POLICY

A nudge toward participation: Improving clinical trial enrollment with behavioral economics

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Interventions informed by behavioral economics can address barriers to patient enrollment in clinical trials and improve recruitment efforts.

Participant recruitment represents one of the largest costs of conducting randomized controlled trials (RCTs) (*1*), and barriers to recruitment can generate problems of selective enrollment and under-enrollment (*2*). These problems have long plagued efforts to evaluate medical interventions by limiting generalizability and reducing statistical power. In recent decades, behavioral economics has provided considerable insights into how people make decisions, blending findings from economics and psychology to generate better descriptive and normative models of behavior. Systematic efforts to apply this approach to problems such as patient enrollment in RCTs have not been attempted. In this article, we provide a taxonomy of proposed interventions (Table 1) informed by behavioral economic theory to address low enrollment in clinical trials by addressing the patient barriers of imperfect information, desire for autonomy in making enrollment decisions, and resource constraints. This taxonomy is not exhaustive, but it provides a range of behaviorally informed interventions, or "nudges," that might feasibly be tested and, if successful, implemented.

SELECTING INFORMATION TO PROVIDE

After funding is secured, patients meet eligibility requirements, appropriate protocols are in place, and physicians decide to refer eligible patients (aspects that are not always guaranteed), presenting information to patients in a digestible way is a major challenge to enrollment. Potential participants—with or without a scientific or medical background—must attempt to make informed decisions with limited information in a limited amount of time. However, given the absence of perfect information about all plausible or tested medical interventions, individuals instead rely on contextual signals (i.e., social influences) to decide whether or not an RCT is attractive to them.

Social norms, both descriptive (what others are doing) and injunctive (what others approve of), can encourage participation via a "safety in numbers" mentality. Just as a long waiting list or a friend's recommendation can communicate a restaurant's quality, the social proof provided by normative information may resolve anxiety regarding RCTs (Table 1). These norms can be communicated directly, such as by relaying physicians' recommendations or the number of other people who have elected to participate. Of course, when enrollment rates are low, including at a trial's onset, approaches that imply norms without explicitly describing enrollment numbers may be preferable.

Individuals could also receive personalized information regarding how they were chosen to participate to signal that the trial is tailored to patients like them. Communicating that others have invested time and effort in designing the RCT can also leverage individuals' duties of reciprocity. For example, a field experiment with more than 1 million individuals tested eight different messages to encourage organ donation registration and demonstrated that a reciprocity-based message ("If you needed an organ transplant would you have one? If so, please help others.") led to the largest increase in registration rates (*3*).

Objective information regarding the medical risks of a particular trial may be more difficult to present strategically and may perhaps be best addressed by careful design of the clinical trial itself, rather than through behavioral economic approaches that may (inappropriately) diminish the salience of these risks for potential research participants. Side effects of medications or procedures and burden of procedures (multiple blood draws, multiple physical examinations, and time commitment) should be clearly presented to avoid misperceptions of possible harms or adverse events.

CHOOSING HOW TO PROVIDE INFORMATION

A consent form that comprehensively lists all risks and benefits might seem to ensure patients make informed decisions. However, long forms may engender misunderstandings and deemphasize important information. Electronic forms that provide links to supplemental information would simplify consent forms while still granting access to all information to those interested in learning more. Fortunately, current revisions to the Common Rule, a set of ethical regulations for most human research, promote consent procedures that highlight key information and shorten form length (*4*). These potential revisions could determine whether simple text or format changes, such as the use of bullet points or different fonts for important information, might help patients better understand their rights and responsibilities.

Additional consideration could be given to when and where information is provided (Table 1). For instance, the presence of a physician in the room while patients are considering participation may reduce time spent reading information if patients assume the risks have been vetted by the physician or if patients feel pressured to not waste the physician's time. Providing consent documents at the end of an appointment may unwittingly discourage attention to the information, as patients may be impatient to move on with their days. When possible, we encourage leveraging otherwise-empty times in patients' schedules, such as time spent waiting to see a clinician, to direct their attention to clinical trial opportunities.

CHOICE ARCHITECTURE: HOW DECISIONS ARE STRUCTURED

A major contribution of behavioral economics to public policy has been the use of defaults to increase engagement in activities ranging from 401(k) savings (*5*) to organ donor consent (*6*). These rules establish what will occur if no further action is taken, and many individuals who would have otherwise let inertia hold sway end up engaging by default. Default enrollment is now increasingly common in minimal risk, pragmatic clinical trials. In an ongoing trial we are leading (NCT02328794), smokers at several companies are automatically enrolled

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Table 1. Taxonomy of proposed interventions.

	Approach	Benefits	Concerns
Information provision	• Descriptive norms • Injunctive norms • Reciprocity • Personalization • Simplified consent forms • Providing information at appropriate times	• Relatively inexpensive • Informed participants are less likely to make mistakes during clinical trial • Serves ethical goal of informed consent	• If norm of participation is low, normative information may reduce desire to participate • Too much information can reduce desire to engage • Depends on trust in the source of the information

Choice architecture	• Defaults
	• Active choice
	  ◦ Enhanced active choice
	  ◦ Expanded active choice
	• Structured decision flow
	  ◦ Foot-in-the-door
	  ◦ Self-prophecy
		• Recruitment procedure has to be developed anyway, so little added effort to incorporate choice architecture
		• Grant greater sense of control/autonomy to participants
		• Relatively inexpensive
			• Some procedures are not fully transparent
			• May backfire, by introducing "no" options or by asking wrong questions
			• Ethical concerns about fully informed consent

Incentives	• Direct financial payment • Lottery payment • Material prizes • Rewards that facilitate participation (e.g., bus pass) • Social recognition • Providing RCT results	• Compensates participants for time, opportunity cost, and taking on risk • Delivery of incentives can be structured to motivate continued participation	• Can be expensive • Undue inducement • Unjust inducement • Potential participants may fail to disclose exclusion criteria

and randomized to different smoking cessation programs unless they explicitly opt-out from participation. This enhances both the rate and diversity of patient accrual. For trials that are greater than minimal risk or that require more active engagement, specific steps can be determined by default, such as automatically scheduling appointments to discuss the enrollment decision (with the opportunity to reschedule), thus removing a logistical planning hurdle to eventual participation. In most cases, participants should ultimately be debriefed to inform them that such defaults were used and why they were chosen.

Alternatively, patients may be required to make an active choice—an explicit decision to participate or not before proceeding. Thus, patients cannot avoid enrollment by mere inaction or inattention but instead are encouraged to ask for more information, express any concerns, and evaluate the pros and cons of participation (Table 1). To further motivate participation, researchers might implement "enhanced" active choice, where the stated options highlight the costs and benefits of participating versus not participating, or ask patients to choose among multiple options ("expanded" active choice), where the numerous "yes" options imply that enrollment is normative:

- Yes, morning appointments
- Yes, afternoon appointments
- Yes, evening appointments
- No

By directly choosing their appointment timing, patients retain control over an aspect of participation that is largely irrelevant to the study's outcome but potentially important to patients. Concerns about these appointments can be addressed up-front, and enrollees make clearer commitments to participate in the full trial protocol. The mere existence of these appointments, in turn, can increase engagement, making the overall procedure more efficient.

Researchers can also design recruitment as a series of decisions that filter toward the enrollment decision. The "foot-in-the-door" technique first makes a small request, such as completion of a survey, and then follows with a larger request: the decision to enroll. The initial request can even facilitate enrollment by embedding eligibility screening questions in the survey. If this initial request might be too onerous to complete during the enrollment procedures, a simpler approach is to ask patients to hypothetically participate in an RCT before making the actual enrollment request. This "self-prophecy" procedure leverages the fact that people are likely to say they would perform a prosocial action in hypothetical contexts, and the desire for self-consistency then increases compliance with the actual request.

INCENTIVES

There are, inevitably, resource constraints that patients face. Incentives can reimburse individuals for the foregone working hours and transportation costs of attending appointments and may attract those who otherwise consider the burdens of enrollment to be too high. Financial incentives, such as direct payments, payments to charity, or deductions from insurance premiums, can carry large up-front costs but may prove cost-effective or even cost-saving if they reduce the accrual time required to complete enrollment. Additionally, there may be ways to reduce costs, such as using lottery payments—which leverage people's tendency to overestimate the likelihood of a small probability event—rather than fixed payments (Table 1).

Despite concerns that incentives may represent "undue inducements" by blinding

people to risk, studies have shown that payments may actually serve to signal the risk level of the trial and prompt participants to take more time to carefully assess risks (*7*). Further, incentives do not appear to cloud patients' abilities to make trade-offs between risks and benefits (*8*). Additional concerns that incentives represent "unjust inducements" by preferentially encouraging enrollment among the poor, or that they may reduce participants' willingness to disclose disqualifying information, have also not manifested in hypothetical enrollment decisions (*9*), but definitive evidence is needed from real RCTs; the RETAIN trial has been launched to determine how incentives influence cancer patients' decisions to enroll in a real therapeutic trial (NCT02697799).

Researchers can also encourage participation through nonmonetary prizes (e.g., iPads), although matching the gift to the target population would be essential. Prizes not valued at levels commensurate with the costs of provision are inefficient, or what economists call a "deadweight loss." Alternative incentives include gifts that facilitate participation, such as fuel vouchers to offset transportation costs. These incentives may involve extra effort to procure and implement but may add value by specifically targeting barriers to participation.

Social incentives, such as peer encouragement or mentorship from other patients, can be relatively inexpensive and, by involving other nonclinicians, might reduce any sense of hierarchy between patients and medical providers. Rather than checking up on patients directly, researchers can contact friends and families of patients and leverage these social ties as sources of participant motivation, transportation to appointments, and oversight. Additionally, clinical trial researchers could partner with foundations to recognize consenting participants at community fun runs or through social media phenomena, like the ALS Ice Bucket Challenge, further raising awareness of research and helping patients feel like part of a larger movement. Such efforts may change social norms and attitudes toward research, make other incentives for participation seem even more attractive, and encourage potential participants to seek out enrollment opportunities. Other nonmaterial rewards, such as providing patients with RCT results, also reimburse patients for their efforts while fostering transparency.

THE ETHICS OF THE NUDGE

Nudges may be considered to mitigate the goals of informed consent. However, the present taxonomy promotes nudges that help patients understand relevant information and promote open conversations with physicians. By definition, such nudges cannot "coerce" participation, because they imply no threat of harm for nonenrollment. Although these nudges are explicitly intended to augment enrollment, they may have salutary effects by correcting misperceptions and guiding people to better-informed choices. Nonetheless, informed consideration of the ethics of enrollment nudges requires that they be tested in future research. Such studies should assess whether nudges lead patients to make decisions they would rather not make, are preferentially effective among vulnerable populations, or lead to reduced understanding of the trials in which patients enroll.

IN CLOSING

Behavioral economics has much to contribute to public health, including a focus on the specific contexts in which decisions are made. The interventions described in our taxonomy (Table 1) may not be applicable across all types of patients, settings, and studies. However, these are empirically testable questions, and much could be learned about intervention design with laboratory or hypothetical choice studies. Once relevant barriers to participation are identified and resolved in behavioral labs, interventions can be tested with real patients, as many issues will only arise with patients who must weigh the costs and benefits of actual enrollment. The process of testing in both controlled lab settings and more generalizable field settings might appear onerous but promises better understanding of patient barriers, protects patients from suboptimally designed interventions, and provides more reliable answers regarding the effectiveness and ethics of these interventions. Perhaps most importantly, such work will increase the probabilities that RCTs have adequate statistical power to answer their research questions, thereby enabling clinical trials to achieve their goals of advancing science, improving public health, and saving lives.

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