Published in final edited form as:

Contemp Clin Trials. 2019 January ; 76: 1–8. doi:10.1016/j.cct.2018.11.007.

Randomized Evaluation of Trial Acceptability by INcentive (RETAIN): Study protocol for two embedded randomized controlled trials

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Author's Contributions

JM, AJS, BB, SB, BLH, RAS, RRG, MSP, FB, DL, JK, KGV, and SDH contributed to the study design and protocol. DCK, JM and SDH drafted the protocol manuscript. AJS, BLH, RAS, RRG, MSP, DL, JK, and KGV provided critical feedback and revisions. All authors have provided final approval of the study protocol.

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Competing Interests: None

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Abstract

Introduction—The most common and conceptually sound ethical concerns with financial incentives for research participation are that they may (1) represent undue inducements by blunting peoples’ perceptions of research risks, thereby preventing fully informed consent; or (2) represent unjust inducements by encouraging enrollment preferentially among the poor. Neither of these concerns has been shown to manifest in studies testing the effects of incentives on decisions to participate in hypothetical randomized clinical trials (RCTs), but neither has been assessed in real RCTs.

Methods and analyses—We are conducting randomized trials of real incentives embedded within two parent RCTs. In each of two trials conducted in parallel, we are randomizing 576 participants to one of three incentive groups. Following preliminary determination of patients’ eligibility in the parent RCT, we assess patients’ research attitudes, demographic characteristics, perceived research risks, time spent reviewing consent documents, ability to distinguish research from patient care, and comprehension of key trial features. These quantitative assessments will be supplemented by semi-structured interviews for a selected group of participants that more deeply explore patients’ motivations for trial participation. The trials are each designed to have adequate power to rule out undue and unjust inducement. We are also exploring potential benefits of incentives, including possible increased attention to research risks and cost-effectiveness.

Keywords

randomized controlled trials; behavioral economics; incentives; ethics; nudge

Introduction

Recruitment Difficulties Plague Randomized Clinical Trials

An Institute of Medicine report revealed that more than 40% of clinical trials sponsored by the National Cancer Institute are never completed, typically due to enrollment difficulties, [1–4] which have been called the “ultimate inefficiency[5]” and “the most difficult and challenging aspect of clinical trials [6]”. Even when investigators enroll an adequate number of participants, they rarely do so on schedule [4, 7], or in a manner that attracts the full range of eligible participants [8, 9]. Further, participant recruitment represents one of the largest

costs of conducting clinical trials, requiring an average of 13 hours and \$500 per subject in cancer trials at academic medical centers [10].

Given the resources needed to successfully recruit patients to RCTs, and the gap between important research questions and available research funding, it is essential to find ways to enhance recruitment of patients to clinical trials [11]. To address this challenge, authorities have suggested that trialists should embed evaluations of recruitment strategies within their trials [12, 13].

Financial Incentives for RCT participation

Investigators increasingly have sought to understand how people make decisions to participate in research, and specifically what investigators ethically can do to improve study enrollment [14–16]. This work has revealed that, among several reasons why potential subjects would or would not participate in research, the opportunity for financial compensation or benefit often figures prominently among both patients [17–19] and volunteers [20] [21] [22]. Indeed, common sense, anecdotal experiences, and the few empirical analyses conducted to date all suggest that financial incentives can increase study enrollment and that larger incentives are more effective than are smaller ones [23–25].

Ethical Concerns with Incentivizing Research Participation

Despite these potential benefits, an often-cited concern with paying people to participate in research is that incentives may represent undue inducements – that is, by offering money, investigators may alter peoples’ perceptions of the risks associated with research participation, thereby preventing fully informed consent [26–35]. A second common concern with incentives is that they may represent unjust inducements – that is, incentives could encourage enrollment preferentially among less-wealthy persons [36–38]. To address these controversial matters requires definitive evidence of the impact payments have on risk perception and whether or how payments differentially motivate participation among persons with different incomes or financial needs.

We are conducting the Randomized Evaluation of Trial Acceptability by INcentive (RETAIN) study to test the efficacy and potential risks of providing financial incentives for participation in clinical trials. RETAIN is supported by the National Cancer Institute (RO1CA197332) and registered on [ClinicalTrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT02697799) (NCT02697799). The results will inform research regulations and guide the use of incentives in future RCTs to expedite medical innovation and improve health. The following protocol and future publication of results will conform to the guidelines for reporting embedded recruitment trials [12].

Objectives

The aims of RETAIN are to (1) determine if the ethical concerns with incentives for research participation actually manifest; (2) assess the possible scientific and ethical benefits of financial incentives for RCT participation; and (3) evaluate the cost-effectiveness of using financial incentives to increase RCT enrollment rates.

Methods

Study Design

RETAIN is a social-behavioral study, representing two trials conducted in parallel, each embedded within a different parent RCT, and each comparing three intervention arms (Table 1). Each parent trial includes distinct objectives, risks, benefits, and eligibility criteria. RETAIN procedures have been layered onto each trial to maximize practicability for research staff and to align with the scientific goals of each parent trial in which it is embedded (Figure 1). The first parent trial is the Behavioral Activation and Varenicline for Smoking Cessation in Depressed Smokers Study (BASC). BASC tests two behavioral interventions in combination with Varenicline in a population of daily smokers with current or lifetime major depressive disorder (NCT 02378714). The second parent trial is the Mobility and Outcomes for Validated Evidence – Incentive Trial (MOVE IT). MOVE IT aims to examine the impact of a supportive social incentive-based gamification intervention in the three months post-hospital discharge among general medical and cancer patients using wearable technology (NCT 03321279).

Study Setting

Study sites for BASC include outpatient clinic settings at the University of Pennsylvania and Northwestern University. MOVE IT is being conducted across several inpatient wards at the Hospital of the University of Pennsylvania.

Participants

Eligibility for RETAIN is contingent on eligibility for the BASC and MOVE IT parent trials. The BASC parent trial is enrolling adults age 18 years or older who are daily smokers with major depressive disorder without psychotic features. The MOVE IT parent trial is enrolling adults age 18 years or older who are admitted for inpatient care to the Hospital of the University of Pennsylvania (HUP) on six medicine or oncology floors.

Coupling RETAIN with these two parent trials enables the evaluation of research incentives for studies using both medication and behavioral interventions, and conducted in both inpatient and outpatient settings.

Recruitment

Recruitment for RETAIN is closely linked to recruitment for the parent RCTs. Participants eligible for the parent trials are assessed for eligibility in RETAIN. A waiver of consent has been granted for RETAIN (see Ethics section) so that participants do not have knowledge of the different incentive amounts offered to each of three arms. However, because RETAIN participants in the BASC target population may communicate with future prospective participants, potential participants' prior knowledge of specific incentives or randomization used for RETAIN is assessed via open-ended probes. Potential participants whose responses to probes suggest any possibility that they are familiar with the incentives are allowed to participate in the parent trial without RETAIN randomization. Patients in the MOVE IT trial are not assessed for prior knowledge, as we have designed our recruitment plan to limit

prospective participant approaches to only one patient per hospital room to mitigate contamination concerns.

Intervention

Randomization and Masking

In each embedded trial, assignment to the three incentive arms is determined by computerized random-number generation with block randomization using variable block sizes of 3 and 6. In the BASC and MOVE IT parent trials, randomization is also stratified by the research site or clinical research coordinator conducting the recruitment, respectively. Participants in both embedded trials have 33.3% probabilities of being assigned to each RETAIN arm. Eligible patients approached for the BASC trial are randomized to \$0, \$200, or \$500 for participation. Eligible patients approached for the MOVE IT trial are randomized to \$0, \$100, or \$300 for participation. Amounts offered for each trial differ based on the relative time and effort being asked of the participant for each parent trial. By necessity, clinical research coordinators administering the consent process in both parent trials are unmasked to the incentive information being messaged to prospective participants. However, because trial recruitment information and the consent process have been fully scripted for both parent trials, biases associated with recruiter non-blinding are minimized.

Presentation of incentive information

All subjects receive scripted verbal messaging and a parent trial consent form that indicates the payment for research participation. The differences across RETAIN arms relate only to the information regarding payment. In both trials, the first page of the consent form and the subsequent sections of the consent forms describing the costs to participate indicate the appropriate trial remuneration. In the \$0 arm, these sections indicate that participants will not be paid for enrolling in the study; in the middle and high incentive arms, these sections indicate the specific amounts that participants will be paid. All other information in the parent trial consent form is identical across arms, designed by the parent trial investigators, and governed by separate IRB approval.

Debriefing and Payment Equalization

Following the parent trial consent process and collection of post-consent outcomes (Figure 1), each participant undergoes a debriefing process. During debriefing, the parent trial research coordinator informs patients that: (1) recruitment for the parent trial included a study of the effects of incentives on enrollment and decision making; (2) patients were randomly assigned to receive no incentive, moderate incentives, or high incentives; (3) patients were not informed about the incentives study to enable the research questions to be answered validly; (4) patients should not disclose their incentives to others to prevent biasing future patients' enrollment decisions and to prevent future patients from being disqualified from RETAIN; and (5) no further data will be collected as part of RETAIN after the incentives are disbursed. These consenting patients also learn that regardless of their randomly assigned incentive, they will all earn the maximal incentive amount for their participation.¹ Such payment equalization promotes fairness by rewarding people equally for making equal contributions to the parent RCTs.

Ethics

To promote the scientific integrity of RETAIN, parent trial clinical research coordinators temporarily withhold information regarding patients' randomization to one of three incentives. The Institutional Review Boards at the University of Pennsylvania and Northwestern University via a reliance agreement with Penn have approved a Waiver of Informed Consent whereby RETAIN-eligible patients are randomized without notification. These IRBs have also approved the foregoing debriefing process, including the foregoing rationale for providing all patients who enroll in the parent trial the highest incentive level. Debriefing has long been used in studies for which the research questions could not be answered if certain study procedures were disclosed up front. Debriefing increases the moral accountability of the researchers, promotes transparency for patients, and fulfills a federal criterion for using interventions not described during the informed consent process [39–41]. Participants who do not consent to the parent trials will not be debriefed or paid. This decision was made in consultation with Internal and External Ethics Boards that have been convened to oversee RETAIN. Collectively, members of these Boards and the trial investigators determined that it would be inappropriate to identify a person who has declined to participate for no money or for the moderate-level incentive, and to then offer that person the chance to participate for the high-level incentive. Board members opined that such a process would be akin to treating declining patients' initial choices as insufficient and negotiable. Others were concerned that although it was important to promote participant dignity by informing them through debriefing, this must be balanced against the larger risk that if the researchers debriefed patients who did not participate, without offering them a second chance to participate, they may cause distress and potentially degrade patients' trust in the healthcare system.

Sample Size and Power

We plan to enroll 576 patients in RETAIN in association with each parent trial. If this goal is achieved, there would be a total of 1,152 patients in RETAIN overall. RETAIN data associated with each of the two parent trials will be analyzed separately in primary analyses. If meta-analytic tests for heterogeneity across trials are null, then secondary analyses will be conducted using data from both trials together. Within each parent trial, we anticipate that 50% of RETAIN patients (288 of 576) will choose to enroll in the parent trial. Patient recruitment began in September 2017 in BASC and in January 2018 in MOVE IT. RETAIN is slated to conclude June 30, 2020, but this date may be modified based on accrual and recommendations of the Data and Safety Monitoring Board (DSMB).

The target enrollment of 576 patients in each RETAIN sub-trial was determined based on the primary goal of ruling out the possibility that incentives represent an undue inducement. Statistically, the presence of an undue inducement is represented by the interaction term between incentive amount and risk on the outcome of enrollment in the parent trial[24].

¹The high-level incentive arm in the BASC-RETAIN study is \$500. This amount accounts for a \$200 payment for time, effort, and travel paid for by the BASC study team, which existed prior to partnering with RETAIN, as well as \$300 of incentives paid for by the RETAIN team. At the time of debriefing, participants across all arms learn of the division in payment structure. The time, effort, and travel payments are disbursed on a per-session basis; the RETAIN incentives are disbursed in two installments.

Thus, we seek to rule out the possibility that the odds ratio associated with this interaction term is appreciably greater than a null value. To facilitate such a power estimation, we considered groups of participants with greater or less than a median level of risk perception who are randomized to either a high or a low incentive. We assumed that with an overall sample size of 576 participants in each embedded trial, 192 participants would be randomized to each of the three incentive arms. Further assuming that randomization balances the incentives distributions within each risk-perception group, 96 participants would be assigned to each of the three incentives within both the high and low risk-perception groups. Among patients assigned to receive \$0, we set the odds ratio (OR) contrasting the odds of enrollment between risk-perception groups to 1, such that the OR for those assigned to receive the highest incentive (\$300 and \$500 in MOVE IT and BASC, respectively) represents the interaction odds ratio. We assume a true interaction OR of 1 and use a one-sided significance level of 0.0427 such that the upper 95.73% confidence limit on the observed OR falls entirely below the non-inferiority threshold. If the enrollment rate in the parent trials is 50%, we will have at least 80% power to rule out undue inducement, as represented by an interaction odds ratio of 2.0 or greater between risk and incentive amount on the outcome of parent trial enrollment. We will have similar levels of power to rule out unjust inducement, as indicated by an interaction odds ratio of 2.0 or greater between either (a) income and incentive amount, or (b) financial well-being and incentive amount, on the outcome of parent trial enrollment. We specify an interaction OR of 2.0 using the dichotomized levels of risk perception and payment used to facilitate power calculations. In reality, we will analyze risk perception as a continuous variable and incentive size as a 3-level variable, and adjust the corresponding odds ratio accordingly to maintain equivalent type I and II error rates.

Quality Assurance and Control

We have chartered a DSMB to monitor RETAIN, with purview over both embedded trials. Monitoring occurs through at least annual reviews and a priori stopping rules have been established based on early evidence of undue inducement or unjust inducement (see Interim analyses). Any serious adverse events, protocol deviations/violations, and unanticipated events are reported to the IRBs, DSMB and funding agency.

Data Management

BASC survey data are collected via phone and in-person using a Case Report Form and transferred to an MS Access database that permits real-time data entry and storage by secured network remote access. The Case Report Forms are scanned into the database, increasing standardization across personnel. MOVE IT survey data are collected via Qualtrics.

Outcome Measures

Primary Outcome

The primary outcome of RETAIN is the decision to consent to participate in the parent RCTs. Patients who are randomized in RETAIN are considered to achieve the primary outcome if they sign the parent trial consent form. Thus, randomized participants who do not

allow research staff to complete the assessments prior to handing them the informed consent form are considered to have not consented. In BASC, for example, this could arise if participants learn of their assigned incentive but do not complete their phone screening assessment, or complete the phone screen assessment but refuse or fail to show up for their in-person intake visit, when the informed consent form itself would otherwise be reviewed.

Secondary Outcomes

Secondary outcomes include quantitative measures of attitudes towards research; patient-reported motivations for participation; time spent attending to the informed consent document; perceived risks of research; therapeutic misconceptions; perceptions of influence or coercion; understanding of the research study; and retention through the end of the parent trial's treatment sessions. Participants' attitudes towards research are measured using the Research Attitudes Questionnaire-7 (RAQ-7) [42]. The RAQ-7 has high internal consistency and factorial validity [43, 44]. We measure the RAQ-7 before disclosure of incentives to 1) assess patients' broad reasons to participate in research or not without being biased by prior discussions of payment, and 2) assess whether the hypothesized relationship between RAQ-7 score and the odds of enrolling is modified by incentives. If present, such effect modification would be considered as secondary evidence of the potential for incentives to represent undue inducements. We also plan to assess a subset of participants' motivations for participating in trials through semi-structured interviews.

We have obtained approval to present the informed consent form electronically to patients before viewing the paper consent. Patients are asked to first read the informed consent form on-screen without interruption.² Attention to the informed consent document is assessed by measuring the amount of time patients spend reading each part of the parent trial consent form by setting up each section as a "survey" in REDCap. The data extract includes the time – to the second – at which the participant moved to another section through a timestamp. The primary measure of attention is time spent reviewing the risk section of the informed consent document; the secondary measure is total time spent on the consent form. Attending more carefully to informed consent documents may promote informed choice [45, 46].

Perceived risks of the research are measured by the 10-item "compared riskiness" scale, which assesses perceptions of research risk [46]. Following pilot work that suggested the presence of floor effects with the original compared riskiness scale developed by Cryder et al, we modified several items to make the scale more responsive to the risk profiles of the parent trials.

Incidence of therapeutic misconception is assessed with a 4-item therapeutic misconception tool [47–49]. It has been hypothesized that the use of financial incentives could reduce therapeutic misconception, and thereby promote informed decision-making [50]. Because patients are not accustomed to being paid for their clinical care, offering incentives could signal that research is different. We are testing the hypothesized benefit of research incentives by measuring the incidence of therapeutic misconception in each incentive arm.

²All patients are given the opportunity to review the paper consent form and ask questions with the parent trial clinical research coordinator after this electronic consent process and the completion of several RETAIN measures.

To measure general perception of coercion and voluntariness of research participation, we use the five-item Perceived Coercion Scale of the MacArthur Admission Experience Survey [51]. The true/false scale is tailored to measure patients' perceptions of coercion in the inpatient psychiatric treatment admission process; we have edited the wording to make it relevant to participation in the parent trials.

Understanding of the trial is assessed with a 6-item Trial Elements Quiz, featuring core elements of the parent trial's consent form. The quiz distills key elements of the parent trials' respective informed consent forms, such as the duration of the parent trial intervention, the main purpose of the study, and the key risks of participation. In preliminary work, we have shown that research incentives may encourage potential participants to spend more time learning about study elements [46], which may translate into an improved understanding of the parent trial.

To enable exploration of the possibility that incentives may also enhance trial retention (i.e., in addition to trial enrollment), we disburse incentive payments in two installments. The first payment is given as soon as possible after debriefing. The second payment is disbursed during the patient's last week of treatment therapy or study intervention. Retention will be defined as completion of treatment or study intervention, and the denominator for analyses of retention will include all those who received the first payment. This will not be a randomized comparison, because participants in all RETAIN arms will have been debriefed by the time retention is measured, and all will be receiving the same incentive. Instead, we will compare retention rates in BASC before and after the roll-out of RETAIN. Because BASC was offering up to \$200 in reimbursement payments prior to the launch of RETAIN, we will specifically compare retention during that period with retention in the \$0 and \$500 arms of RETAIN. Similar comparisons will not be possible in MOVE IT because RETAIN and MOVE IT launched simultaneously.

Analysis Plan

Primary Analytic Approaches

We will assess bivariate relationships of incentives with the outcomes using ANOVA or Kruskal-Wallis/Wilcoxon rank-sum tests for normally and non-normally distributed continuous variables, and chi-square tests for comparisons of proportions. To examine the hypothesized statistical interactions, we will use logistic, linear, or quantile regression, as appropriate based on outcome parameterizations and distributions. For all outcomes other than tests for undue or unjust inducement, we will adjust significance levels for multiple comparisons using the Sidak-Holm method [52].

In all analyses in which the parent trial enrolls in multiple centers, we will model the center from which patients are recruited as a fixed effect, thereby mitigating confounding by center and adjusting variance estimates for clustering of participants within centers [53]. To adjust for chance covariate imbalance among arms, we will include covariates in multivariable models if they are significantly associated with the intervention arm and predictive of enrollment in the parent trials in bivariate analyses. We will explore temporal trends in incentives' effects over the study period using stratified analyses. If temporal trends are

noted, as may occur if prospective patients learn of the incentives study, we will adjust for their influence by entering time as a covariate, modeled as a spline. To avoid problems in estimating odds ratios due to sparse data, we will limit the number of covariates to no more than 1 per 10 participants enrolling in the parent trials. We will evaluate the potential effect modifiers using stratified analyses. If differences among strata appear, we will formally test their corresponding interactions with the incentives term. All analyses will be conducted using the intention-to-treat approach to avoid selection bias.

Approach to Missing Data

The analytic sample for the RETAIN primary endpoint analysis will consist of all patients randomized in RETAIN, regardless of ultimate eligibility status for the parent trials. If missingness due to parent trial ineligibility does not exceed 10%, the primary analysis will be limited to participants with complete data. If missingness exceeds 10%, the outcomes for ineligible subjects will first be imputed based on all participants with observed outcome data. For missingness > 10%, logistic models will be fit separately among observed data within each arm with consent (yes or no) as the outcome and screening variables as predictors. For each ineligible participant, the probability of consent will then be determined according to the intervention-specific models and their respective screening covariates. Binary consent outcomes will then be generated for ineligible participants, and outcome generation will be repeated within the context of a multiple imputation algorithm.

Once the analytic dataset is formed according to our level of ineligibility-induced missingness, our analyses to rule out undue and unjust inducements entail three primary covariates: risk perception, annual household income, and financial well-being, and all models will have the primary outcome of enrollment as the outcome. First, to determine whether incentives represent undue inducements for research participation, we will test the statistical interaction between incentive size and the primary covariate of risk perception on the outcome of enrollment in the parent trials. Second, to determine whether incentives represent unjust inducements for research participation, we will test two interactions, each in a separate model to avoid collinearity: that between incentive size and the primary covariate of annual household income, and that between incentive size and the primary covariate of financial well-being. All analyses will be stratified by parent study.

Analyses of these interaction terms will be structured as tests of non-inferiority, such that the null hypotheses are that incentives do meet criteria for undue or unjust inducement, and we reject the null, and conclude the absence of undue or unjust inducement, if the interaction terms are “small” according to pre-specified criteria (in technical terms, the inferiority margin). Specifically, our analyses are designed to determine whether we can exclude the possibility that incentives represent undue or unjust inducements if the resulting interaction terms are sufficiently small, defined as the ability to exclude, with 95% confidence, the possibility that any of these interaction odds ratios are >2.0.

Cost-Effectiveness Analysis

We will also evaluate the cost-effectiveness of using research incentives to recruit a fixed sample size from the perspective of the research sponsor and investigators. We define cost-

effectiveness as the incremental costs of conducting the trial with vs. without a given incentive (or with one incentive vs. another), divided by the time required to conduct the study with vs. without a given incentive. This approach recognizes that there are several potential benefits to reducing the time required to achieve a target sample size. Some of these, such as the reduced costs attributable to lower expenditures on recruitment expenses including staff salaries, will be reflected in the numerator. Others, such as greater public health benefits attributable to expedited dissemination of study results, are more difficult to quantify, but will be revealed by the denominator based in units of time. This will enable different stakeholders to determine whether the benefits are worth the costs. We will evaluate the cost-effectiveness of the following: (i) high vs. no incentive (ii) moderate vs. no incentive, and high vs. moderate incentive. Relevant costs to be analyzed include the total costs of the incentives themselves (the incentive amount multiplied by the number of patients receiving it) and the costs of conducting the parent trials for sufficiently long to recruit that number of patients. These latter costs include, for example, the costs of direct recruitment activities such as mailings, advertisements, and phone charges, and the duration of salary and benefits support needed for relevant study personnel. In a sensitivity analysis, we will also determine how heavily one would have to weigh the “costs” of any observed adverse effects of incentives (e.g., undue or unjust inducement) to nullify the hypothesized cost savings of incentives if they improved accrual rate sufficiently to lower total trial costs.

Interim Analyses

During the trial, we will conduct two interim tests of these interactions to evaluate evidence of undue or unjust inducement. Interim analyses will be conducted following accrual of 50% and 75% of the target sample size in each parent trial. In contrast to the final analyses, the interim analyses will be conducted as superiority tests of the interactions, such that rejection of the null hypothesis indicates evidence of the presence of an interaction between incentive size and one of our three primary covariates. This approach maximizes the possibility of meeting pre-specified stopping rules if evidence of undue or unjust inducement emerges. For these analyses, we will use 1-sided significance levels of 0.0056 and 0.0219 in the interim analyses to occur after 50%, and 75% of the data have accrued within each parent study, respectively. The DSMB will be empowered to stop the trial early if the lower confidence bound exceeds the non-inferiority bound of 2.0, which suggests undue or unjust inducement.

Discussion

The concomitant problems of under-enrollment and selective enrollment in RCTs have long plagued efforts to evaluate new and existing medical interventions [54–58]. Under-enrollment occurs when too few research participants are enrolled to provide adequate statistical power to answer the study’s primary research question, degrading the study’s scientific value and hence, ethics [3, 59, 60]. Selective enrollment occurs when certain subgroups within the target population enroll in proportions greater or less than their representation in that population, limiting the generalizability of the trial’s results and curtailing scientific value [9].

If financial incentives do indeed increase the enrollment fraction – the number of patients enrolled among all patients recruited – they could enhance the scientific value and validity of the research by augmenting the precision (i.e., statistical power) of RCTs. Further, because studies suggest that payments may influence participation decisions across socioeconomic and racial groups,[19, 24, 46] it is possible that incentives could combat selective enrollment, augmenting the generalizability of RCT results.

An often-cited concern with paying people to participate in research is that incentives may represent undue inducements – that is, by offering money, investigators may alter peoples’ perceptions of the risks associated with research participation, thereby preventing fully informed consent [26–35]. Importantly, an inducement is not undue if it merely encourages people to do things they would not do for free; rather, to be undue requires that the inducement prevents people from thinking as clearly about risks or burdens as they otherwise would [30]. Comparing participants’ assessments of risk for participation in parent trials across each financial incentive amount allows detection of undue inducement.

A second common concern with incentives is that they may represent unjust inducements – that is, incentives could encourage enrollment preferentially among less-wealthy persons [36–38]. These concerns persist despite observations that less-advantaged persons commonly incur risks for the benefit of others (e.g., military service, coal mining) [38, 61], and that larger payments – rather than none – may be needed to counter concerns regarding exploitation [38]. Thus, to address this concern, we will analyze whether or how payments differentially motivate participation among persons with different incomes or financial needs.

Despite the conceptual merits of incentives for research participation and the fact that they are commonly provided [62, 63], the preceding ethical concerns have led to inconsistent policies for regulating incentives by institutional review boards (IRBs) and funding agencies [62–64]. Thus, to rationalize and appropriately regulate the use of research incentives, high-quality evidence is needed to gauge their intended and unintended consequences, and the cost-effectiveness of plausible incentive sizes.

The two embedded trials being conducted within the RETAIN program represent the first large, multicenter randomized trials to test the effectiveness and ethics of financial incentives to augment trial recruitment in the context of real clinical trials. The financial incentive interventions are being tested in two urban centers in the country, paired with parent trials with diverse diagnostic criteria and testing multiple “doses” of the intervention with no, medium, and high compensation. We are also examining the cost effectiveness of the interventions. If the trials show that incentives increase trial enrollment and have favorable cost effectiveness without meeting our definitions of undue and unjust inducements, payment for research participation may become more widely accepted and consistently regulated, benefiting both scientific progress and study participants.

Acknowledgments

Funding Statement

This work was supported by National Institutes of Health: National Cancer Institute grants numbered RO1CA197332 and 5RO1CA184211. The funding source has no role in the study design, data collection, analytic plans or manuscript preparation.

Abbreviations

RCTs	Randomized clinical trials
IRBs	Institutional review boards
RETAIN	Randomized evaluation of trial acceptability by incentive
BASC	Behavioral activation and varenicline for smoking cessation in depressed smokers study
MOVE IT	Mobility and outcomes for validated evidence – incentive trial
HUP	Hospital of the University of Pennsylvania
DSMB	Data and safety monitoring board
RAQ-7	Research attitudes questionnaire-7

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Figure 1:
RETAIN flow diagram in the context two parent RCTs

Table 1:

Key Characteristics by Parent Trial

	BASC	MOVE IT
Parent trial participants	Daily smokers with current or lifetime major depressive disorder.	Adults admitted for inpatient care on general medicine or oncology units.
Parent trial intervention	Two behavioral interventions in combination with varenicline	Supportive social incentive-based gamification intervention in the three months post-hospital discharge. Hospital-implemented mobility protocol using wearable technology.
Parent trial outcome(s)	Point-prevalence abstinence post- target quit date.	Change in mean daily step count.
Is there a separate step to screen for RETAIN-specific eligibility?	Yes Patients are probed for prior knowledge of incentive randomization, equalization, or the maximum amount offered under RETAIN.	No
Do patients actively consent to RETAIN ?	No A waiver of consent for RETAIN has been approved by the IRB.	No A waiver of consent for RETAIN has been approved by the IRB.
Can anyone enroll in the parent trial without enrolling in RETAIN?	Yes , if they screen ineligible specifically for RETAIN	No
Incentive for parent trial subjects not enrolled in RETAIN	Up to \$200	Not applicable
Incentive levels	None: \$0 Moderate: \$200 High: \$500	None: \$0 Moderate: \$100 High: \$300
Debriefing Plan	On the phone , before the first day of the assigned intervention for the parent trial.	In-person , during the same encounter as all RETAIN procedures and prior to beginning the assigned intervention for the parent trial.
Payments to subjects consented to RETAIN and the parent trial	\$300 in two \$150 installments, plus up to \$200 from individual session/travel payments.¹	\$300 in two \$150 installments