Part I
Model design

In the main text, we mentioned three main parameters: the placebo rate p_{placebo} (hereafter shortened to p_{pl}), the efficacy of efficacious stool p_{eff}, and the frequency of efficacious donors f_{eff}.

As will be discussed below, correctly relating p_{pl} and p_{eff} requires a hidden parameter. This parameter is not important for the simulations in the main text, but it is important when drawing random variates $(p_{\text{pl}}, p_{\text{eff}})$ from a distribution.

1 Placebo rate and treatment efficacy

In our model, a patient in the treatment arm can respond to the treatment under one of three scenarios:

1. the donor was inefficacious and the patient responded because of the placebo effect,
2. the donor was efficacious and the patient would have responded even if they had been given a placebo, or
3. the donor was efficacious and the patient would *not* have responded if they had been given only the placebo.

We account for these three possibilities by treating the two effects—an effect from efficacious stool and the placebo effect—as independent.

Specifically, we say that efficacious stool has some "active ingredient" that, in the absence of a placebo effect, would cause a fraction p_{ing} of patients to respond. The efficacy rate p_{eff} of treatment with efficacious stool will be higher than this active ingredient efficacy p_{ing} because a patient can respond to the placebo. If a fraction p_{pl} of patients would respond to the placebo alone, then:

$$1 - p_{\text{eff}} = (1 - p_{\text{ing}})(1 - p_{\text{pl}}), \tag{1}$$

that is, when a patient is administered efficacious stool, the patient does not respond only if they do not respond to the active ingredient *and* they do not respond to the placebo. Eq. (1) is equivalent to

$$p_{\text{eff}} = p_{\text{ing}} + p_{\text{pl}} - p_{\text{ing}}p_{\text{pl}}. \tag{2}$$

2 Drawing random variates

2.1 Distribution of parameters values

In the simplest use case for the model, the model parameters are fixed point estimates. In a more complex use, the parameters are each drawn from a probability distribution, allowing for some uncertainty about the exact values of the parameters while simulating. "Drawing from" a distribution could either mean drawing random sets of parameters or specifying a Bayesian prior distribution for the parameter.

In this study, we used the beta distribution for the parameters because:

- The parameters are all probabilities of Bernoulli trials (i.e., a "coin flip" that answers, for example, whether a patient responds to treatment) and the beta distribution is the conjugate prior for the binomial distribution.

- The hyperparameters of the beta distribution are easy to interpret. Beta(s, f) corresponds to s Bernoulli trial successes and f failures. It has a "strength" of $s+f$ (i.e., the prior data and the collected data will have equal weight in determining the posterior after $s + f$ "coin flips" have been observed in the experimental data) and places the mean estimate of the parameter at $s/(s + f)$.

In clinical practice, it is the patient who responds to treatment or not. For the purposes of the mathematics, it is more convenient to say that the *donor* succeeded (i.e., a patient treated with stool from that donor responded) or failed (i.e., the patient did not respond to treatment).

For example, consider the clinical trial results [3] presented in main text, where 1 of 6 donors appeared efficacious. The point estimate for f_{eff} is just 1/6, but finding 1 of 6 donors efficacious would be inconsistent with, say, $f_{\text{eff}} = 1/3$. It could be more conservative, then, to run simulations in which:

- f_{eff} is drawn from Beta$(A_{\text{feff}}, B_{\text{feff}})$, where A_{feff} is the number of efficacious donors previously observed and B_{feff} is the number of inefficacious donors

- p_{pl} is drawn from Beta$(A_{\text{pl}}, B_{\text{pl}})$, where A_{pl} is the number of patients in the placebo arm who responded and B_{pl} is the number who did not respond, and

Clinical trial result	Parameter	Point estimate	A	B
2 of 37 in placebo arm responded	p_{placebo}	$2/37 = 0.054$	2	35
1 of 6 donors appeared efficacious	f_{eff}	$1/6 = 0.17$	1	5
7 of 18 patients allocated to the efficacious donor responded	p_{eff}	$7/18 = 0.39$	7	11

Table 1: Point estimates and hyperparameters for model parameters using clinical data [3]. Compare against main text Table 1. A and B are hyperparameters for a beta distribution.

- p_{eff} is drawn from $\text{Beta}(A_{\text{peff}}, B_{\text{peff}})$, where A_{peff} is the number of patients in the *treatment* arm who responded and B_{peff} is the number who did not respond.

Specifically, we define the distribution on the model parameters as:

$$P_{\text{pl,ing}}(p_{\text{pl}}, p_{\text{ing}}) = \text{Beta}(p_{\text{pl}}; A_{\text{pl}}, B_{\text{pl}}) \times \text{Beta}(p_{\text{eff}}; A_{\text{peff}}, B_{\text{peff}}) \tag{3}$$

$$P_{\text{feff}}(f_{\text{eff}}) = \text{Beta}(f_{\text{eff}}; A_{\text{feff}}, B_{\text{feff}}), \tag{4}$$

where the hyperparameters A and B are shown in Table 1.

2.2 Dependence of parameters

Note that, although f_{eff} is treated as independent from p_{pl} and p_{ing}, the priors on p_{pl} and p_{eff} constitute a joint distribution on p_{pl} and p_{ing}. It is *not* true that p_{pl} can be drawn from $\text{Beta}(A_{\text{pl}}, B_{\text{pl}})$ and p_{eff} separately drawn from $\text{Beta}(A_{\text{peff}}, B_{\text{peff}})$ because this will violate the requirement that $p_{\text{eff}} > p_{\text{pl}}$. We sampled $(p_{\text{pl}}, p_{\text{eff}})$ using rejection sampling:

1. Draw p_{pl}, p_{ing}, and a threshold T from the uniform distribution on $[0, 1]$.
2. Compute $p_{\text{eff}} = p_{\text{pl}} + p_{\text{ing}} - p_{\text{pl}}p_{\text{ing}}$.
3. Accept the pair $(p_{\text{pl}}, p_{\text{ing}})$ if

$$\text{Beta}(p_{\text{pl}}; A_{\text{pl}}, B_{\text{pl}}) \times \text{Beta}(p_{\text{eff}}; A_{\text{peff}}, B_{\text{peff}}) < T. \tag{5}$$

In our implementation, we speed up this sampling by using numerical optimization to find the maximum M of the product of the two beta distributions and then draw T from $[0, M]$.

3 Incorporating inefficacious donors as placebos

Here we articulated a prior on the placebo rate p_{pl} using only the results from the placebo arm. We could also have lumped the patients assigned to inefficacious donors, who we assert respond to efficacious treatment with probability p_{pl}, in with patients from the the placebo arm, who also respond with probability p_{pl}. In the clinical trial whose results are summarized in Table 1, 2 of 20 patients assigned to the 5 apparently inefficacious donors responded [3], so the prior on p_{pl} would be informed by $2 + 2 = 4$ successful and $35 + 18 = 53$ failed placebo-or-inefficacious treatments.

Part II
Utility & decision theory

4 Theory

The model of differences in donor stool efficacy that we laid out can be used as a framework for optimizing non-adaptive trial designs with respect to some *utility function*, i.e., a single number that encodes the desirability of some outcome. In the main text, we reported on statistical powers, which are the expected utilities of a utility function that assigns a utility 1 to trials with $p < 0.05$ and a utility 0 to other trials. A researcher might be interested in optimizing trial design with respect to some other utility, say, the number of efficacious donors identified.

5 Methods

We used the model to optimize the design of a forthcoming two-stage Phase II clinical trial that uses FMT to treat ulcerative colitis. In this trial, the researchers were limited to a non-adaptive trial design in the trial's first stage, but the results of the first stage could be used to assign donors in the second stage. Therefore, the trial's researchers aimed to optimize the probability that they would be able to identify and discover an efficacious donor in the

first stage so that they could use that donor in the second stage. [swo: cite Russell?]

There were 30 patients in each arm. We evaluated the following allocations: use one donor for all patients, use one donor for every two patients, one for every three, and so forth, up to using a new donor for every patient. Using the fixed model parameters shown in Table 1, 10,000 simulations were performed for each allocation and the number of trials in which the the donor with the best ratio of successes to failures was tabulated. (In the case of a tie among donors, one of the best donors was selected at random.)

To evaluate the robustness of these results, the same simulations were performed but, instead of using point estimates for the model parameters, drawing the model parameters from the distributions shown in Table 1.

6 Results

The trial designs most likely to produce a "best" donor (i.e., with the best ratio of responding patients to patients treated) assigns 2 or 3 patients to each donor (i.e., evenly distributes patients across 10 or 15 donors; Table 2, column "point estimates"). The difference between the best strategy (2 or 3 patients per donor) and the worst strategy (one single donor for all patients) was large: the best strategy was 62% likely to provide a best donor who was also an efficacious donor, while the worst strategy was only 17% likely. Using a new donor for every patient produced intermediate results (58% likely to identify an efficacious donor).

When including this uncertainty in the model parameters, the ranking of strategies remains about the same (e.g., 3 patients per donor is optimal), but the probability that the best donor is an efficacious one decreases for most strategies (Table 2, column "distributions").

Part III
Bayesian assignment strategies

Adaptive donor assignment strategies aim to use the information derived from the patients' outcomes—and possibly some *a priori* beliefs about the values of the model parameters—to make decisions about how to assign

	Probability (%)	
N_{donors}	point estimates	distributions
30	58	32
15	62	39
10	62	40
6	56	38
5	54	37
3	41	31
2	32	25
1	17	17

Table 2: Probability that a donor allocation yields a best donor that is actually efficacious. All confidence intervals were within 1% of the reported value.

donors. The donor assignment problem, then, is amenable to a Bayesian treatment. For example, the myopic Bayesian algorithm reported in the main text (and described in more detail below) assigns donors such that the patient has the highest probability of responding to treatment given our prior expectations about donors' efficacies and the data so far accumulated during the trial. In Bayesian statistics, this "updated" probability is a posterior predictive probability.

7 Predictive posterior distributions

7.1 Derivation of predictive posterior

To derive the posterior predictive probability, we first need to articulate the posterior probability on the core parameters p_{pl}, p_{ing}, and f_{eff} as well as a new parameter that indicates whether each donor is efficacious or not. Let $\boldsymbol{q}$ be a vector of entries "efficacious" or "inefficacious" with a length equal to the number of donors. Let q_i be called the *quality* of the i-th donor. The posterior probability is then

$$P(p_{\text{pl}}, p_{\text{ing}}, f_{\text{eff}}, \boldsymbol{q}|\boldsymbol{X}) \propto \underbrace{P(\boldsymbol{X}|p_{\text{pl}}, p_{\text{ing}}, f_{\text{eff}}, \boldsymbol{q})}_{\text{likelihood}} \times \underbrace{P(p_{\text{pl}}, p_{\text{ing}}, f_{\text{eff}}, \boldsymbol{q})}_{\text{prior}}, \quad (6)$$

where $\boldsymbol{X}$ is the data: the number of patients who responded (or not) for each donor. More specifically, we say that donor i's stool was administered to n_i patients, of which s_i patients responded.

As per Section 2, we assume that the prior can be separated into parts:

$$P(p_{\text{pl}}, p_{\text{ing}}, f_{\text{eff}}, \boldsymbol{q}) = P_{\text{pl,ing}}(p_{\text{pl}}, p_{\text{ing}}) P_{\text{feff}}(f_{\text{eff}}) P(\boldsymbol{q}|f_{\text{eff}}), \tag{7}$$

that is, that the placebo rate p_{pl} and active ingredient efficacy p_{ing} are independent of the frequence of efficacious donors f_{eff}, which is in turn independent of the qualities $\boldsymbol{q}$ of the particular donors. The prior on $\boldsymbol{q}$ can be broken up by donor because the donors' qualities are all independent of one another:

$$P(\boldsymbol{q}|f_{\text{eff}}) = \prod_{i=1}^{D} \begin{Bmatrix} f_{\text{eff}} & \text{if } q_i \text{ is efficacious} \\ 1 - f_{\text{eff}} & \text{if not} \end{Bmatrix}, \tag{8}$$

where D is the number of donors. We assume that the outcomes of the patients are independent, so the likelihood of the data $\boldsymbol{X}$ is probability of the observed combinations of successes and failures for each donor:

$$P(\boldsymbol{X}|p_{\text{pl}}, p_{\text{ing}}, f_{\text{eff}}, \boldsymbol{q}) = \prod_{i=1}^{D} \begin{Bmatrix} \text{Bin}(s_i; n_i, p_{\text{eff}}) & \text{if } q_i \text{ is efficacious} \\ \text{Bin}(s_i; n_i, p_{\text{pl}}) & \text{if not} \end{Bmatrix}, \tag{9}$$

where $\text{Bin}(s_i; n_i, p_{\text{eff}})$ is the probability mass function of the binomial distribution with s_i successes out of n_i trials with probability of success p_{eff}. Equations (6), (8) and (9) can be combined:

$$\begin{aligned} P(p_{\text{pl}}, p_{\text{ing}}, f_{\text{eff}}, \boldsymbol{q}|\boldsymbol{X}) \propto & \\ \prod_{i=1}^{D} & \begin{Bmatrix} f_{\text{eff}} \times \text{Bin}(s_i; n_i, p_{\text{eff}}) & \text{if } q_i \text{ is ``efficacious''} \\ (1 - f_{\text{eff}}) \times \text{Bin}(s_i; n_i, p_{\text{pl}}) & \text{if not} \end{Bmatrix} \\ & \times P_{\text{pl,ing}}(p_{\text{pl}}, p_{\text{ing}}) P_{\text{feff}}(f_{\text{eff}}). \end{aligned} \tag{10}$$

To simplify the notation, we will write the core parameters and their prior as:

$$\boldsymbol{\pi} \equiv (p_{\text{ing}}, p_{\text{pl}}, f_{\text{eff}}) \tag{11}$$

$$P_{\pi}(\boldsymbol{\pi}) \equiv P_{\text{pl,ing}}(p_{\text{pl}}, p_{\text{ing}}) P_{\text{feff}}(f_{\text{eff}}). \tag{12}$$

It will be convenient to treat $\boldsymbol{\pi}$ and $\boldsymbol{q}$ separately.

To compute the posterior predictive probability that the next patient will respond to treatment with stool from donor i, we marginalize over the parameters $\boldsymbol{\pi}$ (i.e., integrate over p_{pl}, p_{ing}, and f_{eff}) and the qualities $\boldsymbol{q}$ (i.e., sum over the 2^D possibilities for the q_i). Let σ_i represent the event where the next patient responds when treated with stool from donor i. Then the posterior predictive probability is

$$P(\sigma_i|\boldsymbol{X}) = \int \sum_{\boldsymbol{q}} P(\sigma_i|\boldsymbol{\pi}, \boldsymbol{q}) \underbrace{P(\boldsymbol{\pi}, \boldsymbol{q}|\boldsymbol{X})}_{\text{posterior}} \, \mathrm{d}\boldsymbol{\pi} \tag{13}$$

The probability that the next patient responds to treatment is p_{eff} if the donor is efficacious or p_{pl} if not:

$$P(\sigma_i|\boldsymbol{\pi}, \boldsymbol{q}) = \left\{ \begin{matrix} p_{\text{eff}} & \text{if } q_i \text{ is "efficacious"} \\ p_{\text{pl}} & \text{if not} \end{matrix} \right\}. \tag{14}$$

Combining Eqs. (10), (13) and (14) yields a computable predictive posterior:

$$\begin{aligned} P(\sigma_i|\boldsymbol{X}) \propto \int & \underbrace{[p_{\text{eff}} f_{\text{eff}} \operatorname{Bin}(s_i; n_i, p_{\text{eff}}) + p_{\text{pl}}(1 - f_{\text{eff}}) \operatorname{Bin}(s_i; n_i, p_{\text{pl}})]}_{\text{term for donor } i} \\ & \times \prod_{j \neq i} \underbrace{[f_{\text{eff}} \operatorname{Bin}(s_j; n_j, p_{\text{eff}}) + (1 - f_{\text{eff}}) \operatorname{Bin}(s_j; n_j, p_{\text{pl}})]}_{\text{terms for other donors}} \times \underbrace{P_\pi(\boldsymbol{\pi})}_{\text{priors}} \, \mathrm{d}\boldsymbol{\pi} \end{aligned} \tag{15}$$

7.2 Computing the predictive posterior

Eq. (15) is unwieldy and there are some notational and computational simplifications that can make it easier to use. First define

$$\boldsymbol{s} \equiv \{s_1, s_2, \ldots, s_D\}, \tag{16}$$

where s_i is the number of "successes" for donor i (i.e., the number of patients who responded to treatment with stool from donor i) and

$$\boldsymbol{f} \equiv \{f_1, f_2, \ldots, f_D\}, \tag{17}$$

the number of "failures" for donor i. We then define a shorthand $Q(\boldsymbol{s}; \boldsymbol{f})$ for dealing with all these data and parameters:

$$\begin{aligned} & Q(\boldsymbol{s}; \boldsymbol{f}) \equiv \\ & \qquad \int \prod_{i=1}^{D} \left[f_{\text{eff}} p_{\text{eff}}^{s_i} (1 - p_{\text{eff}})^{f_i} + (1 - f_{\text{eff}}) p_{\text{pl}}^{s_i} (1 - p_{\text{pl}})^{f_i} \right] \times P_\pi(\boldsymbol{\pi}) \, \mathrm{d}\boldsymbol{\pi}. \end{aligned} \tag{18}$$

Lemma 1. *The posterior predictive probability that the next patient will respond to treatment with stool from donor 1 is*

$$\frac{Q(s_1+1, s_2, s_3, \ldots; \boldsymbol{f})}{Q(\boldsymbol{s}; \boldsymbol{f})}. \tag{19}$$

It could just as well been any donor i; no generality is lost.

Proof. Let σ_1 be the event where donor 1 cures the next patient. We are trying to show that

$$P(\sigma_1|\boldsymbol{s}, \boldsymbol{f}) = \frac{Q(s_1+1, s_2, s_3, \ldots; \boldsymbol{f})}{Q(\boldsymbol{s}; \boldsymbol{f})}. \tag{20}$$

The predictive posterior probability requires integrating over $\boldsymbol{\pi}$ and summing over $\boldsymbol{q}$:

$$P(\sigma_1|\boldsymbol{s}, \boldsymbol{f}) \propto \int \sum_{\boldsymbol{q}} P(\sigma_1|\boldsymbol{\pi}, \boldsymbol{q})\, P(\boldsymbol{\pi}, \boldsymbol{q}|\boldsymbol{s}, \boldsymbol{f})\, \mathrm{d}\boldsymbol{\pi}. \tag{21}$$

The first term is easy, and follow directly from our model assumptions:

$$P(\sigma_1|\boldsymbol{s}, \boldsymbol{f}) = \begin{Bmatrix} p_{\text{eff}} & \text{if donor 1 is efficacious} \\ p_{\text{pl}} & \text{otherwise} \end{Bmatrix} \tag{22}$$

The second probability is the posterior probability of the parameters:

$$P(\boldsymbol{\pi}, \boldsymbol{q}|\boldsymbol{s}, \boldsymbol{f}) \propto P(\boldsymbol{s}, \boldsymbol{f}|\boldsymbol{\pi}, \boldsymbol{q})\, P(\boldsymbol{\pi}, \boldsymbol{q}). \tag{23}$$

Each donor is independent of the others, and each patient's response to treatment is a Bernoulli trial, so the first probability (the likelihood) is a product of binomial probability densities:

$$P(\boldsymbol{s}, \boldsymbol{f}|\boldsymbol{\pi}, \boldsymbol{q}) = \prod_{i=1}^{D} \begin{Bmatrix} \mathrm{Bin}(s_i; n_i, p_{\text{eff}}) & \text{if donor } i \text{ efficacious} \\ \mathrm{Bin}(s_i; n_i, p_{\text{pl}}) & \text{if not} \end{Bmatrix} \tag{24}$$

The constants in the binomials depend on the $\boldsymbol{s}$ and $\boldsymbol{f}$, not on any of the varying parameters in the integral/sum, so they can be pulled out:

$$P(\boldsymbol{s}, \boldsymbol{f}|\boldsymbol{\pi}, \boldsymbol{q}) \propto \prod_{i=1}^{D} \begin{Bmatrix} p_{\text{eff}}^{s_i}(1-p_{\text{eff}})^{f_i} & \text{if donor } i \text{ efficacious} \\ p_{\text{pl}}^{s_i}(1-p_{\text{pl}})^{f_i} & \text{if not} \end{Bmatrix} \tag{25}$$

The prior $P(\boldsymbol{\pi}, \boldsymbol{q})$ in Eq. (23) broken up to reveal the more familiar prior $P_\pi(\boldsymbol{\pi})$:

$$P(\boldsymbol{\pi}, \boldsymbol{q}) = \prod_{i=1}^{D} \begin{Bmatrix} f_{\text{eff}} & \text{if donor } i \text{ is efficacious} \\ 1 - f_{\text{eff}} & \text{if not} \end{Bmatrix} \times P_\pi(\boldsymbol{\pi}) \tag{26}$$

Some algebra shows that the products in the definitions for $P(\boldsymbol{\pi}, \boldsymbol{q})$ and $P(\boldsymbol{s}, \boldsymbol{f}|\boldsymbol{\pi}, \boldsymbol{q})$ move nicely through the sum in the definition of the posterior probability, and the extra p_{eff} or p_{pl} from the predictive probability moves right inside the donor 1 term:

$$\begin{aligned} P(\sigma_1|\boldsymbol{s}, \boldsymbol{f}) \propto \int & \left[f_{\text{eff}} p_{\text{eff}}^{s_1+1} (1 - p_{\text{eff}})^{f_1} + (1 - f_{\text{eff}}) p_{\text{pl}}^{s_1+1} (1 - p_{\text{pl}})^{f_1} \right] \\ & \times \prod_{i=2}^{D} \left[f_{\text{eff}} p_{\text{eff}}^{s_i} (1 - p_{\text{eff}})^{f_i} + (1 - f_{\text{eff}}) p_{\text{pl}}^{s_i} (1 - p_{\text{pl}})^{f_i} \right] P(\boldsymbol{\pi}) \, \mathrm{d}\boldsymbol{\pi} \end{aligned} \tag{27}$$

But this is just Q as if donor 1 already had another success:

$$P(\sigma_1|\boldsymbol{s}, \boldsymbol{f}) \propto Q(s_1 + 1, s_2, s_3, \ldots; \boldsymbol{f}). \tag{28}$$

A little more algebra along these lines will show that the posterior of donor 1 causing a failure means replacing the p_{eff} and p_{pl} with $1 - p_{\text{eff}}$ and $1 - p_{\text{pl}}$, which shows that

$$Q(s_1 + 1, s_2, s_3, \ldots; \boldsymbol{f}) + Q(\boldsymbol{s}; f_1 + 1, f_2, f_3, \ldots) = Q(\boldsymbol{s}, \boldsymbol{f}), \tag{29}$$

and therefore that the denominator shown in the lemma statement is the right one. □

7.3 New donors in the predictive posterior

Donors that have no successes or failures (i.e., whose stool has not been administered to any patient) are "hiding in the background" in $Q(\boldsymbol{s}; \boldsymbol{f})$. A new donor with $s_i = f_i = 0$ does not contribute to the product over donors i shown in (18):

$$f_{\text{eff}} p_{\text{eff}}^{s_i} (1 - p_{\text{eff}})^{f_i} + (1 - f_{\text{eff}}) p_{\text{pl}}^{s_i} (1 - p_{\text{pl}})^{f_i} = f_{\text{eff}} + (1 - f_{\text{eff}}) = 1. \tag{30}$$

Thus, there is nothing special in the math about new donors.

7.4 Incorporating placebo arm data

Information from the placebo arm of an ongoing trial can be incorporated just like the successes and failures of each donor. In this way, the results from the placebo arm can be used to continuously refine the posterior distribution on p_{pl}.

The placebo arm is mathematically equivalent to a donor that we know is not efficacious. Whereas most donors get terms in $Q(\boldsymbol{s};\boldsymbol{f})$ that are equal to $[f_{\text{eff}}p_{\text{eff}}^{s_i}(1-p_{\text{eff}})^{f_i}+(1-f_{\text{eff}})p_{\text{pl}}^{s_i}(1-p_{\text{pl}})^{f_i}]$, the placebo arm "donor" gets a term $p_{\text{pl}}^{s_{\text{pl}}}(1-p_{\text{pl}})^{f_{\text{pl}}}$, where s_{pl} is the number of patients in the placebo arm who responded and f_{pl} is the number who did not.

8 The myopic Bayesian strategy

A donor selection *strategy* determines what donor should be used next in light of the history of the trial thus far (i.e., the number of successes and failures attributed to each donor), the priors on the model parameters, and the number of patients remaining. Technically speaking, the strategy is a function that takes those inputs and returns the identity of the donor to be used next.

In the *myopic* (or "greedy") strategy, each donor is selected because, at that moment, they appear to be the one that maximizes the probability that the next patient will respond to treatment. Thus, before each patient is assigned, Eq. (15), and the donor i that maximizes $P(\sigma_i|\boldsymbol{X})$ is used for that patient. This kind of algorithm is called "myopic" or "greedy" because it makes the best immediate choice, which is not necessarily the choice that will lead to the optimal outcome for the entire trial [2, 1]. The optimal strategy will be examined below.

The myopic strategy has a property that makes it intuitive in many scenarios: if some donor has at least as many successes as and no more failures than any other donor, then that donor is the myopic choice.

Theorem 1. *If $s_i \geq s_j$ and $f_i \leq f_j$, then $P(\sigma_i|\boldsymbol{X}) > P(\sigma_j|\boldsymbol{X})$.*

Proof. Without loss of generality, let $i = 1$ and $j = 2$. By Lemma 1, the difference in predictive posteriors is proportional to the difference of two Q values:

$$P(\sigma_1|\boldsymbol{X})-P(\sigma_2|\boldsymbol{X}) \propto Q(s_1+1,s_2,s_3,\ldots;\boldsymbol{f})-Q(s_1,s_2+1,s_3,\ldots;\boldsymbol{f}). \quad (31)$$

Eq. (18) shows that the difference between these two Q values will be a new integral. The terms in the integral corresponding to the other donors ($i > 2$) and the prior on $\boldsymbol{\pi}$ will remain the same. Only the product of the $i = 1$ and $i = 2$ terms will change. Those terms will be:

$$\begin{aligned}&(\text{1 term with an extra success}) \times (\text{normal 2 term}) - \\ &\qquad (\text{normal 1 term}) \times (\text{2 term with an extra success}). \quad (32)\end{aligned}$$

In gory detail:

$$\begin{aligned}&\left[f_{\text{eff}} p_{\text{eff}}^{s_1+1}(1-p_{\text{eff}})^{f_1} + (1-f_{\text{eff}}) p_{\text{pl}}^{s_1+1}(1-p_{\text{pl}})^{f_1}\right] \times \\ &\qquad \left[f_{\text{eff}} p_{\text{eff}}^{s_2}(1-p_{\text{eff}})^{f_2} + (1-f_{\text{eff}}) p_{\text{pl}}^{s_2}(1-p_{\text{pl}})^{f_2}\right] - \\ &\qquad \left[f_{\text{eff}} p_{\text{eff}}^{s_1}(1-p_{\text{eff}})^{f_1} + (1-f_{\text{eff}}) p_{\text{pl}}^{s_1}(1-p_{\text{pl}})^{f_1}\right] \times \\ &\qquad\qquad \left[f_{\text{eff}} p_{\text{eff}}^{s_2+1}(1-p_{\text{eff}})^{f_2} + (1-f_{\text{eff}}) p_{\text{pl}}^{s_2+1}(1-p_{\text{pl}})^{f_2}\right]. \quad (33)\end{aligned}$$

This produces two terms with f_{eff}^2, two with $(1-f_{\text{eff}})^2$, and four with $f_{\text{eff}}(1-f_{\text{eff}})$. The f_{eff}^2 terms cancel: they both have $p_{\text{eff}}^{s_1+s_2+1}$. Similarly, the $(1-f_{\text{eff}})^2$ terms cancel: they both have $p_{\text{pl}}^{s_1+s_2+1}$. This leaves four terms:

$$\begin{aligned}&f_{\text{eff}}(1-f_{\text{eff}}) \times \\ &\quad \Big[p_{\text{eff}}^{s_1+1}(1-p_{\text{eff}})^{f_1} p_{\text{pl}}^{s_2}(1-p_{\text{pl}})^{f_2} + p_{\text{eff}}^{s_2}(1-p_{\text{eff}})^{f_2} p_{\text{pl}}^{s_1+1}(1-p_{\text{pl}})^{f_2} - \\ &\quad p_{\text{eff}}^{s_1}(1-p_{\text{eff}})^{f_1} p_{\text{pl}}^{s_2+1}(1-p_{\text{pl}})^{f_2} - p_{\text{eff}}^{s_2+1}(1-p_{\text{eff}})^{f_2} p_{\text{pl}}^{s_1}(1-p_{\text{pl}})^{f_2}\Big]. \quad (34)\end{aligned}$$

These terms can be rearranged into:

$$\begin{aligned}&f_{\text{eff}}(1-f_{\text{eff}})(p_{\text{eff}}-p_{\text{pl}}) p_{\text{eff}}^{s_1}(1-p_{\text{eff}})^{f_1} p_{\text{pl}}^{s_2}(1-p_{\text{pl}})^{f_2} \times \\ &\qquad\qquad \left[1 - \left(\frac{p_{\text{pl}}}{p_{\text{eff}}}\right)^{s_1-s_2} \left(\frac{1-p_{\text{eff}}}{1-p_{\text{pl}}}\right)^{f_2-f_1}\right]. \quad (35)\end{aligned}$$

So long as $s_1 \geq s_2$ and $f_1 \leq f_2$, then all these terms are positive. Because every other term in the integral is positive, the difference in Eq. (31) will be positive, so $P(\sigma_i|\boldsymbol{X}) > P(\sigma_j|\boldsymbol{X})$. □

This is a theorem about the myopic Bayesian strategy. Even though donor A might be better than B (in the sense that $s_A \geq s_B$ and $f_A \leq f_B$), it could be that somehow, it is more favorable to the trial's final outcome to

assign the next patient to B. That possibility will be discussed below when comparing the myopic and optimal Bayesian strategies.

This theorem has a simple corollary that shows that there is a common situation when the best-choice donor is a new donor (one that has not yet been used to treat any patients).

Corollary 1. *A patient is more likely to respond to treatment with stool from a new donor than to treatment with stool from a donor with no successes and at least one failure.*

Thus, the myopic Bayesian strategy requires that, at the beginning of the trial, you use a new donor until you get at least one positive patient outcome.

9 The optimal Bayesian strategy

A strategy is *optimal* with respect to some *utility function* and some true model parameters (or distribution of model parameters) if there is no other strategy that has a higher expected utility averaged over the donor's random outcomes (or also averaged over values of the model parameters drawn from those true distributions). In other words, a strategy is the optimal one if, in performing many simulated trials, the strategy makes decisions about donor assignment that lead to the best average results.

9.1 Trial trees

The greedy strategy has the advantage that, when implemented, it need only compute the answer to a small number of questions: for each patient, where should that patient be assigned? The optimal strategy, on the other hand, needs to look ahead to all possible outcomes. It is easy to express these possibility in terms of a tree that represent the trial's possible outcomes.

The root of the tree (denoted as $\varnothing$) is the current trial state. The root has a number of child *donor nodes*, which represent the possibility of choosing to allocate the next patient to each donor. In the case where there are two available donors, call these nodes A and B. Each donor node has two *state nodes*. The left child represents the new trial state in which the patient responded to treatment (i.e., the donor "succeeded"); the right child represents the new trial state in which the patient did not respond. We label these nodes with the donor node label and either s or f to indicate success

or failure. (This is an adaptation of the notation used by Zelen [5]). A tree representing a trial with two donors A and B and two remaining patients is shown in Figure 1.

A strategy's expected utility is the expected utility of the root (trial state) node. A state node's expected utility is just the expected utility of the donor choice node corresponding to the donor that the strategy would select given that trial state. The expected utility of a donor choice node is the weighted average of the expected utilities of its two (trial state) children. For example, if the next patient will respond to stool from donor A with probability p and the expected utilities of the two outcome nodes As and Af as $U(As)$ and $U(Af)$, then the exected utility of the donor choice node A is $pU(As) + (1-p)U(Af)$.

The recursion ends at the leaves (the trial state in which there are no remaining patients), which are each assigned a utility by the utility function. One choice for utility is the number of patients that responded to treatment. Another choice would be to assign a utility 0 to a leaf if the outcome is not statistically significant and assign a utility 1 is if the outcome is significant.

9.2 Counting trial states

Because the optimal strategy will require recursion through the entire tree, it will eventually require computing the posterior predictive probability for every possible trial state. For modest numbers of patients (e.g., 30), the number of trial states is large (tens of millions).

How many unique trial states are there for a given number of patients N? We specify "unique" because two donors with the same number of successes and the same number of failures are indistinguishable. If donors were distinguishable, then the number of unique trial states would be the number of ways of distributing the indistinguishable N balls (i.e., the patients) among $2N$ bins (i.e., donor A successes, donor A failures, donor B successes, etc.). This value is described by the multiset number. In our case, the donors are indistinguishable, but they have two distinguishable "sub-bins": you can tell a donor who has 1 success and 0 failures from a donor who has 0 successes and 1 failure, but you can't tell apart two donors who each have 1 success and 1 failure.

First, we show a formula to compute the number of ways to put n indistinguishable balls into indistinguishable bins.

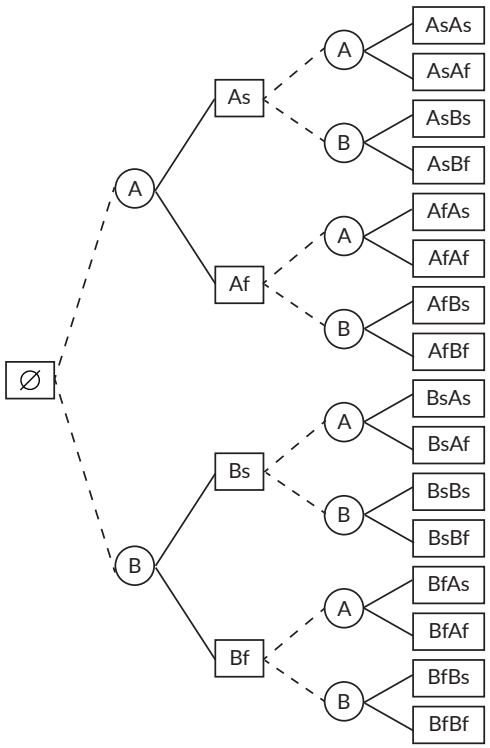

Figure 1: **A depth-2 trial tree.** Trial states are marked in square boxes; donor decision nodes in circles. Starting at the initial trials state $\varnothing$, donor A or B can be assigned to the next patient. If donor A is assigned, that patient can either experience a success (leading to trial state As) or a failure (Af). The solid line have probabilities associated with them: given the priors and the donors' histories, there is some probability associated with the transition between $\varnothing$ and As, i.e., the probability that the next patient will respond to treatment with stool from donor A. The dotted lines indicate a choice: different donor strategies can assign different donors to the next patient given the same trial state.

Lemma 2. *Let the number of ways to distribute n indistinguishable balls into indistinguishable bins with at most m balls per bin be written $W(n, m)$. The number of ways to distribute n indistinguishable balls into indistinguishable bins is $W(n, n)$, where $W(n, m)$ is defined by the recursion:*

$$W(0, m) = W(1, m) = 1 \tag{36}$$

$$W(n, 1) = 1 \tag{37}$$

$$W(n, m) = \sum_{i=0}^{\left\lfloor \frac{n}{m} \right\rfloor} W(n - im, m - 1) \tag{38}$$

Proof. Because the bins are only distinguished by the number of balls they contain, we can enumerate the distributions by writing the number of bins that have a certain number of balls. For example, for the $n = 4$ case, there are 5 ways to distribute the balls:

1. 1 bin has 4 balls.
2. 1 bin has 3 balls; 1 bin has 1 ball.
3. 2 bins have 2 balls.
4. 1 bin has 2 balls; 2 bins have 1 ball.
5. 4 bins have 1 ball.

This enumeration suggests a recursion: for some m, the number of bins that could have m balls is $i \in \left\{0, 1, \ldots, \left\lfloor \frac{n}{m} \right\rfloor\right\}$. For each of those situations, we ask how many ways there are to arrange the remaining $n - im$ balls among bins with at most $m - 1$ balls per bin.

For $n = 0$, there is only one arrangement: all the bins have 0 balls. For $n = 1$, there is also only one arrangement: one bin has one ball. If $m = 1$, there is only one arrangement: n bins having 1 ball. □

We can extend this logic to ask the number of ways to distibute the N patients among the (at most N) indistinguishable donors.

Theorem 2. *Let a double-bin be an ordered pair of integers (i.e., a bin with distinguishable "success" and "failure" sub-bins). Let $H(n, m)$ be the number of ways to put n indistinguishable balls into double-bins with at most m balls*

per double-bin. Then the number of ways to put n indistinguishable balls into double-bins is $H(n, n)$ where $H(n, m)$ is defined by the recursion:

$$H(0, m) = 1 \tag{39}$$
$$H(1, m) = 2 \tag{40}$$
$$H(n, 1) = n + 1 \tag{41}$$
$$H(n, m) = \sum_{i=0}^{\lfloor \frac{n}{m} \rfloor} \binom{m+i}{m} \times H(n - im, m - 1) \tag{42}$$

Proof. This proof is like the lemma except that there is an extra degree of freedom. Now the bins with m donors fall into $m + 1$ subcategories: they can have 0 in the left sub-bin and m in the right, 1 in the left and $m - 1$ in the right, and so forth, up to m in the left and 0 in the right. The number of ways to distribute the i bins that have m donors among the possible $m + 1$ subcategories is $\binom{m+i}{m}$.

For $n = 0$, there is only one way to distribute the balls: 0 successes and 0 failures. For $n = 1$, there are two ways to distribute the balls: either 1 success or 1 failure. For $m = 1$, there are $n + 1$ ways to distribute the balls: 0 successes and n failures, 1 success and $n - 1$ failures, and so forth, up to n successes and 0 failures. □

Note that this recursion relationship for $H(n, n)$ will yield the same number as an algorithmic approach:

1. Make a string of n stars and $2n - 1$ bars.
2. For every possible permutation of that string, make a list of the length of run of stars. (This is equivalent to enumerating all ways to write n non-negative integers that add up to n.)
3. Group that list of run lengths into pairs. (These are the left and right sub-bins.)
4. Sort the list. (This accounts for indistinguishability of the double-bins.)
5. Count the number of unique sorted lists of tuples.

This approach is slow because it requires enumerating all $(3n - 1)!$ permutations of the stars and bars.

# patients	# trial states
1	2
2	6
3	14
4	33
5	70
6	149
7	298
8	591
9	$1,132$
10	$2,139$
15	$39,894$
20	5.58×10^5
25	6.39×10^6
30	6.29×10^7
40	4.34×10^9
50	2.14×10^{11}
60	8.22×10^{12}

Table 3: The number of possible trial states for a given number of patients, assuming that the number of available donors is equal to the number of patients.

Some representative results are shown in Table 3. These results argue for the difficulty of an exact, optimal calculation: for a moderate-size trial with 30 donors, the tree will have 60 million unique leaf trial states.

9.3 Optimality of the myopic strategy

9.3.1 Utility in an optimal strategy

Is the myopic strategy optimal with respect to some utility function and priors? The myopic strategy locally optimizes the number of patients with successful outcomes, so we will compare the myopic strategy against the strategy that is optimal with respect to the number of patients with successful outcomes at the end of the trial.

For convenience, we will merge the notation $Q(\boldsymbol{s}; \boldsymbol{f})$ and the node labels

in Figure 1 to define:

$$Q(\varnothing) \equiv Q(\boldsymbol{s}; \boldsymbol{f}) \tag{43}$$
$$Q(As) \equiv Q(s_A + 1, s_B, s_C, \ldots; \boldsymbol{f}) \tag{44}$$
$$Q(AsAf) \equiv Q(s_A + 1, s_B, s_C, \ldots; f_A + 1, f_B, f_C, \ldots) \tag{45}$$

and so forth. For example, As can be read as "donor $\underline{A}$ has had a $\underline{s}$uccess." One line of algebra shows that the probability of donor A having two successes, for example, is $Q(AsAs)/Q(\varnothing)$.

As mentioned above, the optimal strategy propagates expected utilities up through the tree, weighting the utilities by the probability of the patient outcome. Thus, the utility of a donor node is:

$$\begin{aligned} U(A) &= P(As)U(As) + P(Af)U(Af) \\ &= \frac{1}{Q(\varnothing)} \left[Q(As)U(As) + Q(Af)U(Af) \right]. \end{aligned} \tag{46}$$

The utility of a state node is the utility of its child donor node that has the greatest utility:

$$U(\varnothing) = \max \left\{ U(A), U(B) \right\}. \tag{47}$$

The myopic strategy is optimal if $P(As)$ being greater than (or equal to) $P(Bs)$ for all other donors B implies that $U(A) \geq U(B)$ for all other donors B, that is, that no donor has a greater utility than the donor who is most likely to succeed.

We do not have a proof for the conjecture that the myopic strategy is optimal with respect to the stated utility function. That conjecture may indeed be false.

9.3.2 Optimality of the myopic strategy for two patients remaining

To simplify the question, we concentrate on the case in which there are two remaining patients and only two donors (A and B) to choose from.

Theorem 3. *In a trial where:*

- *there are two patients remainings*
- *there are two donor (where donor A has had s_A successes and f_A failures and donor B has had s_B successes and f_B failures),*

- $s_A \geq s_B$ *and* $f_A \leq f_B$, *and*
- *the utility is an increasing function of the number of patients with successful outcomes,*

then A is the optimal donor.

Proof. We need to show that $U(A) \geq U(B)$. (If $U(A) = U(B)$, then both donor choices are optimal.)

First, define the utilities $U_0 < U_1 < U_2$, where U_0 is the utility of final trial outcomes in which neither of the two patients responded, U_1 is the utility for one patient responding, and U_2 is the utility for two patients responding.

Next, expand the definitions of expected utility and substitute these utility values. Expanding Eq. (46),

$$\begin{aligned} U(A) = \frac{1}{Q(\varnothing)} \Big\{ & \max \Big[Q(AsAs)U(AsAs) + Q(AsAf)U(AsAf), \\ & \qquad Q(AsBs)U(AsBs) + Q(AsBf)U(AsBf) \Big] \\ & + \max \Big[Q(AfAs)U(AfAs) + Q(AfAf)U(AfAf), \\ & \qquad Q(AfBs)U(AfBs) + Q(AfBf)U(AfBf) \Big] \Big\}. \end{aligned} \tag{48}$$

This is the sum of two terms, each of which is the maximum of two other terms, so the entire value is the maximum over four terms, each with four subterms. Making that replacement and converting the, e.g., $U(AsAs)$ into U_2 yields:

$$\begin{aligned} U(A) = \frac{1}{Q(\varnothing)} \max \Big\{ & \\ & Q(AsAs)U_2 + 2Q(AsAf)U_1 + Q(AfAf)U_0, \\ & Q(AsAs)U_2 + [Q(AsAf) + QU(AfBs)]\, U_1 + Q(AfBf)U_0, \\ & Q(AsBs)U_2 + [Q(AsBf) + QU(AfAs)]\, U_1 + Q(AfAf)U_0, \\ & Q(AsBs)U_2 + [Q(AsBf) + QU(AfBs)]\, U_1 + Q(AfBf)U_0 \Big\}. \end{aligned} \tag{49}$$

Repeating the same algebra for $U(B)$ gives the same result, but with A and

B swapped:

$$U(B) = \frac{1}{Q(\varnothing)} \max \Big\{ \begin{array}{l} Q(BsBs)U_2 + 2Q(BsBf)U_1 + Q(BfBf)U_0, \\ Q(BsBs)U_2 + \left[Q(BsBf) + QU(BfAs)\right] U_1 + Q(BfAf)U_0, \\ Q(BsAs)U_2 + \left[Q(BsAf) + QU(BfBs)\right] U_1 + Q(BfBf)U_0, \\ Q(BsAs)U_2 + \left[Q(BsAf) + QU(BfAs)\right] U_1 + Q(BfAf)U_0 \Big\}. \end{array} \tag{50}$$

Note that, by Eq. (29), all the Q terms on each line in Eqs. (49) and (50) sum to $Q(\varnothing)$. Thus, each line in the two equations represents a different of U_2, U_1, and U_0.

To show that $Q(A) > Q(B)$, we need to be able to compare the Q coefficients in the two equations. We can use an approach like the one used in Theorem 1. In Eq. (35), a term $(p_{\text{eff}} - p_{\text{pl}})$ appeared. Performing the same algebra with different pairs of Q values will produce the same results but with that one term changed:

$$Q(As) - Q(Bs) \to (p_{\text{eff}} - p_{\text{pl}}) \tag{51}$$

$$Q(AsAs) - Q(BsBs) \to (p_{\text{eff}}^2 - p_{\text{pl}}^2) \tag{52}$$

$$Q(BfBf) - Q(AfAf) \to \left[(1 - p_{\text{pl}})^2 - (1 - p_{\text{eff}})^2\right] \tag{53}$$

By the same logic as was used in Theorem 1, because each of the terms on the right of the arrow is positive, the terms on the left are all positive. Thus, we have:

$$Q(AsAs) \geq Q(BsBs) \tag{54}$$

$$Q(AfAf) \leq Q(BfBf) \tag{55}$$

Using these two inequalities and the fact that the Q coefficients on each line in the big equations all sum to 1, we can see that the first line in Eq. (49) is at least as great as first line in Eq. (50). Similar comparisons shows that the second line in the first equation is at least as great as the second line in the second equation, that the third line in the first is at least as great as the third in the second equation, and that the fourth lines of both equations are equal to one another.

Thus, no matter which line in Eq. (50) is the maximum, there is a line in Eq. (49) that is at least as great, and therefore $U(A) \geq U(B)$. □

Thus, when there are only two patients remaining, in cases in which it is easy to assert that a donor is the myopic choice, that donor is also the optimal choice.

10 Multiple donor assignment

In FMT trials, the outcome from the patient is not immediate; some time will pass between the assignment of a patient to a donor and that patient's outcome. It can be that a patient will need to be assigned to a donor before the outcome from the previously-assigned patient is known.

Notable, the urn-based donor allocation strategy does not need any modification to work in these situations: balls are drawn from the urn to select donors, and balls are put into the urn once a patient outcome is known.

The tree formalism discussed in Section 9.1 assumes that only one patient is assigned at a time. In the case of donor being assigned in sequence before their outcomes are known, a few modifications are required. Say, for example, a patient has been assigned to donor A but the outcome is not yet known, and a new patient needs to be assigned to A or B. The same formalism described above can assigned expected utilities to the donor nodes under As and Af. Call AsA the donor node where the first patient was assigned to A, that patient was (or will be) successful, and the second patient is assigned to A as well. Similarly name AsB, AfA, and AfB. Then the expected utilities in question are the assignment of *two* donors, AA or AB, where AA's utility is a mixture over the utilities of AsA and AfA (and the mixing term is still A's probability of success) and AB's utility is, similarly, a mixture over AsB and AfB. This configuration is summarized in Figure 2.

For practical purposes, patients could be assigned in a way that optimizes the expected number of successes given the probabilities computed using the known outcomes. For example, if donor i has a probability of success $p_i \equiv P(\sigma_i|\boldsymbol{X})$ and donor j has $p_j \equiv P(\sigma_j|\boldsymbol{X})$, then the ratio of patients assigned to them should approach $\sqrt{p_i/p_j}$ (as per the calculation in [4], p. 195).

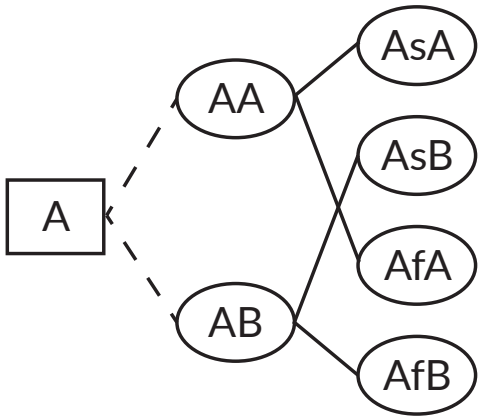

Figure 2: **A trial tree with two successive donor choices.** The current state of the trial, A, indicates that the next patient has been assigned to donor A but the outcome is not known. The dotted lines indicate that the expected utility of the current state A is the maximum over the utilities of the two donor choice nodes AA and AB. The solid lines indicate that the expected utility of AA is the weighted average of the utilities of AsA and AfA, whose utilities are computed as described previously.

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