University of Bremen

Oncology Phase II Adaptive Designs

Efficacy estimates and their use in planning Phase III trials

Arsénio Nhacolo

Supervisor:
Prof. Werner Brannath

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Outline

Background

Knowledge gained in clinical trials of a particular phase is often used to plan trials of subsequent phases.

Effect estimates of successful Phase II trials used to plan Phase III sample size.

Phase II estimates are often biased and imprecise, resulting in inadequately powered Phase III trials.

High failure rate of Phase III trials has been reported in the literature (about 40% in general, over 60% in adult cancer).

The actual magnitude of benefit achieved in clinical trials is nearly always less than what was predicted at the time trials were designed (Gan et al.,2012).

Adjustment methods: literature review
(1)

Different approaches to deal with bias/imprecision of Phase II estimates when planning Phase III sample size (SS).

Conservative SS estimation (CSSE) strategies:

- *Frequentist:* Use a conservative value ($\hat{\theta}_f$,) of Phase II effect estimate ($\hat{\theta}$) to determine Phase III SS. Achieved by
  - subtracting a certain amount from $\hat{\theta}$, e.g., one standard error (i.e., $\hat{\theta}_f = \hat{\theta} - \text{SE}(\hat{\theta})$) (`Wang et al., 2006`)
  - applying a discounting factor $f \in]0, 1]$ (i.e., $\hat{\theta}_f = \hat{\theta} \times f$) (`Kirby et al., 2012`)
- *Bayesian:* Put a probability mass around the observed Phase II effect and computes the averaged success probability (SP) at a given SS. Then the Phase III SS estimate is the minimum SS whose Bayesian SP exceeds a certain desired power.

Adjustment methods: literature review
(2)

Where many similar Phase II trials on the same therapy exist, meta-analytic approaches can also be used to better plan subsequent Phase III trials.

E.g.: In the context of randomized Phase II trials with binary endpoints, `Burke et al.(2014)` deemed the meta-analysis using a Bayesian random effects logistic regression model to be the most appropriate.

The model can predict the probability that

- the therapy will be truly effective in a new trial
- in a new trial with a given SS, the 95% credible interval for the odds ratio will be entirely in favour of the therapy.

Adjustment methods: new proposal
(1)

Despite the approaches above, the question of how to appropriately employ Phase II effect estimates to plan Phase III trials still remains a challenge.

- No clear guidelines on the amount of effect to discount for the frequentist CSSE strategies;
- The Bayesian strategies rely on adequate choice of conservative prior distribution, for which universally valid guidelines are hard to establish.

We propose a new approach to estimate a multiplicative adjustment factor to be applied to Phase II estimates before employing them to plan the SS of Phase III trials.

Adjustment methods: new proposal
Method 1

The approach is based on parametric bootstrapping.

Method 1

- Let θ be the true efficacy parameter of interest
- $\mathcal{F}_\theta$ the corresponding distribution from which data is drawn
- After a successful Phase II trial, estimate of θ, $\hat{\theta}$, is obtained and, under specific α and β, the Phase III SS, $\hat{n} = n(\hat{\theta}, \alpha, \beta)$, is calculated
- Phase II trials τ_i, $i = 1, \ldots, m$, similar to the actual trial are simulated, with data points drawn from $\mathcal{F}_{\hat{\theta}}$
- Let J be the index set of all simulated trials in which H_0 was rejected, and $|J|$ its cardinality ($|J| \leq m$)
- For each τ_j, $j \in J$, the estimate of $\hat{\theta}$, denoted by θ_j^*, is obtained and, the Phase III SS, $n_j^* = n(\theta_j^*, \alpha, \beta)$, is calculated.

Adjustment methods: new proposal
(Method 1)

- Individual estimates of the multiplicative adjustment factors for effect size and SS, f_j and ρ_j, are calculated as $f_j = \hat{\theta}/\theta_j^*$ and $\rho_j = \hat{n}/n_j^*$.
- The average values of these factors are taken to be their final estimates, i.e., $f = \frac{1}{|J|}\sum_{j\in J} f_j$ and $\rho = \frac{1}{|J|}\sum_{j\in J} \rho_j$.
- The adjusted Phase II estimate for calculating Phase III SS is $\theta_f = \hat{\theta} \times f$.
- Alternatively, if unadjusted Phase II estimate is used to obtain Phase III SS, the adjusted SS is $n_\rho = \hat{n} \times \rho$.

Method 2

Let $\mathfrak{p}_j^* = \mathfrak{p}(n_j^*, \hat{\theta}, \alpha)$ be the power a phase III trial would attain, calculated using the sample size n_j^* and the observed efficacy estimate $\hat{\theta}$

The sample size multiplicative adjustment factor is calculated such that the expected value of phase III power is equal to the target (desired) power, i.e.,

$$\rho = \left\{ \tilde{\rho} | E_{\hat{\theta}} \left[\mathfrak{p}(\tilde{\rho} n_j^*, \hat{\theta}, \alpha) \right] = 1 - \beta \right\}.$$

Simulation study
(1)

Objective:

- Evaluate the proposed methods with respect to power of Phase III trials.

Procedure:

1. Assuming specific true treatment effect, we simulate Phase II trials.
2. For each simulated trial in which H_0 was rejected, we calculate the effect estimate and we apply our methods to obtain the adjustment factors which we then use to estimate the Phase III sample size N.
3. The power that N would yield is then calculated.

Simulation study
(2)

Phase II trial design:

- Adaptive two-stage designs by `Englert and Kieser (2013)`, testing $H_0 : \pi \leq \pi_0$ vs $H_1 : \pi \geq \pi_1$, with $\pi_1 > \pi_0$
  - Design 1: $(\pi_0, \pi_1, \alpha, \beta, n_1) = (0.2, 0.4, 0.05, 0.1, 20)$
  - Design 2 : $(\pi_0, \pi_1, \alpha, \beta, n_1) = (0.4, 0.6, 0.05, 0.1, 22)$

Phase III trial design:

- Single-stage parallel-group RCT (`Halabi,2008`), testing
  - $H_0 : \pi_c = \pi_t$ vs $H_1 : \pi_c \neq \pi_t$,
  - Type I error rate α and target power $1 - \beta$.

Phase II estimation methods:

- Naïve (fixed-sample) maximum likelihood estimator
- Estimators proposed by `Nhacolo and Brannath (2018)`

Simulation runs: 5000 trials simulated, and for each another 5000 trials simulated to estimate adjustment factors.

Results: Adjustment factors

	Method 1				Method 2	
	f		ρ		ρ	
Est.	Mean	SD	Mean	SD	Mean	SD
$\hat{\pi}_{nml}$	0.951	0.034	1.591	0.367	1.731	0.393
$\hat{\pi}_{m1}$	0.982	0.047	1.406	0.348	1.513	0.356
$\hat{\pi}_{m2}$	0.983	0.048	1.414	0.371	1.526	0.385
$\hat{\pi}_{m2v2}$	0.980	0.057	1.427	0.382	1.548	0.409
$\hat{\pi}_{m3}$	0.983	0.047	1.413	0.369	1.524	0.382
$\hat{\pi}_{nml}$	0.966	0.017	1.591	0.320	1.706	0.308
$\hat{\pi}_{m1}$	0.984	0.026	1.405	0.320	1.492	0.311
$\hat{\pi}_{m2}$	0.984	0.026	1.411	0.339	1.502	0.333
$\hat{\pi}_{m2v2}$	0.982	0.034	1.450	0.394	1.572	0.416
$\hat{\pi}_{m3}$	0.985	0.026	1.409	0.336	1.499	0.330

Results: Power (p)

Target: 90%

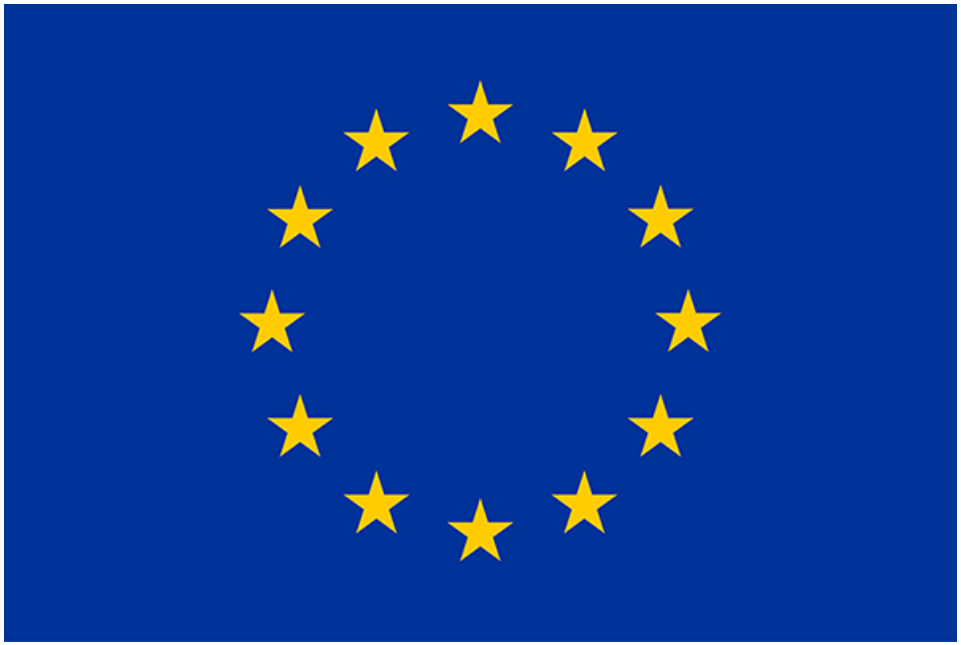
No adjustment		Method 1				Method 2	
$\mathfrak{p}[n(\hat{\pi}), \theta, \alpha]$		$\mathfrak{p}[n(f\hat{\pi}), \pi, \alpha]$		$\mathfrak{p}[\rho n(\hat{\pi}), \pi, \alpha]$		$\mathfrak{p}[\rho n(\hat{\pi}), \pi, \alpha]$	
Mea	Med	Mea	Med	Mea	Med	Mea	Med
77.8	84.1	80.7	88.7	85.2	95.0	86.6	96.6
82.1	90.6	81.4	91.6	85.9	96.3	87.3	97.4
82.3	89.9	81.5	90.7	85.9	95.9	87.3	97.2
81.3	87.5	80.4	89.0	85.1	94.5	86.7	96.0
82.3	89.4	81.4	90.2	85.9	95.6	87.3	97.0
78.8	86.2	82.5	91.2	86.2	96.2	87.5	97.6
82.2	90.5	82.6	92.3	86.3	96.4	87.5	97.4
82.5	90.0	82.7	91.7	86.4	96.1	87.6	97.3
80.3	86.6	80.3	89.2	84.4	94.3	86.0	96.0
82.4	89.8	82.7	91.6	86.4	96.0	87.6	97.2

*Target: 90%

Discussion

- “Discounting” the Phase II effect estimate is necessary regardless of the estimator.
- However, the estimators that take into account the adaptive nature of the designs require less “discounting”.
- Method 1 seems to attain the target only with respect to the median power.
- Method 2 is better, its mean power is closer to the target.
- The attained power similar across different estimation methods and design scenarios.

Acknowledgements



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Thank you!