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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 ED-based trials is unknown.

Objectives—To characterize the quantity and quality of incentives and other forms of compensation used in clinical trials of human subjects recruited in U.S. 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 U.S. emergency departments from 2009-2013. 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 papers 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 $10-195. 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 employ 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.

Keywords

clinical trials; clinical research; incentives; research ethics

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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. In the Discussion, we also provide an ethical and historical perspective on the use of incentive payments in clinical trials. The paper 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 2009-2013. The search terms used were "emergency medicine" or "emergency department" 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 U.S. emergency departments.

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 papers 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 four papers 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 Table 1. Two studies addressed smoking cessation in ED patients; two 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 one study was extramurally funded; one study[1] was supported by internal funds from a hospital-affiliated foundation. Over half the studies (5 of 8) were supported by federal agencies, with the National Institutes of Health 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, while four others offered additional payments at varying waves of follow-up. The range of maximum payments varied from $10-$195. The study by Flores[2] 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[3] offered the largest potential payment, a $100 gift card, to return at three 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 one a debit card for groceries.

4. Discussion

4.1. Study results

Incentives to subjects in emergency department-based clinical trials are uncommon. Of 77 trials reviewed in the past five 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 endpoint. For one study, which required in-person biochemical confirmation of smoking abstinence, a larger payment of $100 was offered.[3] Total payments for all trials reviewed was 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.[1] 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 one study, we estimate about 5% of mailed incentives were returned.[3]

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 U.S. There has been a longstanding 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 U.S. 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 from yellow fever.[4-6] 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 in order to participate in sleep studies that paid $100 per day at the National Institutes of Health in 1980, was a more recent reminder of the potential for financial incentives to adversely affect participant safety in research.[7]

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.[8] 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 or other overture in order to obtain compliance" and the same reward could become "undue" "if the subject is especially vulnerable."[8]

The federal research regulations issued in response to the Belmont report in the Common Rule (45CFR46) addressed the role of financial (and non-financial) compensation to research participants. The regulations that address informed consent (45CFR46.116) state that an investigator should seek informed consent only under circumstances that "minimize the possibility of undue influence or coercion." The federal Office of Human Subjects Protection (OHRP) noted in its policy guidance that compensation should be "just and fair" but "in no case should remuneration be viewed as a way of offsetting risks; that is, it should not be considered a benefit to be weighed against study risks.[9] This guidance was revised in

2013 to address the concern that any level of compensation based on research risks could be considered unacceptable. OHRP also indicated that while Institutional Review Boards (IRBs) "should not consider remuneration as a way of offsetting risks," subjects "may include compensation for risks associated with their participation in research and that compensation may be an acceptable motive for agreeing to participate in research."[9] Although the Food and Drug Administration (FDA) indicated in 1989 that payment could be considered a research benefit as well as a potential source of undue influence, by 1995 the FDA indicated that payment should not be viewed as a benefit, but could be considered to be a recruiting incentive.[4]

4.3. Ethical considerations

The ethical application of the research regulations that frame the role of financial incentives and compensation are highly relevant to emergency medicine researchers. Patients in the ED may be considered vulnerable by the acuity or nature of their disease, lack of health insurance and other socioeconomic factors. The emergency medicine researcher has an obligation to perform ethically and scientifically sound research. This requires an appropriate sample of subjects who meet the study's inclusion criteria and can complete all study-related activities. Are financial incentives acceptable to encourage participation or study completion? If financial incentives are permissible, should one use an absolute or relative compensation structure for the same research activity when performed in different populations? How do IRBs consider these issues and determine what payment if any is "fair and just?"

Whether to pay healthy volunteers and patient subjects and what is "appropriate payment" remains a controversial topic in human subjects research.[5,10-14] Dickert provided one conceptual model for research compensation.[11] Dickert recommended a "wage payment model" over a "market model" where payment is an incentive and based on supply and demand or a "reimbursement model" that only pays for expenses. The market model pays subjects based on standard wage for unskilled labor that is augmented for particularly uncomfortable procedures.[11] Other models such as the NIH compensation based on "inconvenience units" for research activities have been described.[11] However, although many IRBs recognize or accept financial compensation for time, effort, inconvenience, study-related expenses (travel, childcare, parking, etc.), compensation based on research risk is not considered acceptable.

Recent studies have confirmed that IRBs struggle to translate the ethical principles about compensation to their evaluation of specific research protocols. Klitzman observed that IRB members often used the terms coercion and undue influence interchangeably when considering financial incentives and struggle with "how much is too much?" and "how high is too high?"[15] In a national survey of IRB members and staff, Largent et al. concluded that "excessively expansive or inconsistent views about coercion and undue influence held by IRB members and human subjects professionals may interfere with the recruitment of research participants by needlessly limiting the payments offered to them and may thereby impede valuable research without true cause."[16]

One important concern is that financial compensation could influence the ability of a research subject to make an unbiased evaluation of the risks and benefits of participating in a study, or could encourage subjects, especially those who are vulnerable, to agree to participate. However, empirical studies have not confirmed that any amount of compensation distorts an individual's ability to understand risk.[17,18] Wertheimer has argued that financial incentives are "never coercive" in terms of directly threatening someone to participate in research and Dickert has suggested that undue inducement concerns are "largely overestimated."[12,19]

Given the many issues and complexities that surround the role of financial compensation and financial incentives in research, it is important for the emergency medicine researcher to recognize that she/he can find common ground with the IRB. Both the investigator and the IRB share an ethical and regulatory commitment to sound scientific design. Emergency medicine researchers may consider financial compensation or incentives if these are needed to recruit an adequate sample size and assure that enrolled subjects complete the required study activities. Conducting research that is underpowered or biased due to loss to follow up or not having accurate follow up data to determine the outcome of a research study should be as much of a concern for the researcher as for those charged with review and oversight of the research.

5. Limitations

In our literature review, we examined only the previous five years of ED-based clinical trials. Studies conducted earlier may have used additional incentive mechanisms. Neither did we examine the possible use of incentives for non-randomized trials, such as surveys, observational cohort studies, and before-/after studies. Similarly, we excluded trials where the physician or provider was the subject, such as the use of various training techniques in a simulation laboratory.

We did not review the use of incentives in trials conducted in other clinical venues, or in healthy subjects. We chose to focus on ED trials involving patients. We limited our search to U.S.-based trials, printed in English, to better understand practice in the country with the most extensive infrastructure for ED-based patient-oriented research.

It is possible that incentives or payments were made to subjects, but not reported. To the extent that incentives are sufficiently important to trial methodology to merit reporting, we hope and expect that investigators would have reported them.

Finally, having studies reviewed by a second abstractor with formal assessment of interrater reliability might have increased the accuracy of search results. We did not seek to examine the use of incentives in trials that were unpublished.

6. Conclusions

Incentives for recruitment and retention are infrequently used in clinical trials in emergency medicine. This may reflect several factors, including the relative ease of subject recruitment, the infrequent need to continue follow-up after discharge, and the relative lack of extramural

funding for ED-based trials. ED-based trials that employ incentives are generally extramurally funded and require several timepoints of subject follow-up after discharge. Incentives are an important mechanism to recruit and retain subjects in high-quality trials, but must be offered in ways that avoid coercion and undue influence.

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References

1. Drendel AL, Gorelick MH, Weisman SJ, Lyon R, Brousseau DC, Kim MK. A randomized clinical trial of ibuprofen versus acetaminophen with codeine for acute pediatric arm fracture pain. Ann Emerg Med. 2009; 54:553–60. [PubMed: 19692147]
2. Flores G, Bridon C, Torres S, et al. Improving asthma outcomes in minority children: a randomized, controlled trial of parent mentors. Pediatrics. 2009; 124:1522–32. [PubMed: 19948624]
3. Bernstein SL, Rosner J, O'Malley S, et al. Successful Tobacco Dependence Treatment Achieved via Pharmacotherapy and Motivational Interviewing in Low-Income Emergency Department Patients. Ann Emerg Med. 2015 doi:10.1016/j.annemergmed.2015.03.030.
4. Hutt LE. Paying research subjects: historical considerations. Health Law Rev. 2003; 12:16–21. [PubMed: 15742492]
5. Grady C. Payment of clinical research subjects. J Clin Invest. 2005; 115:1681–7. [PubMed: 16007244]
6. Neumann T, Neuner B, Gentilello LM, et al. Gender differences in the performance of a computerized version of the alcohol use disorders identification test in subcritically injured patients who are admitted to the emergency department. Alcoholism: Clinical & Experimental Research. 2004; 28:1693–701.
7. Kolata GB. The death of a research subject. Hastings Center Rep. 1980; 10:5–6.
8. National Commission for the Proptection of Human Subjects of Biomedical Behavioral Research. The Belmont report: Ethical principles and guidelines for the protection of human subjects of research. ERIC Clearinghouse; Bethesda, MD: 1978.
9. McDonough KH, Giaimo ME, Miller HI, et al. Low-dose ethanol alters the cardiovascular, metabolic, and respiratory compensation for severe blood loss.[see comment]. J Trauma-Injury Infection & Critical Care. 2002; 53:541–8. discussion 8.
10. Czarny MJ, Kass NE, Flexner C, Carson KA, Myers RK, Fuchs EJ. Payment to healthy volunteers in clinical research: the research subject's perspective. Clin Pharmacol Ther. 2010; 87:286–93. [PubMed: 20090675]
11. Dickert N, Grady C. What's the price of a research subject? Approaches to payment for research participation. N Engl J Med. 1999; 341:198–203. [PubMed: 10403861]
12. Dickert N. Enrollment of economically disadvantaged participants in clinical research. Virtual Mentor. 2009; 11:54–60. [PubMed: 23190487]
13. Macklin R. On paying money to research subjects: ‘due’ and ‘undue’ inducements. IRB. 1981; 3:1–6. [PubMed: 11649367]
14. Wong JC, Bernstein M. Payment of research subjects for more than minimal risk trials is unethical. Am J Med Sci. 2011; 342:294–6. [PubMed: 21804364]
15. Klitzman R. How IRBs view and make decisions about coercion and undue influence. J Med Ethics. 2013; 39:224–9. [PubMed: 22982492]
16. Largent E, Grady C, Miller FG, Wertheimer A. Misconceptions about coercion and undue influence: reflections on the views of IRB members. Bioethics. 2013; 27:500–7. Bioethics 2013;27:500-7. [PubMed: 22493972]
17. Festinger DS, Marlowe DB, Dugosh KL, Croft JR, Arabia PL. Higher magnitude cash payments improve research follow-up rates without increasing drug use or perceived coercion. Drug Alcohol Depend. 2008; 96:128–35. [PubMed: 18395365]

18. Bentley JP, Thacker PG. The influence of risk and monetary payment on the research participation decision making process. J Med Ethics. 2004; 30:293–8. [PubMed: 15173366]
19. Wertheimer A, Miller FG. Payment for research participation: a coercive offer? J Med Ethics. 2008; 34:389–92. [PubMed: 18448723]
20. Bernstein SL, Bijur P, Cooperman N, et al. A randomized trial of a multicomponent cessation strategy for emergency department smokers. Acad Emerg Med. 2011; 18:575–83. [PubMed: 21676054]
21. Currier GW, Fisher SG, Caine ED. Mobile crisis team intervention to enhance linkage of discharged suicidal emergency department patients to outpatient psychiatric services: a randomized controlled trial. Acad Emerg Med. 2010; 17:36–43. [PubMed: 20015106]
22. McCarthy ML, Ding R, Roderer NK, et al. Does providing prescription information or services improve medication adherence among patients discharged from the emergency department? A randomized controlled trial. Ann Emerg Med. 2013; 62:212–23. e1. [PubMed: 23561463]
23. Stein JC, Navab B, Frazee B, et al. A randomized trial of computer kiosk-expedited management of cystitis in the emergency department. Acad Emerg Med. 2011; 18:1053–9. [PubMed: 21996070]
24. Walton MA, Chermack ST, Shope JT, et al. Effects of a brief intervention for reducing violence and alcohol misuse among adolescents: a randomized controlled trial. JAMA. 2010; 304:527–35. [PubMed: 20682932]

Table

Emergency medicine trials providing incentive payments to study subjects.

Study	Topic	Funder	Type of Incentive	No. of potential payments	Total value
Bernstein 2011[20]	Smoking cessation	National Institutes of Health (NIH)	Cash, Metrocard	1	$29
Currier 2010[21]	Suicidality	NIH	Groceries debit card	3	$150
Drendel 2009[1]	Pediatric fracture pain	Children's Hospital Foundation	Toy store gift card	1	$10
Flores 2009[2]	Pediatric asthma	Commonwealth Fund, Robert Wood Johnson Foundation	Checks	13	$170
McCarthy 2013[22]	Medication adherence	NIH, Agency for Healthcare Research and Quality	CVS gift card	1	$10
Stein 2011[23]	Urinary tract infection/kiosk	California Healthcare Foundation	Gift card	1	$10
Walton 2010[24]	Alcohol/violence	NIH	Cash	3	$76
Bernstein 2015[3]	Smoking cessation	NIH	Walmart gift cards	5	$195