Incentivizing Recruitment and Retention to Address Enrollment Challenges in Clinical Research

Neal W. Dickert, MD, PhD; Scott D. Halpern, MD, PhD; Javed Butler, MD, MPH

Pervasive problems related to the recruitment and retention of participants in clinical research threaten our ability to produce timely data necessary to guide practice and policy. For example, the Warfarin Versus Aspirin in Reduced Cardiac Ejection Fraction trial took >7 years to recruit, averaging 1 patient per center every 6.25 months.[1] The Efficacy of Vasopressin Antagonism in Heart Failure: Outcome Study With Tolvaptan (EVEREST) trial involved 436 sites to enroll 4133 patients; 77 sites enrolled no patients; and the median enrollment among active sites was only 6.[2,3] Related to this, a major barrier to both Food and Drug Administration approval and acceptance among cardiologists of rivaroxaban in the setting of acute coronary syndrome seems to have been uncertainty related to high rates of loss to follow-up among enrolled subjects in the Anti-Xa Therapy to Lower Cardiovascular Events in Addition to Standard Therapy in Subjects With Acute Coronary Syndrome–Thrombolysis in Myocardial Infarction (ATLAS ACS–TIMI 51) trial.[4,5] These problems are not universal. The Acute Study of Clinical Effectiveness of Nesiritidein Decompensated Heart Failure (ASCEND-HF) study, for example, successfully randomized 7141 patients in just >3 years (although it did involve ≈400 sites).[6] The precise reasons for the variability in recruitment and retention are poorly understood and likely vary by center, by condition, and by study.[7]

Slow recruitment and inadequate retention delay clinical knowledge, and differences in participant characteristics, withdrawal rates, and outcomes introduce uncertainty and limit generalizability. Despite uniform and extensive inclusion and exclusion criteria, low-enrolling sites in EVEREST enrolled sicker patients, had higher rates of protocol noncompletion for reasons other than adverse events, and had a greater incidence of primary adverse outcomes.[3] Low enrollment also depletes resources, escalates costs, and fuels migration of research away from the United States, further limiting generalizability to US populations.[8] Similar trends have been observed outside of cardiology. According to a recent Institute of Medicine–National Cancer Institute report, 40% of National Cancer Institute–funded trials do not complete enrollment.[9] These systemic challenges threaten our ability to evaluate potentially beneficial new interventions and to perform trials examining comparative effectiveness of existing therapies, both of which represent integral elements of health system improvement. In light of these problems and in recognition of important ethical reasons to facilitate clinical research, there have been calls for increased integration of clinical medicine and research and suggestions that regulatory requirements should be relaxed to facilitate low-risk comparative effectiveness trials—often using simple or practical designs—in particular.[10–14]

It is clear that we need to explore multiple methods for improving trial recruitment and retention, given the numerous causes of poor recruitment and retention in clinical trials today.[7] Challenges exist in terms of public awareness and engagement; regulatory requirements have continued to grow and become more complex; and the process of sequential development and dismantling of clinical trial infrastructure is burdensome and inefficient.[10,15] Moreover, financing and executing trials involve complex coordination of multiple entities, often including sponsors, contract research organizations, regulators, site investigators, and patients, each of whom may have different interests and motivations. The leadership and institutional culture at the individual centers certainly play a major role in recruitment and retention as well.

Among potential barriers, the dearth of incentives in clinical research also looms large.[15] Treating clinicians are uncompensated for identifying and referring participants; medical school faculty are rarely promoted for serving as investigators in multicenter trials; and research staff salaries are unrelated to recruitment success. Important ethical and financial arguments exist against incentives, and these arguments are grounded in appropriate concern for the protection of research subjects and the appreciation of historical research abuses. However, few are grounded in evidence. Interestingly, some data exist on the effects of providing incentives to research participants. Although limited, these data suggest that long-held concerns about undue inducement in particular may not manifest in practice.[16] Incentives to providers and researchers raise concerns that are distinct from those about incentives to participants, but the implications of incentive strategies may be similarly amenable to empirical investigation and warrant exploration, given their potential role in addressing important enrollment challenges.

From the Department of Medicine, Division of Cardiology, Emory University School of Medicine, Atlanta, GA (N.W.D., J.B.); Atlanta Veterans Affairs Medical Center, Atlanta, GA (N.W.D.).; and Department of Medical Ethics and Health Policy, Division of Pulmonary, Allergy, and Critical Care Medicine, Leonard Davis Institute Center for Health Incentives and Behavioral Economics, Perelman School of Medicine, University of Pennsylvania, Philadelphia (S.D.H.).

Correspondence to Neal Dickert, MD, PhD, Emory University School of Medicine, 1462 Clifton Rd, No. 508, Atlanta, GA 30322.

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Targets for Incentives and Ethical Implications

Referring Providers

Clinical providers play a critical role in research. Busy clinicians must learn about protocols, screen patients, discuss trials, and make referrals. These activities may involve substantial efforts yet are typically uncompensated. Payments for referrals (finder's fees) to overcome these barriers have been, at times, commonly used, particularly in industry-funded research.[17] Finder's fees, however, have fallen out of favor and are largely prohibited in academic centers because of concerns about conflict of interest, about patients feeling pressured or losing trust in providers, or about researchers competing by offering providers more money than other studies.[18–20]

These concerns are serious but not unique. Incentives are widely used at both the policy and practice levels and considered legitimate in the context of clinical care to improve quality, contain cost, and avoid waste; how to structure these incentives to minimize conflicts and maximize desirable results is an area of active research. Because the role of research in facilitating a learning health system is increasingly recognized as essential to quality health care,[12] comparable efforts focusing on understanding ways to compensate physicians who evaluate and refer patients for clinical trials could be invaluable. Could payment based only on referral or screening increase enrollment with less pressure on participants than payment contingent on enrollment? Will disclosure of providers' interests foster or erode trust? Could regulation of payment minimize competition for referrals? These are critical ethical questions, but they are not intrinsic problems. In other words, incentive structures are problematic only to the extent that undesirable consequences materialize in practice. Fortunately, most of these consequences can be studied.

To evaluate these questions, investigators could randomize trial sites (stratified by factors such as type of site or geographic area) to provide enrollment-based payments, referral-based payments, or no payment to referring physicians. Ethical outcome measures could include quality of consent, patients' perceptions of referring physicians, and socioeconomic distribution of enrollment. Effectiveness could be measured by the number of referrals, referred patients' eligibility, distribution of patient characteristics across sites, and actual enrollment. Incremental cost-effectiveness could be evaluated by comparing trial costs with and without incentives, inclusive of costs associated with longer recruitment periods (Table). To the best of our knowledge, no such study has ever been performed, and experimentally designed ethics trials within trials are uncommon but have been successfully completed with regard to practices such as informed consent procedures.[21,22] Moreover, the outcome measures for such a study would involve standard interview and survey methods combined with data that would already be collected as part of the parent trial. With proper upfront coordination, such a study seems feasible and likely to yield important insights.

Site Investigators

Site investigators are already compensated for research efforts; however, there is typically little reward to academic investigators unless a study brings sizable resources to the institution, and budgets are often slim. Because of institutional costs and funding constraints, salary support is often minimal, and many investigators, under pressure to cover salary with clinical activity, relegate trial management to coordinators. This practice may reduce recruitment and quality. Incentives for meeting or exceeding quality goals are widely accepted in the clinical realm, and trials use incentives for meeting regulatory requirements or infrastructure-related milestones. They may be harnessed to improve both initial recruitment and retention of subjects as well.

The principal concern is that incentivizing investigators may compromise science and participant protection. Investigators might pressure staff to enroll more aggressively, pressure participants to enroll or remain in a study, overstate benefits or understate risks, or skirt eligibility criteria. Concerns about patient interactions may be most acute when researchers are also clinicians. Although there has been fraud in the context of enrollment incentives,[23] this area has not been effectively studied; the extent to which concerns would materialize under different incentive structures is unknown. Obviously, different incentives will have different ethical implications. Incentivizing screening, for example, rather than enrollment may result in less pressure on patients. There are also real concerns about the appearance of conflict of interest in incentive arrangements. Interestingly, there is some evidence that patients generally do not find per capita investigator payments problematic, although they have greater concern when equity interests are present.[24] Adequately disclosing incentive arrangements and studying patients' reactions are a central element of assessing their ethical impact.[25]

Study Coordinators

Finally, coordinators play pivotal roles in identifying, recruiting, and retaining participants. They solicit referrals and interact directly with participants. Typically, coordinators are salaried; incentive structures are rarely used to encourage productivity, although there are reports of industry-funded incentives.[17] By virtue of their employment, there are intrinsic incentives to enroll patients; however, bonuses may increase productivity and could be made contingent on screening, enrollment, or completion of important follow-up data points. The last point in particular could importantly improve subject retention and mirror payments to subjects across the course of a study. As with payments to investigators, paying coordinators could alter communication with participants in ways that undermine autonomy or erode trust. Adherence to protection measures and data quality could also suffer. However, enrollment may improve, data completeness and retention could increase, and trial costs could decrease.

Ethical concerns about incentives to coordinators or site investigators differ somewhat from concerns about referring physicians. Although they will need to account for these differences (Table), study designs fundamentally similar to those proposed for referring clinicians could be used to assess their impact in practice.

Table. Potential Concerns and Outcome Measures

Incentivized Role	Potential Incentives	Ethical Concerns	Measures to Track Effects of Incentives
Referring providers	Payment per referred patient based on hourly rates and estimated time screening and discussing the trial Payment per enrolled patient based on hourly rates and estimated time screening and discussing the trial Payment per enrolled patient based on perceived amount necessary to generate adequate enrollment	• Conflict of interest • Pressure on patient • Loss of trust • Compromised consent	• Referral/enrollment rates and time to completion • Rate of eligibility • Rate of refusals/acceptance • Patients' perceptions of conflict, trust in providers • Participant understanding • Quality of consent conversations (eg, duration, comprehensiveness, absence of pressure, content) • Demographic distribution of enrollment • Cost
Investigators/coinvestigators	Per-patient payments for successful screening/presentation of the study to patients based on hourly rate and estimated work of screening; payments are in addition to standard payment for enrolled patients Increases in per-patient enrollment payments for sites meeting or exceeding enrollment targets Bonuses for meeting enrollment targets and follow-up data points (eg, fixed bonuses for every 5 patients enrolled)	• Conflict of interest • Pressure on patients • Loss of trust • Compromised consent • Scientific integrity	• Enrollment/recruitment rates and time to completion • Rate of eligibility • Data integrity and adherence to good clinical practice (eg, accuracy of data, adequacy of documentation, protocol deviations) • Rate of refusal/acceptance • Participant understanding and trust • Quality of consent conversations (eg, duration, comprehensiveness, absence of pressure, content) • Cost
Research staff	Bonuses on a per-patient basis for identifying eligible patients Per-patient bonuses for number of patients contacted above a certain minimum Per-patient bonuses for successful enrollment/consent Per-patient bonuses for completion of follow-up data or for percentage of enrollees completing the study	• Pressure on patients • Undermining informed consent • Scientific integrity • Loss of trust	• Enrollment/recruitment rates and time to completion • Rate of eligibility • Data integrity and adherence to good clinical practice (eg, accuracy of data, adequacy of documentation, protocol deviations) • Rate of refusal/acceptance and retention • Participant understanding and trust • Quality of consent conversations (duration, comprehensiveness, absence of pressure, content) • Cost

A Way Forward

Incentives for recruitment and retention raise real ethical concerns rooted in a strong and appropriate desire to protect participants and to foster trust. However, incentives are not intrinsically problematic. Rather, performing and participating in research is something we as a society encourage and respect; adequate evaluation of existing and emerging therapies is an integral component of health and health system improvement.[12,26] Because declining research activity and quality in the United States has the potential to negatively impact public health, there are moral reasons to explore strategies to improve enrollment. We have argued that incentives represent one important mechanism that may be relatively straightforward to implement and evaluate.

Fortunately, most ethical concerns related to incentives can be empirically studied. We propose implementing reasonable, well-designed incentives within planned studies with dedicated budgets sufficient to enable rigorous evaluation and systematic monitoring of intended and unintended consequences. Of course, proposed incentives for evaluation will need to be reviewed by both local institutional review boards and experts in ethics and clinical research to ensure that they are practical (and thus worthy of evaluation) and do not pose obvious significant risks to participant welfare or informed consent. We suspect that many incentives may improve enrollment without posing undue risks, but if evidence emerges that trust is eroded, inappropriate enrollments are increased, or consent is compromised, these incentives should not be used regardless of enrollment effects.

Incentives will surely have different implications in different contexts. The same incentive may influence a referring physician differently on the basis of local reimbursement standards and cost of living. And although the focus of this analysis is on US researchers, incentives may function very differently in low- and middle-income countries. Similarly, the proper role of incentives may vary for different studies. Because the ethical justification is greater for a trial addressing an important policy or public health priority than for a trial of a drug designed principally to achieve a marketing indication or that is likely to have little impact on treatment outcomes. Like all issues in research ethics, context matters and numerous complexities exist; oversight and review must be context sensitive but should be informed by data when possible.

The impact of incentives on recruitment and retention and their ethical implications in practice are unknown, as is the relative effect of barriers addressed by incentives compared

with the numerous other barriers in clinical research today. However, data-free guesses have led to the present quagmire and offer no insights into balancing important considerations to advance research. Cardiology has led the way toward evidence-based medicine; it is time to lead a more evidence-based approach to ethics that adopts the same standards of evidence that undergird research itself. Fundamental ethical principles are not amendable to empirical investigation, but many of the practices that address ethical concerns are. Investing in such studies now could yield exponential returns if effective and ethical approaches to improving recruitment are identified.

Disclosures

None.

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