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EXTENDING A BAYESIAN DECISION-THEORETIC APPROACH TO VALUE-BASED SEQUENTIAL CLINICAL TRIAL DESIGN

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ABSTRACT

Recent work has illustrated how Bayesian approaches to discrete simulation optimization can be applied to clinical trial design. These approaches balance the expected cost of running the trial with the expected economic benefits of adopting one of the treatments, based on the information which accumulates during the trial. Some work in this space has presented a model of a fully sequential trial, but with simplifying assumptions; other work has incorporated some special features of pragmatic clinical trials into a one-stage (that is, non-sequential) framework. This paper shows how simulation optimization ideas can be used to model fully sequential sampling for trials which contain these features.

1 INTRODUCTION

The link between ranking, selection and experimental design is well-established (e.g., Bechhofer 1954) and the ranking and selection literature has provided ideas which have proven useful in discrete optimization via simulation, or DOvS (Kim and Nelson 2006; Xu et al. 2010; Chick and Inoue 2001; Frazier et al. 2008; Branke and Schmidt 2004; Chen et al. 2010). Applying new ideas from simulation optimization to experimental design for clinical trials is therefore of interest.

In this paper, we first recall some recent applications of one version of DOvS for clinical trial design, based on a Bayesian expected value of information approach for sampling choices (Chick and Inoue 2001; Frazier et al. 2008). We then relax a number of the restrictive assumptions made in recent published work on fully sequential clinical trials (Chick et al. 2017), referencing work on a one-stage, i.e. non-sequential, Bayesian model (Alban et al. 2018) and some literature on what are termed 'pragmatic' clinical trials (Schwartz et al. 1961; Roland and Torgerson 1998). In a fully sequential trial, the sample size may be 'adapted' as data are observed; in a one-stage trial, the sample size is selected prior to collecting the data. We provide new results which show how some clinical trials may be run in a fully sequential manner, under the conditions identified below.

These extensions are proposed with a view to adapting simulation optimization research to reflect better some of the developing trends in delivering 'value-based health care'. At a conceptual level, the work is motivated by three important forces. Firstly, national health care budgets are placing greater emphasis on achieving value for money in their delivery systems. For example, the United Kingdom (NICE 2014) and France (HAS 2012), among other countries, now have guidelines for conducting cost-benefit analyses of new health technologies. And clinical trials for new technologies are a non-trivial part of health budgets: the cost of bringing a new molecular entity to market has passed an estimated US$1.7bil (Paul et al. 2014). Health technology assessments often use quality adjusted life year (QALY) and cost assessments (Gold et al. 1996) which are informed by the mathematical modeling techniques which are best suited to the

analysis in question (Brennan et al. 2006). We propose bringing mathematical tools further upstream, so as to improve the cost effectiveness of the trials themselves.

The second force is the push to *adaptive clinical trial design* (Pallmann et al. 2018). This seeks to adjust features of the trial dynamically as data become available, retaining good inferential properties about the effectiveness, or cost-effectiveness, of an intervention, while reducing the time and number of patients required to achieve that inference.

The third force is the push to *multi-arm clinical trials* (Wason et al. 2016; Villar and Rosenberger 2018). Restricting attention to two-arm designs which compare a new and existing health technology, when multiple technologies may be tested for the same condition, results in multiple trials with similar control arms. Comparing multiple new therapies with a single standard in one trial may reduce overall costs.

In earlier work, two of the coauthors of the present paper worked on a project which accounted for the first two of these forces. The result was a fully sequential clinical trial for comparing two arms in a way which jointly maximizes the net health benefit minus the costs of the trial and the adoption decision (Chick, Forster, and Pertile 2017, hereafter referred to as CFP). Some follow-on work resulted in highly-sequential, multiarm, trials which account for all three forces above, by modelling the simultaneous comparison of multiple, competing, new health technologies with a known standard. Trial designs explored include combinations of different, mutually compatible, treatments, as well as seamless phase II/phase III dose-finding trials, where different dose levels represent different arms. Preliminary work was presented at WSC (Yapar et al. 2016) and has resulted in a recently submitted paper (Chick et al. 2018).

In the present paper, we focus on the first two of the forces. We relax some assumptions in CFP to explore some of the practical issues which can arise in some pragmatic clinical trials. We reference the ProFHER trial (Handoll et al. 2015; Rangan et al. 2015; Corbacho et al. 2016; Handoll et al. 2017), a pragmatic, multi-site, randomised controlled trial funded by the United Kingdom National Institute for Health Research, which compared surgery and sling for the treatment of displaced fractures of the proximal humerus. Two features of the ProFHER trial are used to extend the literature discussed above:

1. The trial compared two health technologies – surgery and sling – which were both being used to treat the fractures of interest at the time the trial was commissioned. This differs from the situation which faces clinical trial design for a new drug which needs to pass the hurdles of efficacy and cost-effectiveness (as well as quality and safety) before approval.
2. The trial operated multiple sites, meaning that the rate of recruitment may also be a decision variable: lower recruitment rates require fewer trial sites, but delay the time to selecting an alternative.

In addition to incorporating these two features, we extend earlier work by valuing more fully the benefits accruing to trial and non-trial participants. Delayed decisions due to long trials may prevent such patients from benefiting from a better technology.

Alban et al. (2018) present a one-stage (non-sequential) model which accounts for these three practical issues. Their model seeks to maximize the expected net health benefit, minus trial costs, within a Bayesian expected value of information framework. Forster et al. (2018) present a detailed application of the theory presented here to the ProFHER trial. Below we first recall the key elements of the one-stage trial design model of Alban et al. (2018) before going on to show how this design may be extended to a fully-sequential trial in several interesting cases. Section 4 applies some of these techniques to the ProFHER trial.

2 MATH MODEL OF FIXED-LENGTH CLINICAL TRIAL

This section presents a variation on the model of Alban et al. (2018) for optimizing the duration and recruitment rate for a two-arm clinical trial. Pairs of patients are sampled and assigned to each of the two arms. The number of patient pairs is to be fixed before any patients are enrolled. We call the arms the standard arm, S, and new arm, N, for consistency with CFP. However, we do not necessarily consider the standard technology to be the current practice. Instead, we assume that a fraction of patients p_{N} is treated

with technology N in practice prior to the start of the trial. Thus, a fraction $1-p_{\mathrm{N}}$ is treated with S. Without loss of generality, we assume that $p_{\mathrm{N}} \in [0,1/2]$, because we can always relabel the standard and new technologies to satisfy this constraint. In Section 4, we explore two currently active choices, surgery (N) and sling (S), to treat displaced proximal humeral fracture.

The goal of the trial is to assess which of the two technologies should be used to treat patients once the trial concludes. At the end of the trial, an adoption decision is made to stay with the current mix, switch everybody to treatment S, or switch everybody to treatment N. Define the adoption decision $\mathscr{D} \in \{\mathrm{S},\mathrm{N},\mathrm{M}\}$, where M means that the decision is to continue with current practice of a mix of the two technologies.

Following CFP and other literature (e.g., Jackson et al. 2010), we use the incremental net monetary benefit (INMB) as the outcome, X_i, of pairwise allocation, i. Denote the effectiveness of the two technologies by the random variables $E_{\mathrm{N}} \in \mathbb{R}$ (for the new technology) and $E_{\mathrm{S}} \in \mathbb{R}$ (for the standard) and define the patient-level costs of using the technologies as the random variables $C_{\mathrm{N}}, C_{\mathrm{S}} \in \mathbb{R}$. The INMB for pairwise allocation i is

$$X_i = \lambda(E_{\mathrm{N},i} - E_{\mathrm{S},i}) - (C_{\mathrm{N},i} - C_{\mathrm{S},i}), \tag{1}$$

where $\lambda > 0$ is the monetary value of one unit of effectiveness. It is assumed that $X_i \mid W \overset{\text{i.i.d.}}{\sim} \mathscr{N}(W, \sigma_X^2)$, $i = 1,2,\ldots,Q_{\max}$, where $Q_{\max}$ is the maximum number of pairwise allocations that can be made in the trial, σ_X^2 is the known sampling variance, and W is the sampling mean, which is assumed to have a $\mathscr{N}(\mu_0, \sigma_0^2)$ prior distribution. We define $n_0 = \sigma_X^2/\sigma_0^2$ as the effective sample size of the prior distribution and denote the information set at the start of the trial by $K_0 = (\mu_0, n_0)$.

We consider the length of the trial in time units instead of the number of patients. We let $\zeta > 0$ be the annual incidence rate of the condition and let $r \in [0, r_{\max}]$ be the annual rate of recruitment to each arm of the trial, where $r_{\max} \in (0, \zeta/2]$ is the maximum possible rate of recruitment which depends on the number of recruitment sites, s. Let T be the recruitment period duration (in years), so that there are $Q = rT$ pairwise allocations, which requires $2rT$ enrolled patients. We assume that r and T are continuous for purposes of analysis, but we will round Q as necessary for implementation.

As the trial progresses, realisations of X arrive with a delay of $\Delta \geq 0$ units of time and are used to update the prior distribution of W. We require that the outcomes of all patients recruited to the trial be observed before the adoption decision may be made. The adoption decision is made at time $T + \Delta$ if $T > 0$ and is done with immediate effect. If there is no trial, then $T = 0$ and the adoption decision is assumed to take immediate effect at time 0. Further assume that the adoption decision has to be made at, or before, a time horizon $H > \Delta$, so that $T \in [0, H - \Delta]$ and $Q_{\max} = \lfloor r_{\max}(H - \Delta) \rfloor$.

We consider two types of learning: 'online' and 'offline'. Online learning takes into account the health benefits to patients during the trial period while offline learning ignores them. We define δ_{on} to be 1 for online learning, and 0 for offline learning. Online learning in simulation optimization and in web-based machine learning applications usually accounts only for outcomes from sampled participants, i.e. it assumes that the recruitment rate and the incidence rate are the same. Our online learning approach additionally accounts for non-participants during the trial and waiting period in addition to the trial participants (see e.g., Eckermann and Willan (2007)).

We assume that $P(T)$ patients will benefit from the trial adoption decision. We allow $P(T)$ to be a function of T to capture different settings of the adoption decision type. Alban et al. (2018) analyse two special cases:

1. 'Market exclusivity': this represents the case in which $P(T) = P$, so that a fixed number of patients will be treated post-adoption. The term originates from the granting of exclusive rights to market a drug post-authorisation (see e.g., FDA 2015), but we use it in a more general sense to refer to situations in which there exists a fixed patient population to be treated post-adoption (for example, when a regulator approves a health technology for a defined period post-authorisation and prior to updating evidence).

2. 'Patent protection': this represents the case in which a patent protection agreement is guaranteed for a fixed time horizon H, during which time the trial is run and the adoption decision is implemented; we let $P(T) = \zeta(H - T - \mathbf{1}_{T>0}\Delta)$. As FDA (2015) explains, patent protection may be applied for at any time during the development process of a new drug. Our use of the term is more restrictive, in that the protection is assumed to apply over the interval $[0,H]$.

With this framework, we model the health outcomes and treatment costs of four types of patients: (1) patients who are recruited to the trial during the time interval $[0,T]$; (2) patients who do not participate in the trial during this recruitment; (3) patients needing care after the end of the recruitment period but prior to an adoption decision, during the waiting period $[T,T+\Delta]$; (4) patients treated after the adoption decision. The number of patients of types (1)–(3) are the same for both market exclusivity and for patent protection. The number of patients, $P(T)$, of type (4) is constant for market exclusivity but depends on T for patent protection.

Define $I_{\mathscr{D}}$ as the total switching cost for each decision, where $I_{\mathrm{M}} = 0$, because continuing with current practice incurs no switching cost and $I_{\mathrm{N}}, I_{\mathrm{S}} \geq 0$ are the total fixed costs of switching practice to N or S, respectively (these could reflect retraining costs, or costs of communicating the decision).

Assume that the costs of the trial are given by a cost per patient recruited c, as well as a cost $c_{\mathrm{cap}}(r_{\max})$ which is nondecreasing in $r_{\max}$. We assume $c_{\mathrm{cap}}(r_{\max})$ is piecewise continuous, with the possibility of jumps at points where an additional site might be needed to achieve a given capacity. For example, if 10 patients per unit time can be entered into a trial at a given site, then one model might be $c_{\mathrm{cap}}(r_{\max}) = c_{\mathrm{fixed}} + c_{\mathrm{site}} s$, where c_{fixed} is the fixed cost of running a trial, $s = \lceil r_{\max}/10 \rceil$ is the number of sites required to recruit patient pairs at rate $r_{\max}$, and c_{site} is a fixed cost per site.

Define the expected total net benefit as the sum of patient health benefits minus the costs of running the trial. Let W_{N} and W_{S} be the expected monetary benefit of treating a patient with N and S, respectively, that is $W_{\mathrm{N}} = \mathbb{E}[\lambda E_{\mathrm{N}} - C_{\mathrm{N}}]$ and $W_{\mathrm{S}} = \mathbb{E}[\lambda E_{\mathrm{S}} - C_{\mathrm{S}}]$, so that $W = W_{\mathrm{N}} - W_{\mathrm{S}}$. We also define the expected net monetary benefit for the current mix as $W_{\mathrm{M}} = p_{\mathrm{N}} W_{\mathrm{N}} + (1 - p_{\mathrm{N}}) W_{\mathrm{S}}$.

Alban et al. (2018) assume that T will be chosen prior to the start of the trial (a so-called 'one-shot' trial). Let $\bar{V}(T,r;K_0)$ be the expected total net benefit for a trial with recruitment period duration T and recruitment rate r given the initial beliefs K_0. We assume that, if $T = 0$ or $r = 0$, the trial is not run and the option with the largest expected net benefit is chosen. For the case in which costs and benefits are not discounted:

$$\bar{V}(T,0;K_0) = \bar{V}(0,r;K_0) = \max_{\mathscr{D} \in \{\mathrm{M,N,S}\}} \{\mathbb{E}[P(0) W_{\mathscr{D}} - I_{\mathscr{D}} \mid K_0]\}.$$

For given fixed $T > 0$ and $r > 0$, the expected total net benefit is

$$\begin{aligned} \bar{V}(T,r;K_0) \quad = \quad & -\underbrace{(c_{\mathrm{cap}}(r_{\max}) + 2crT)}_{\text{trial costs}} + \underbrace{\delta_{\mathrm{on}} rT \mathbb{E}[W_{\mathrm{N}} + W_{\mathrm{S}} \mid K_0]}_{\text{trial participants}} \\ & + \underbrace{\delta_{\mathrm{on}}(\zeta - 2r) T \mathbb{E}[W_{\mathrm{M}} \mid K_0]}_{\text{non-participants during trial period}} + \underbrace{\delta_{\mathrm{on}} \zeta \Delta \mathbb{E}[W_{\mathrm{M}} \mid K_0]}_{\text{current practice during } (T,T+\Delta]} + \underbrace{\mathbb{E}[(P(T) W_{\mathscr{D}} - I_{\mathscr{D}}) \mid K_0]}_{\text{post-decision}}. \end{aligned} \tag{2}$$

Instead of maximising the expected total net benefit $\bar{V}$, we will maximise the expected net gain, V, defined as the difference between $\bar{V}(T,r;K_0)$ and the expected benefits of continuing to implement the current mix for all patients, $\zeta(\delta_{\mathrm{on}} T + \mathbf{1}_{T>0}\Delta)\mathbb{E}[W_{\mathrm{M}} \mid K_0]$. This definition of expected net gain differs from the one given by Raiffa and Schlaifer (1961) who define the expected net gain with sampling before selecting, here $\bar{V}(T,r;K_0)$, and adopting the optimal decision without collecting information, $\bar{V}(0,0;K_0)$.

If $T = 0$ or $r = 0$, the expected net gain (relative to retaining the current mix) is the maximum increment in expected reward of immediately selecting the current mix, or switching to N, or switching to S:

$$V(T,0;K_0) = V(0,r;K_0) = \max\{0, \mathbb{E}[(1 - p_{\mathrm{N}}) P(0) W - I_{\mathrm{N}} \mid K_0], \mathbb{E}[-p_{\mathrm{N}} P(0) W - I_{\mathrm{S}} \mid K_0]\}. \tag{3}$$

For $T > 0$ and $r > 0$, and for this case of no time discounting, we get

$$V(T,r;K_0) = -\underbrace{(c_{\text{cap}}(r_{\max}) + 2crT)}_{\text{trial cost}} + \underbrace{\delta_{\text{on}} rT(1-2p_{\text{N}})\mathbb{E}[W \mid K_0]}_{\text{trial participants}} + \underbrace{\mathbb{E}[\mathbf{1}_{\mathscr{D}=\text{N}}((1-p_{\text{N}})P(T)W - I_{\text{N}}) + \mathbf{1}_{\mathscr{D}=\text{S}}(-p_{\text{N}}P(T)W - I_{\text{S}}) \mid K_0]}_{\text{post-decision}}. \tag{4}$$

The benefits to non-participants and patients treated in the waiting period do not appear in Eq. (4) as they are treated the same with or without trial. However, they are still accounted for by the function $P(T)$: a decreasing $P(T)$ reduces the number patients that benefit from the adoption decision of the trial, which can be interpreted as the losses due to non-participants not being able to benefit from the adoption decision.

In some applications, we may wish to allow for a discount factor. For example, the UK's National Institute for Health and Care Excellence (NICE) may use an annual discount factor of 3.5%. To model discounted rewards, we first introduce some additional notation. We define $\tau = \lceil r\Delta \rceil$ as the delay as measured by the number of pairwise allocations (equal to the number of decision epochs). (We may relax integrality and consider real valued $\tau = r\Delta$ when derivatives are needed). We let $\rho_{\text{year}} \geq 0$ be the annual discount rate (e.g., $\rho_{\text{year}} = 0.035$ for UK NICE; and $\rho_{\text{year}} = 0$ if no discounting is desired). Then the discount rate over the time between patient pairs is $\tilde{\rho} = (1+\rho_{\text{year}})^{1/r} - 1$ (T is measured in years). We now define the time-discounted number of patient pairs as $Q_{\tilde{\rho}} = Q = rT$ if the discount rate is 0, and as $Q_{\tilde{\rho}} = 1 + (1+\tilde{\rho})^{-1} + \ldots + (1+\tilde{\rho})^{-(Q-1)} = (1-(1+\tilde{\rho})^{-Q})(1+\tilde{\rho})/\tilde{\rho}$ if the discount rate exceeds 0. We also adapt the post-trial effective number of patients. If $\tilde{\rho} = 0$, $P_{\tilde{\rho}}(T) = P(T)$ as above for the cases of market exclusivity and patent protection as described above. If $\tilde{\rho} > 0$ and we assume that all $P(T)$ patients arrive with constant incidence rate ζ in the interval $[T+\Delta, T+\Delta+P/\zeta]$, we have a post-trial effective number of patients $P_{\tilde{\rho}}(T) = (\zeta/r)(1-(1+\tilde{\rho})^{-r(H-T-\Delta)})(1+\tilde{\rho})/\tilde{\rho}$ for patent protection, and $P_{\tilde{\rho}}(T) = (\zeta/r)(1-(1+\tilde{\rho})^{-rP/\zeta})(1+\tilde{\rho})/\tilde{\rho}$ for market exclusivity.

With this notation we can generalize Eq. (4) to also account for discounted rewards when $T, r > 0$:

$$\begin{aligned} V(T,r;K_0) \;=\; & -(c_{\text{cap}}(r_{\max}) + 2cQ_{\tilde{\rho}}) + \delta_{\text{on}} Q_{\tilde{\rho}}(1-2p_{\text{N}})\mathbb{E}[W \mid K_0] \\ & + \mathbb{E}\left[\left(\frac{1}{1+\tilde{\rho}}\right)^{Q+\tau}\left(\mathbf{1}_{\mathscr{D}=\text{N}}((1-p_{\text{N}})P_{\tilde{\rho}}(T)W - I_{\text{N}}) + \mathbf{1}_{\mathscr{D}=\text{S}}(-p_{\text{N}}P_{\tilde{\rho}}(T)W - I_{\text{S}})\right) \middle| K_0\right]. \end{aligned} \tag{5}$$

The objective here is to maximise the expected net gain, $V(T,r;K_0)$, defined in Eq. (3) and Eq. (5), by finding an optimal trial design given by the optimal recruitment rate and duration, (r^*, T^*):

$$\begin{aligned} \sup_{T,r} \quad & V(T,r;K_0) \\ \text{s.t.} \quad & T \in [0, H-\Delta], r \in [0, r_{\max}] \end{aligned} \tag{6}$$

Although the number of sites is a decision variable, we assume for this paper that $r_{\max}$ and s are fixed, and that we might also optimize over $r_{\max}$ in applications.

3 WHEN CAN THE TRIAL BE RUN SEQUENTIALLY?

In this section we formulate the sequential version of the problem in Eq. (6), presenting three special cases for which it can be solved using the methods presented in CFP. Alban et al. (2018) show that, assuming that r is fixed and can not be adapted during the trial, it is optimal to select $r = r_{\max}$. In this section, we therefore fix the number of sites at s and assume that the recruitment rate, r, is fixed at $r_{\max}$. We assume that neither s nor r may be adjusted during the course of the sequential trial. We allow the length of the trial to be extended or shortened as outcomes are observed.

3.1 The Sequential Problem as a Stopping Problem

To formulate the sequential version of the problem in Eq. (6), we define the decision epochs and actions. It is natural to define every patient pair allocation time/arrival time as a decision epoch. The decision epochs are therefore $t = 0, \ldots, Q_{\max} - 1$ such that, at each epoch, action a_t is chosen from the action space $\mathscr{A}_t = \{0,1\}$ so that we either make another pairwise allocation ($a_t = 1$) or stop recruitment ($a_t = 0$). We assume that it is not possible to stop recruitment for a few epochs and then restart it (allowing for this possibility would make the recruitment rate a decision variable) so that, once recruitment has stopped, the outcomes for all patients in the pipeline are observed prior to an adoption decision being made.

To clarify, we are using t to index decision epochs, at each patient pair, in this section, rather than measuring time. The recruitment period duration of a one-shot trial will continue to be called T. The possibly random number of patient pairs Q is determined by the actions at the decision epochs, with $Q = \min\{Q_{\max}\} \cup \{t : a_t = 0\}$ for each sample path.

Beliefs are updated as new information, in the form of outcome data, arrives. By the normality assumptions in Section 2 and Bayes' rule, the posterior mean, μ_t, and the effective number of samples, n_t, are sufficient statistics for the posterior distribution of W:

$$\mu_t = \frac{n_0\mu_0 + \sum_{i=1}^{(t-\tau)^+} X_i}{n_0 + (t-\tau)^+}, \qquad n_t = n_0 + (t-\tau)^+,$$

where $(m)^+ = \max(0,m)$. Because we can obtain the effective number of samples from t, we let the state at epoch t, K_t, be defined by $K_t = (\mu_t, t)$ which is still sufficient for the posterior distribution of W. This definition of state also allows us to track the number of patients in the pipeline for epochs $t = 0, 1, \ldots, \tau$.

Let $\pi \in \Pi$ be the policy that maps each state to available actions and the adoption decision, where Π is the set of valid (nonanticipative) policies. At each epoch t, π determines whether sampling should continue, or whether it should stop, so that a decision is made at epoch $t + \tau$ (or time $t/r + \Delta$). We can formulate the expected net gain of such a trial as follows:

$$\begin{aligned} V(\pi; K_0) \quad = \quad & -\mathbf{1}_{a_0=1} c_{\text{cap}}(r_{\max}) + \mathbb{E}_\pi \left[\sum_{t=0}^{Q-1} \frac{\delta_{\text{on}}(1-2p_{\text{N}})X_{t+1} - 2c}{(1+\tilde{\rho})^t} \,\middle|\, K_0 \right] \\ & + \mathbb{E}_\pi \left[\frac{\mathbf{1}_{\mathscr{D}=\text{N}}((1-p_{\text{N}})P_{\tilde{\rho}}(Q/r)W - I_{\text{N}}) + \mathbf{1}_{\mathscr{D}=\text{S}}(-p_{\text{N}}P_{\tilde{\rho}}(Q/r)W - I_{\text{S}})}{(1+\tilde{\rho})^{\mathbf{1}_{Q>0}(Q+\tau)}} \,\middle|\, K_0 \right], \end{aligned} \tag{7}$$

where $\mathbb{E}_\pi[\cdot]$ is the expectation induced by policy π, which in turn determines the stopping epoch Q. The objective is now to assess the existence and nature of an optimal policy, π^*, that maximises Eq. (7).

3.1.1 Recollection of Value Function from CFP

In our analysis, we would like to see if there are interesting special cases for which the identification of the optimal policy, π^*, to maximize Eq. (7) can be done by reducing the problem to a form consistent with the formulation of CFP. For such cases, there exists an optimal non-anticipative policy which satisfies an associated Bellman's equation (Chick et al. 2017). We therefore recall the value function for CFP's model. Using the notation of this paper, the value function of CFP is

$$V^\pi(K_0) = \mathbb{E}_\pi \left[\left\{ \sum_{t=0}^{Q-1} \frac{-c + \delta_{\text{on}} X_{t+1}}{(1+\tilde{\rho})^t} \right\} + \frac{\mathbf{1}_{\mathscr{D}=\text{N}}(P_{\tilde{\rho}}(Q/r)W - I)}{(1+\tilde{\rho})^{\mathbf{1}_{Q>0}(Q+\tau)}} \,\middle|\, K_0 \right]. \tag{8}$$

The first term in the expectation represents the cost of sampling plus rewards (if any) associated with online learning as patient outcomes are observed. The second term in the expectation represents the INMB of the adoption decision, net fixed costs of implementing the alternative selected as best. The term $\mathbf{1}_{Q>0}(Q+\tau)$

indicates that a penalty for discounting is only relevant for the terminal reward if at least one pairwise allocation is made. CFP assumed the case of no discounting and market exclusivity, with $P_{\tilde{\rho}}(T) = P$ in the main paper and some extensions in the appendix.

3.1.2 Bellman Equations of the Stopping Problem

The existence of an optimal policy for Eq. (7) can be assessed via the Bellman equation even for special cases which do not reduce the problem to the form in Eq. (8). We let $Z_{t,u}$ be the expected posterior mean of W, given the information at epoch t and u patients in the pipeline to be observed:

$$Z_{t,u} = \mathbb{E}\left[W \mid K_t, X_{t-u+1}, X_{t-u+2}, \ldots, X_t\right].$$

It is easy to check that $Z_{t,u} \sim \mathcal{N}(\mu_t, \sigma_X^2 u/n_t(n_t+u))$. The terminal reward is the expected reward when sampling stops and an alternative is selected, and for Eq. (7) is given by:

$$G_t(K_t) = \mathbb{E}\left[\mathbf{1}_{\mathscr{D}=\mathrm{N}}((1-p_\mathrm{N})P_{\tilde{\rho}}(t/r)Z_{t,\min\{\tau,t\}} - I_\mathrm{N}) + \mathbf{1}_{\mathscr{D}=\mathrm{S}}(-p_\mathrm{N}P_{\tilde{\rho}}(t/r)Z_{t,\min\{\tau,t\}} - I_\mathrm{S}) \mid K_t\right] / (1+\tilde{\rho})^{\mathbf{1}_{t>0}\tau}$$

for $t = 0, 1, \ldots, Q_{\max}$. Bellman's equation is given by:

$$B_t(K_t) = \max\{G_t(K_t), \delta_{\mathrm{on}}(1-2p_\mathrm{N})\mu_t - 2c + (1+\tilde{\rho})^{-1}\mathbb{E}_\pi\left[B_{t+1}(\mu_{t+1}) \mid K_t\right]\}, \quad \text{for } t = 0, 1, \ldots, Q_{\max}-1,$$
$$B_{Q_{\max}}(K_{Q_{\max}}) = G_{Q_{\max}}(K_{Q_{\max}}).$$

When $G_t(K_t)$ exceeds the second term in the maximization for $B_t(K_t)$, Bellman's equation says to stop at epoch t, wait for the observations on the pipeline patients to arrive, and then implement the best of $(\mathrm{S}, \mathrm{N}, \mathrm{M})$ depending on which adoption decision gives the best reward. Otherwise, Bellman's equation says to continue sampling the next patient pair and reevaluate the choice to stop or to continue.

3.2 The Stopping Problem Simplified to the Model of CFP

We describe the three special cases in which the sequential formulation simplifies to the problem presented in CFP. Such a simplification means that the algorithms from that paper can be applied to provide a fully sequential algorithm for the special cases considered here. Henceforth, we ignore the costs of capacity, which are fixed constants once $r_{\max}$ is selected. One might optimize over values of $r_{\max}$ as an extra level of optimization. The costs of capacity do not influence the optimal stopping time once the trial is determined to run. The decision to carry out the trial is made once the design is optimized and the value of the trial can be computed.

With these assumptions, we can rewrite Eq. (7) as follows:

$$\begin{aligned} V(\pi; K_0) &= \mathbb{E}_\pi\left[\sum_{t=0}^{Q-1} \frac{\delta_{\mathrm{on}}(1-2p_\mathrm{N})X_{t+1} - 2c}{(1+\tilde{\rho})^t}\,\Big|\, K_0\right] \\ &\quad + \mathbb{E}_\pi\left[\frac{\mathbf{1}_{\mathscr{D}=\mathrm{N}}((1-p_\mathrm{N})P_{\tilde{\rho}}(Q/r)W - I_\mathrm{N}) + \mathbf{1}_{\mathscr{D}=\mathrm{S}}(-p_\mathrm{N}P_{\tilde{\rho}}(Q/r)W - I_\mathrm{S})}{(1+\tilde{\rho})^{\mathbf{1}_{Q>0}(Q+\tau)}}\Big| K_0\right]. \end{aligned} \tag{9}$$

In our conversion of the one-shot trial to a fully sequential trial, we retain the notation $P_{\tilde{\rho}}(Q/r)$ to allow for both market exclusivity and patent protection where possible. That said, to take advantage of the computations of CFP we require market exclusivity, with a fixed $P_{\tilde{\rho}}(Q/r) = P$.

3.2.1 Current Practice is the Standard Treatment

If the current practice is the standard treatment, then $p_\mathrm{N} = 0$ and there is no fixed cost associated with switching to the current practice, $I_\mathrm{S} = 0$, and Eq. (9) simplifies to:

$$V(\pi; K_0) = \mathbb{E}_\pi\left[\sum_{t=0}^{Q-1} \frac{\delta_{\mathrm{on}}X_{t+1} - 2c}{(1+\tilde{\rho})^t} + \frac{\mathbf{1}_{\mathscr{D}=\mathrm{N}}(P_{\tilde{\rho}}(Q/r)W - I_\mathrm{N})}{(1+\tilde{\rho})^{\mathbf{1}_{Q>0}(Q+\tau)}}\Big| K_0\right].$$

If we let $c' = 2c$, $P' = P_{\tilde{\rho}}(Q/r)$, and $I' = I_{\mathrm{N}}$, then this objective function is in the form of Eq. (8). It is therefore solvable with the sequential trial methods of CFP if $P_{\tilde{\rho}}(Q/r) = P$ is constant.

3.2.2 Force the Decision to Adopt One of the Two Technologies

Suppose that the mix of treatments is not an available adoption decision, so that $\mathscr{D} \in \{\mathrm{N}, \mathrm{S}\}$. Suppose too that $P_{\tilde{\rho}}(Q/r) = P$. Then $\mathbf{1}_{\mathscr{D}=\mathrm{S}} = 1 - \mathbf{1}_{\mathscr{D}=\mathrm{N}}$ and Eq. (9) becomes:

$$V(\pi; K_0) = \mathbb{E}_\pi \left[\sum_{t=0}^{Q-1} \frac{\delta_{\mathrm{on}}(1-2p_{\mathrm{N}})X_{t+1} - 2c}{(1+\tilde{\rho})^t} + \frac{\mathbf{1}_{\mathscr{D}=\mathrm{N}}(PW - (I_{\mathrm{N}} - I_{\mathrm{S}}))}{(1+\tilde{\rho})^{\mathbf{1}_{Q>0}(Q+\tau)}} \Big| K_0 \right] - p_{\mathrm{N}} P \mu_0 - I_{\mathrm{S}}. \tag{10}$$

We have used the facts that $\mathbb{E}_\pi[W \mid K_0] = \mu_0$ and that $P_{\tilde{\rho}}(Q/r)$ is constant with market exclusivity.

If $p_{\mathrm{N}} < 1/2$, then we can divide through by $1 - 2p_{\mathrm{N}}$. Further, adding the constant $P p_{\mathrm{N}} \mu_0 - I_{\mathrm{S}}$ does not change the optimal π to maximize Eq. (10). We thus seek π to maximize:

$$\mathbb{E}_\pi \left[\sum_{t=0}^{Q-1} \frac{\delta_{\mathrm{on}} X_{t+1} - \frac{2c}{1-2p_{\mathrm{N}}}}{(1+\tilde{\rho})^t} + \frac{\mathbf{1}_{\mathscr{D}=\mathrm{N}} \left(\frac{P}{1-2p_{\mathrm{N}}} W - \frac{I_{\mathrm{N}} - I_{\mathrm{S}}}{1-2p_{\mathrm{N}}} \right)}{(1+\tilde{\rho})^{\mathbf{1}_{Q>0}(Q+\tau)}} \Bigg| K_0 \right], \tag{11}$$

which is in the form of the objective in CFP when we let $c' = 2c/(1-2p_{\mathrm{N}})$, $P' = P/(1-2p_{\mathrm{N}})$, and $I' = (I_{\mathrm{N}} - I_{\mathrm{S}})/(1-2p_{\mathrm{N}})$. We can multiply the maximum of Eq. (11) with $1-2p_{\mathrm{N}}$ and add $-P p_{\mathrm{N}} \mu_0 - I_{\mathrm{S}}$ to obtain $\max_{\pi \in \Pi} V(\pi; K_0)$.

If $p_{\mathrm{N}} = 1/2$, we seek π to maximize

$$\mathbb{E}_\pi \left[\sum_{t=0}^{Q-1} \frac{-2c}{(1+\tilde{\rho})^t} + \frac{\mathbf{1}_{\mathscr{D}=\mathrm{N}}(PW - (I_{\mathrm{N}} - I_{\mathrm{S}}))}{(1+\tilde{\rho})^{\mathbf{1}_{Q>0}(Q+\tau)}} \Big| \mu_0 \right], \tag{12}$$

which is the same problem solved in CFP when $c' = 2c$, $P' = P$, and $I' = I_{\mathrm{N}} - I_{\mathrm{S}}$. By adding $-P p_{\mathrm{N}} \mu_0 - I_{\mathrm{S}}$ to the maximum of Eq. (12) we obtain $\max_{\pi \in \Pi} V(\pi; K_0)$.

If $I_{\mathrm{N}} < I_{\mathrm{S}}$ then I' is negative, while CFP have assumed that I' is nonnegative. The assumption of $I' \geq 0$ does not seem to be needed in their derivation. Thus, the methods in CFP are applicable here.

3.2.3 No Switching Costs

Suppose that both treatments have no switching costs, i.e. $I_{\mathrm{N}} = I_{\mathrm{S}} = 0$. In this case, adopting the better of N and S is at least as good as adopting the mix of treatments M. Therefore, we can restrict the adoption decision to either N or S and use the formulation of forcing the decision to be N or S. Thus, we can use the transformation in Section 3.2.2 to obtain a fully sequential trial, and can solve it using the techniques of CFP for the case of market exclusivity.

4 APPLICATION TO PROFHER TRIAL

We illustrate the above methods using the ProFHER trial. This investigated the use of surgery (N) versus sling (S) to treat patients with a displaced proximal humeral fracture. Details of the clinical and economic analysis may be found in Handoll et al. (2015), Rangan et al. (2015), Corbacho et al. (2016) and Handoll et al. (2017). Forster et al. (2018) examine the practicalities of implementing the Bayesian sequential design in the ProFHER trial, and discuss how statistics from the trial inform parameter values.

The following parameter values are used for the present application: $\delta_{\mathrm{on}} = 0$, $r_{\max} = r = 47$/yr, $p_{\mathrm{N}} = 0.39$, $\mu_0 = £0$, $n_0 = 2$, $Q_{\max} = 250$ $H = Q_{\max}/r_{\max} + \Delta = 6.32$yr, $\zeta = 7{,}000$/yr, $\Delta = 1$yr, annual discount rate of $\rho_{\mathrm{year}} = 0.035$ for a discount rate of $\tilde{\rho} = (1+\rho_{\mathrm{year}})^{(1/r)} - 1 = 7.322 \times 10^{-4}$ per patient pair, market exclusivity with $P = 42{,}000$ and $P_{\tilde{\rho}}(T) = 37{,}963$, $\sigma_X = £4{,}400$, $I_{\mathrm{N}} = £0$, $I_{\mathrm{S}} = £0$ and $c = £1{,}600$.

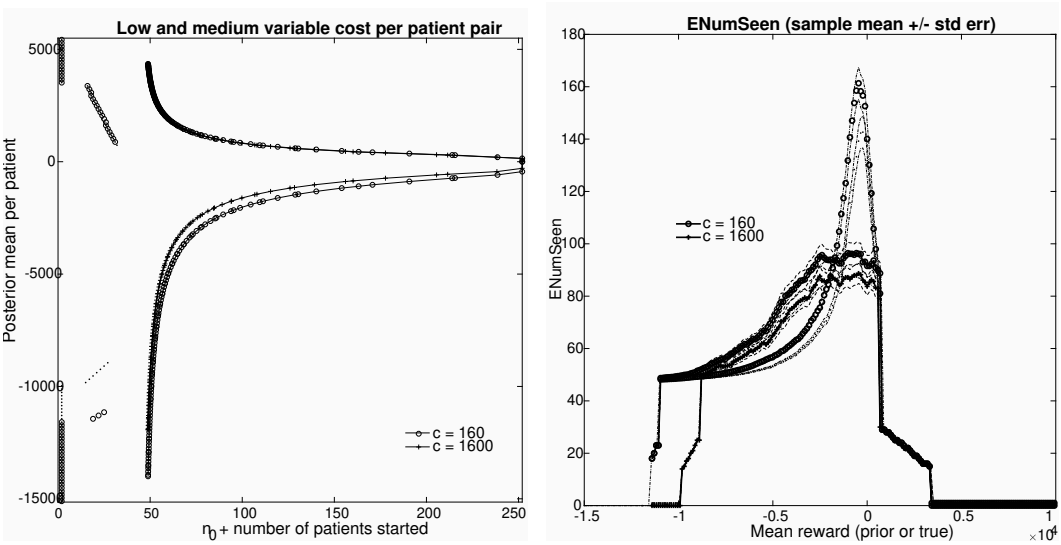

Figure 1: Stopping boundaries (left panel) and expected number of samples (right panel) for the new trials.

Figure 1 displays some operating characteristics for the fully sequential trial. The left panel displays the optimal stopping boundaries as a function of the posterior mean μ_t (vertical axis) and the effective number of samples in the prior plus the number of patient pairs started, $n_0 + t$ (horizontal axis). We look first at the circles, which correspond to $c = £1,600$ per patient. If the prior mean μ_0 is left of the vertical circles at $n_0 = 2$ on the horizontal axis, it is optimal to not run any trial and instead immediately select the better alternative on the basis of μ_0. For $\mu_0 > 3000$ it is optimal to immediately select N, and for $\mu_0 < -12000$ it is optimal to select S. In the range between $n_0 = 2$ and $n_0 + \tau = 50$, we see additional circles: for values of μ_0 corresponding to the points in that range, it is optimal to run fewer than τ samples, wait for the samples to be observed, then select the best alternative. For values of μ_0 in between those regions, in the range $\mu_0 \in -11500, 1000$, it is optimal to run a sequential trial with at least τ samples. In this case, the first observations start to arrive at $n_0 + \tau = 49$, after which the prior/posterior mean is updated. If the posterior mean hits the upper or lower boundary, the trial stops, the remaining observations are collected, and the 'better' option (N or S) is selected. The other boundaries, with dots and '+' signs, correspond to a lower cost of $c = £160$ per patient. The lower sampling cost leads to a wider 'continuation region' (the area between the two boundaries) and which encourages more sampling. Graphs not shown indicate that a decrease in the discount rate ρ_{year} results in the upper stopping boundary increasing.

The right panel of Figure 1 displays results from four separate Monte Carlo simulations. Once more, simulations were run assuming $c = £1,600$ and $c = £160$. The 'jumps' in the graph in the right panel correspond to the points in the left panel which demarcate whether no trial, a fixed duration recruitment period of less than τ samples or a fully sequential trial, is optimal. The dashed lines in the right panel of Figure 1, which are more peaked in the region of $\mu_0 = 0$, present the expected number of samples when the modeler adopts the prior distribution with $n_0 = 2$, but in which all problem configurations have the true mean specified on the horizontal axis. The lighter curves immediately above and below those curves illustrate the size of $\pm$ 1 standard error based on 15,000 replications of the trial. This is a frequentist analysis in which the problems presented to the modeler do not match the modeler's prior distribution. These results show that the trial can take longer, in expectation, than did the original trial (which had 125 patient pairs) for a narrow range of values near $\mu_0 = 0$. For a broad range of values of μ_0, however, the trial will be shorter, in expectation.

The less peaked, more solid lines, show the average number of samples taken prior to stopping the trial, illustrate the mean number of samples in a Bayesian setting, with random problem instances selected to match the prior distribution of the modeler. This panel confirms that lower sampling costs result in more

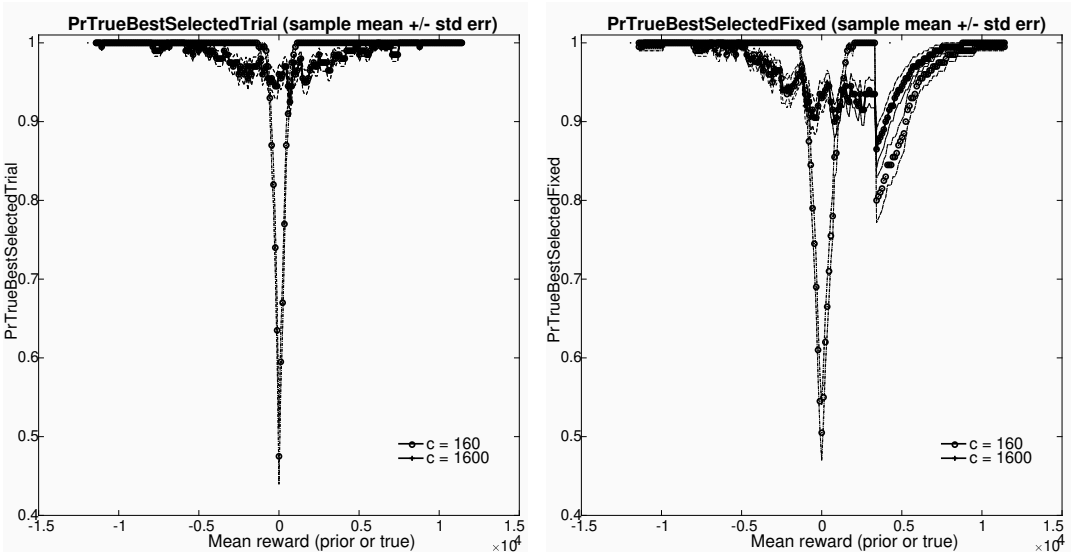

Figure 2: P[CS] for fixed duration trial with 125 patient pairs (left panel) and for new trials (right panel).

sampling, in expectation. It also shows that the mean number of patient pairs required is below the 125 seen in the actual trial, at least for the parameters selected in this analysis.

Figure 2 reports the probability of making the correct technology selection, P[CS], for a trial with 125 patient pairs, versus the P[CS] of the new trial presented here as a function of the prior mean. As before, the dashed lines correspond to sampling problem instances where the mean is exactly that of the horizontal axis (frequentist), and thus the P[CS] becomes approximately 0.5 when the mean is 0 for those curves. These can be used for power curves. The power of the new proposal is somewhat less: lower sampling costs increases power due to an increase in the expected number of observations. The more solid lines correspond to assuming the horizontal axis has the prior mean and that nature gives problems which match the modeler's prior distribution (RPI). The P[CS] for the true trial with RPI drops down to approximately 95% (left panel), and drops further in the right panel. The P[CS] drops particularly in the area where the upper stopping boundary drops due to the discount factor being positive. Despite having a somewhat lower P[CS] relative to the fixed duration trial (which tends to sample more), the sequential sampling procedure does better than the fixed duration trial for maximizing INMB (graphs not shown due to space limitations).

5 CONCLUSIONS

There are numerous opportunities for the clinical trial design field and the simulation optimization field to cross-fertilize. This paper explored the extension of certain one-stage Bayes' optimal trial designs to fully sequential trial design. We showed that this can be done in a computationally feasible way for an application to a pragmatic clinical trial carried out in the UK NHS which was not immediately amenable to a fully sequential analysis using existing techniques. In particular, this work shows how a sequential trial can account for (i) scenarios where the two treatments tested are both used in existing practice, and evidence is to be collected as to which is the more appropriate, as is the case for the ProFHER trial, (ii) the relationship between the rate of recruitment and the incidence of a condition in the population, with either online or offline learning, for patients in and not in the trial, (iii) tradeoffs in the cost of sites and the expected value of information for sampling, when future benefits to patients and the cost of the trial are to both be considered.

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