Online Companion: Appendices

Appendix A summarizes the principal notation in the main paper. Appendix B gives technical details for the derivatives of the focal objective function. Appendix C justifies mathematical claims in section 3. Appendix D presents numerical comparative statics analysis. Appendix E provides formalism for the probabilistic performance measures in the experiments of section 4. Appendix F shows how the one-shot trial design of the main paper can be transformed to a response adaptive trial. Appendix G displays supplemental figures for the application to the ProFHER trial. We provide Matlab code to reproduce the results at https://github.com/andres-alban/ValueBasedTrials.

Appendix A: Table of principal notation

Table EC.1 Table of principal notation.

Parameter	*Description*
$p_{\mathrm{N}} \in [0, 1/2]$	Fraction of patients treated with HT N under the current practice
$E_{\mathrm{N}}, E_{\mathrm{S}} \in \mathbb{R}$	Effectiveness of technologies N and S, respectively
$C_{\mathrm{N}}, C_{\mathrm{S}} \in \mathbb{R}_{\geq 0}$	Patient-level costs of using technologies N and S, respectively
$\lambda \in \mathbb{R}_{\geq 0}$	Monetary value of one unit of effectiveness (e.g., £30,000 / QALY)
$X \in \mathbb{R}$ (random variable)	Incremental net monetary benefit of technology N over S
$W \in \mathbb{R}$	Unknown expected value of X
$\sigma_X^2 \in \mathbb{R}_{>0}$	Known variance of X
$\mu_0 \in \mathbb{R}$, $\sigma_0^2 \in \mathbb{R}_{>0}$	Mean and variance of prior distribution for W
$n_0 = \sigma_X^2/\sigma_0^2$	Effective sample size of prior distribution
$T_{\max} \in \mathbb{R}_{>0}$	Maximum time duration of recruitment in trial
$\zeta \in \mathbb{R}_{>0}$	Incidence rate of the condition in the population
$r_{\max} \in [0, \zeta]$	Capacity of rate of recruitment
$Q_{\max} \in \mathbb{N}$	Maximum sample size for the trial
$T \in [0, T_{\max}]$	Recruitment period duration (decision variable)
$r \in [0, r_{\max}]$	Average recruitment rate to the trial (decision variable)
$Q = Tr/2$	Sample size of the trial
$\mathcal{D} \in \{\mathrm{M}, \mathrm{N}, \mathrm{S}\}$	Adoption decision to implement the current practice (mix of technologies) M, the new technology N, or the standard technology S (decision variable)
Z_{Tr}	Posterior mean to be obtained, given μ_0 and Tr patients to be observed
$\Delta \in [0, H)$	Delay in observing realization of pairwise allocation (in time units)
$P(T) \in \mathbb{R}_{\geq 0}$	Number of patients to receive implemented technology once adoption decision is made at $T + \Delta$
$H \in \mathbb{R}_{>0}$	Maximum time horizon for decision, in the case of fixed horizon
$P \in \mathbb{R}_{>0}$	Number of patients affected by adoption decision, in the case of fixed patient pool
ρ_{yr}	Annual discount rate, e.g., 3.5% for UK NICE
$\rho \in [0, 1)$	Continuous time discount rate, $\rho = \ln(1 + \rho_{\mathrm{yr}})$
$\tilde{T}_\rho(T)$	Effective discounted recruitment period duration
$P_\rho(T)$	Effective discounted number of patients to receive implemented technology once adoption decision is made at $T + \Delta$
δ_{on}	1 = online learning; 0 = offline learning
$c \in \mathbb{R}_{\geq 0}$	Variable per-patient cost per patient completing the trial
$c_{\mathrm{cap}}(r)$	Fixed setup cost of a trial to achieve recruitment rate r
$c_{\mathrm{fix}}, c_r, \theta$	Parameters of setup cost function, e.g., $c_{\mathrm{cap}}(r) = c_{\mathrm{fix}} + c_r r^\theta$
$I_{\mathcal{D}} \in \mathbb{R}_{\geq 0}$	Fixed cost of switching to technology $\mathcal{D}$ from standard technology
$\alpha_{\mathrm{N}}(T), \alpha_{\mathrm{S}}(T) \in \mathbb{R}$	Expected costs per patient if technology N or S is adopted
$\Psi(z)$	Standard normal loss function, $\Psi(z) \equiv \mathbb{E}[(Z - z)^+] = \phi(z) - z(1 - \Phi(z))$

Appendix B: Derivation of partial derivatives of V

The first order conditions for interior solutions of (5), assuming that $P(T)$ and $c_{\text{cap}}(r)$ are differentiable, are given by

$$\frac{\partial V(T,r)}{\partial T}=0 \text{ and } \frac{\partial V(T,r)}{\partial r}=0.$$

In this appendix, we show the main steps to find the partial derivatives of V with respect to T and r. We first introduce some derivatives that will be used repeatedly:

$$\frac{\partial \alpha_{\text{N}}(T)}{\partial T}=-\frac{\alpha_{\text{N}}(T)}{P_\rho(T)}\frac{dP_\rho(T)}{dT}, \quad \frac{\partial \alpha_{\text{S}}(T)}{\partial T}=-\frac{\alpha_{\text{S}}(T)}{P_\rho(T)}\frac{dP_\rho(T)}{dT},$$
$$\frac{\partial \sigma_Z}{\partial T}=\sqrt{\frac{n_0\sigma_X^2 r}{(2n_0+Tr)^3T}}, \qquad \frac{\partial \sigma_Z}{\partial r}=\sqrt{\frac{n_0\sigma_X^2 T}{(2n_0+Tr)^3r}}.$$

The following equations are useful relationships in deriving the partial derivatives:

$$\frac{\partial((\alpha_{\text{N}}(T))/\sigma_Z)}{\partial T}=-\frac{\alpha_{\text{N}}(T)}{\sigma_Z}\left(\frac{1}{P_\rho(T)}\frac{dP_\rho(T)}{dT}+\frac{1}{\sigma_Z}\frac{\partial\sigma_Z}{\partial T}\right)$$
$$\frac{\partial((\alpha_{\text{S}}(T))/\sigma_Z)}{\partial T}=-\frac{\alpha_{\text{S}}(T)}{\sigma_Z}\left(\frac{1}{P_\rho(T)}\frac{dP_\rho(T)}{dT}+\frac{1}{\sigma_Z}\frac{\partial\sigma_Z}{\partial T}\right)$$
$$\frac{\partial\sigma_Z}{\partial T}=\frac{\sigma_X^2 r}{\sigma_Z(2n_0+Tr)^2}=\frac{n_0\sigma_Z}{(2n_0+Tr)T}$$
$$\frac{\partial\sigma_Z}{\partial r}=\frac{\sigma_X^2 T}{\sigma_Z(2n_0+Tr)^2}=\frac{n_0\sigma_Z}{(2n_0+Tr)r}.$$

Consider first

$$\begin{aligned}
&\frac{\partial}{\partial T}\left(e^{-\rho(T+\Delta)}P_\rho(T)\sigma_Z\Psi\left(\frac{\alpha_{\text{N}}(T)-\mu_0}{\sigma_Z}\right)\right)\\
&=-\rho e^{-\rho(T+\Delta)}P_\rho(T)\sigma_Z\Psi\left(\frac{\alpha_{\text{N}}(T)-\mu_0}{\sigma_Z}\right)+e^{-\rho(T+\Delta)}\frac{dP_\rho(T)}{dT}\sigma_Z\Psi\left(\frac{\alpha_{\text{N}}(T)-\mu_0}{\sigma_Z}\right)\\
&\quad+e^{-\rho(T+\Delta)}P_\rho(T)\frac{\partial\sigma_Z}{\partial T}\Psi\left(\frac{\alpha_{\text{N}}(T)-\mu_0}{\sigma_Z}\right)\\
&\quad+e^{-\rho(T+\Delta)}P_\rho(T)\sigma_Z\left(\Phi\left(\frac{\alpha_{\text{N}}(T)-\mu_0}{\sigma_Z}\right)-1\right)\left(-\frac{\alpha_{\text{N}}(T)}{\sigma_Z}\left(\frac{1}{P_\rho(T)}\frac{dP_\rho(T)}{dT}+\frac{1}{\sigma_Z}\frac{\partial\sigma_Z}{\partial T}\right)+\frac{\mu_0}{\sigma_Z^2}\frac{\partial\sigma_Z}{\partial T}\right)\\
&=e^{-\rho(T+\Delta)}\Bigg[\left(\sigma_Z\frac{dP_\rho(T)}{dT}+P_\rho(T)\frac{\partial\sigma_Z}{\partial T}-P_\rho(T)\sigma_Z\rho\right)\Psi\left(\frac{\alpha_{\text{N}}(T)-\mu_0}{\sigma_Z}\right)\\
&\quad+\left(\frac{\alpha_{\text{N}}(T)}{\sigma_Z}\left(\sigma_Z\frac{dP_\rho(T)}{dT}+P_\rho(T)\frac{\partial\sigma_Z}{\partial T}\right)-\frac{P_\rho(T)\mu_0}{\sigma_Z}\frac{\partial\sigma_Z}{\partial T}\right)\left(1-\Phi\left(\frac{\alpha_{\text{N}}(T)-\mu_0}{\sigma_Z}\right)\right)\Bigg].
\end{aligned}$$

Similarly,

$$\begin{aligned}
&\frac{\partial}{\partial T}\left(e^{-\rho(T+\Delta)}P_\rho(T)\sigma_Z\Psi\left(\frac{\alpha_{\text{S}}(T)+\mu_0}{\sigma_Z}\right)\right)\\
&=e^{-\rho(T+\Delta)}\Bigg[\left(\sigma_Z\frac{dP_\rho(T)}{dT}+P_\rho(T)\frac{\partial\sigma_Z}{\partial T}-P_\rho(T)\sigma_Z\rho\right)\Psi\left(\frac{\alpha_{\text{S}}(T)+\mu_0}{\sigma_Z}\right)\\
&\quad+\left(\frac{\alpha_{\text{S}}(T)}{\sigma_Z}\left(\sigma_Z\frac{dP_\rho(T)}{dT}+P_\rho(T)\frac{\partial\sigma_Z}{\partial T}\right)+\frac{P_\rho(T)\mu_0}{\sigma_Z}\frac{\partial\sigma_Z}{\partial T}\right)\left(1-\Phi\left(\frac{\alpha_{\text{S}}(T)+\mu_0}{\sigma_Z}\right)\right)\Bigg].
\end{aligned}$$

Thus, we get

$$\begin{aligned}\frac{\partial V(T,r)}{\partial T} &= e^{-\rho T}\left(\frac{1}{2}\delta_{\text{on}} r(1-2p_{\text{N}})\mu_0 - cr\right) \qquad \text{(EC.1)}\\ &+ (1-p_{\text{N}})e^{-\rho(T+\Delta)}\Bigg[\left(\sigma_Z\frac{dP_\rho(T)}{dT} + P_\rho(T)\frac{\partial\sigma_Z}{\partial T} - P_\rho(T)\sigma_Z\rho\right)\Psi\left(\frac{\alpha_{\text{N}}(T)-\mu_0}{\sigma_Z}\right)\\ &+ \left(\frac{\alpha_{\text{N}}(T)}{\sigma_Z}\left(\sigma_Z\frac{dP_\rho(T)}{dT} + P_\rho(T)\frac{\partial\sigma_Z}{\partial T}\right) - \frac{P_\rho(T)\mu_0}{\sigma_Z}\frac{\partial\sigma_Z}{\partial T}\right)\left(1-\Phi\left(\frac{\alpha_{\text{N}}(T)-\mu_0}{\sigma_Z}\right)\right)\Bigg]\\ &+ p_{\text{N}}e^{-\rho(T+\Delta)}\Bigg[\left(\sigma_Z\frac{dP_\rho(T)}{dT} + P_\rho(T)\frac{\partial\sigma_Z}{\partial T} - P_\rho(T)\sigma_Z\rho\right)\Psi\left(\frac{\alpha_{\text{S}}(T)+\mu_0}{\sigma_Z}\right)\\ &+ \left(\frac{\alpha_{\text{S}}(T)}{\sigma_Z}\left(\sigma_Z\frac{dP_\rho(T)}{dT} + P_\rho(T)\frac{\partial\sigma_Z}{\partial T}\right) + \frac{P_\rho(T)\mu_0}{\sigma_Z}\frac{\partial\sigma_Z}{\partial T}\right)\left(1-\Phi\left(\frac{\alpha_{\text{S}}(T)+\mu_0}{\sigma_Z}\right)\right)\Bigg].\end{aligned}$$

The partial derivative with respect to r follows similar steps to the ones to find the derivatives with respect to T, so we only present the final result:

$$\begin{aligned}\frac{\partial V(T,r)}{\partial r} = -\frac{\partial c_{\text{cap}}(r)}{\partial r} &- c\tilde{T}_\rho(T) + \delta_{\text{on}}\tilde{T}_\rho(T)(1-2p_{\text{N}})\mu_0/2\\ &+ e^{\rho(T+\Delta)}P_\rho(T)\frac{\partial\sigma_Z}{\partial r}\left[(1-p_{\text{N}})\phi\left(\frac{\alpha_{\text{N}}(T)-\mu_0}{\sigma_Z}\right) + p_{\text{N}}\phi\left(\frac{\alpha_{\text{S}}(T)+\mu_0}{\sigma_Z}\right)\right]\end{aligned}$$

Appendix C: Proofs of mathematical claims

C.1. Proofs in section 3.3

Proof of Prop. 1. Weierstrass' theorem states that the optimal solution of $\max_{x\in S} f(x)$ exists if f is upper semi-continuous and S is closed and bounded (Andreasson et al. 2007, section 4.2). A function $f: S \to \mathbb{R}$ is upper semi-continuous at x_0 if $\limsup_{x\to x_0} f(x) \le f(x_0)$, or equivalently, if for every $\epsilon > 0$ there is a neighborhood S' around x_0 such that $f(x) \le f(x_0) + \epsilon$ for all $x \in S'$.

The domain of $V(T,r)$ is $D = \{(T,r) \mid 0 \le T \le T_{\max},\ 0 \le r \le r_{\max}\}$, which is closed and bounded. Hence, to prove the existence of a solution, it is sufficient to show that $V(T,r)$ is upper semi-continuous.

It is easy to check that $P_\rho(T)$ is upper semi-continuous given that $P(T)$ is upper semi-continuous. Because $c_{\text{cap}}(r)$ is lower semi-continuous, $-c_{\text{cap}}(r)$ is upper semi-continuous. It follows that $V(T,r)$ is upper semi-continuous in $\{(T,r) \mid 0 < T \le T_{\max},\ 0 < r \le r_{\max}\}$ and we only need to show that $V(T,r)$ is upper semi-continuous when either $T = 0$ or $r = 0$.

For $T = 0$, first consider the neighborhood when T is exactly zero. Then, $V(0, r+\delta_r) = V(0,r)$ for any δ_r in the domain D by the definition in (9). Now, let $\delta_T > 0$ and consider the following inequality using (8):

$$V(\delta_T, r+\delta_r) = -(c_{\text{cap}}(r+\delta_r) + c(r+\delta_r)\tilde{T}_\rho(\delta_T)) + \delta_{\text{on}}[(r+\delta_r)\tilde{T}_\rho(\delta_T)/2](1-2p_{\text{N}})\mu_0$$

$$+e^{-\rho(\delta_T+\Delta)}\mathbb{E}\left[(P_\rho(\delta_T)(1-p_{\rm N})Z_{\delta_T(r+\delta_r)}-I_{\rm N})^+ + (-P_\rho(\delta_T)p_{\rm N}Z_{\delta_T(r+\delta_r)}-I_{\rm S})^+\right]$$
$$\le \delta_{\rm on}[(r+\delta_r)\tilde{T}_\rho(\delta_T)/2](1-2p_{\rm N})\mu_0$$
$$+e^{-\rho\delta_T}e^{-\rho\Delta}\mathbb{E}\left[(P_\rho(0)(1-p_{\rm N})Z_{\delta_T(r+\delta_r)}-I_{\rm N})^+ + (-P_\rho(0)p_{\rm N}Z_{\delta_T(r+\delta_r)}-I_{\rm S})^+\right].$$

The inequality holds because $c_{\rm cap}(r)\ge 0$ and $P_\rho(T)$ is non-increasing, so $P_\rho(\delta_T)\le P_\rho(0)$. The right-hand side of the inequality is further continuous in δ_T and is such that it converges to $V(0,r)$ as $\delta_T\to 0$. Thus, we can conclude that $V(\delta_T,r+\delta_r)\le V(0,r)+\epsilon$ for any $\epsilon>0$ if we make δ_T small enough, and that $V(T,r)$ is upper semi-continuous at $T=0$.

For $r=0$, consider first the neighborhood when r is exactly zero. Then, $V(T+\delta_T,0)=V(T,0)$ for any δ_T in the domain of $V(T,r)$, by the definition of V in (4a). Now, let $\delta_r>0$ and consider the following inequality that follows from $c_{\rm cap}(r)\ge 0$ and $P(T)$ being non-increasing:

$$V(T+\delta_T,\delta_r) = -(c_{\rm cap}(\delta_r)+c\delta_r\tilde{T}_\rho(T+\delta_T)) + \delta_{\rm on}[(\delta_r)\tilde{T}_\rho(T+\delta_T)/2](1-2p_{\rm N})\mu_0$$
$$+e^{-\rho(T+\delta_T+\Delta)}\mathbb{E}[(P_\rho(T+\delta_T)(1-p_{\rm N})Z_{(T+\delta_T)\delta_r}-I_{\rm N})^+$$
$$+(-P_\rho(T+\delta_T)p_{\rm N}Z_{(T+\delta_T)\delta_r}-I_{\rm S})^+]$$
$$\le \delta_{\rm on}[\delta_r\tilde{T}_\rho(\delta_T)/2](1-2p_{\rm N})\mu_0$$
$$+e^{-\rho\delta_T}e^{-\rho(T+\Delta)}\mathbb{E}[(P_\rho(0)(1-p_{\rm N})Z_{(T+\delta_T)\delta_r}-I_{\rm N})^+$$
$$+(-P_\rho(0)p_{\rm N}Z_{(T+\delta_T)\delta_r}-I_{\rm S})^+].$$

The right-hand side of the inequality is continuous in δ_T and δ_r and is such that it converges to $V(T,0)$ as $\delta_T\to 0$ and $\delta_r\to 0$. Therefore, we can conclude that $V(T+\delta_T,\delta_r)\le V(T,0)+\epsilon$ for any $\epsilon>0$ if we make $|\delta_T|$ and δ_r small enough, and that $V(T,r)$ is upper semi-continuous at $r=0$. □

C.2. Proofs in section 3.4

Proof of Prop. 2. It is sufficient to show that $V(T,r)$ is the same for all members of the set $\mathcal{S}=\{(T,r)\in[0,T_{\max}]\times[0,r_{\max}]: Tr/2=Q\}$. If $Q=0$, then $V(T,r)=V(0,0)$ for all members $\mathcal{S}$. This follows directly from the definition of V in (4a). Now suppose that $Q>0$, and let $\sigma_Z^2=\sigma_X^2 Q/(n_0(2n_0+Q))$. Then, we obtain, for all members of the set $\mathcal{S}$, the same expected net gain:

$$V(T,r)=\delta_{\rm on}Q(1-2p_{\rm N})\mu_0/2-2cQ-c_{\rm cap}+P\sigma_Z\left[(1-p_{\rm N})\Psi\left(\frac{\alpha_{\rm N}-\mu_0}{\sigma_Z}\right)+p_{\rm N}\Psi\left(\frac{\alpha_{\rm S}+\mu_0}{\sigma_Z}\right)\right]. \quad \square$$

Proof of Prop. 3. Let (T^*,r^*) be an optimal solution to (5). First, observe that if $T^*=0$ or $r^*=0$, then $(0,r_{\max})$ is also an optimal solution by the definition of V in (4a).

Now, consider the case $T^*>0$ and $r^*>0$ such that $Q^*=T^*r^*/2>0$. We will show that any trial design with the same sample size Q^* but with a larger recruitment rate ($r\ge r^*$) and shorter duration ($T=2Q^*/r\le T^*$) obtains equal or larger expected net gain.

The posterior mean variance, σ_Z^2, is the same for any design that has the same sample size. The non-increasing assumption of $P(T)$ implies that $P_\rho(T)$ is non-increasing, and, hence, $P_\rho(T^*) \le P_\rho(2Q^*/r)$, $\alpha_{\mathrm{N}}(T^*) \ge \alpha_{\mathrm{N}}(2Q^*/r)$, and $\alpha_{\mathrm{S}}(T^*) \ge \alpha_{\mathrm{S}}(2Q^*/r)$. Because $\Psi(\cdot)$ is decreasing, we can show that the post-trial rewards, R^*, under the optimal design are smaller than the post-trial rewards obtained when the recruitment rate r is larger than r^* while maintaining the same sample size Q^*:

$$\begin{aligned} R^* &= P_\rho(T^*)\sigma_Z \left[(1-p_{\mathrm{N}})\Psi\left(\frac{\alpha_{\mathrm{N}}(T^*)-\mu_0}{\sigma_Z}\right) + p_{\mathrm{N}}\Psi\left(\frac{\alpha_{\mathrm{S}}(T^*)+\mu_0}{\sigma_Z}\right)\right] \\ &\le P_\rho(2Q^*/r)\sigma_Z \left[(1-p_{\mathrm{N}})\Psi\left(\frac{\alpha_{\mathrm{N}}(2Q^*/r)-\mu_0}{\sigma_Z}\right) + p_{\mathrm{N}}\Psi\left(\frac{\alpha_{\mathrm{S}}(2Q^*/r)+\mu_0}{\sigma_Z}\right)\right]. \end{aligned}$$

The cost and online rewards may however be larger with a larger recruitment rate. Therefore, it is not clear that increasing the recruitment rate obtains larger expected net gain, which is what we will now prove.

To simplify notation, let $C = c - \delta_{\mathrm{on}}(1-2p_{\mathrm{N}})\mu_0/2$ be the per patient cost net of online rewards, such that the optimal expected net gain is given by

$$V^* = -c_{\mathrm{cap}} - Cr^*\tilde{T}_\rho(T^*) + e^{-\rho(T^*+\Delta)}R^*.$$

Because $Q^* > 0$, we know that the optimal expected net gain is positive: $c_{\mathrm{cap}} + Cr^*\tilde{T}_\rho(T^*) \le e^{-\rho(T^*+\Delta)}R^*$. The expected net gain for the design that maintains the same sample size but uses a larger recruitment rate can be bounded below by the function $f(r)$:

$$V(Q^*/r, r) \ge f(r) = -c_{\mathrm{cap}} - Cr\tilde{T}_\rho(2Q^*/r) + e^{-\rho(2Q^*/r+\Delta)}R^*$$

because we have shown that the post-trial rewards are larger when the recruitment rate is larger.

We show that the derivative of $f(r)$ is non-negative for $r \ge r^*$, which will show that expected net gain is non-decreasing as the recruitment rate increases. Basic calculus gives us

$$f'(r) = -\frac{C}{\rho}\left(1 - e^{-2\rho Q^*/r} - \frac{2\rho Q^*}{r}e^{-2\rho Q^*/r}\right) + \frac{2\rho Q^*}{r^2}e^{-2\rho Q^*/r}e^{-\rho\Delta}R^*,$$

and because the optimal expected net gain is positive, we can use $e^{-\rho\Delta}R^* \ge Cr^*(1 - e^{-2\rho Q^*/r^*})/(\rho e^{-2\rho Q^*/r^*})$ to obtain

$$\begin{aligned} f'(r) &\ge -\frac{C}{\rho}\left(1 - e^{-2\rho Q^*/r} - \frac{2\rho Q^*}{r}e^{-2\rho Q^*/r}\right) + \frac{2\rho Q^*}{r^2}e^{-2\rho Q^*/r}\frac{Cr^*(1-e^{-2\rho Q^*/r^*})}{\rho e^{-2\rho Q^*/r^*}} \\ &= -\frac{C}{\rho}\left(1 - e^{-\rho T} - \rho T e^{-\rho T} - \frac{\rho T^2}{T^*}e^{-\rho T}\frac{1-e^{-\rho T^*}}{e^{-\rho T^*}}\right). \end{aligned}$$

The second line inputs $T = 2Q^*/r$ and $T^* = 2Q^*/r^*$ and is a function of r through T. To show that $f'(r) \ge 0$ for $r \ge r^*$, it is sufficient to show that

$$g(T, T^*) = \left(1 - e^{-\rho T} - \rho T e^{-\rho T} - \frac{\rho T^2}{T^*}e^{-\rho T}\frac{1-e^{-\rho T^*}}{e^{-\rho T^*}}\right) \le 0$$

for any $T \leq T^*$.

It can be shown that $g(T,T^*)$ is increasing in T^* by taking partial derivatives with respect to T^*. Thus, it is sufficient to show that $g(T,T) = 1 - e^{-\rho T} - \rho T \leq 0$, which can be easily shown by taking derivatives with respect to T. We can conclude that $f(r)$ is nondecreasing.

We have shown that the expected net gain is nondecreasing when the recruitment rate is increased and duration shortened to maintain the same sample size. Thus, we have shown that the design given $T = T^* r^*/r_{\max}$ and $r = r_{\max}$ obtains at least the same expected net gain as the optimal design: $V(T^* r^*/r_{\max}, r_{\max}) \geq V(T^*, r^*)$. Because (T^*, r^*) is optimal, we have established that $V(T^* r^*/r_{\max}, r_{\max}) = V(T^*, r^*)$ and that an optimal solution with $r = r_{\max}$ exists. □

Proof of Prop. 4. Let (T^*, r^*) be an optimal solution and consider the alternative solution $(T_{\max}, T^* r^*/T_{\max})$. It is straightforward to show that the alternative solution is also optimal by following the same procedure as in the proof of Prop. 3. □

C.3. Comparative statics results in section 3.5

In this appendix, we present the algebra that leads to the results of comparative statics of (5) presented in section 3.5. For simplicity, we present the results with undiscounted rewards for Cases I and II ($c_{\text{cap}}(r) = c_{\text{cap}}$), i.e., it is sufficient to optimize only T for a fixed r ($V^* = \max_{T \in [0, T_{\max}]} V(T, r)$). The results are, however, as general as presented in section 3.5.

We aim to find the sign of the derivatives $\mathrm{d}V^*/\mathrm{d}b = \partial V(T^*, r_{\max})/\partial b$ and $\mathrm{d}V(T^*, r_{\max})/\mathrm{d}b = -(\partial^2 V(T^*, r_{\max})/\partial T \partial b)/(\partial^2 V(T^*, r_{\max})/\partial T^2)$. The right-hand side of the second equation only holds when $\partial^2 V(T^*, r_{\max})/\partial T^2 < 0$. While it is guaranteed to be non-positive at an interior solution by the second order necessary conditions (Andreasson et al. 2007, Theorem 4.17), we assume that it is strictly negative to exclude the rare cases when it is zero. Thus, the algebra we show in this section only shows the sign of the numerator $\partial^2 V(T^*, r)/\partial T \partial b$.

C.3.1. Post-adoption population. For fixed patient pool, the optimal expected net gain is increasing in P:

$$\begin{aligned}\frac{\partial V(T,r)}{\partial P} &= (1-p_{\mathrm{N}})\sigma_Z \Psi\left(\frac{\alpha_{\mathrm{N}} - \mu_0}{\sigma_Z}\right) + p_{\mathrm{N}} \sigma_Z \Psi\left(\frac{\alpha_{\mathrm{S}} + \mu_0}{\sigma_Z}\right) \\ &\quad + (1-p_{\mathrm{N}})\alpha_{\mathrm{N}}\left(1 - \Phi\left(\frac{\alpha_{\mathrm{N}} - \mu_0}{\sigma_Z}\right)\right) + p_{\mathrm{N}}\alpha_{\mathrm{S}}\left(1 - \Phi\left(\frac{\alpha_{\mathrm{S}} + \mu_0}{\sigma_Z}\right)\right) > 0.\end{aligned}$$

Using the implicit function theorem, the sign of $\partial T^*/\partial P$ is the same as the sign of:

$$\begin{aligned}\frac{\partial^2 V(T,r)}{\partial T \partial P} &= \frac{\partial \sigma_Z}{\partial T}\Bigg[(1-p_{\mathrm{N}})\phi\left(\frac{\alpha_{\mathrm{N}} - \mu_0}{\sigma_Z}\right) + p_{\mathrm{N}}\phi\left(\frac{\alpha_{\mathrm{S}} + \mu_0}{\sigma_Z}\right) \\ &\quad + (1-p_{\mathrm{N}})\frac{\alpha_{\mathrm{N}}(\alpha_{\mathrm{N}} - \mu_0)}{\sigma_Z^2}\phi\left(\frac{\alpha_{\mathrm{N}} - \mu_0}{\sigma_Z}\right) + p_{\mathrm{N}}\frac{\alpha_{\mathrm{S}}(\alpha_{\mathrm{S}} + \mu_0)}{\sigma_Z^2}\phi\left(\frac{\alpha_{\mathrm{S}} + \mu_0}{\sigma_Z}\right)\Bigg].\end{aligned}$$

The first two terms in brackets have a positive effect on the optimal trial length, because the value of information is higher when P is higher. The third and fourth terms come from the change in the adoption decision rule because α_{N} and α_{S} decrease as P increases. When $\alpha_{\text{N}} < \mu_0$ there is a negative contribution from the third term but positive from all other terms. Similarly, when $\alpha_{\text{S}} < -\mu_0$ there is a negative contribution from the fourth term but negative from all other terms. In general, we cannot conclude that the optimal T is increasing with P, but this is often the case. For instance, if $-\alpha_{\text{S}} \le \mu_0 \le \alpha_{\text{N}}$, or equivalently, it is a priori optimal to adopt M, then T^* is increasing with P.

For fixed horizon, we perform the sensitivity analysis on the time horizon H. The results are very similar to fixed patient pool. The expected net gain is again increasing in H:

$$\begin{aligned}\frac{\partial V(T,r)}{\partial H} =& \zeta\Bigg[(1-p_{\text{N}})\sigma_Z\Psi\left(\frac{\alpha_{\text{N}}(T)-\mu_0}{\sigma_Z}\right)+p_{\text{N}}\sigma_Z\Psi\left(\frac{\alpha_{\text{S}}(T)+\mu_0}{\sigma_Z}\right)\\ &+(1-p_{\text{N}})\alpha_{\text{N}}(T)\left(1-\Phi\left(\frac{\alpha_{\text{N}}(T)-\mu_0}{\sigma_Z}\right)\right)+p_{\text{N}}\alpha_{\text{S}}(T)\left(1-\Phi\left(\frac{\alpha_{\text{S}}(T)+\mu_0}{\sigma_Z}\right)\right)\Bigg]>0\end{aligned}$$

The derivative that determines the direction of change of the optimal trial length is

$$\begin{aligned}\frac{\partial^2 V(T,r)}{\partial T\partial H} =& \zeta\frac{\partial\sigma_Z}{\partial T}\Bigg[(1-p_{\text{N}})\phi\left(\frac{\alpha_{\text{N}}(T)-\mu_0}{\sigma_Z}\right)+p_{\text{N}}\phi\left(\frac{\alpha_{\text{S}}(T)+\mu_0}{\sigma_Z}\right)\\ &+(1-p_{\text{N}})\frac{\alpha_{\text{N}}(T)(\alpha_{\text{N}}(T)-\mu_0)}{\sigma_Z^2}\phi\left(\frac{\alpha_{\text{N}}(T)-\mu_0}{\sigma_Z}\right)+p_{\text{N}}\frac{\alpha_{\text{S}}(T)(\alpha_{\text{S}}(T)+\mu_0)}{\sigma_Z^2}\phi\left(\frac{\alpha_{\text{S}}(T)+\mu_0}{\sigma_Z}\right)\Bigg]\\ &-\frac{\zeta(1-p_{\text{N}})\alpha_{\text{N}}(T)^2}{\sigma_Z(H-\Delta-T)}\phi\left(\frac{\alpha_{\text{N}}(T)-\mu_0}{\sigma_Z}\right)-\frac{\zeta p_{\text{N}}\alpha_{\text{S}}(T)^2}{\sigma_Z(H-\Delta-T)}\phi\left(\frac{\alpha_{\text{S}}(T)+\mu_0}{\sigma_Z}\right).\end{aligned}$$

Comparing this expression to that for $\partial^2 V(T,r)/\partial T\partial P$, we have two additional terms with a negative effect which capture the reduction in the post-trial patients for a longer trial. The direction of change of T^* is not definitive through comparative statics.

C.3.2. Discount rate ρ. To show the effect of the discount rate, we need to assume here discounted rewards. Instead, to make the algebraic expressions more manageable, we assume that $p_{\text{N}} = 0$ noting that the results hold equally for any p_{N}. We obtain

$$\begin{aligned}\frac{\partial V(T,r)}{\partial \rho} =& (-cr+\delta_{\text{on}}r(1-2p_{\text{N}})\mu_0/2)\frac{\partial \tilde{T}_\rho(T)}{\partial\rho}-(T+\Delta)e^{-\rho(T+\Delta)}P_\rho(T)\sigma_Z\Psi\left(\frac{\alpha_{\text{N}}(T)-\mu_0}{\sigma_Z}\right)\\ &+e^{-\rho(T+\Delta)}\frac{\partial P_\rho(T)}{\partial\rho}\sigma_Z\Psi\left(\frac{\alpha_{\text{N}}(T)-\mu_0}{\sigma_Z}\right)+e^{-\rho(T+\Delta)}\left(1-\Phi\left(\frac{\alpha_{\text{N}}(T)-\mu_0}{\sigma_Z}\right)\right)\alpha_{\text{N}}(T)\frac{\partial P_\rho(T)}{\partial\rho}\end{aligned}$$

The second line above is negative so we only need to show that the first line is negative:

$$\begin{aligned}(-cr+\delta_{\text{on}}r(1-2p_{\text{N}})\mu_0/2)\frac{\partial\tilde{T}_\rho(T)}{\partial\rho} &\le (T+\Delta)e^{-\rho(T+\Delta)}P_\rho(T)\sigma_Z\Psi\left(\frac{\alpha_{\text{N}}(T)-\mu_0}{\sigma_Z}\right)\\ (cr-\delta_{\text{on}}r(1-2p_{\text{N}})\mu_0/2)\tilde{T}_\rho(T)\left(-\frac{1}{\tilde{T}_\rho(T)}\frac{\partial\tilde{T}_\rho(T)}{\partial\rho}\right) &\le (T+\Delta)e^{-\rho(T+\Delta)}P_\rho(T)\sigma_Z\Psi\left(\frac{\alpha_{\text{N}}(T)-\mu_0}{\sigma_Z}\right)\end{aligned}$$

To show that the first line is negative at the optimal design, we need to make use of the non-negativity of the optimal expected net gain, $V(T^*, r^*) \geq 0$, equivalent to

$$(c_{\text{cap}} + cr^* - \delta_{\text{on}} r^*(1-2p_{\text{N}})\mu_0/2)\tilde{T}_\rho(T^*) \leq e^{-\rho(T^*+\Delta)} P_\rho(T^*)\sigma_Z^* \Psi\left(\frac{\alpha_{\text{N}}(T^*) - \mu_0}{\sigma_Z^*}\right)$$
$$(cr^* - \delta_{\text{on}} r^*(1-2p_{\text{N}})\mu_0/2)\tilde{T}_\rho(T^*) \leq e^{-\rho(T^*+\Delta)} P_\rho(T^*)\sigma_Z^* \Psi\left(\frac{\alpha_{\text{N}}(T^*) - \mu_0}{\sigma_Z^*}\right)$$

Thus, the problem simplifies to showing that

$$-\frac{1}{\tilde{T}_\rho(T)}\frac{\partial \tilde{T}_\rho(T)}{\partial \rho} \leq T + \Delta$$
$$\frac{1 - e^{-\rho T}(\rho T + 1)}{\rho(1 - e^{-\rho T})} \leq T + \Delta,$$

which requires some simple additional algebra to show that it indeed holds.

The comparative statics for T^* require the calculation of $\partial^2 V(T,r)/\partial T \partial \rho$. While it is straightforward to calculate, it results in a long expression that does not elucidate any interesting results and we do not show it here.

C.3.3. Effective sample size of the prior distribution. To analyze the sensitivity of V to n_0, we compute

$$\frac{\partial V(T,r)}{\partial n_0} = P\frac{\partial \sigma_Z}{\partial n_0}\left[(1-p_{\text{N}})\phi\left(\frac{\alpha_{\text{N}}(T) - \mu_0}{\sigma_Z}\right) + p_{\text{N}}\phi\left(\frac{\alpha_{\text{S}}(T) + \mu_0}{\sigma_Z}\right)\right] < 0,$$

where $\partial \sigma_Z/\partial n_0 = -\sigma_Z^2(2n_0 + Tr)/(2n_0(n_0 + Tr)) < 0$. The optimal expected net gain is decreasing in n_0 because n_0 is a measure of the confidence in the beliefs, and therefore, the lower the confidence, the higher the rewards obtained from learning through a trial.

To analyze the sensitivity on the optimal recruitment duration, we obtain the following derivative:

$$\begin{aligned}\frac{\partial^2 V(T,r)}{\partial T \partial n_0} =& P\frac{\partial^2 \sigma_Z}{\partial T \partial n_0}\left[(1-p_{\text{N}})\phi\left(\frac{\alpha_{\text{N}}(T) - \mu_0}{\sigma_Z}\right) + p_{\text{N}}\phi\left(\frac{\alpha_{\text{S}}(T) + \mu_0}{\sigma_Z}\right)\right] \\ &+ (1-p_{\text{N}})P\phi\left(\frac{\alpha_{\text{N}}(T) - \mu_0}{\sigma_Z}\right)\frac{(\alpha_{\text{N}}(T) - \mu_0)^2}{\sigma_Z^3}\frac{\partial \sigma_Z}{\partial T}\frac{\partial \sigma_Z}{\partial n_0} \\ &+ p_{\text{N}}P\phi\left(\frac{\alpha_{\text{S}}(T) + \mu_0}{\sigma_Z}\right)\frac{(\alpha_{\text{S}}(T) + \mu_0)^2}{\sigma_Z^3}\frac{\partial \sigma_Z}{\partial T}\frac{\partial \sigma_Z}{\partial n_0}.\end{aligned}$$

The terms in the second and third line are negative because $\partial \sigma_Z/\partial n_0 < 0$, which correspond to the effect of a larger n_0 requiring a smaller sample size to achieve the required confidence in a decision. These two terms correspond to the intuitive effect of a less informative prior requiring more evidence to be gathered. However, an additional effect is found in the first term which is positive for $n_0 < Tr/4$ because $\partial^2 \sigma_Z/\partial T \partial n_0 = \sigma_Z(-4n_0 + Tr)/4(2n_0 + Tr)^2 T$. Therefore, T^* often increases with n_0 when n_0 is small, as we observe in the numerical results of Appendix D.

C.3.4. Sampling standard deviation σ_X. The analysis here is similar to the analysis for n_0:

$$\frac{\partial V(T,r)}{\partial \sigma_X} = P\frac{\partial \sigma_Z}{\partial \sigma_X}\left[(1-p_{\mathrm{N}})\phi\left(\frac{\alpha_{\mathrm{N}}(T)-\mu_0}{\sigma_Z}\right)+p_{\mathrm{N}}\phi\left(\frac{\alpha_{\mathrm{S}}(T)+\mu_0}{\sigma_Z}\right)\right]>0,$$

where $\partial\sigma_Z/\partial\sigma_X = \sqrt{Tr/(2n_0(n_0+Tr/2))}>0$.

$$\begin{aligned}\frac{\partial^2 V(T,r)}{\partial T\partial \sigma_X} =& P\frac{\partial^2 \sigma_Z}{\partial T\partial \sigma_X}\left[(1-p_{\mathrm{N}})\phi\left(\frac{\alpha_{\mathrm{N}}(T)-\mu_0}{\sigma_Z}\right)+p_{\mathrm{N}}\phi\left(\frac{\alpha_{\mathrm{S}}(T)+\mu_0}{\sigma_Z}\right)\right]\\ &+(1-p_{\mathrm{N}})P\phi\left(\frac{\alpha_{\mathrm{N}}(T)-\mu_0}{\sigma_Z}\right)\frac{(\alpha_{\mathrm{N}}(T)-\mu_0)^2}{\sigma_Z^3}\frac{\partial\sigma_Z}{\partial T}\frac{\partial\sigma_Z}{\partial\sigma_X}\\ &+p_{\mathrm{N}}P\phi\left(\frac{\alpha_{\mathrm{S}}(T)+\mu_0}{\sigma_Z}\right)\frac{(\alpha_{\mathrm{S}}(T)+\mu_0)^2}{\sigma_Z^3}\frac{\partial\sigma_Z}{\partial T}\frac{\partial\sigma_Z}{\partial\sigma_X}>0.\end{aligned}$$

Here we obtain a definitive sign because $\partial^2\sigma_Z/\partial T\partial\sigma_X = \sqrt{n_0 r/((2n_0+Tr)^3 T)}>0$.

C.3.5. Per-patient cost c. We can easily obtain

$$\frac{\partial V}{\partial c} = -Tr<0$$
$$\frac{\partial^2 V}{\partial T\partial c} = -r<0,$$

which confirms the intuitive result that the optimal expected net gain and optimal enrolled patients in Cases I–III is decreasing with variable per-patient cost.

C.3.6. Delay in observing outcomes Δ. We obtain

$$\frac{\partial V}{\partial \Delta} = -\rho e^{-\rho(T+\Delta)}\sigma_Z P_\rho\left[(1-p_{\mathrm{N}})\Psi\left(\frac{\alpha_{\mathrm{N}}-\mu_0}{\sigma_Z}\right)+p_{\mathrm{N}}\Psi\left(\frac{\alpha_{\mathrm{S}}+\mu_0}{\sigma_Z}\right)\right]\le 0$$

C.3.7. Cost of recruitment c_r. We obtain

$$\frac{\partial V}{\partial c_r} = -r^\theta \le 0$$

and for Case III trials (only recruitment rate is optimized), we obtain

$$\frac{\partial^2 V}{\partial r\partial c_r} = -\theta r^{\theta-1}\le 0.$$

C.3.8. Fraction of patients in new technology p_{N}. It is straightforward to check that

$$\begin{aligned}\frac{\partial V(T,r)}{\partial p_{\mathrm{N}}} =& -2\delta_{\mathrm{on}}Tr\mu_0 + P(T)\sigma_Z\left(\Psi\left(\frac{\alpha_{\mathrm{S}}(T)+\mu_0}{\sigma_Z}\right)-\Psi\left(\frac{\alpha_{\mathrm{N}}(T)-\mu_0}{\sigma_Z}\right)\right)\\ &+P(T)\left[\alpha_{\mathrm{S}}(T)\left(1-\Phi\left(\frac{\alpha_{\mathrm{S}}(T)+\mu_0}{\sigma_Z}\right)\right)-\alpha_{\mathrm{N}}(T)\left(1-\Phi\left(\frac{\alpha_{\mathrm{N}}(T)-\mu_0}{\sigma_Z}\right)\right)\right].\end{aligned}$$

There are three summands in this expression. The first is the online learning effect. The second is the effect due to post-trial benefits. The third is a correction due to the change of the optimal adoption decision rule. The magnitude of the second summand depends on the magnitude of $P(T)\sigma_Z$, while the magnitude of the third summand depends on the magnitudes of $P(T)\alpha_{\rm N}(T)$ and $P(T)\alpha_{\rm S}(T)$. When $P(T)\sigma_Z$ dominates, the effect depends on the expected gains of adopting technologies N or S; if $\Psi\left((\alpha_{\rm S}(T)+\mu_0)/\sigma_Z\right) > \Psi\left((\alpha_{\rm N}(T)-\mu_0)/\sigma_Z\right)$, then an increase in $p_{\rm N}$ (increase in the number of people who would benefit from the adoption of S) would increase the expected net gain.

The second derivative $\partial^2 V(T,r)/\partial T\partial p_{\rm N}$ is a long expression that does not elucidate any interesting insights. We present a special scenario, $I_{\rm N}=I_{\rm S}=0$, with some interesting results. Note that $\alpha_{\rm N}(T)=\alpha_{\rm S}(T)=0$ and we obtain

$$\frac{\partial^2 V(T,r)}{\partial T\partial p_{\rm N}} = -2\delta_{\rm on} r\mu_0 - 2\frac{dP(T)}{dT}\mu_0\left(1-\Phi\left(\frac{\mu_0}{\sigma_Z}\right)\right).$$

From this expression, observe that under some additional conditions the optimal trial length becomes independent of $p_{\rm N}$. One possibility is $\mu_0=0$. The second possibility is under fixed patient pool and offline learning. The optimal expected net gain is independent of $p_{\rm N}$ under the former, but not the latter, condition.

C.4. Proofs for asymptotic results of Prop. 5 in section 3.6.1

Claims are proved separately for the four cases of section 3.4 in Lemmas EC.1 to EC.4. The combination of the four lemmas completes the proof of Prop. 5. The proofs assume that $c-\delta_{\rm on}(1-2p_{\rm N})\mu_0/2>0$ and that there is no discounting, $\rho=0$. The proofs further assume that $c_{\rm cap}(r)=c_{\rm fix}+c_r r$ where $c_r=0$ for Cases I and II with constant setup costs and where $c_r>0$ for Cases III and IV with variable costs.

C.4.1. Case I: constant setup costs, no discounting, fixed patient pool. If $c-\delta_{\rm on}(1-2p_{\rm N})\mu_0/2\le 0$ in this case, the effective cost of sampling is less than or equal to zero, and, given the trial is run, it is optimal to sample infinitely for any P. We, therefore, analyze the more interesting setting where $c-\delta_{\rm on}(1-2p_{\rm N})\mu_0/2>0$. Because Q^* grows unbounded with P (shown below), we let $r_{\max}=\infty$ and $T_{\max}=\infty$, i.e., there is no upper bound on the decision variables.

LEMMA EC.1. *If $c_{cap}(r)=c_{cap}$, $\rho=0$, $P(T)=P$ and $c-\delta_{\rm on}(1-2p_N)\mu_0/2>0$, then*

$$\lim_{P\to\infty}\frac{Q^*}{\sqrt{P}} = \left(\frac{\sqrt{n_0\sigma_X^2}\,\phi(\mu_0/\sigma_0)}{4(c-\delta_{\rm on}(1-2p_N)\mu_0/2)}\right)^{1/2},$$

$$\lim_{P\to\infty}\frac{V^*}{P} = (1-p_N)\sigma_0\Psi(-\mu_0/\sigma_0)+p_N\sigma_0\Psi(\mu_0/\sigma_0).$$

Proof of Lemma EC.1. For functions f and g, we use the notation $f(P)\sim g(P)$ to denote $\lim_{P\to\infty} f(P)/g(P)=1$. Without loss of generality, the proof assumes that r is fixed and T is the decision variable. For clarity, we make the dependence of T^* on P explicit with $T^*(P)$. We need to show that

$$rT^*(P)\sim\left(\frac{\sqrt{n_0\sigma_X^2}\,\phi(\sqrt{n_0}\mu_0/\sigma_X)P}{c-\delta_{\rm on}(1-2p_{\rm N})\mu_0/2}\right)^{1/2}.$$

We know that $T^*(P)$ either satisfies the first order condition $\partial V(T,r)/\partial T = 0$ or $T^*(P) = 0$. However, $T^*(P) = 0$ is not optimal for sufficiently large P. The expression $\partial V(T,r)/\partial T = 0$ was derived in Appendix B. By rearranging terms, we obtain

$$P\left(\frac{1-p_{\mathrm{N}}}{\sqrt{2\pi}}e^{-\frac{n_0(2n_0+rT^*(P))}{2\sigma_X^2 rT^*(P)}(\alpha_{\mathrm{N}}-\mu_0)^2}+\frac{p_{\mathrm{N}}}{\sqrt{2\pi}}e^{-\frac{n_0(2n_0+rT^*(P))}{2\sigma_X^2 rT^*(P)}(\alpha_{\mathrm{S}}+\mu_0)^2}\right) = \sqrt{\frac{(2n_0+rT^*(P))^3T^*(P)}{n_0\sigma_X^2 r}}(cr-\delta_{\mathrm{on}}r(1-2p_{\mathrm{N}})\mu_0/2). \tag{EC.2}$$

The left-hand side approaches infinity as $P\to\infty$, so that the right-hand side needs to approach infinity as $P\to\infty$. Hence, $\lim_{P\to\infty}T^*(P)=\infty$, and the right-hand side satisfies the following relationship:

$$\sqrt{\frac{(2n_0+rT^*(P))^3T^*(P)}{n_0\sigma_X^2 r}}(cr-\delta_{\mathrm{on}}r(1-2p_{\mathrm{N}})\mu_0/2)\sim\frac{c-\delta_{\mathrm{on}}(1-2p_{\mathrm{N}})\mu_0/2}{\sqrt{n_0\sigma_X^2}}r^2(T^*(P))^2$$

Because $\alpha_{\mathrm{N}} = I_{\mathrm{N}}/(1-p_{\mathrm{N}})P$ and $\alpha_{\mathrm{S}} = I_{\mathrm{S}}/p_{\mathrm{N}}P$, which approach zero as $P\to\infty$, the left-hand side of (EC.2) satisfies the following relationship:

$$P\left(\frac{1-p_{\mathrm{N}}}{\sqrt{2\pi}}e^{-\frac{n_0(2n_0+rT^*(P))}{2\sigma_X^2 rT^*(P)}(\alpha_{\mathrm{N}}-\mu_0)^2}+\frac{p_{\mathrm{N}}}{\sqrt{2\pi}}e^{-\frac{n_0(2n_0+rT^*(P))}{2\sigma_X^2 rT^*(P)}(\alpha_{\mathrm{S}}+\mu_0)^2}\right)\sim\frac{P}{\sqrt{2\pi}}e^{-\frac{n_0}{2\sigma_X^2}\mu_0^2}.$$

Combining results, we obtain

$$\frac{P}{\sqrt{2\pi}}e^{-\frac{n_0}{2\sigma_X^2}\mu_0^2}\sim\frac{c-\delta_{\mathrm{on}}(1-2p_{\mathrm{N}})\mu_0/2}{\sqrt{n_0\sigma_X^2}}r^2(T^*(P))^2$$

and, by rearranging terms, the desired result for $Q^*/\sqrt{P}$.

Using the previous result, the asymptotic result for $V^* = V(T^*)$ is straightforward to find. Let σ_Z^* be σ_Z evaluated at T^*. Because $\lim_{P\to\infty}T^*=\infty$, we know that $\lim_{P\to\infty}\sigma_Z^*=\sigma_X/\sqrt{n_0}=\sigma_0$. Then,

$$\begin{aligned}
V^* &= -c_{\mathrm{cap}}-crT^*+\delta_{\mathrm{on}}\ (1-2p_{\mathrm{N}})\mu_0 rT^*/2+P\sigma_Z^*\left((1-p_{\mathrm{N}})\Psi\left(\frac{\alpha_{\mathrm{N}}-\mu_0}{\sigma_Z^*}\right)+p_{\mathrm{N}}\Psi\left(\frac{\alpha_{\mathrm{S}}+\mu_0}{\sigma_Z^*}\right)\right)\\
V^* &\sim -crT^*+\delta_{\mathrm{on}}(1-2p_{\mathrm{N}})\mu_0 rT^*/2+P\sigma_Z^*\left((1-p_{\mathrm{N}})\Psi\left(\frac{-\mu_0}{\sigma_Z^*}\right)+p_{\mathrm{N}}\Psi\left(\frac{\mu_0}{\sigma_Z^*}\right)\right)\\
V^* &\sim -crT^*+\delta_{\mathrm{on}}(1-2p_{\mathrm{N}})\mu_0 rT^*/2+P\sigma_0\left((1-p_{\mathrm{N}})\Psi\left(\frac{-\mu_0}{\sigma_0}\right)+p_{\mathrm{N}}\Psi\left(\frac{\mu_0}{\sigma_0}\right)\right)\\
V^* &\sim (-c+\delta_{\mathrm{on}}(1-2p_{\mathrm{N}})\mu_0/2)\left(\frac{\sqrt{n_0\sigma_X^2}\phi(\sqrt{n_0}\mu_0/\sigma_X)}{(c-\delta_{\mathrm{on}}(1-2p_{\mathrm{N}})\mu_0/2)r^2}\right)^{1/2}\sqrt{P}+P\sigma_0\left((1-p_{\mathrm{N}})\Psi\left(\frac{-\mu_0}{\sigma_0}\right)+p_{\mathrm{N}}\Psi\left(\frac{\mu_0}{\sigma_0}\right)\right)\\
V^* &\sim P\sigma_0\left((1-p_{\mathrm{N}})\Psi\left(\frac{-\mu_0}{\sigma_0}\right)+p_{\mathrm{N}}\Psi\left(\frac{\mu_0}{\sigma_0}\right)\right),
\end{aligned}$$

and the last line is the statement in the lemma. □

C.4.2. Case II: constant setup costs, no discounting, fixed horizon. Because we assume undiscounted rewards, Case II is necessarily fixed horizon. If $c-\delta_{\rm on}(1-2p_{\rm N})\mu_0/2\le 0$ in this case, then the first order condition for T^* is never satisfied, and it is optimal to sample infinitely. We therefore analyze the setting where $c-\delta_{\rm on}(1-2p_{\rm N})\mu_0/2>0$. In addition, we allow $T_{\max}=\infty$, i.e., there is no upper bound on T, because $T^*\to\infty$ as $P\to\infty$, as shown below. Prop. 3 shows that $r^*=r_{\max}$ is optimal. By multiplying T^* with $r_{\max}/2$, we obtain asymptotic results for Q^*.

Lemma EC.2. *If $c_{cap}(r)=c_{cap}$, $\rho=0$, $P(T)=\zeta(H-T-\mathbf{1}_{T>0}\Delta)$, $c-\delta_{\rm on}(1-2p_N)\mu_0/2>0$, and $T_{\max}=\infty$, then*

$$\lim_{H\to\infty}\frac{T^*}{\sqrt{\zeta(H-\Delta)}}=\left(\frac{\sqrt{n_0\sigma_X^2}\phi(\mu_0/\sigma_0)}{(c-\delta_{\rm on}(1-2p_N)\mu_0/2)r_{\max}^2+\zeta r_{\max}\sigma_0(\Psi(\mu_0/\sigma_0)+(1-p_N)\mu_0/\sigma_0)}\right)^{1/2},$$
$$\lim_{H\to\infty}\frac{V^*}{\zeta(H-\Delta)}=(1-p_N)\sigma_0\Psi(-\mu_0/\sigma_0)+p_N\sigma_0\Psi(\mu_0/\sigma_0). \tag{EC.3}$$

Proof of Lemma EC.2. For functions f and g, we use the notation $f(H)\sim g(H)$ to denote $\lim_{H\to\infty}f(H)/g(H)=1$. For clarity, we make the dependence of T^* on H explicit with $T^*(H)$. We need to show that

$$T^*(H)\sim\left(\frac{\sqrt{n_0\sigma_X^2}\phi(\sqrt{n_0}\mu_0/\sigma_X)\zeta(H-\Delta)}{(c-\delta_{\rm on}(1-2p_{\rm N})\mu_0/2)r^2+\zeta r\sigma_X/\sqrt{n_0}(\Psi(\mu_0\sqrt{n_0}/\sigma_X)+(1-p_{\rm N})\mu_0\sqrt{n_0}/\sigma_X)}\right)^{1/2}.$$

We know that $T^*(H)$ either satisfies the first order condition $\partial V(T^*(H))/\partial T=0$ or $T^*(H)=0$. Because $T^*(H)=0$ is not optimal for sufficiently large H, $T^*(H)$ satisfies $\partial V(T^*(H))/\partial T=0$. Using the expression derived in Appendix B, $dV(T^*(H))/dT=0$ is equivalent to

$$\begin{aligned}cr-\delta_{\rm on}r(1-2p_{\rm N})\mu_0/2=&(1-p_{\rm N})\Bigg[\zeta(H-T^*(H)-\Delta)\frac{\partial\sigma_Z^*(H)}{\partial T}\phi\left(\frac{\alpha_{\rm N}(T^*(H))-\mu_0}{\sigma_Z^*(H)}\right)\\&-\sigma_Z^*(H)\zeta\Psi\left(\frac{\alpha_{\rm N}(T^*(H))-\mu_0}{\sigma_Z^*(H)}\right)-\alpha_{\rm N}(T^*(H))\zeta\left(1-\Phi\left(\frac{\alpha_{\rm N}(T^*(H))-\mu_0}{\sigma_Z^*(H)}\right)\right)\Bigg]\\&+p_{\rm N}\Bigg[\zeta(H-T^*(H)-\Delta)\frac{\partial\sigma_Z^*(H)}{\partial T}\phi\left(\frac{\alpha_{\rm S}(T^*(H))+\mu_0}{\sigma_Z^*(H)}\right)\\&-\sigma_Z^*(H)\zeta\Psi\left(\frac{\alpha_{\rm S}(T^*(H))+\mu_0}{\sigma_Z^*(H)}\right)-\alpha_{\rm S}(T^*(H))\zeta\left(1-\Phi\left(\frac{\alpha_{\rm S}(T^*(H))+\mu_0}{\sigma_Z^*(H)}\right)\right)\Bigg],\end{aligned}$$

where $\sigma_Z^*(H)$ is σ_Z evaluated at $T^*(H)$. Because the left side of the equation is bounded for any H, the right side must be as well. Thus, $(H-T^*(H)-\Delta)\partial\sigma_Z^*(H)/\partial T$ is bounded and implies that $\lim_{H\to\infty}T^*(H)=\infty$, $\lim_{H\to\infty}(H-T^*(H)-\Delta)=\infty$, and $(H-\Delta)\sim(H-T^*(H)-\Delta)$, with the use of expression for $\partial\sigma_Z/\partial T$ derived in Appendix B. Using this observation on the above equation, we obtain the following relationship:

$$cr-\delta_{\text{on}}r(1-2p_{\text{N}})\mu_0/2+\zeta\frac{\sigma_X}{\sqrt{n_0}}\left(\Psi\left(\frac{\mu_0\sqrt{n_0}}{\sigma_X}\right)+(1-p_{\text{N}})\frac{\mu_0\sqrt{n_0}}{\sigma_X}\right)$$
$$\sim\zeta(H-T^*(H)-\Delta)\sqrt{\frac{n_0\sigma_X^2 r}{(2n_0+rT^*(H))^3T^*(H)}}\phi\left(\frac{\mu_0\sqrt{n_0}}{\sigma_X}\right).$$

By rearranging and some additional asymptotic approximations, we obtain

$$\left(cr-\delta_{\text{on}}r(1-2p_{\text{N}})\mu_0/2+\zeta\frac{\sigma_X}{\sqrt{n_0}}\left(\Psi\left(\frac{\mu_0\sqrt{n_0}}{\sigma_X}\right)+(1-p_{\text{N}})\frac{\mu_0\sqrt{n_0}}{\sigma_X}\right)\right)\frac{r(T^*(H))^2}{\sqrt{n_0}\sigma_X\phi\left(\frac{\mu_0\sqrt{n_0}}{\sigma_X}\right)}\sim\zeta(H-\Delta).$$

The desired result is obtained by rearranging the terms and setting $r=r_{\max}$, which we know to be an optimal decision from Prop. 3. Using this result and following a similar procedure as in the proof of lemma EC.1, we can obtain the asymptotic result for V^*:

$$V^*=-c_{\text{cap}}(r)-crT^*+\delta_{\text{on}}\ (1-2p_{\text{N}})\mu_0rT^*/2+P(T^*)\sigma_Z^*\left((1-p_{\text{N}})\Psi\left(\frac{\alpha_{\text{N}}(T^*)-\mu_0}{\sigma_Z^*}\right)+p_{\text{N}}\Psi\left(\frac{\alpha_{\text{S}}(T^*)+\mu_0}{\sigma_Z^*}\right)\right)$$
$$V^*\sim-crT^*+\delta_{\text{on}}(1-2p_{\text{N}})\mu_0rT^*/2+\zeta(H-T^*-\Delta)\sigma_0\left((1-p_{\text{N}})\Psi\left(\frac{-\mu_0}{\sigma_0}\right)+p_{\text{N}}\Psi\left(\frac{\mu_0}{\sigma_0}\right)\right)$$
$$V^*\sim\zeta(H-\Delta)\sigma_0\left((1-p_{\text{N}})\Psi\left(\frac{-\mu_0}{\sigma_0}\right)+p_{\text{N}}\Psi\left(\frac{\mu_0}{\sigma_0}\right)\right).\quad\square$$

C.4.3. Case III: affine setup costs, no discounting, fixed patient pool. If $c-\delta_{\text{on}}(1-2p_{\text{N}})\mu_0/2\le 0$, then the first order condition is never satisfied and it is optimal to sample infinitely. In that scenario, a solution to (5) does not exist unless r is constrained and $r^*=r_{\max}$. We therefore analyze the setting where $c-\delta_{\text{on}}(1-2p_{\text{N}})\mu_0/2>0$. Because the optimal recruitment rate grows unboundedly with P (as shown below), we assume that $r_{\max}=\infty$, i.e., no upper bound on r. To obtain asymptotic results on Q^*, we only need to multiply the results of r^* with $T_{\max}/2$, as Prop. 4 shows that $T=T_{\max}$ is optimal.

LEMMA EC.3. *If $c_{cap}(r)=c_{fix}+c_r r$ where $c_r>0$, $\rho=0$, $P(T)=P$ and $c-\delta_{\text{on}}(1-2p_N)\mu_0/2>0$ then*

$$\lim_{P\to\infty}\frac{r^*}{\sqrt{P}}=\left(\frac{\sqrt{n_0\sigma_X^2}\phi(\mu_0/\sigma_0)}{[cT_{\max}+c_r-\delta_{\text{on}}(1-2p_N)\mu_0T_{\max}/2]}\right)^{1/2},\tag{EC.4}$$
$$\lim_{P\to\infty}\frac{V^*}{P}=\sigma_0[\Psi(\mu_0/\sigma_0)+(1-p_N)\mu_0/\sigma_0].$$

Proof of Lemma EC.3. Prop. 4 shows that it is optimal to have $T^*=T_{\max}$. The optimal r has to satisfy the first order optimality condition $\partial V(T_{\max},r)/\partial r=0$ for large enough P. The optimality condition is equivalent to

$$P\left(\frac{1-p_{\text{N}}}{\sqrt{2\pi}}e^{-\frac{n_0(2n_0+r^*(P)T_{\max})}{2\sigma_X^2r^*(P)T_{\max}}(\alpha_{\text{N}}-\mu_0)^2}+\frac{p_{\text{N}}}{\sqrt{2\pi}}e^{-\frac{n_0(2n_0+r^*(P)T_{\max})}{2\sigma_X^2r^*(P)T_{\max}}(\alpha_{\text{S}}+\mu_0)^2}\right)$$
$$=\sqrt{\frac{(2n_0+r^*(P)T_{\max})^3r^*(P)}{n_0\sigma_X^2T_{\max}}}(c_r+cT_{\max}-\delta_{\text{on}}T_{\max}(1-2p_{\text{N}})\mu_0/2).$$

The optimality condition is the same as (EC.2) with the exception of exchanging $T^*(P)$ with $r^*(P)$, exchanging r with $T_{\max}$, and an additional c_r on the right-hand side. The rest of the proof follows as the proof of Lemma EC.1 and is not reproduced here. □

C.4.4. Case IV: affine setup costs, no discounting, fixed horizon. If $c-\delta_{\text{on}}(1-2p_{\text{N}})\mu_0/2<0$ in this case, the effective cost of sampling is less than zero, and, given the trial is run, it is optimal to sample infinitely for large H. We, therefore, analyze the more interesting setting where $c-\delta_{\text{on}}(1-2p_{\text{N}})\mu_0/2\geq 0$. Notice that, unlike the previous cases, $c-\delta_{\text{on}}(1-2p_{\text{N}})\mu_0/2=0$ is considered here and gives interesting results that differ substantially from the scenario when $c-\delta_{\text{on}}(1-2p_{\text{N}})\mu_0/2>0$. Because both T^* and r^* grow unbounded with P (shown below), we let $T_{\max}=\infty$ and $r_{\max}=\infty$, i.e., there is no upper bound on the decision variables.

LEMMA EC.4. *If $\rho=0$, $c_{cap}(r)=c_{fix}+c_r r$, where $c_r>0$, $P(T)=\zeta(H-T-\mathbf{1}_{T>0}\Delta)$, $c-\delta_{\text{on}}(1-2p_N)\mu_0/2\geq 0$, and $T_{\max}=\infty$ and $r_{\max}=\infty$, then*

$$\lim_{H\to\infty}\frac{V^*}{\zeta(H-\Delta)}=(1-p_N)\sigma_0\Psi(-\mu_0/\sigma_0)+p_N\sigma_0\Psi(\mu_0/\sigma_0).$$

In addition, if $c-\delta_{\text{on}}(1-2p_N)\mu_0/2>0$, then

$$\lim_{H\to\infty}\frac{r^*}{(\zeta(H-\Delta))^{1/4}}=\lim_{H\to\infty}\frac{KT^*}{(\zeta(H-\Delta))^{1/4}}=\left(\frac{K^2\sqrt{n_0\sigma_X^2}\phi(\mu_0/\sigma_0)}{c-\delta_{\text{on}}(1-2p_N)\mu_0/2}\right)^{1/4},$$

if $c-\delta_{\text{on}}(1-2p_N)\mu_0/2=0$, and

$$\lim_{H\to\infty}\frac{r^*}{(\zeta(H-\Delta))^{1/3}}=\lim_{H\to\infty}\frac{KT^*}{(\zeta(H-\Delta))^{1/3}}=\left(\frac{K^2\sqrt{n_0\sigma_X^2}\phi(\mu_0/\sigma_0)}{c_r}\right)^{1/3},$$

if $c-\delta_{\text{on}}(1-2p_N)\mu_0/2=0$, where $K=\sigma_X\zeta(\Psi(\mu_0/\sigma_0)+(1-p_N)\mu_0/\sigma_0)/(\sqrt{n_0}c_r)$.

Proof of Lemma EC.4. For large enough H, the optimal trial design satisfies $T^*r^*>0$ and the first order optimality conditions $\partial V(r^*,T^*)/\partial T=0$ and $\partial V(r^*,T^*)/\partial r=0$. Using the expressions derived in Appendix B and the property $\partial\sigma_Z/\partial r=(r/T)\partial\sigma_Z/\partial T$, the first order optimality conditions are equivalent to

$$\begin{aligned}(c-\delta_{\text{on}}(1-2p_{\text{N}})\mu_0/2)r^*+(1-p_{\text{N}})\left[\zeta\alpha_{\text{N}}(T^*)\left(1-\Phi\left(\frac{\alpha_{\text{N}}(T^*)-\mu_0}{\sigma_Z^*}\right)\right)+\sigma_Z^*\zeta\Psi(\left(\frac{\alpha_{\text{N}}(T^*)-\mu_0}{\sigma_Z^*}\right)\right]\\ +p_{\text{N}}\left[\zeta\alpha_{\text{S}}(T^*)\left(1-\Phi\left(\frac{\alpha_{\text{S}}(T^*)+\mu_0}{\sigma_Z^*}\right)\right)+\sigma_Z^*\zeta\Psi(\left(\frac{\alpha_{\text{S}}(T^*)+\mu_0}{\sigma_Z^*}\right)\right]\\ =\zeta(H-T^*-\Delta)\frac{\partial\sigma_Z^*}{\partial T}\left[(1-p_{\text{N}})\phi\left(\frac{\alpha_{\text{N}}(T^*)-\mu_0}{\sigma_Z^*}\right)+p_{\text{N}}\phi\left(\frac{\alpha_{\text{S}}(T^*)+\mu_0}{\sigma_Z^*}\right)\right]\end{aligned}\tag{EC.5}$$

and

$$(c_r+(c-\delta_{\text{on}}(1-2p_{\text{N}})\mu_0/2)T^*)\frac{r^*}{T^*}=\zeta(H-T-\Delta)\frac{\partial\sigma_Z^*}{\partial T}\left[(1-p_{\text{N}})\phi\left(\frac{\alpha_{\text{N}}(T^*)-\mu_0}{\sigma_Z^*}\right)+p_{\text{N}}\phi\left(\frac{\alpha_{\text{S}}(T^*)+\mu_0}{\sigma_Z^*}\right)\right],\tag{EC.6}$$

where σ_Z^* is σ_Z evaluated at (T^*, r^*). Notice that the right-hand side of both conditions are the same so we can formulate a third condition:

$$(1-p_{\mathrm{N}})\left[\zeta\alpha_{\mathrm{N}}(T^*)\left(1-\Phi\left(\frac{\alpha_{\mathrm{N}}(T^*)-\mu_0}{\sigma_Z^*}\right)\right)+\sigma_Z^*\zeta\Psi(\left(\frac{\alpha_{\mathrm{N}}(T^*)-\mu_0}{\sigma_Z^*}\right)\right] \\ +p_{\mathrm{N}}\left[\zeta\alpha_{\mathrm{S}}(T^*)\left(1-\Phi\left(\frac{\alpha_{\mathrm{S}}(T^*)+\mu_0}{\sigma_Z^*}\right)\right)+\sigma_Z^*\zeta\Psi\left(\frac{\alpha_{\mathrm{S}}(T^*)+\mu_0}{\sigma_Z^*}\right)\right]=c_r\frac{r^*}{T^*} \tag{EC.7}$$

We first show that $\lim_{H\to\infty} H - T^* - \Delta = \infty$ by means of contradiction. Assuming that $\lim_{H\to\infty} H - T^* - \Delta < \infty$ implies that $\lim_{H\to\infty} T^* = \infty$. Then, the right-hand side of (EC.5) approaches zero as $H\to\infty$. But the left-hand side is larger than zero so that (EC.5) cannot be satisfied for large enough H and we have reached a contradiction.

Next, we show that $\lim_{H\to\infty} T^* = \infty$ by contradiction. Assuming that $\lim_{H\to\infty} T^* < \infty$, (EC.5) implies that $\lim_{H\to\infty} r^* = \infty$. We reach a contradiction in (EC.7) because the left-hand side is bounded and the right-hand side is not.

Because we have established that $\lim_{H\to\infty} T^* = \infty$, (EC.7) implies $\lim_{H\to\infty} r^* = \infty$. In fact, (EC.7) implies

$$\begin{aligned} r^* &= \left[\zeta(1-p_{\mathrm{N}})\left[\alpha_{\mathrm{N}}(T^*)\left(1-\Phi\left(\frac{\alpha_{\mathrm{N}}(T^*)-\mu_0}{\sigma_Z^*}\right)\right)+\sigma_Z^*\Psi\left(\frac{\alpha_{\mathrm{N}}(T^*)-\mu_0}{\sigma_Z^*}\right)\right]\right. \\ &\qquad \left.+\zeta p_{\mathrm{N}}\left[\alpha_{\mathrm{S}}(T^*)\left(1-\Phi\left(\frac{\alpha_{\mathrm{S}}(T^*)+\mu_0}{\sigma_Z^*}\right)\right)+\sigma_Z^*\Psi\left(\frac{\alpha_{\mathrm{S}}(T^*)+\mu_0}{\sigma_Z^*}\right)\right]\right]\frac{T^*}{c_r} \\ &\sim KT^*, \end{aligned} \tag{EC.8}$$

where $K = \sigma_X\zeta(\Psi(\mu_0/\sigma_0) + (1-p_{\mathrm{N}})\mu_0/\sigma_0)/(\sqrt{n_0}c_r)$. The asymptotic equivalence follows due to $\lim_{H\to\infty} T^* = \infty$ and $\lim_{H\to\infty} r^* = \infty$.

The rest of the proof has to consider the two cases $c - \delta_{\mathrm{on}}(1-2p_{\mathrm{N}})\mu_0/2 = 0$ and $c - \delta_{\mathrm{on}}(1-2p_{\mathrm{N}})\mu_0/2 > 0$ separately.

Assume first that $c - \delta_{\mathrm{on}}(1-2p_{\mathrm{N}})\mu_0/2 > 0$. Combining (EC.6) and (EC.8), we obtain

$$K(c_r + (c-\delta_{\mathrm{on}}(1-2p_{\mathrm{N}})\mu_0/2)T^*) \sim \zeta(H-T^*-\Delta)\sqrt{\frac{n_0\sigma_X^2 K}{(2n_0+K(T^*)^2)^3}}\phi(\sqrt{n_0}\mu_0/\sigma_X),$$

and with further simplifications

$$T^* \sim \left(\frac{\sqrt{n_0}\sigma_X\phi(\sqrt{n_0}\mu_0/\sigma_X)}{K^2(c-\delta_{\mathrm{on}}(1-2p_{\mathrm{N}})\mu_0/2)}\zeta(H-\Delta)\right)^{1/4}.$$

From (EC.8) it follows

$$r^* \sim \left(\frac{K^2\sqrt{n_0}\sigma_X\phi(\sqrt{n_0}\mu_0/\sigma_X)}{c-\delta_{\mathrm{on}}(1-2p_{\mathrm{N}})\mu_0/2}\zeta(H-\Delta)\right)^{1/4},$$

and we are done with the proof for the case $c - \delta_{\text{on}}(1 - 2p_{\text{N}})\mu_0/2 > 0$.

Now, assume $c - \delta_{\text{on}}(1 - 2p_{\text{N}})\mu_0/2 = 0$. Combining (EC.6) and (EC.8), we obtain

$$Kc_r \sim \zeta(H - T^* - \Delta)\sqrt{\frac{n_0\sigma_X^2 K}{(2n_0 + K(T^*)^2)^3}}\phi(\sqrt{n_0}\mu_0/\sigma_X),$$

and with further simplifications

$$T^* \sim \left(\frac{\sqrt{n_0}\sigma_X\phi(\sqrt{n_0}\mu_0/\sigma_X)}{K^2 c_r}\zeta(H - \Delta)\right)^{1/3}.$$

From (EC.8) it follows

$$r^* \sim \left(\frac{K\sqrt{n_0}\sigma_X\phi(\sqrt{n_0}\mu_0/\sigma_X)}{c_r}\zeta(H - \Delta)\right)^{1/3},$$

and we are done with the proof for the case $c - \delta_{\text{on}}(1 - 2p_{\text{N}})\mu_0/2 = 0$.

Using the asymptotic behavior of T^* and r^*, it is easy to show that

$$V^* \sim \zeta(H - \Delta)\left((1 - p_{\text{N}})\sigma_0\Psi(-\mu_0/\sigma_0) + p_{\text{N}}\sigma_0\Psi(\mu_0/\sigma_0)\right). \quad \square$$

C.5. Proofs for asymptotic results of Prop. 6 in section 3.6.2

Proof of Prop. 6 It is easy to check that $\lim_{P\to\infty} P_\rho = \zeta/\rho$ with fixed patient pool and that $\lim_{H\to\infty} P_\rho(T) = \zeta/\rho$ with fixed horizon, where convergence is uniform on the bounded domain $0 \le T \le T_{\max}$. Similarly, $\alpha'_{\text{N}} = I_{\text{N}}\rho/((1 - p_{\text{N}})\zeta) = \lim_{P\to\infty}\alpha_{\text{N}} = \lim_{H\to\infty}\alpha_{\text{N}}(T)$, and $\alpha'_{\text{S}} = I_{\text{S}}\rho/(p_{\text{N}}\zeta = \lim_{P\to\infty}\alpha_{\text{S}} = \lim_{H\to\infty}\alpha_{\text{S}}(T)$. Consider first $Tr > 0$:

$$\begin{aligned}
|V_\infty(T,r) - V(T,r)| &= e^{-\rho(T+\Delta)}\sigma_Z\left|\frac{\zeta}{\rho} - P_\rho(T)\right|\left((1 - p_{\text{N}})\left|\Psi\left(\frac{\alpha'_{\text{N}} - \mu_0}{\sigma_Z}\right) - \Psi\left(\frac{\alpha_{\text{N}}(T) - \mu_0}{\sigma_Z}\right)\right|\right.\\
&\qquad \left. + p_{\text{N}}\left|\Psi\left(\frac{\alpha'_{\text{S}} + \mu_0}{\sigma_Z}\right) - \Psi\left(\frac{\alpha_{\text{S}}(T) + \mu_0}{\sigma_Z}\right)\right|\right)\\
&\le \sigma_0\left|\frac{\zeta}{\rho} - P_\rho(T)\right|\left((1 - p_{\text{N}})\left|\Psi\left(\frac{\alpha'_{\text{N}} - \mu_0}{\sigma_Z}\right) - \Psi\left(\frac{\alpha_{\text{N}}(T) - \mu_0}{\sigma_Z}\right)\right|\right.\\
&\qquad \left. + p_{\text{N}}\left|\Psi\left(\frac{\alpha'_{\text{S}} + \mu_0}{\sigma_Z}\right) - \Psi\left(\frac{\alpha_{\text{S}}(T) + \mu_0}{\sigma_Z}\right)\right|\right),
\end{aligned}$$

where the inequality uses $\sigma_Z \le \sigma_0$ and $e^{-\rho(T+\Delta)} \le 1$. Because $\Psi(\cdot)$ is a bounded function in the domain, there is a constant C, independent of T and r, such that

$$|V_\infty(T,r) - V(T,r)| \le C\left|\frac{\zeta}{\rho} - P_\rho(T)\right|.$$

Because $P_\rho(T)$ converges uniformly to ζ/ρ, it follows that $V(T,r)$ converges uniformly to $V_\infty(T,r)$ when $Tr>0$. Consider now $Tr=0$:

$$\begin{aligned}|V_\infty(T,r)-V(T,r)| = \Big|&\frac{\zeta}{\rho}\max\{0,\,(1-p_{\rm N})\mu_0 - I_{\rm N}\rho/\zeta,\,-p_{\rm N}\mu_0 - I_{\rm S}\rho/\zeta\}\\ &- P_\rho(T)\max\{0,\,(1-p_{\rm N})\mu_0 - I_{\rm N}/P_\rho(T),\,-p_{\rm N}\mu_0 - I_{\rm S}/P_\rho(T)\}\Big|\\ \le &\left|\frac{\zeta}{\rho} - P_\rho(T)\right|\max\{0,\,(1-p_{\rm N})\mu_0 - I_{\rm N}\rho/\zeta,\,-p_{\rm N}\mu_0 - I_{\rm S}\rho/\zeta\}.\end{aligned}$$

Again, because $P_\rho(T)$ converges uniformly to ζ/ρ, it follows that $V(T,r)$ converges uniformly to $V_\infty(T,r)$ when $Tr=0$ and we are done proving that $V(T,r)$ converges uniformly to $V_\infty(T,r)$ as $P\to\infty$ or $H\to\infty$.

Due to uniform convergence, it follows that $\lim_{P\to\infty} V^*_{\rm P} = \lim_{H\to\infty} V^*_{\rm H} = \max_{T,r} V_\infty(T,r)$. We cannot guarantee a unique maximizer of $V_\infty(T,r)$. However, uniform convergence also guarantees that, if a unique maximizer $(T_\infty, r_\infty) = \arg\max_{T,r} V_\infty(T,r)$ exists, then $\lim_{P\to\infty} T^*_{\rm P} = \lim_{H\to\infty} T^*_{\rm H} = T_\infty$ and $\lim_{P\to\infty} r^*_{\rm P} = \lim_{H\to\infty} r^*_{\rm H} = r_\infty$. Thus, $\lim_{P\to\infty} Q^*_{\rm P} = \lim_{H\to\infty} Q^*_{\rm H} = r_\infty T_\infty/2$. □

Appendix D: Numerical comparative statics

This appendix provides the technical details for the numerical investigation of the sign of the following derivatives with respect to parameter b: $\mathrm{d}V^*/\mathrm{d}b$, $\mathrm{d}T^*/\mathrm{d}b$, $\mathrm{d}r^*/\mathrm{d}b$, and $\mathrm{d}Q^*/\mathrm{d}b$. The results are based on exploring the parameter space by evaluating the optimal design and expected net gain at representative points in the parameter space and recording the finite difference computation of the derivatives at each point using the envelope and implicit function theorems.

We consider only offline learning ($\delta_{\rm on}=0$) because it is equivalent to a shift in per-patient cost as discussed in section 3.5. We consider both fixed patient pool and fixed horizon, and let $P=\zeta H$ for fixed patient pool. To explore different shapes of setup costs, we consider polynomial functions $c_{\rm cap}(r) = c_r r^\theta$ and explore values for $c_r \ge 0$ and $\theta \ge 1$. We assume no fixed costs because those only affect the decision whether to run the trial or not, while we are interested in the effects when the trial is run. We use $\theta \ge 1$ to consider the more realistic scenario of convex setup costs because recruitment becomes harder as the trial size increases.

To explore the parameter space, we split the procedure in the four cases described in section 3.4 which are defined based on the setup cost function $c_{\rm cap}(r)$, the post-adoption population, either fixed patient pool or fixed horizon, and discount rate ρ.

We consider the range of parameters in Table EC.2 chosen with the following reasoning. We need to set a scale for value/money and time. We set the scale for value and money by fixing the sampling cost $c=1{,}000$ and sampling standard deviation $\sigma_X = 1{,}000$; this is without loss of generality because it is easy to check that a change in these parameters is equivalent to a scaled problem with appropriate compensation in other parameters[13]:

$$V(T,r;\beta c,c_r,\zeta) = \beta V(T,r;c,c_r/\beta,\zeta/\beta)$$
$$V(T,r;\gamma\sigma_X,\zeta,\mu_0) = V(T,r;\sigma_X,\gamma\zeta,\mu_0/\gamma)$$
$$V(T,r;\beta c,\gamma\sigma_X,c_r,\zeta,\mu_0,I_{\mathrm{N}},I_{\mathrm{S}}) = \beta V(T,r;c,\sigma_X,c_r/\beta,\zeta\gamma/\beta,\mu_0/\gamma,I_{\mathrm{N}}/\beta,I_{\mathrm{S}}/\beta)$$

for any $\beta > 0$ and $\gamma > 0$. We choose 1,000 as the fixed value to keep the units in the same scale as the application in section 4 for ease of interpretation.

We set the scale of time by fixing the time horizon at $H = 200$. We choose 200 again to keep the units in the same scale as the application in section 4, where each unit is a month.

Thus, we set all parameters in terms of c, σ_X, and H, using base case values similar in magnitude with the application in section 4, and exploring values one or two orders of magnitudes smaller or larger than the base case values.

Table EC.2 includes the parameters for all four cases but we present the results for each case independently because some parameters are only relevant for some cases (e.g., the discount rate is not relevant for Cases I and II because the discount rate needs to be zero) and to identify trends that differ in different cases. There are 10 degrees of freedom in these 13 parameters, after normalization of the values of c, σ_X, and H.

Table EC.2 Parameters explored in the numerical results

Parameter	Range of values
$c_{\mathrm{cap}}(r) = c_r r^\theta$	$c_r = 0; 1{,}000; 100; 10{,}000,\ \theta = 1,2,3$
$H\ (P = \zeta H)$	200
Post-adoption	fixed patient pool, fixed horizon
ρ	$0, 0.5, 0.1, 0.01/H$
σ_X	1,000
n_0	1,0.1,10
μ_0	$0; -1{,}000; 1{,}000$
c	1,000
$I_{\mathrm{N}}, I_{\mathrm{S}}$	$0, 0.01, 0.1 \times P\sigma_X/\sqrt{n_0}$
p_{N}	$0, 0.2, 0.4$
Δ	$0.1, 0.01, 0.3 \times H$
ζ	$100{,}000; 10{,}000; 1{,}000{,}000/H$
$T_{\max}, r_{\max}$	$H - \Delta$, 200

We report the fraction of instances where the derivatives are larger than zero. We exclude instances where the optimal design is found at a boundary, i.e., $Q^* = 0$, or $T^* = T_{\max}$ (for Cases I,

[13] The notation $V(T,r;b)$ makes the dependence of V on the parameters b explicit.

II, and IV), or $r^* = r_{\max}$ (for Cases I, III, and IV). We exclude this instances because the derivatives of the design variables are zero at these points (small changes cannot push the design out of extreme points) and we do not want the fractions to be biased by these instances.

Two computational issues are present in this analysis. First, the optimization problem to find T^* and r^* is nonconvex. We find the optimal design by initializing local optimization algorithms[14] at ten random starting points. To validate that errors in the optimization algorithm do not significantly bias the results, we compared the optimal design for 10,000 randomly selected instances using 100 vs. 10 random starting points and found a discrepancy in the optimal value in less than 0.2% instances. Second, we use finite centered differences to compute the derivatives at the optimal points. These computational issues explain a slight inconsistency between a few of the theoretical results in Appendix C.3 above and three of the entries in the numerical results of Table EC.4 and EC.6 below. However, the errors are not large enough to alter the insights of this analysis.

In Table EC.3, we summarize the results of the numerical comparative statics for Case IV trials. The "number of instances" column represents the number of instances with an optimal design found in the interior of the domain. The number of instances for P and H are smaller than the rest because they are only valid for fixed patient pool and fixed horizon, respectively. The other derivatives pool the results for fixed patient pool and fixed horizon together. The number of parameter combinations tested for Case IV were 137,781 and we found an optimal design in the interior of the domain for 56,272 (41%). We discuss these results in section 3.5.

Table EC.3 **Numerical comparative statics for Case IV trials**

Parameter b	Number of instances	$\mathrm{d}V^*/\mathrm{d}b > 0$	$\mathrm{d}T^*/\mathrm{d}b > 0$	$\mathrm{d}r^*/\mathrm{d}b > 0$	$\mathrm{d}Q^*/\mathrm{d}b > 0$
P	28,224	100%	1.3%	99.3%	98.7%
H	28,048	100%	100%	100%	100%
ρ	56,272	0.0%	2.0%	54.9%	0.0%
Δ	56,272	0.0%	49.8%	0.0%	0.0%
n_0	56,272	0.0%	99.9%	11.7%	96.2%
σ_X	56,272	100%	21.8%	100%	97.6%
c	56,272	0.0%	0.0%	0.0%	0.0%
c_r	56,272	0.0%	99.8%	0.0%	0.2%

In Table EC.4, we present the results for Case I trials. Because Δ has no impact on the expected net gain in such trials, we only considered $\Delta = 0$. The number of parameter combinations tested was 729 of which 648 (89%) were in the interior of the domain. We see the presence of numerical error due the optimization and numerical computation of derivatives: $\mathrm{d}V^*/\mathrm{d}\sigma_X$ and $\mathrm{d}Q^*/\mathrm{d}\sigma_X$ are theoretically greater than zero but we find 1.1% and 1.9%, respectively, of instances where this does not hold and $\mathrm{d}V^*/\mathrm{d}n_0$ is theoretically smaller than zero but we find 0.2% instances where

[14] We use the MATLAB® fmincon function with the SQP algorithm.

this does not hold. This provides further evidence that the errors induced by the analysis exist but are small enough not to affect the insights of the analysis.

The results yield similar insights to those yielded by the discussion of Case IV trials with some notable differences. First, 92.0% of instances have $\mathrm{d}Q^*/\mathrm{d}P > 0$ compared to 98.7% in Case IV trials. While both have the same direction in a majority of instances, the proportion is significantly different. Second, 72.7% of instances have $\mathrm{d}Q^*/\mathrm{d}n_0 > 0$ compared with 96.2% in Case IV trials. The difference between Case I and IV may be due to the optimal sample size for Case I (mean=1,630) being much larger than the that for Case IV (mean=210).

Table EC.4 **Numerical comparative statics for Case I trials**

Parameter b	Number of instances	$\mathrm{d}V^*/\mathrm{d}b > 0$	$\mathrm{d}Q^*/\mathrm{d}b > 0$
P	648	100%	92.0%
n_0	648	0.2%	72.7%
σ_X	648	98.9%	98.1%
c	648	0.0%	0.0%

In Table EC.5, we present the results for Case II trials. Of 15,309 parameter combinations, we find interior solutions for 10,957 (72%). We see small errors in the expected net gain derivative with respect to σ_X. The most notable difference with the results for Case IV is that $\mathrm{d}T^*/\mathrm{d}\sigma_X > 0$ for 73.2% of instances compared to 97.6% of Case IV in which $\mathrm{d}Q^*/\mathrm{d}\sigma_X > 0$.

Table EC.5 **Numerical comparative statics for Case II trials**

Parameter b	Number of instances	$\mathrm{d}V^*/\mathrm{d}b > 0$	$\mathrm{d}T^*/\mathrm{d}b > 0$
P	5,093	100%	63.2%
H	5,864	100%	100%
ρ	10,957	0.0%	0.0%
Δ	10,957	0.0%	0.0%
n_0	10,957	0.0%	97.7%
σ_X	10,957	100%	73.2%
c	10,957	0.0%	0.0%

Finally, Table EC.6 presents the results for Case III trials. Of 6,561 parameter combinations, we find interior solutions for 5,624 (86%). We have small numerical errors that do not match the theoretical results for the derivatives with respect to σ_X and n_0. The most relevant result is that $\mathrm{d}r^*/\mathrm{d}n_0 > 0$ for 75.2% of instances compared to 96.2% of Case IV trials in which $\mathrm{d}Q^*/\mathrm{d}n_0 > 0$.

Appendix E: Computation of CPCS and power

In section 4, we defined the CPCS as the conditional probability of correct selection of a technology for adoption, given $W = w$:

$$\mathrm{CPCS}(w) = \Pr(\mathcal{D} = \mathcal{D}^{orac} \mid W = w),$$

Table EC.6 **Numerical comparative statics for Case III trials**

Parameter b	Number of instances	$\mathrm{d}V^*/\mathrm{d}b>0$	$\mathrm{d}r^*/\mathrm{d}b>0$
P	5,624	100%	95.7%
n_0	5,624	0.1%	75.2%
σ_X	5,624	99.6%	99.3%
c	5,624	0.0%	0.0%
c_r	5,624	0.0%	0.0%

where $\mathcal{D}^{orac}$ is the oracle's adoption decision. In this section, we show how to compute it.

First of all, note that the optimal adoption decision depends on Z_{Tr}, which given W has the following distribution:

$$Z_{Tr}\mid W\sim\mathcal{N}\left(\frac{n_0\mu_0+TrW/2}{n_0+Tr/2}\ ,\ \frac{2Tr\sigma_X^2}{(2n_0+Tr)^2}\right).$$

If $W>\alpha_{\mathrm{N}}(T)$, the oracle adoption decision is N. Thus, the CPCS simplifies to

$$\mathrm{CPCS}(w)=\Pr(Z_{Tr}>\alpha_{\mathrm{N}}(T)\mid W=w).$$

We can then compute $\mathrm{CPCS}(w)=1-\Phi(U_{\mathrm{N}})$, where

$$U_{\mathrm{N}}=\frac{2n_0(\alpha_{\mathrm{N}}(T)-\mu_0)+Tr(\alpha_{\mathrm{N}}(T)-w)}{\sigma_X\sqrt{2Tr}}.$$

If $w<-\alpha_{\mathrm{S}}(T)$, the oracle's adoption decision is S, and we obtain $\mathrm{CPCS}(w)=\Pr(Z_{Tr}<-\alpha_{\mathrm{S}}(T)\mid W=w)=1-\Phi(U_{\mathrm{S}})$, where

$$U_{\mathrm{S}}=\frac{2n_0(\alpha_{\mathrm{S}}(T)+\mu_0)+Tr(\alpha_{\mathrm{S}}(T)+w)}{\sigma_X\sqrt{2Tr}}.$$

Similarly, if $-\alpha_{\mathrm{S}}(T)\le w\le\alpha_{\mathrm{N}}(T)$, the oracle adoption decision is M, and we obtain $\mathrm{CPCS}(w)=\Pr(-\alpha_{\mathrm{S}}(T)\le Z_{Tr}\le\alpha_{\mathrm{N}}(T)\mid W=w)=\Phi(U_{\mathrm{N}})+\Phi(U_{\mathrm{S}})-1$.

The final closed-form expression of CPCS is then

$$\mathrm{CPCS}(w)=\begin{cases}1-\Phi(U_{\mathrm{N}}), & w>\alpha_{\mathrm{N}}(T)\\ 1-\Phi(U_{\mathrm{S}}), & w<-\alpha_{\mathrm{S}}(T)\\ \Phi(U_{\mathrm{N}})+\Phi(U_{\mathrm{S}})-1, & -\alpha_{\mathrm{S}}(T)\le w\le\alpha_{\mathrm{N}}(T)\end{cases}$$

The computation of power requires the following definitions. Let α be the type I error and q_x be the $1-x$ quantile of a standard normal distribution. A two-sided hypothesis test, rejects the (null) hypothesis that the population mean W is zero if the sample average $\bar{X}=2/(Tr)\sum_{i=1}^{Tr/2}X_i$ is larger than $q_{\alpha/2}\sigma_X/\sqrt{Tr/2}$, or smaller than $-q_{\alpha/2}\sigma_X/\sqrt{Tr/2}$. The power is the probability of rejection given $W=w$:

$$\begin{aligned}\mathrm{power}(w)&=\Pr\left(\bar{X}>\frac{\sigma_X}{\sqrt{Tr/2}}q_{\alpha/2}\cup\bar{X}<-\frac{\sigma_X}{\sqrt{Tr/2}}q_{\alpha/2}\,\middle|\,W=w\right)\\&=\Pr\left(\bar{X}>\frac{\sigma_X q_{\alpha/2}}{\sqrt{Tr/2}}\,\middle|\,W=w\right)+\Pr\left(\bar{X}<-\frac{\sigma_X q_{\alpha/2}}{\sqrt{Tr/2}}\,\middle|\,W=w\right)\\&=1-\Phi\left(q_{\alpha/2}-\sqrt{\frac{Tr}{2\sigma_X^2}}w\right)+1-\Phi\left(q_{\alpha/2}+\sqrt{\frac{Tr}{2\sigma_X^2}}w\right).\end{aligned}$$

Appendix F: Some special parameter settings that allow fully sequential trials

In a fully sequential trial, the decision to continue the trial or to stop sampling is made after the outcome of each patient pair is observed, as for an optimal stopping time problem. The sequential version of the one-stage optimal trial design problem in section 2.5, with fixed rate of recruitment r, is written in Appendix F.1 below. If we can show that this problem is equivalent (after suitable reparameterization) to an existing fully sequential trial model, then the one-shot trials proposed in section 2.5 can be run as fully adaptive trials, at least for the case of a fixed rate of recruitment. The fixed recruitment rate can then be optimized. Appendix F.2 affirms that this can be done for four special parameter settings to match the model of Chick et al. (2017a). For these special settings, then, we can allow the duration of the trial T to be response adaptive to observed outcomes, for any given fixed rate of recruitment $r > 0$, with a simple transformation of a few parameters.

This section assumes a fixed patient pool ($P(T) = P$) and that the recruitment rate r is fixed. The results of this section are used in numerical experiments in section 5 to assess the benefit of optimizing recruitment rate in a one-shot trial, of shifting from a one-stage trial to a sequential trial that adapts trial duration, or of optimizing the recruitment rate of a sequential trial that adapts trial duration (if one of the four special parameter settings holds).

F.1. Optimize fixed recruitment, with optimal adaptive stopping time.

The model in section 2 assumes that T and r are continuous, whereas the decision epochs are discrete. We first recall a related discrete-time sequential model to introduce notation and fix ideas. We then adapt the continuous-time model of section 2 to a corresponding discrete-time model.

Chick et al. (2017a) provided a fully sequential two-armed trial with optimal adaptive stopping time, and which essentially assumes $p_{\mathrm{N}} = 0$ and fixed patient pool in terms of our model. Alban et al. (2018) extended that model to allow for pragmatic trials with more general p_{N}. Following that model, we define decision epochs $t = 0, 1, \dots, Q_{\max} - 1$. At each decision epoch, measurements of health outcome and treatment cost are observed (with appropriate delay) for a pair of patients randomized to each arm of the trial. An action $a_t \in \{0, 1\}$ is made to continue sampling ($a_t = 1$) or stop sampling ($a_t = 0$) before enrolling each patient pair (hence the term fully sequential). Once recruitment stops, at stopping time $Q = \min\{t : a_t = 0\}$, we observe the outcomes of patients in the *pipeline* – those who have been randomized but whose outcomes have not been observed yet – before making the adoption decision. A policy, π, maps available knowledge (prior information, plus acquired data) to an action at each decision epoch. Let $\mathbb{E}_\pi[\,\cdot \mid K_0\,]$ denote the expectation induced by policy π given the prior information set $K_0 = (\mu_0, n_0)$. If $Q = 0$, the trial does not run, and the adoption decision is made immediately, based on the prior information alone.

We now adapt the model in section 2 to discrete-time. Let $\tau = \lceil r\Delta/2 \rceil$ be the number of patient pairs enrolled in the trial during the follow-up period of length Δ and let $\tilde{\rho} = e^{2\rho/r} - 1$ be the discrete discount rate per patient pair. We write the expected net gain for a discrete time trial with recruitment rate r and policy π, which sequentially determines $Q \in \{0,1,\ldots,Q_{\max}\}$, as:

$$V(\pi,r) = -\mathbf{1}_{Q>0} c_{\text{cap}}(r) + \mathbb{E}_\pi \left[\sum_{t=0}^{Q-1} \frac{\delta_{\text{on}}(1-2p_{\text{N}})X_{t+1} - 2c}{(1+\tilde{\rho})^t} \middle| K_0 \right] + \mathbb{E}_\pi \left[\frac{\mathbf{1}_{\mathcal{D}=\text{N}}((1-p_{\text{N}})P_\rho(2Q/r)W - I_{\text{N}}) + \mathbf{1}_{\mathcal{D}=\text{S}}(-p_{\text{N}}P_\rho(2Q/r)W - I_{\text{S}})}{(1+\tilde{\rho})^{\mathbf{1}_{Q>0}(Q+\tau)}} \middle| K_0 \right]. \tag{EC.9}$$

A policy π_r^* that maximizes $V(\pi,r)$ over non-anticipative policies π is said to optimize the trial duration for a given fixed r. An optimum can be found by solving the univariate optimization $\max_r V(\pi_r^*,r)$, assuming the computability of π_r^* and $V(\pi_r^*,r)$, for $r \in [0,r_{\max}]$.

F.2. Equivalence for four special cases

If we assume a fixed patient pool ($P(T) = P$), we may identify four special parameter settings that permit the computation of the optimal sequential policy π_r^* and expected net gain $V(\pi_r^*,r)$ in (EC.9) for any given r using the methods of Chick et al. (2017a,b):

To this end, we recall the objective function of the fully sequential trial in Chick et al. (2017a).

$$V(\pi) = \mathbb{E}_\pi \left[\left\{ \sum_{t=0}^{Q-1} \frac{-c + \delta_{\text{on}} X_{t+1}}{(1+\tilde{\rho})^t} \right\} + \frac{\mathbf{1}_{\mathcal{D}=\text{N}}(P_\rho W - I)}{(1+\tilde{\rho})^{\mathbf{1}_{Q>0}(Q+\tau)}} \right]. \tag{EC.10}$$

Here, the policy π is a nonanticipative function which selects an action a_t to either continue sampling, or to stop, on the basis of prior knowledge and any observations seen by time t, for $t = 0,1,2,\ldots,Q$. After stopping and observing all the data, the new alternative is selected as best if $P_\rho W - I \geq 0$.

We first explore the differences between (EC.9) and (EC.10) related to the fixed costs of the trial. The fixed cost $c_{\text{cap}}(r)$ in (EC.9) only affects the decision of running the trial or not, captured by action a_0. Such decision can also be made by computing the value of the optimal design with zero fixed costs, and then evaluating whether it overcomes the fixed costs. Thus, fixed costs do not disturb the equivalence of the optimal trial design once the decision to observe the first patient pair is taken, even though they do affect the optimal choice of a_0.

We now explore equivalence of the sequential sampling models, assuming a_0 indicates the first patient pair is to be observed, for some parameter settings.

F.2.1. Current practice is standard treatment. When $p_{\text{N}} = 0$, (EC.9) becomes

$$V(\pi) = -\mathbf{1}_{Q>0} c_{\text{cap}}(r) + \mathbb{E}_\pi \left[\sum_{t=0}^{Q-1} \frac{\delta_{\text{on}} X_{t+1} - 2c}{(1+\tilde{\rho})^t} \right] + \mathbb{E}_\pi \left[\frac{\mathbf{1}_{\mathcal{D}=\text{N}}(P_\rho W - I_{\text{N}})}{(1+\tilde{\rho})^{\mathbf{1}_{Q>0}(Q+\tau)}} \right],$$

which is equivalent to (EC.10) by letting $c' = 2c$ and $I' = I_{\text{N}}$.

F.2.2. Forcing the decision to adopt one of the two HTs, undiscounted rewards. When the adoption decision is forced to be N or S with undiscounted rewards[15] ($\tilde{\rho}=0$), we can use $\mathbf{1}_{\mathcal{D}=\mathrm{S}} = 1-\mathbf{1}_{\mathcal{D}=\mathrm{N}}$ such that (EC.9) becomes

$$V(\pi) = -\mathbf{1}_{Q>0}c_{\mathrm{cap}}(r) - p_{\mathrm{N}}P\mu_0 - I_{\mathrm{S}} + \mathbb{E}_\pi\left[\sum_{t=0}^{Q-1}\delta_{\mathrm{on}}(1-2p_{\mathrm{N}})X_{t+1} - 2c + \mathbf{1}_{\mathcal{D}=\mathrm{N}}(PW - (I_{\mathrm{N}} - I_{\mathrm{S}}))\right]$$

If $p_{\mathrm{N}} < 1/2$, then we can divide through by $1-2p_{\mathrm{N}}$ and add the constant $Pp_{\mathrm{N}}\mu_0 - I_{\mathrm{S}}$ without changing the optimal π. Thus, the optimal π maximizes:

$$\mathbb{E}_\pi\left[\sum_{t=0}^{Q-1}\delta_{\mathrm{on}}X_{t+1} - \frac{2c}{1-2p_{\mathrm{N}}} + \mathbf{1}_{\mathcal{D}=\mathrm{N}}\left(\frac{P}{1-2p_{\mathrm{N}}}W - \frac{I_{\mathrm{N}}-I_{\mathrm{S}}}{1-2p_{\mathrm{N}}}\right)\right],$$

which is in the form of (EC.10) when we let $c' = 2c/(1-2p_{\mathrm{N}})$, $P' = P/(1-2p_{\mathrm{N}})$, and $I' = (I_{\mathrm{N}} - I_{\mathrm{S}})/(1-2p_{\mathrm{N}})$.

If $p_{\mathrm{N}} = 1/2$, the optimal π maximizes

$$\mathbb{E}_\pi\left[\sum_{t=0}^{Q-1}2c + \mathbf{1}_{\mathcal{D}=\mathrm{N}}(PW - (I_{\mathrm{N}} - I_{\mathrm{S}}))\right],$$

which is in the form of (EC.10) when $\delta'_{\mathrm{on}} = 0$, $c' = 2c$, $P' = P$, and $I' = I_{\mathrm{N}} - I_{\mathrm{S}}$.

F.2.3. No switching costs and undiscounted rewards. When $I_{\mathrm{N}} = I_{\mathrm{S}} = 0$, then it is optimal to adopt N or S. When rewards are not discounted ($\tilde{\rho}=0$) the transformation in Appendix F.2.2 is also valid in this setting.

F.2.4. No switching costs and $\mu_0 = 0$. When $I_{\mathrm{N}} = I_{\mathrm{S}} = \mu_0 = 0$, whether rewards are discounted or not, we obtain a special case of the above subsection that can additionally accommodate scenarios with discounted rewards. We again use $\mathbf{1}_{\mathcal{D}=\mathrm{S}} = 1-\mathbf{1}_{\mathcal{D}=\mathrm{N}}$ in (EC.9) to obtain

$$V(\pi) = -\mathbf{1}_{Q>0}c_{\mathrm{cap}}(r) + \mathbb{E}_\pi\left[\sum_{t=0}^{Q-1}\frac{\delta_{\mathrm{on}}(1-2p_{\mathrm{N}})X_{t+1} - 2c}{(1+\tilde{\rho})^t} + \frac{\mathbf{1}_{\mathcal{D}=\mathrm{N}}(P_\rho W)}{(1+\tilde{\rho})^{\mathbf{1}_{Q>0}(Q+\tau)}}\right].$$

If $p_{\mathrm{N}} < 1/2$, then we can divide through by $1-2p_{\mathrm{N}}$ and obtain the optimal π by solving (EC.10) with $c' = 2c/(1-2p_{\mathrm{N}})$ and $P'_\rho = P_\rho/(1-2p_{\mathrm{N}})$. If $p_{\mathrm{N}} = 1/2$ we obtain the optimal π by solving (EC.10) with $\delta'_{\mathrm{on}} = 0$, $c' = 2c$, and $P'_\rho = P_\rho$.

Appendix G: Supplementary figures for the application to the ProFHER trial

This section provides supplementary numerical analysis for the application to the ProFHER trial in section 4. Appendix G.1 gives sensitivity analysis for the expected net gain of a trial and optimal trial as a function of several key parameters that describe the value of a trial. Appendix G.2 illustrates numerically the quality of the asymptotic results for the various scenarios. Appendix G.1.4 explores online versus offline learning.

[15] Alban et al. (2018) incorrectly claim that this result is also valid with discounted rewards.

G.1. Additional sensitivity analysis

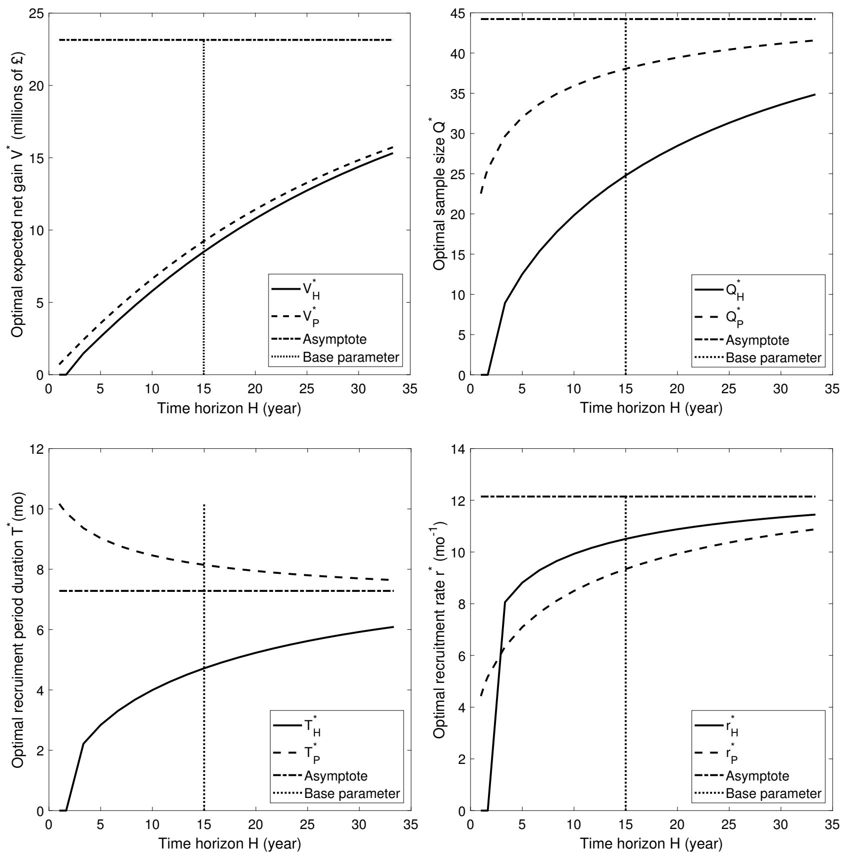
Appendix G.1.1 gives sensitivity analysis to assumptions to the size of the post-adoption population. Appendix G.1.2 does so for the discount rate. Appendix G.1.3 gives sensitivity analysis for the fixed costs of changing technology, and the fraction of patients on the new health technology.

G.1.1. Sensitivity to the post-adoption population. For ease of exposition, we fix $P = \zeta H$ and analyze the effect of a change in H for both fixed horizon and fixed patient pool, while keeping the remaining base case parameters constant. Figure EC.1 presents the results for the optimal expected net gain, sample size, recruitment duration, and recruitment rate, along with the asymptotes derived in section 3.6.2. The optimal sample size is increasing in H. The more interesting result is how the additional patients are obtained in terms of recruitment duration and rate. The optimal recruitment rate is increasing under both fixed horizon and fixed patient pool. However, the optimal recruitment duration is increasing for fixed horizon but decreasing for fixed patient pool: T^*_{H} approaches the asymptote from below, while T^*_{P} approaches it from above. In numerical experiments for fixed patient pool, a longer trial penalizes the expected net gain more for larger P than for smaller P due to greater discounting of a larger value. In contrast, for fixed horizon, the penalty of discounting is moderated by a decreasing value of the post-adoption population for longer trials. The optimal expected net gain V^* is increasing in H as shown in section 3.5. Due to the high incidence rate in this application, it is optimal to run the trial even for a short time horizon. However, a time horizon shorter than 20 months does not justify the trial under a fixed horizon.

While the asymptotic approximations are accurate for Cases I–III, particularly in undiscounted scenarios (see Appendix G.2 below), the asymptotes are not good approximations in the range of interest of our application. However, the optimal expected net gain and trial design do approach the asymptotes for larger time horizons.

G.1.2. Sensitivity to the discount rate. Figure EC.2 shows the optimal expected net gain, sample size, recruitment duration, and recruitment rate as a function of the discount rate, keeping all other parameters constant. We note two important observations. First, the optimal expected net gain and design for a fixed patient pool are much more sensitive to the discount rate than for the fixed horizon: the recruitment duration increases steeply as the discount rate goes to zero. In section 3.4 we showed that in a scenario with fixed patient pool and no discounting, it is optimal to set the recruitment duration to $T_{\max}$, where $T_{\max}$ can be arbitrarily large. If $T_{\max} = 10$ years, the optimal sample size under the undiscounted fixed patient pool scenario is 170, an example of a situation where the value-based design recruits more patients than the classical design.

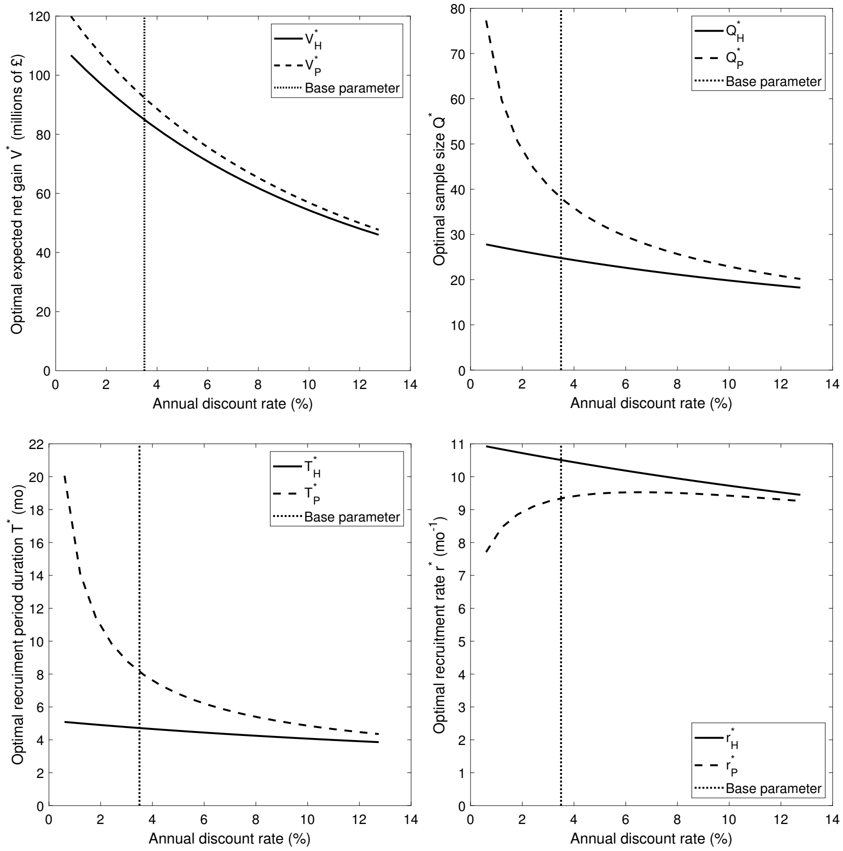
Figure EC.1 Optimal expected net gain, sample size, recruitment duration, and recruitment rate as a function of the time horizon.



Second, with a fixed horizon, both recruitment duration and rate are decreasing with the discount rate. With a fixed patient pool, we observe a decrease in recruitment duration but an inverse U-shaped optimal recruitment rate, increasing for an annual discount rate below 7%. The U-shaped behavior illustrates two opposing effects: (i) a larger discount rate prompts quicker action through a larger recruitment rate; (ii) a larger discount rate reduces the potential gains by reducing the effective post-adoption population, prompting reduced spending and lower recruitment rates.

G.1.3. Sensitivity to the fraction of patients on the new HT, p_{N} and fixed costs of changing technology. Our base case parameters include $I_{\mathrm{N}} = I_{\mathrm{S}} = \mu_0 = 0$, so there are no fixed costs associated with changing health technology, which imply that p_{N} has no effect on the expected net gain or optimal trial length (see section 3.5). Here, we consider scenarios where $I_{\mathrm{N}} = I_{\mathrm{S}} = £10$Mill and $I_{\mathrm{N}} = I_{\mathrm{S}} = £100$Mill and a range of values for p_{N} while keeping the remaining base case parameters fixed. Figure EC.3 shows the optimal expected net gain and sample size as a function of p_{N}. For $I_{\mathrm{N}} = I_{\mathrm{S}} = £10$Mill, p_{N} has a negligible effect on Q^* and a small effect on the expected net gain. For $I_{\mathrm{N}} = I_{\mathrm{S}} = £100$Mill, there is a substantial effect on expected net gain and a noticeable difference in the sample size for the fixed patient pool scenario.

Figure EC.2 Optimal expected net gain, sample size, recruitment duration, and recruitment rate as a function of the discount rate.



We observe that I_{N}, I_{S}, and p_{N} are only relevant to the optimal design when the switching costs are large. By inspecting (8), we see that the switching costs only appear in $\alpha_{\mathrm{N}}(T)$ and $\alpha_{\mathrm{S}}(T)$, which are further divided by σ_Z. If $\alpha_{\mathrm{N}}(T)$ or $\alpha_{\mathrm{S}}(T)$ are similar in magnitude to σ_Z, then the design will have a significant dependency on I_{N}, I_{S}, and p_{N}. As an example, for a fixed horizon with $p_{\mathrm{N}} = 0.39$, the ratio $\alpha_{\mathrm{N}}(T^*_{\mathrm{H}})/\sigma_Z$ is 0.072 for $I_{\mathrm{N}} = £10$Mill and 0.723 for $I_{\mathrm{N}} = £100$Mill, respectively, explaining why we observe a noticeable difference only for the latter scenario.

G.1.4. Online vs. offline learning. Consider the base case parameters introduced in section 4. Because online and offline learning are equivalent when $\mu_0 = 0$, we evaluate the difference between online and offline learning for a range of values taken by μ_0. We do not see any difference in Figure EC.4 as the lines overlap. We do not observe much larger differences by reducing the post-adoption population (P for fixed patient pool and H for fixed horizon).

G.2. Asymptotic analysis

This section provides numerical results for variations on the ProFHER trial, in order to give insights as to the asymptotic behavior for the four cases in the taxonomy of value-based designs in Table 1 of the main paper.

Figure EC.3 Optimal expected net gain (left) and sample size (right) as a function of p_{N}.

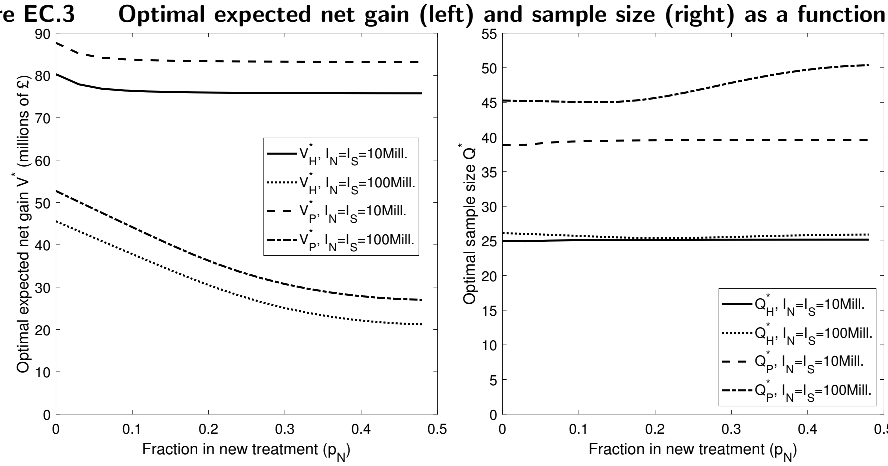
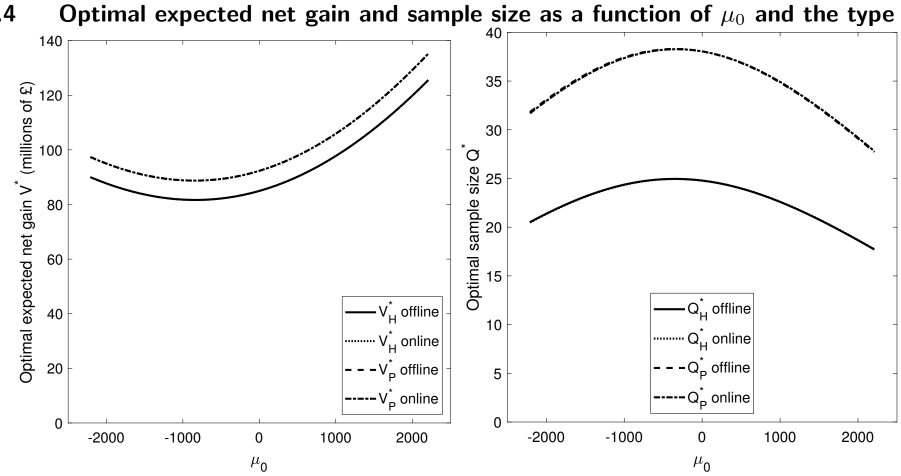


Figure EC.4 Optimal expected net gain and sample size as a function of μ_0 and the type of learning.



G.2.1. Asymptotics ($P(T) \to \infty$) for Cases I and II. Consider the base case parameters introduced in section 4. To force Cases I and II, we let $c_{\text{cap}}(r) = £960,000$ independent of the recruitment rate, and let $r_{\max} = \check{r} = 7.8$/month. Figure EC.5 shows how the optimal sample size increases as a function of H (left subfigure, for the fixed horizon case) and P (right subfigure, for the fixed patient pool case) when ρ is as in the base case parameters and $\rho = 0$. Similarly, Figure EC.6 plots the optimal expected net gain. Plotted with dotted and dash-dotted lines are the asymptotic approximations that were derived in section 3.6. Horizontal dotted lines correspond to the approximations with discounted rewards, increasing dash-dotted lines to those without discounted rewards.

The approximations with undiscounted rewards are close to the actual values in the range plotted, with a better fit for fixed patient pool (the lines are overlapping in the figures). This is due to $I_{\mathrm{N}} = I_{\mathrm{S}} = \mu_0 = 0$, and $P(T^*)\sigma_0 \gg c\check{r}T^*$. The approximations for discounted rewards are accurate for the optimal sample size under a fixed patient pool, but, for the range of values under consideration, the discounted approximations are less accurate.

Figure EC.5 The optimal sample size as a function of H for fixed horizon (left) and P for fixed patient pool (right) for Cases I and II.

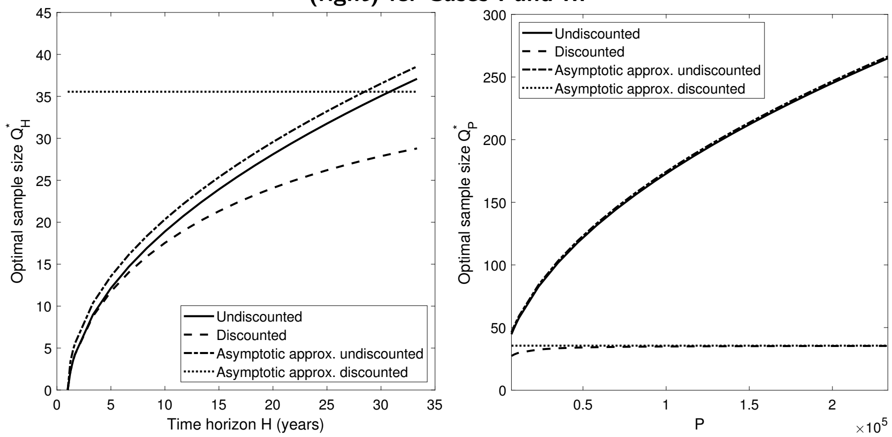
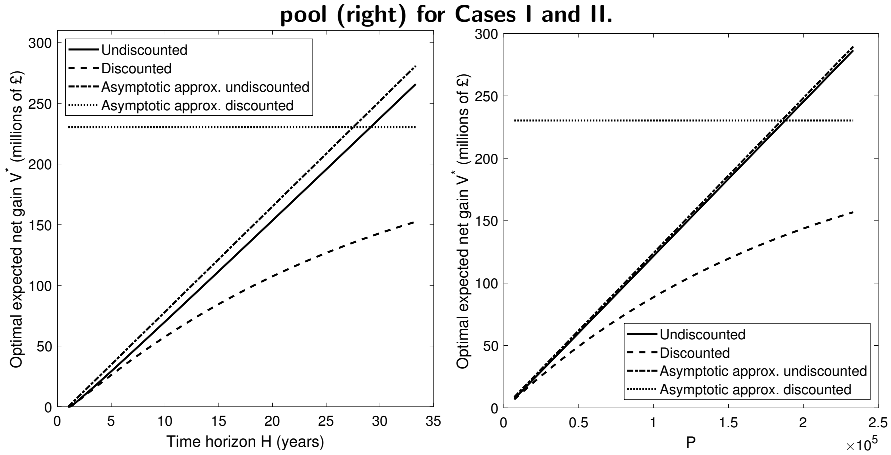


Figure EC.6 The optimal expected net gain as a function of H for fixed horizon (left) and P for fixed patient pool (right) for Cases I and II.



G.2.2. Asymptotics $P(T) \to \infty$ for Case III. We can force Case III by letting $c_{\text{cap}}(r) = c_{\text{fix}} + c_r r$, $\rho = 0$ and a fixed patient pool. The results are similar to Cases I and II (data not shown).

G.2.3. Asymptotics ($P(T) \to \infty$) for Case IV. In Appendix G.1.1, we showed the asymptotic approximations for Case IV with $\rho > 0$. Here, we explore the asymptotic approximations with undiscounted rewards ($\rho = 0$). We assume a setup cost function of the form: $c_{\text{cap}}(r) = c_{\text{fix}} + c_r r$. We assume that half of the setup costs of the trial were fixed (as in section 4) and the other half represent marginal costs, obtaining the following estimates: $c_{\text{fix}} = c_{\text{cap}}(\check{r})/2 = £480{,}000$; $c_r = c_{\text{cap}}(\check{r})/2/\check{r} = £5{,}080$ per year. Figure EC.7 shows the results for the optimal expected net gain and design variables. We find that the approximations for the optimal design variables are poor but for the expected net gain are reasonably close.

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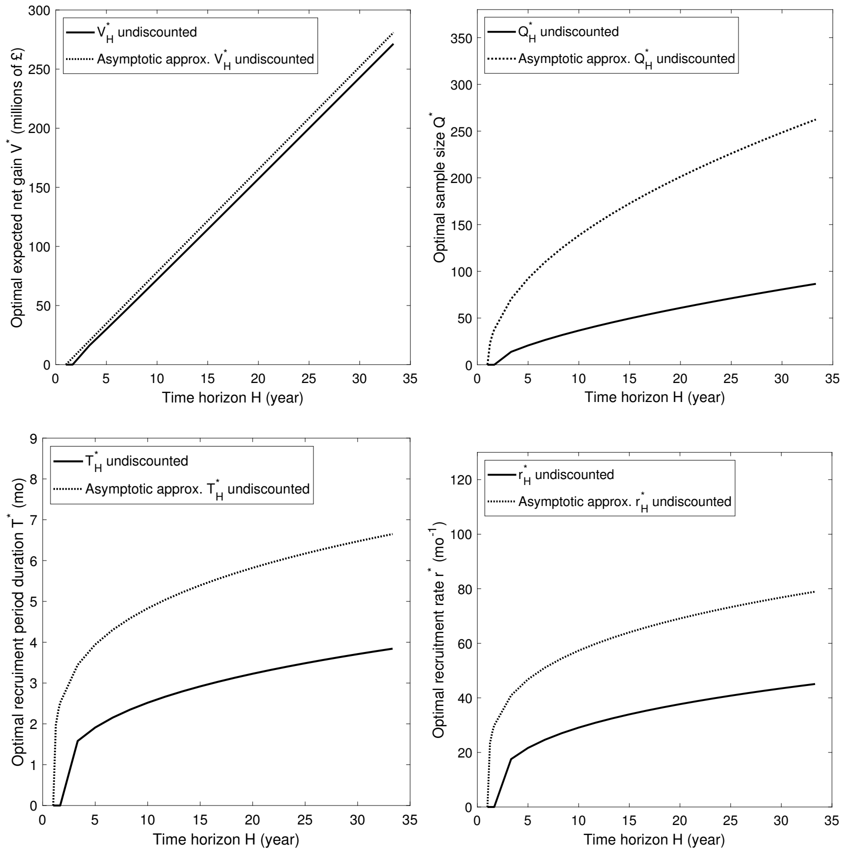
Figure EC.7 Optimal expected net gain, sample size, recruitment duration, and recruitment rate as a function of the time horizon.



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