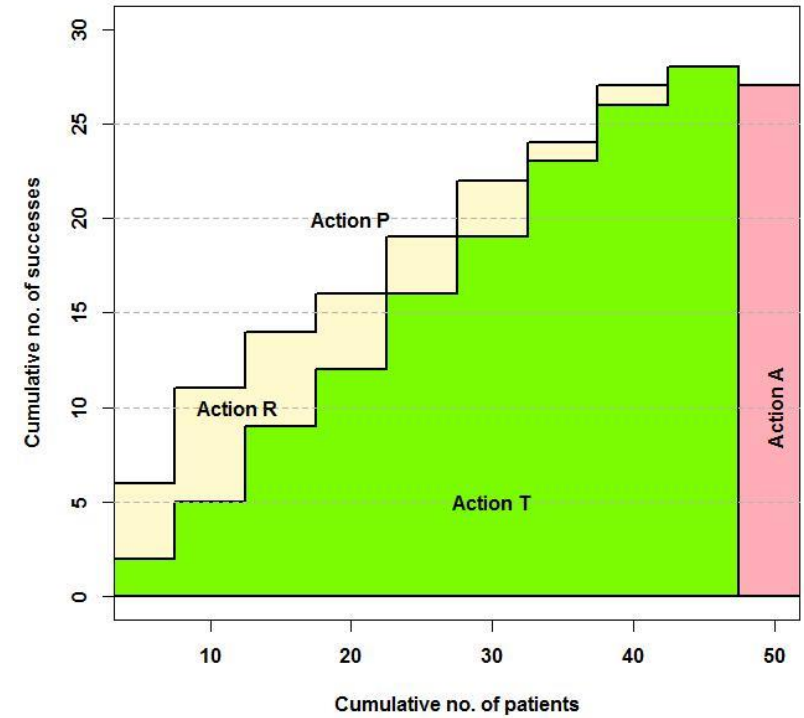# Trivariate case

$Beta(2, 3)$           $Beta(1, 1)$           $Beta(3, 2)$

# Conclusion

▶ Ordering of treatments matters

▶ Different priors:

- $p_1 \sim Beta(1, 1)$, $p_2 \sim Beta(3, 2)$
- $p_1 \sim Beta(3, 2)$, $p_2 \sim Beta(1, 1)$
- $p_1 \sim Beta(12, 8)$, $p_2 \sim Beta(3, 2)$

▶ Start with less informative prior

# **Discussion**

▶ The Sarmanov family of distribution is slightly more flexible than those of the Farlie-Gumbel-Morgenstern (FGM) distribution

▶ For $a$, $b \geq 1$, the correlation is limited to [-1/3, 1/3]

▶ Olkin and Trikalinos (2015) bivariate beta distribution allows $\rho$ in [-1, 1] but has no closed form

# Co-authors/acknowledgment

- Nick Parsons
- Nigel Stallard