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Original Contribution

Incentives to participate in clinical trials: practical and ethical considerations☆,☆☆

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ABSTRACT

Background: Clinical trials often offer incentives to encourage individuals to enroll and to enhance follow-up. The scope and nature of incentives used in emergency department (ED)-based trials are unknown.
Objectives: The objective of this study is to characterize the quantity and quality of incentives and other forms of compensation used in clinical trials of human subjects recruited in US EDs. A secondary goal is to provide an historical and ethical analysis of the use of incentives in clinical trials.
Methods: We reviewed English-language randomized clinical trials conducted in US EDs from 2009 to 2013. Full text of the studies was reviewed to identify whether incentives were used, their value, and timing. Funding source was noted as well. Data are presented with descriptive statistics.
Results: Of 1151 articles identified, 76 (6.6%) fit criteria for review. Of these, 7 (9.2%) provided incentive payments. A recently published eighth trial was included as well. The total cash value of incentives offered ranged from $10 to $195. Four studies offered payment at enrollment only. Incentives included cash, debit cards, and gift cards.
Conclusion: The use of financial incentives in ED-based trials is uncommon. Studies that use incentives are generally extramurally funded, usually by a federal agency, and include waves of follow-up that continue after discharge from the ED. Payment size is modest. Incentives may improve recruitment and retention in ED-based trials, but authoritative data are lacking. Investigators need to take care to avoid incentives that may be coercive or unduly influence research participants.

1. Introduction

A properly conducted clinical trial must do many things. Two of these are to recruit a sufficient number of subjects to meet the projected sample size and to retain those subjects through the various waves of follow-up. Failure to do the former results in an underpowered study; failure to complete the latter results in missing data. Both events pose threats to the internal validity of the trial and limit any inferences that may be drawn about the results.

We should clarify, at the outset, that we wish to distinguish payments made to subjects in clinical trials to encourage their participation and retention from payments made as reward for behaviors desired as specified in the study protocol. These types of payments have a variety of names, such as contingency management or conditional cash transfers. They might be made, for example, to reward a subject in a clinical trial of addiction treatment whose urine specimen remains drug free. In these kinds of studies, the promise of reward is an external motivator and becomes an integral part of the treatment. It is generally reserved for the intervention arm and is not simply a token of appreciation for subjects' time or effort. Contingency management payments are not the subject of this report.

The goal of this report is to describe the use of incentive payments in clinical trials based in emergency departments (EDs). In the discussion, we also provide an ethical and historical perspective on the use of incentive payments in clinical trials. The article is an expanded version of a didactic presentation by the authors at the 2014 Annual Meeting of the Society for Academic Emergency Medicine. Our hope is that this work may inform the use of incentives in future ED-based clinical trials.

2. Methods

We searched English-language articles available on Ovid Medline from the years 2009 to 2013. The search terms used were *emergency medicine* or *ED* and studies of therapy or diagnosis or prognosis, with filters to maximize sensitivity and specificity. We limited the search to *clinical trials* or *controlled clinical trial* or *randomized clinical trial* or *pragmatic clinical trial*. The goal was to identify all published randomized clinical trials conducted in US EDs.

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All titles were examined by a single author (SLB), who then reviewed study abstracts and full text as needed. The search strategy was developed by both authors. Of note, studies that used payments to encourage desired behaviors, such as contingency management trials, were excluded.

We also examined a clinical trials registry, www.clinicaltrials.gov. However, this registry does not contain information on incentives or payments to study subjects and was therefore not considered further.

Data are presented with descriptive statistics only. No inferential testing was performed. The study was exempted from review by the Human Investigation Committee of Yale University.

3. Results

Between 2009 and 2013, 1151 articles were identified using the search strategy described. Of these, 432 represented prospectively conducted trials, and 131 contained the word *random* in the title or abstract. Of these 131 studies, 51 were conducted outside the United States and were excluded from further consideration. An additional 4 articles recruited subjects from outside the ED and were also excluded. This left 76 trials for analysis.

Of these 76 trials, 7 (9%) specified incentive payments to study subjects. Because of the paucity of such trials, an eighth study, conducted by one of the authors and recently published, was included in the final analysis as well.

Trial methods, including incentive payment plans, are presented in the Table. Two studies addressed smoking cessation in ED patients; 2 others were based in the pediatric ED. The others addressed a variety of topics in adult emergency care. Five of the studies addressed health behaviors or behavioral health (smoking cessation, alcohol misuse, suicidality, and alcohol/injury). All but 1 study was extramurally funded; 1 study [3] was supported by internal funds from a hospital-affiliated foundation. More than half the studies (5/8) were supported by federal agencies, with the National Institutes of Health (NIH) as the most common funder. No study was supported solely by in-kind funds.

Incentives were offered at varying time points and in varying amounts. Four studies offered payment only at enrollment, whereas 4 others offered additional payments at varying waves of follow-up. The range of maximum payments varied from $10 to $195. The study by Flores et al [4] offered the largest incentive to enroll ($50) and offered $10 for each successful monthly telephone follow-up over the subsequent 12 months. The 2014 study by Bernstein et al [8] offered the largest potential payment, a $100 gift card, to return at 3 months for an in-person assessment of exhaled carbon monoxide.

A variety of incentives were offered. Most common were gift cards at widely available retail outlets. Two studies offered cash and 1 a debit card for groceries.

4. Discussion

4.1. Study results

Incentives to subjects in ED-based clinical trials are uncommon. Of 77 trials reviewed in the past 5 years, only 8 (10%) offered subjects financial inducements to enroll or continue participation in follow-up. Nearly all trials received support from extramural agencies through a competitive grant process.

Trials typically offer a modest payment at enrollment and additional payments for subsequent telephone or in-person assessments. Often, the largest payment is reserved for assessment of the primary end point. For 1 study, which required in-person biochemical confirmation of smoking abstinence, a larger payment of $100 was offered [8]. Total payments for all trials reviewed were less than $200. That said, for many of the subjects of these trials, who often are from lower socioeconomic groups, $200 may qualify as a sufficient incentive to enroll and maintain participation.

Incentives are easy to spend at commonly available, affordable retail outlets. One study, in a pediatric ED, offered an incentive that was particularly salient—a gift card to a toy store [3]. Although cash is completely fungible and appeals to all subjects, it presents particular challenges regarding of safe and secure storage and bookkeeping. Incentives that are mailed to subjects where follow-up occurs by phone may be returned for an insufficient address or subject relocation. The proportion of incentives received by subjects at follow-up was not reported in the studies reviewed. For 1 study, we estimate that approximately 5% of mailed incentives were returned [8].

4.2. Historical considerations

There is a long history of paying human subjects to participate in research studies and an extensive literature exploring ethical concerns and controversies about this practice in the United States. There has been a long-standing conflict between offering financial compensation to healthy subjects and patient subjects to participate in research studies and the idea that participation in research is a purely voluntary activity. Some notable historical examples include William Beaumont paying Alexis St Martin $150 in food, clothing, and lodging to examine gastric physiology through Mr Martin's unhealed abdominal gunshot wound and US Army researcher Walter Reed offering $100 in gold to “volunteers” in the yellow fever experiments and an additional $100 if subjects became infected with or died of yellow fever [9-11]. From the 1940s to 1960s, financial compensation was a component of exploitive research studies, especially among vulnerable populations such as prisoners. The death of Bernadette Gilchrist, a nursing student who had failed to disclose a history of anorexia nervosa to participate in sleep studies that paid $100 per day at the NIH in 1980, was a more recent reminder of the potential for financial incentives to adversely affect participant safety in research [12].

In response to many serious unethical research studies, including the Tuskegee syphilis studies, The National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research issued the Belmont report in 1978 [13]. These principles have since guided contemporary approaches to financial incentives and compensation in human subjects research. Regulations now frame financial compensation in terms of the principle of respect. Autonomous individuals must provide informed consent to participate in research studies free of “coercion” and “undue influence.” An undue influence could include “an offer of an excessive, unwarranted, inappropriate, or improper reward

Table
Emergency medicine trials providing incentive payments to study subjects

Study	Topic	Funder	Type of incentive	No. of potential payments	Total value
Bernstein et al [1]	Smoking cessation	NIH	Cash, Metrocard	1	$29
Currier et al [2]	Suicidality	NIH	Groceries debit card	3	$150
Drendel et al [3]	Pediatric fracture pain	Children's Hospital Foundation	Toy store gift card	1	$10
Flores et al [4]	Pediatric asthma	Commonwealth Fund, Robert Wood Johnson Foundation	Checks	13	$170
McCarthy et al [5]	Medication adherence	NIH, Agency for Healthcare Research and Quality	CVS gift card	1	$10
Stein et al [6]	Urinary tract infection/kiosk	California Healthcare Foundation	Gift card	1	$10
Walton et al [7]	Alcohol/violence	NIH	Cash	3	$76
Bernstein et al [8]	Smoking cessation	NIH	Walmart gift cards	5	$195