Retrospective application of a Bayesian value-based sequential design to the HERO trial

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Introduction

- Value-based approaches to trial design explicitly weigh up the expected benefits of information gained from the trial against the costs of conducting it
- Value-based principles can be applied to adaptive trial designs – adaptations are informed by the expected net benefit of potential actions. Here we consider a value-based sequential design proposed by Chick et al. [1]
- The only existing application of this design is to data from the ProFHER trial [2], which suggested that it would have:
  - Reduced the sample size by 14% (saving 5% of the trial budget)
  - Reduced the expected sample size by 38% (saving 13% of the trial budget)
- The NIHR funded ENACT project further investigated the strengths and weaknesses of this design via retrospective applications to data from two trials – HERO (presented here) and Big CACTUS (see [3])
- HERO investigated the clinical and cost-effectiveness of hydroxychloroquine (HCQ) vs. placebo for hand osteoarthritis
  - 248 patients were individually randomised 1:1 between September 2012 and May 2014 [4]
  - Incremental costs and QALYs were close to zero – the trial concluded that HCQ is not cost effective [5]
  - 69% of patients had incomplete cost-effectiveness data – multiple imputation was used for the economic analyses
- We used data on HERO trial expenditure and cost-effectiveness over time (see Figure 1) to investigate;
  - Whether there was a stopping point during recruitment (A – B) where the expected monetary benefit of randomising another pair of patients was smaller than the costs
  - The expected increase in overall value delivered by the value-based sequential design over the original fixed design
  - The practicalities of applying this design to a trial with large amounts of incomplete cost-effectiveness data

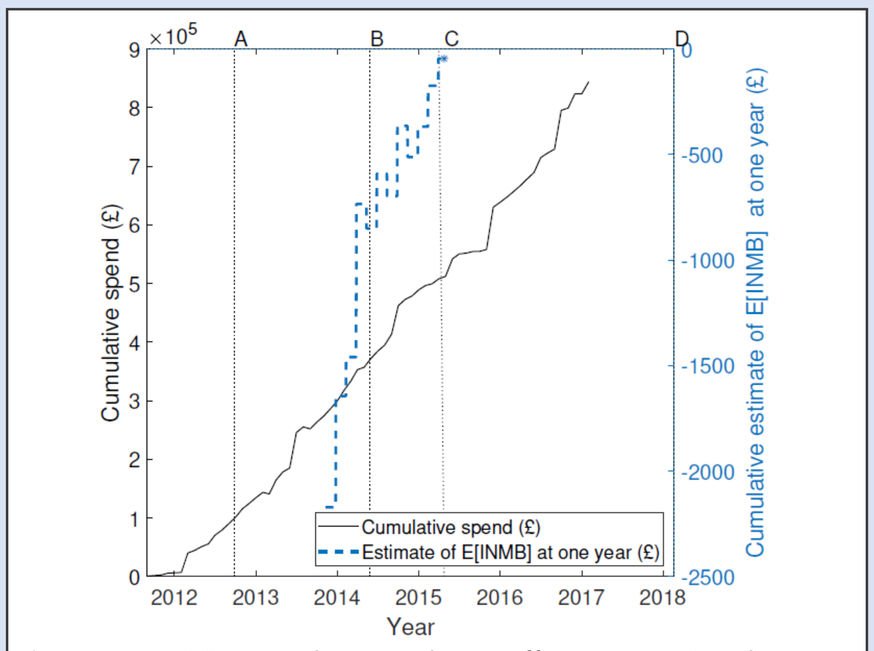

Figure 1: HERO expenditure and cost-effectiveness signal (expected incremental net monetary benefit - $\mathbb{E}$[INMB]) over time. A = Recruitment starts, B = Recruitment finishes, C = One year follow up finishes, D = Results published

Methods

The value-based sequential design

- Bayesian model of a two arm parallel group individually randomised trial
- Patients randomised in pairs to new or standard treatment up to a maximum of $T_{\max}$ pairs
- Cost effectiveness - $\mathbb{E}$[INMB] - observed with delay of $\tau \in \mathbb{Z}_{\geq 0}$ pairwise allocations
- Prior beliefs about $\mathbb{E}$[INMB] are updated as outcomes are observed (normal prior/likelihood)
- The design establishes a stopping boundary for Stage II that maximises the expected benefit resulting from the treatment adoption decision minus the costs of the trial

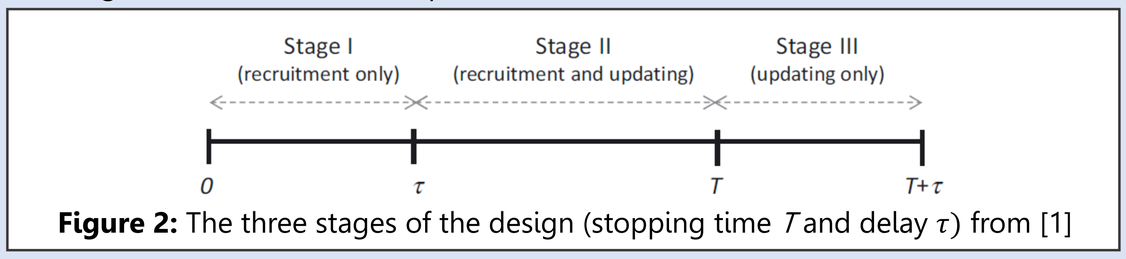

Figure 2: The three stages of the design (stopping time T and delay τ) from [1]

The HERO application

- HERO trial expenditure and cost-effectiveness data were used to retrospectively apply the value-based sequential design to HERO
  - Interim analyses every 10 pairs – estimates obtained using multiply imputed data
  - Cost-effectiveness signal (posterior mean of $\mathbb{E}$[INMB]) compared with the stopping boundary at each interim analysis
- Parameter values used in the application:
  - Size of population to benefit from adoption decision: 24,500 (2,450/year for 10 years)
  - Sampling standard deviation of INMB: £7,615 (estimated from trial data)
  - Prior mean for $\mathbb{E}$[INMB]: £0 (lack of a priori evidence favouring either treatment)
  - Sample size of prior: n_0 = 2 pairwise allocations (diffuse normal prior for $\mathbb{E}$[INMB])
  - Estimated cost per pairwise allocation: £1,650 (estimated from trial accounts)
  - Delay : τ = 1 year = 74 pairwise allocations
  - Maximum sample size: $T_{\max}$ = 124 pairwise allocations (equal to size of the original trial)
- Operating characteristics (e.g. expected sample size) investigated using resampling methods

Results

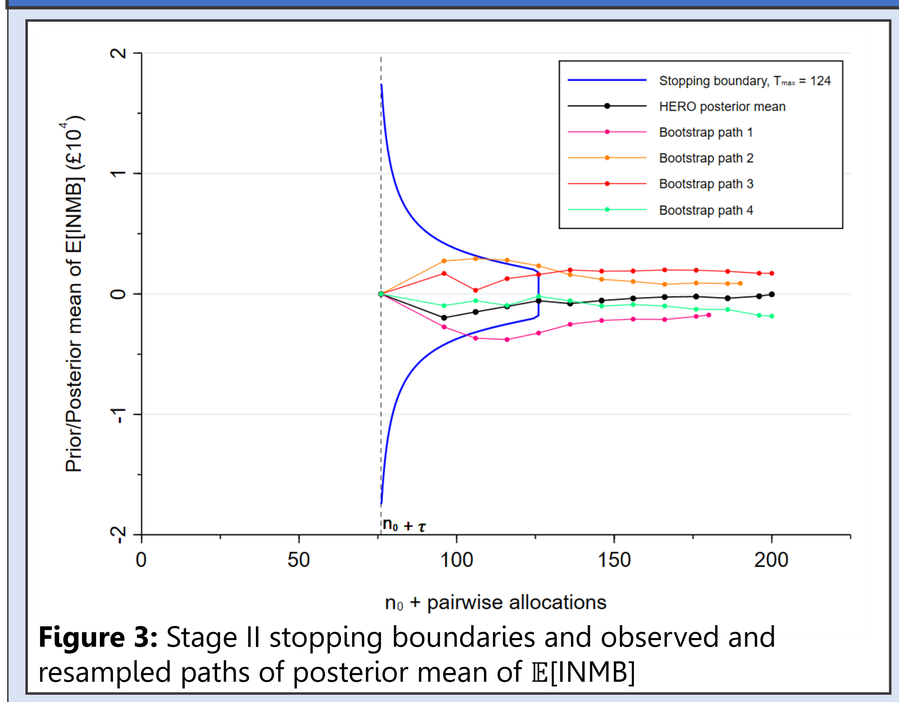

Figure 3: Stage II stopping boundaries and observed and resampled paths of posterior mean of $\mathbb{E}$[INMB]

- **Re-running the trial** - had it been run according to the value-based sequential design, the HERO trial would have:
  - Not stopped early
  - Concluded in favour of placebo – posterior mean of $\mathbb{E}$[INMB] = -£30
- **Expected performance of the design** - Only 151 (3%) of the resampled trials resulted in early stopping - expected sample size was only 0.4% smaller than the sample size of the original trial (Table 1)

	Mean	SD	Min.	Max.
Posterior mean of $\mathbb{E}$[INMB] (£) at end of stage III	-92.8	654.9	2817.3	2538.9
Total sample size recruited (pairwise allocations)	123.5	3.1	94	124
Mean (£) saving (% of total spend)	798.6 (0.1)			

Table 1: Final estimates of $\mathbb{E}$[INMB], overall sample size and cost savings for the 5000 resampled trials

- We estimate that this translates to a saving of approximately £800 (about 0.1% of the trial budget)
- Approximately 55% of the resampled trials resulted in a final estimate of $\mathbb{E}$[INMB] favouring placebo (see Table 2)

	HCQ	Placebo
Final decision	0.448	0.552

Table 2: Proportion of 5000 resampled trials favouring HCQ or placebo

Conclusions

- Value-based adaptive trial designs aim to identify cost-effective interventions via research and decision making processes that are themselves cost-effective.
- We present a further application of the value–based sequential design proposed by Chick et al. [1] to complement the previous application to the ProFHER trial
- For HERO, the value-based sequential approach would have delivered essentially no benefit over the fixed, non-value-based design
- The contrast in results between the HERO and ProFHER case studies show that the potential benefits of the value-based sequential approach vary considerably by application, depending on:
  - The strength of the cost-effectiveness signal
  - Time between randomisation and observation of cost-effectiveness outcomes relative to the length of the recruitment period
  - Cost of the trial relative to the overall expected value of the treatment adoption decision
- Trial teams could use this design to complement existing decision making strategies, particularly when:
  - Cost of sampling is high (in absolute terms or relative to the fixed costs of the trial)
  - Time between recruitment and observation of outcomes is relatively short compared with the total recruitment duration
  - A large difference in costs between the two treatments is expected a priori

References

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