Valuing External Controls in Two Arm Proof of Concept Trials

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https://github.com/sstanhope/ExCtrlValuationTwoArmPOC

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Introduction

Background:

- Augmenting or replacing live control arms with external and historical data can in principle improve compound decision making, and statistical power and time to completion of clinical trials. However, in many cases obtaining this data and performing related analyses are costly. We would like to better value pools of external controls before obtaining them, in order to both justify the expense and avoid wasteful spending.

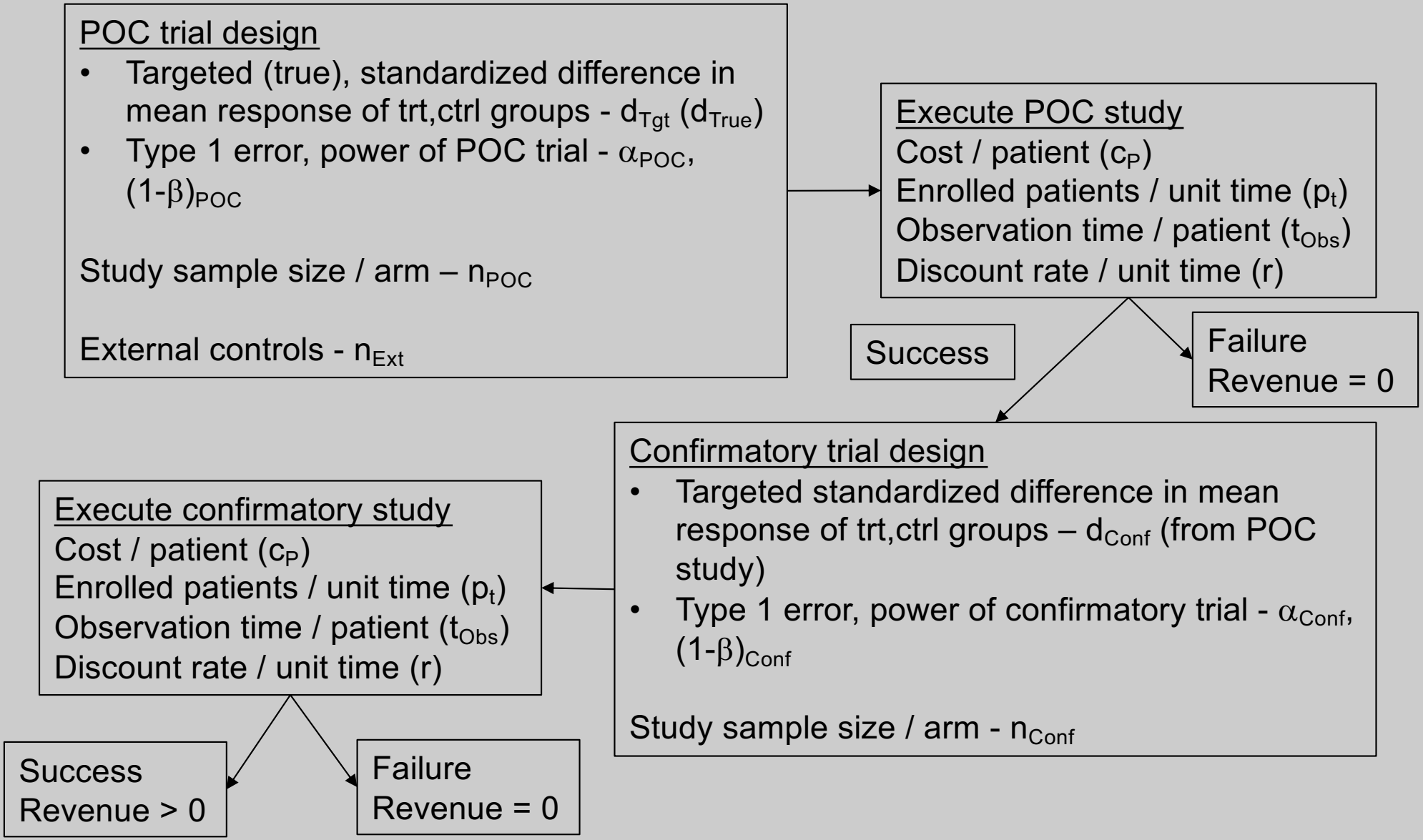
Goals:

- Valuation codes, bounds on value for large pools of potential external controls applied post-hoc to phase II proof of concept (POC) trials with continuous, dichotomous and time to event endpoints

Talk Contents:

- Decision-making flow: POC through confirmatory study;
- Math: POC through confirmatory study, total program valuation (continuous endpoint);
- Valuation example – Belimumab (dichotomous endpoint);
- Extras – Accounting for uncertainty in true effect, lower bound on value of pool, bounds on value for large pools of potential external controls.

Decision-making flow: POC through confirmatory study



Math: *POC* through confirmatory study

$$n_{POC}\left(d_{Tgt}, \alpha_{POC}, (1-\beta)_{POC}\right)$$

$$c_{POC} = (2n_{POC}c_P)(1+r)^{-\left(\frac{2n_{POC}}{p_t} + t_{Obs}\right)}$$

Number of subject / arm from standard power calculations; cost of study borne at end of POC trial.

$$z_{POC} = \Phi^{-1}\left(1 - \frac{\alpha_{POC}}{2}\right)$$

$$Pr^{+}_{POC} = 1 - \Phi\left(z_{POC} - \frac{d_{True}}{\sqrt{(n_{POC})^{-1} + (n_{POC} + n_{Ext})^{-1}}}\right)$$

Prob(+) as a function of p-value criteria, sample size, true effect.

$$E[D_{POC} \mid +] = \frac{1}{\gamma}\int_{LB}^{\infty} x\,\phi\left(\frac{x - d_{True}}{\sqrt{(n_{POC})^{-1} + (n_{POC} + n_{Ext})^{-1}}}\right)dx$$

$$LB = z_{POC}\sqrt{(n_{POC})^{-1} + (n_{POC} + n_{Ext})^{-1}}$$

$$\gamma = \int_{LB}^{\infty} \phi\left(\frac{x - d_{True}}{\sqrt{(n_{POC})^{-1} + (n_{POC} + n_{Ext})^{-1}}}\right)dx$$

Estimated effect size conditional on + trial result used as an input for powering the confirmatory trial (biased up).

Math: POC through *confirmatory study*

$$n_{Conf}\left(E[D_{POC} \mid +], \alpha_{Conf}, (1-\beta)_{Conf}\right)$$

$$c_{Conf} = (2n_{POC}c_P)(1+r)^{-\left(\frac{2n_{Conf}}{p_t} + t_{Obs} + \frac{2n_{POC}}{p_t} + t_{Obs}\right)}$$

Number of subjects based on observed effect from POC trial; cost of study borne at end of confirmatory trial.

$$z_{Conf} = \Phi^{-1}\left(1 - \frac{\alpha_{Conf}}{2}\right)$$

$$Pr^{+}_{Conf} = 1 - \Phi\left(z_{Conf} - \frac{d_{True}}{\sqrt{(n_{Conf})^{-1} + (n_{Conf})^{-1}}}\right)$$

Prob(+) as a function of p-value criteria, sample size, true effect.

Math: Total program valuation

$$n_{Total} = 2n_{POC} + Pr^{+}_{POC}\, 2\, n_{Conf}$$

Expected total subjects

$$Pr^{+} = Pr^{+}_{POC}\, Pr^{+}_{Conf}$$

Probability of program success

$$c_{Total} = c_{POC} + Pr^{+}_{POC}\, c_{Conf}$$

Expected NPV of program costs

$$NPV = -c_{POC} + -Pr^{+}_{POC} c_{Conf} + Pr^{+}_{POC}\, Pr^{+}_{Conf}\, Revenue$$

$$Revenue = R_0(1+r)^{-\left(\frac{2n_{Conf}}{p_t} + t_{Obs} + \frac{2n_{POC}}{p_t} + t_{Obs}\right)}$$

Expected NPV of program (costs and revenue)

$$NPV\left(\begin{matrix} d_{Tgt}, d_{True}, t_{Obs}, \alpha_{POC}, (1-\beta)_{POC}, n_{Ext}, \\ \alpha_{Conf}, (1-\beta)_{Conf}, c_p, p_t, R_0, r \end{matrix}\right)$$

Functional expression of expected NPV of program.

Example: Total program valuation including / excluding external controls

Belimumab for systemic lupus erythematosus

- Phase II – 2009 Wallace et al
  - Co-primary endpoints - 25% absolute, 100% relative change in baseline SLEDAI score (SD = 50%); *reduction of symptom flare by week 52 from 65% to 43%*. 80% power, 5% type I error.
- Phase III – 2011 Navarra et al, Furie et al
  - Primary endpoint – Absolute reduction in SLEDAI. Secondary endpoint – Reduction of symptom flare by week 52. 90% power, 5% type I error.
- NPV given success – $1.07 billion
  - 12 year patent (2011-2023), $100 million - $1 billion / year annually (Ratner 2011), 33% sales-to-operating profit (GSK 2021), 11% discount rate / year (Alacrita)
- Other model parameters / assumptions
  - True reduction in symptom flare = planned; $42,000 / subject, 10 subjects / month (Wallace et al), $n_{Ext} = n_{POC}$

Example: Total program valuation including / excluding external controls

		$N_{Ext} = 0$	$N_{Ext} = N$
Phase II	N	77 / arm	77 / arm
	Cost	$5.01	$5.01
	Pr(+)	80.1%	89.66%
Phase III	N	80 / arm	91 / arm
	Cost	$4.03	$4.46
	Pr(+)	81.65%	86.27%
Total	N	282.29	317.19
	Cost	$8.24	$9.01
	Pr(+)	65.47%	77.35%
	NPV	412.04	474.14

V_{Ext} = $62.10?

Costs, NPV given in mm. Note costs omit fixed components and are given in NPV.
Phase III data given in expectation, conditional on Phase II success.
Total N, costs, NPV given in expectation.

Math: Valuing the external controls

$$V_{Ext} \neq NPV\begin{pmatrix} d_{Tgt}, d_{True}, t_{Obs}, \alpha_{POC}, (1-\beta)_{POC}, n_{Ext} > 0, \\ \alpha_{Conf}, (1-\beta)_{Conf}, c_p, p_t, R_0, r \end{pmatrix} - NPV\begin{pmatrix} d_{Tgt}, d_{True}, t_{Obs}, \alpha_{POC}, (1-\beta)_{POC}, n_{Ext} = 0, \\ \alpha_{Conf}, (1-\beta)_{Conf}, c_p, p_t, R_0, r \end{pmatrix}$$

$$V_{Ext} = NPV\begin{pmatrix} d_{Tgt}, d_{True}, t_{Obs}, \alpha_{POC}, (1-\beta)_{POC}, n_{Ext} > 0, \\ \alpha_{Conf}, (1-\beta)_{Conf}, c_p, p_t, R_0, r \end{pmatrix} - NPV\begin{pmatrix} d_{Tgt}, d_{True}, t_{Obs}, \alpha_{POC}, \big((1-\beta)_{POC}\big)(n_{Ext} > 0), n_{Ext} = 0, \\ \alpha_{Conf}, (1-\beta)_{Conf}, c_p, p_t, R_0, r \end{pmatrix}$$

The value of the external control is the difference in NPVs of the trial incorporating them, and one in which power is controlled and the external controls are replaced (more efficiently wrt total subjects) with randomized subjects.

Example: Value of the external controls

		$N_{Ext} = 0$	$N_{Ext} = N$	$N_{Ext} = 0$ Pr(+) control
Phase II	N	77 / arm	77 / arm	102 / arm
	Cost	$5.01	$5.01	$6.34
	Pr(+)	80.1%	89.66%	89.83%
Phase III	N	80 / arm	91 / arm	91 / arm
	Cost	$4.03	$4.46	$4.26
	Pr(+)	81.65%	86.27%	86.27%
Total	N	282.29	317.19	367.49
	Cost	$8.24	$9.01	$10.17
	Pr(+)	65.47%	77.35%	77.50%
	NPV	$412.04	$474.14	$452.30

V_{Ext} = $21.84

Costs, NPV given in mm. Note costs omit fixed components and are given in NPV.
Phase III data given in expectation, conditional on Phase II success.
Total N, costs, NPV given in expectation.

Extension 1: Monte Carlo over true treatment effect

True symptom flare rates for treated group:

- 65% (no advantage, 50% probability)
- 54% (half planned advantage, 35% probability)
- 43% (full planned advantage, 15%)

		$N_{Ext} = 0$	$N_{Ext} = N$	$N_{Ext} = 0$ Pr(+) control
Total	N	200.83	221.32	271.68
	Cost	$6.14	$6.55	$7.81
	Pr(+)	14.07%	18.00%	18.07%
	NPV	$82.27	$101.95	$96.23

V_{Ext} = $5.72

Costs, NPV given in mm. Note costs omit fixed components and are given in NPV.
Total N, costs, NPV given in expectation.

Extension 2: Lower bound on the value of an external control arm

If we allow the NPV of revenue conditional on success to be zero, we can get a minimum bound for the value of the control arm:

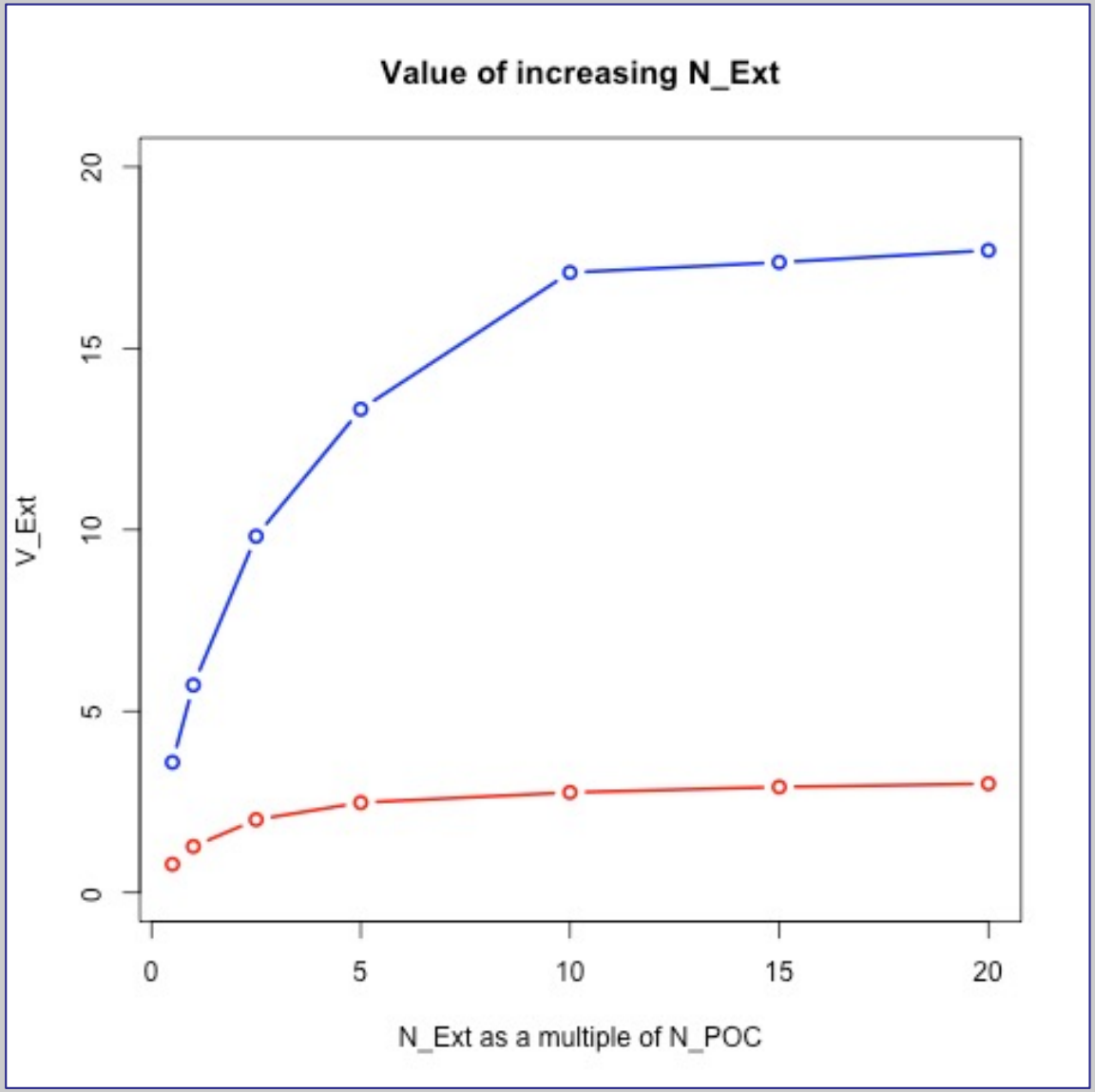
		$N_{Ext} = 0$	$N_{Ext} = N$	$N_{Ext} = 0$ Pr(+) control
Total	N	200.83	221.32	271.68
	Cost	$6.14	$6.55	$7.81
	Pr(+)	14.07%	18.00%	18.07%
	NPV	$82.27	$101.95	$96.23
LB	N	200.12	220.74	271.11
	Cost	$6.12	$6.53	$7.80
	Pr(+)	13.40%	17.26%	17.33%
	NPV	-$6.12	-$6.53	-$7.80

V_{Ext} = $5.72

$\underline{V}_{Ext}$ = $1.27

Costs, NPV given in mm. Note costs omit fixed components and are given in NPV. Total N, costs, NPV given in expectation. Note – wiggle in N, Cost, Pr(+) due to Monte Carlo sampling.

Extension 3: Value of a large pool of prospective external controls



If we have a large enough pool of prospective controls, we can find an external control arm as large as we want.

The pool can be valued according to the value of a very large control arm, since we will have convergence to a single arm statistical test (which maximizes the power of the unbalanced design).

$Max(V_{Ext}) = \$18$ mm
$Max(\underline{V}_{Ext}) = \$3$ mm

Conclusion

Review:

- Problem statement – We want to value pools of exogenous controls applied post-hoc to a phase II POC study, moving into phase III
- Decision flowchart and valuation math – continuous endpoints
- R library implementation – continuous, dichotomous, time-to-event endpoints
- Example calculation (belimumab) – dichotomous endpoint
- Extensions – Uncertainty in true effect size, lower bound on value of pool, valuation of large pools of potential exogenous control data.

Current work:

- One-arm trials (oncology).