Study Protocol and Statistical Analysis Plan for the Randomized Evaluation of Trial Acceptance by INcentive (RETAIN) study

Two randomized controlled trials of financial incentives embedded within two separate parent trials that together examine whether offers of money increase enrollment rates or lead to ethical problems.

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Principal Investigator

Scott D. Halpern, MD, PhD
Perelman School of Medicine at the University of Pennsylvania
301 Blockley Hall, 423 Guardian Drive
Philadelphia, PA 19104
Phone: 215-898-1462
Email: shalpern@ upenn.edu

Contents

Protocol Summary

Title	The Randomized Evaluation of Trial Acceptability by INcentive (RETAIN) Study
Short Title	The RETAIN Study
NCT #	NCT02697799
Principal Investigator	Scott D. Halpern, MD, PhD
Design	This study is a 3-arm prospective randomized controlled trial nested within three parent trials.
Objectives	**Aim I:** To determine if the ethical concerns (i.e., undue and unjust inducement) with incentives for research participation actually manifest. **Aim II:** To assess the possible scientific and ethical benefits of financial incentives for RCT participation. **Aim III:** To evaluate the cost-effectiveness of using financial incentives to increase RCT enrollment rates. This study will provide the first-ever tests of a broad range of intended and unintended consequences of real research incentives, thereby informing research regulations and guiding the use of incentives in future RCTs so as to expedite medical innovation and improve health.
Trial Duration	44 months
Parent Trials and Participating Sites	• Phase III Randomized Trial Comparing Overall Survival After Photon Versus Proton Chemoradiotherapy for Inoperable Stage II-IIIB Non-Small Cell Lung Cancer, or **RTOG 1308** (NCT01993810). Sites: University of Pennsylvania, Massachusetts General Hospital, Washington University, St. Louis, and the University of Texas at MD Anderson Cancer Center. ***(N.B. this was the first parent trial with which RETAIN partnered, but this partnership ended due to insurmountable accrual barriers in the parent RTOG 1308 trial due to insurance denial of proton therapy. Thus, this collaboration ended after only 5 patients were enrolled. We report this history in our original protocol and changes to the protocol).*** • Behavioral Activation and Varenicline for Smoking Cessation in Depressed Smokers Study, or **BASC** (NCT 02378714). Sites: University of Pennsylvania and Northwestern University
Sample Size	576 in RETAIN in association with each parent trial (RTOG 1308, BASC, and MOVE IT)

Target Population	Patients eligible for the parent trials RTOG 1308, BASC, and MOVE IT: • Adults age 18 years or older with histologically or cytologically proven diagnosis of non-small cell lung cancer (stage II-IIIB) (RTOG 1308) • Adults age 18 years or older who are daily smokers with current or lifetime major depressive disorder without psychotic features (BASC) • Adults age 18 years or older who are admitted for inpatient care to the Hospital of the University of Pennsylvania (HUP) on medicine or oncology floors (MOVE IT).
Eligibility	• Eligible for parent trial • 18 years or older • No prior knowledge of specific incentives or randomization used for RETAIN trial (RTOG 1308 and BASC trials) • Speaks English
Randomization	Participants will be randomized to the 3 experimental arms (low-, middle-, and high-level incentive) in equal, 33.3% probabilities. A Penn analyst will implement block randomization stratified by providers across the four sites (RTOG 1308), University of Pennsylvania (Penn), MD Anderson Cancer Center, Massachusetts General Hospital (MGH), and Washington University, St. Louis; by site (BASC) at the University of Pennsylvania (Penn) and (Northwestern); and finally by clinical research coordinator (MOVE IT) at the Hospital of the University of Pennsylvania.
Intervention	The intervention is the randomized incentive amount (low-, middle-, and high-level incentive) to be described during the parent trial consent process, including on the consent forms.
Outcomes	**Primary Outcome:** The proportion of people assigned to each incentive amount who consent to participate in the parent RCTs**.** **Secondary Outcomes:** Attitudes towards research; patient-reported motivations for participation; attention to informed consent document; perceived risks of research; therapeutic misconceptions; perceptions of influence or coercion; understanding of research study; retention through the end of treatment sessions.
Analyses for primary aims	We will assess bivariate relationships of incentives with the primary and secondary outcomes using t-tests or Wilcoxon rank-sum tests for normally and non-normally distributed continuous variables, and chi-square tests for comparisons of proportions. To examine 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 Holm method.

I. Original Protocol

1. Abstract

The most common and conceptually sound[1,2] ethical concerns with incentives for research participation are that they may (1) represent undue inducements by blunting peoples' perceptions of research risks, thereby preventing fully informed consent[3-5]; or (2) represent unjust inducements by encouraging enrollment preferentially among the poor. Neither of these concerns has been shown to manifest in studies using hypothetical incentives for participating in hypothetical RCTs.[6-8] But without evidence of how real incentives influence decision-making for real RCTs, practice variability remains.

We will conduct a randomized trial of 3 real incentives to participate in three parent randomized clinical trials (RCTs). Following clinicians' and research staff's preliminary determination of patients' eligibility in the parent RCT, we will assess patients' research attitudes, demographic characteristics, perceived research risks, time spent reviewing informed consent documents, ability to distinguish research from individualized 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 participating in trials, and the relative influence of incentives on those choices.

After patients make a decision about parent trial enrollment, we will debrief patients consenting to the parent trial about the random assignment of the incentives. The study will have adequate power to rule out between incentive size and risk perception (i.e., undue inducement) and between incentive size and income or economic well-being (i.e., unjust inducement), using formal "non-inferiority" tests, interactions. We also will explore potential benefits of incentives, such as the possibilities that incentives improve informed consent by making people attend more thoroughly to research risks, and that they expedite recruitment enough to be cost-saving on balance.

2. Background and Significance

Recruitment problems often cause randomized clinical trials (RCTs) to fail or accrue excess costs

The concomitant problems of under-enrollment and selective enrollment in randomized clinical trials have long plagued efforts to evaluate new and existing medical interventions. [9-13] For example, a recent Institute of Medicine report found that 40% of cancer RCTs are never completed and published.[14] Under-enrollment occurs when too few research participants are enrolled to provide adequate statistical power to answer the study's primary research question. Because under-enrollment yields unacceptably high probabilities for type II (false negative) errors, these problems reduce the RCT's ability to answer the research question, thereby degrading the trial's scientific value and hence, ethics.[15,16] Selective enrollment occurs when certain subgroups within the target population enroll in proportions greater or less than their representation in that population. By limiting the generalizability of the trial's results, this problem also curtails scientific value. [17]

These problems typically arise due to unexpected impediments to participant recruitment, which has been called "the most difficult and challenging aspect of clinical trials.[18]" Even when investigators enroll an adequate number of participants, they rarely do so on schedule,[13,19,20] or in a manner that attracts the full range of eligible participants.[17,21] 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.[22]

Financial Incentives may augment the precision, generalizability, and efficiency of RCTs

Given the growing gap between the supply of and demand for clinical research participants, 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.[23-27] Among the 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[28-30] and volunteers.[31,32] 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.[6,7,33]

If financial incentives do indeed increase the enrollment fraction – the number of patients enrolled among all patients recruited – they could enhance considerably the scientific value and validity of the research by augmenting the precision (i.e., statistical power) of RCTs. Further, because prior studies by our team[7,8,28] suggest that payments may influence participation decisions across socioeconomic and racial groups, it is possible that incentives could combat selective enrollment, augmenting the generalizability of RCT results. Despite these conceptual merits of incentives for research participation, and the fact that they are commonly provided, [34,35] the practice is controversial due to legitimate concerns regarding their unintended consequences.

There are two primary ethical concerns with providing incentives for research participation

Perhaps the most often-cited concern with paying people to participate in research is that incentives represent undue inducements – that is, they might alter peoples' perceptions of the risks associated with research participation, thereby preventing fully informed consent. [3-5,36-42] In the face of monetary offers, particularly those that are large and immediate, people may overlook or underestimate a study's risks, and hence consent to participate against their own better judgment. Importantly, an inducement is not undue if it merely encourages people to do things they would not do for free.[36,37,39,42]

A second common concern with incentives is that they may represent unjust inducements – that is, incentives could encourage enrollment preferentially among less-wealthy persons. Such differences in the effects of payments may be unjust if they create a system in which the burdens of research participants are borne preferentially by the poor, whereas the knowledge gained from the research would benefit all (or worse, benefit the rich preferentially).[43-45] These concerns persist despite observations that less-advantaged persons commonly incur risks for the benefit of others (e.g., military service, coal mining), [1,44,46]and that larger payments – rather than none – may be needed to counter concerns regarding exploitation.[44] Thus, to address this controversial matter requires definitive evidence of whether or how payments differentially motivate participation among persons with different incomes or financial needs.

These ethical concerns with research incentives have yielded variable policies and practices

Views that research incentives are invariably wrong [3,4,47] have largely been replaced by arguments that payment for research participation can be ethical.[1,36,37,42,46,48,49] Indeed, some scholars have changed the core question from whether participants should be paid to how much is fair.[50] Yet the 2 core concerns noted above continue to engender inconsistent policies for regulating incentives by institutional review boards (IRBs) and funding agencies.[2,34] Indeed, a review of research protocols approved by 11 IRBs revealed marked and unexplained variability in the size of payments used across similar studies, and even across sites within the same study.[35] Such variability is unsurprising given concerns regarding the unintended consequences of research incentives, minimal regulatory guidance on incentive use, and considerable uncertainty regarding what incentive sizes may be cost effective in expediting enrollment.[35] 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.

3. Objectives

a. Aims

Aim I: The primary aim of the RETAIN trial is to determine if the ethical concerns with incentives for research participation actually manifest.

By randomly assigning patients considering participation in three RCTs (see Section 4. Study Organization) to low-, middle-, and high-level incentives for enrolling, and using our established methods for measuring the unintended consequences of incentives for participation[1,7,8,51], we will conclusively determine how incentives influence perceptions of research risks, and the proportion of economically disadvantaged patients who enroll.

Aim II: The secondary aim of the RETAIN trial is to assess the possible scientific and ethical benefits of financial incentives for RCT participation.

The potential benefits of incentives also are grounded more in theory than in evidence. We will empirically examine 3 potential benefits, testing whether incentives (1) increase the enrollment rate, thereby improving the parent trial's efficiency; (2) increase participants' attention to risk information and their understanding of the research study, thereby improving the quality of informed consent; and (3) reduce the rate of "therapeutic misconceptions," defined as patients' failures to appreciate how the goals and processes of research differ from those of clinical care.

Aim III: The third aim of the RETAIN trial is to evaluate the cost-effectiveness of using financial incentives to increase RCT enrollment rates.

To inform the use or nonuse of incentives requires not only that we understand their scientific and ethical

pros and cons, but also their economic costs. To further guide investigators' and funders' decisions regarding incentive use, we will assess the incremental costs relative to the incremental time saved if an otherwise identical RCT was conducted with versus without financial incentives.

b. Primary Outcome Variable

The primary outcome is the proportion of people assigned to each incentive amount that consent to participate in the three parent RCTs (see Section 4. Study Organization).

c. Secondary Outcome Variables

1. Attitudes towards research: Attitudes towards research will be measured using the Research Attitudes Questionnaire-7 (RAQ-7).[52] The RAQ has high internal consistency and factorial validity.[53,54] We will measure the RAQ prior to disclosure of incentives in order to 1) assess patients' broad reasons to participate in research or not without being biased by prior discussions of payment 2) assess whether the hypothesized relationship between RAQ score and the odds of enrolling is modified by incentives. The presence of such effect modification would suggest that incentives represent undue inducements.
2. Attention to the informed consent document: Attending more carefully to informed consent documents may promote informed choice. [55] Visual focus has been established as a measure of attention in several settings, and has been associated with peoples' choices[56,57]and subsequent recall. [58] We will assess 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 will include the time – to the second – at which the participant moved to another section through a timestamp. The primary measure of this assessment will be time spent on the risk section; the secondary measure will be total time spent on the consent form.
3. Perceived risks of the research: Perceived risks of the research will be measured by the 9-item "compared riskiness" scale, which assesses perceptions of research risk.[8]
4. Incidence of therapeutic misconceptions: It has been hypothesized that the use of financial incentives could reduce therapeutic misconceptions, 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 will test the hypothesized benefit of research incentives by measuring the incidence of therapeutic misconceptions in each incentive arm. We will assess this outcome with a 4-item therapeutic misconceptions tool, developed by External Advisory Board member, Dr. Scott Kim. [59-61]
5. Understanding of the trial: In preliminary work, we have shown that research incentives may encourage potential participants to spend more time learning about study elements.[7,27] To assess whether increased attention translates into improved understanding

of the trial, we will use a 6-item Trial Elements Quiz, featuring core elements of the parent trial's consent form.

6. Perceptions of influence or coercion: To measure general perception of coercion and voluntariness of research participation, we will use the five-item Perceived Coercion Scale of the MacArthur Admission Experience Survey[62]. 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.

7. Retention through the end of treatment sessions: To assess the impact of incentives on retention status in the protocol, we will disburse payment in two installments- one as soon as possible after debriefing and one during the patient's last week of treatment therapy or study intervention. The denominator for analyses of this outcome will be all those who received the first payment. We will assess whether patients completed their treatment, and if not, reasons for non-completion.

Please see Section 8. f. Administration of Survey Instruments for additional information on the Study Instruments used to measure outcomes for the RETAIN trial.

4. Study Organization

a. RETAIN Infrastructure

The RETAIN study infrastructure is supported by three individual parent trials among three different patient populations:

1) The Phase III Randomized Trial Comparing Overall Survival After Photon Versus Proton Chemoradiotherapy for Inoperable Stage II-IIIB Non-Small Cell Lung Cancer, or **RTOG 1308**, a two-arm trial comparing conventional, intensity-modulated radiation therapy (IMRT) with proton-beam therapy (PBT) for the treatment of non-small-cell lung cancer (NSCLC). The primary outcome of this trial is overall survival (NCT01993810).

2) The Behavioral Activation and Varenicline for Smoking Cessation in Depressed Smokers Study, or **BASC**, which tests two behavioral interventions in combination with Chantix in a population of daily smokers with current or lifetime major depressive disorder (BASC). The primary outcome of this trial is point-prevalence abstinence post target quit date (NCT 02378714).

3) The Mobility, Outcomes, and Validated Experiences Incentive Trial, or **MOVE IT**, which targets adults admitted for inpatient care on medicine or oncology floors on 6 wards of the Hospital of the University of Pennsylvania. The study aims to examine the impact of a hospital-implemented mobility protocol for general medical and cancer patients using wearable technology. The primary outcome is the change in mean daily step count from the baseline period (week 1 post-discharge) to the intervention period (weeks 2-13 post-discharge) (NCT n/a).

RETAIN procedures have been layered on each study to maximize practicability for parent trial research staff and to align with the scientific goals of each parent trial. Key differences between the RETAIN study design in the context of the three parent trials are further described in Section 5. Study Design.

b. Research Team

The University of Pennsylvania research team includes investigators with expertise in research ethics, clinical trials, biostatistics, health economics, and in the use of financial incentives to motivate a variety of health-related behaviors.

Dr. Scott Halpern (PI) is Associate Professor of Medicine, Epidemiology, and Medical Ethics & Health Policy at Penn, and Deputy Director of the Center for Health Incentives and Behavioral Economics (CHIBE) at the Leonard Davis Institute of Health Economics and Director of the Palliative and Advanced Illness Research (PAIR) Center. He has considerable expertise in the design, ethics, and recruitment barriers of clinical trials, in leading RCTs of financial incentives to modify health behaviors, and in the ethics of using behavioral economic approaches, including incentives, to modify health-related decisions.

Dr. Kevin Volpp (Co-I) is Director of the CHIBE and PENN-CMU Roybal P30 Center on Behavioral Economics and Health. He has successfully completed numerous NIH-funded RCTs of financial incentives to modify health-related behaviors.

Dr. Jason Karlawish (Co-I), Professor of Medicine and Medical Ethics & Health Policy, is one of the nation's leading scholars on patient capacity to consent to research and decisions to enroll in trials. He has extensive experience using many of the instruments to be employed in this study, and is an expert in interpreting the data they produce.

Dr. Frances Barg (Co-I) is Associate Professor of Family Medicine and Co-Director of Penn's Mixed Methods Research Lab. She has great expertise in the use of qualitative methods in medical research and will work closely with Dr. Halpern to oversee the conduct of semi-structured interviews, once implemented, to assess patients' motivations for participating in the RCT.

Dr. Daniel Polsky (Co-I) is Professor of Medicine and Executive Director of the Leonard Davis Institute of Health Economics. He is a leading authority on economic analyses within RCTs, and will guide our analysis of the cost-effectiveness of incentives for RCT enrollment.

Dr. Alisa Stephens-Shields (Co-I), Assistant Professor of Biostatistics in Biostatistics and Epidemiology at the University of Pennsylvania, will be the principal biostatistician for this RCT. She has significant expertise in clinical trials and longitudinal data analysis.

<u>Site Principal Investigators</u>

<u>RTOG 1308</u>

Dr. Samuel Swisher-McClure (Co-I), Assistant Professor of Radiation Oncology at the Hospital of the University of Pennsylvania, has clinical expertise in the multidisciplinary management of patients with thoracic and head and neck malignancies and leads as Site Principal Investigator on the parent trial, RTOG 1308, at the Perelman Center for Advanced Medicine. Dr. Swisher-McClure will provide ongoing support in

the implementation and dissemination phases of the RETAIN trial at Penn.

Dr. Zhongxing Liao (Co-I), Professor and Clinical Medical Director of the Department of Radiation Oncology at the University of Texas MD Anderson Cancer Center, is the National Principal Investigator and Chair of the RTOG 1308 trial.

Dr. Jeffrey Bradley (Co-I), Lee King Professor of Radiation Oncology at Washington University School of Medicine and the Alvin J Siteman Comprehensive Cancer Center, is a Site Principal Investigator on RTOG 1308. Dr. Bradley also serves as Clinical Director of the Kling Proton Therapy Center and as Chief of the Radiation Oncology Thoracic Service at Washington University, St. Louis.

Dr. Noah Choi (Co-I), Professor of Radiation Oncology and Director of Thoracic Radiation Oncology at Massachusetts General Hospital Cancer Center, is a Site Principal Investigator on RTOG 1308.

As the Site PIs, Drs. Swisher-McClure, Liao, Choi, and Bradley will be responsible for managing all aspects of the study at their respective sites. They will oversee coordination, supervise staff, and work with Dr. Halpern to address any issues that arise with recruitment, study execution, or data monitoring.

BASC

Dr. Brian Hitsman (Co-I), Associate Professor of Preventive Medicine and Psychiatry and Behavioral Sciences at Northwestern University, is the Principal Investigator for the NCI-funded parent study Behavioral Activation and Varenicline for Smoking Cessation in Depressed Smokers Study (BASC). Dr. HItsman will lead BASC parent trial research staff at the Northwestern site in RETAIN recruitment efforts.

Dr. Robert Schnoll (Co-I), Associate Professor of Psychology in Psychiatry at the University of Pennsylvania is Site Principal Investigator for the NCI-funded parent study Behavioral Activation and Varenicline for Smoking Cessation in Depressed Smokers Study (BASC). Dr. Schnoll will lead BASC parent trial research staff at the Penn site in RETAIN recruitment efforts. Together with Co-I Hitsman, Dr. Schnoll will work with Dr. Halpern to address any issues that arise with recruitment, study execution, or data monitoring.

MOVE IT

Dr. Ryan Greysen (Co-I), Chief of the Section of Hospital Medicine in the Division of General Internal Medicine and an Assistant Professor of Medicine at the Perelman School of Medicine at the University of Pennsylvania, is the Principal Investigator for the Mobility, Outcomes, and Validated Experiences Incentive Trial, or MOVE IT. Dr. Greysen will oversee recruitment in the inpatient hospital wards for the MOVE IT-RETAIN partnership, in collaboration with Drs. Patel (Co-I) and Halpern.

Dr. Mitesh Patel (Co-I) is an Assistant Professor of Medicine and Health Care Management at the Perelman School of Medicine and The Wharton School at the University of Pennsylvania is the Co-Investigator for the Mobility, Outcomes, and Validated Experiences Incentive Trial, or MOVE IT.

c. Participating Parent Trial Sites

Parent Trial	Site Name	Location
RTOG 1308	The Hospital of the University of Pennsylvania	Philadelphia, PA 19104

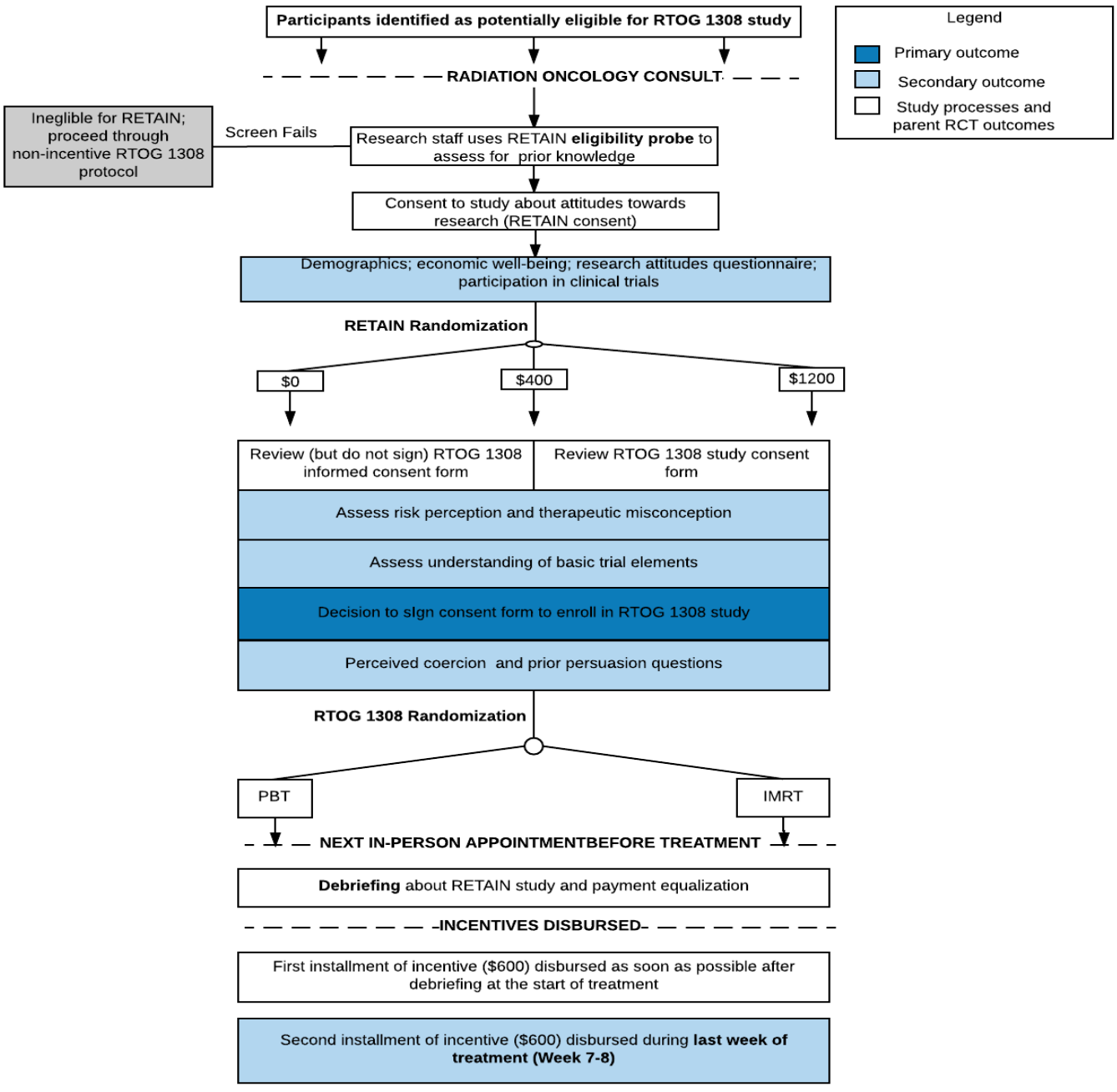
	Massachusetts General Hospital	Boston, MA 02114
	Washington University	St. Louis, MO 63110
	University of Texas MD Anderson Cancer Center	Houston, TX 77030
BASC	Northwestern University	Chicago, IL 60611
	The University of Pennsylvania	Philadelphia, PA 19104
MOVE IT	The Hospital of the University of Pennsylvania	Philadelphia, PA 19104

The RETAIN trial will be conducted at four sites participating in the RTOG 1308 parent trial, the Hospital of the University of Pennsylvania (Penn), MD Anderson Cancer Center, Massachusetts General Hospital (MGH), and Washington University, St. Louis; two sites participating in the BASC parent trial, Northwestern University and the University of Pennsylvania; and one site participation in the MOVE IT parent trial, the Hospital of the University of Pennsylvania. These institutions are imbued with substantial research infrastructures and offer close proximity of site PIs to the clinics from which patients will be recruited. Each parent trial supports research staff; in collaboration with the Site PIs, the parent trial research staff will carry out the protocol at their respective institutions.

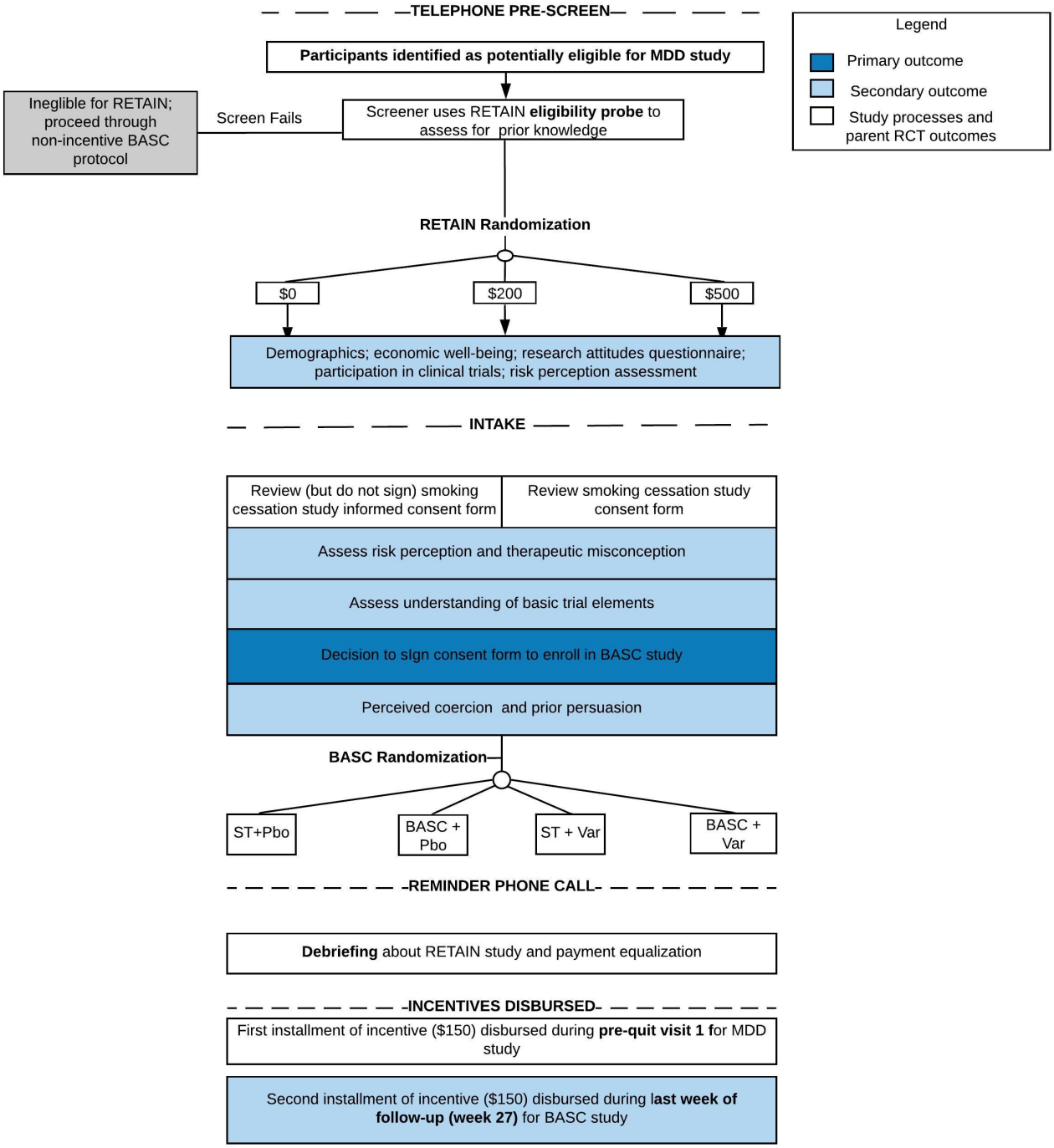
5. Study Design

This study is a prospective randomized controlled trial nested within three real randomized controlled trials.

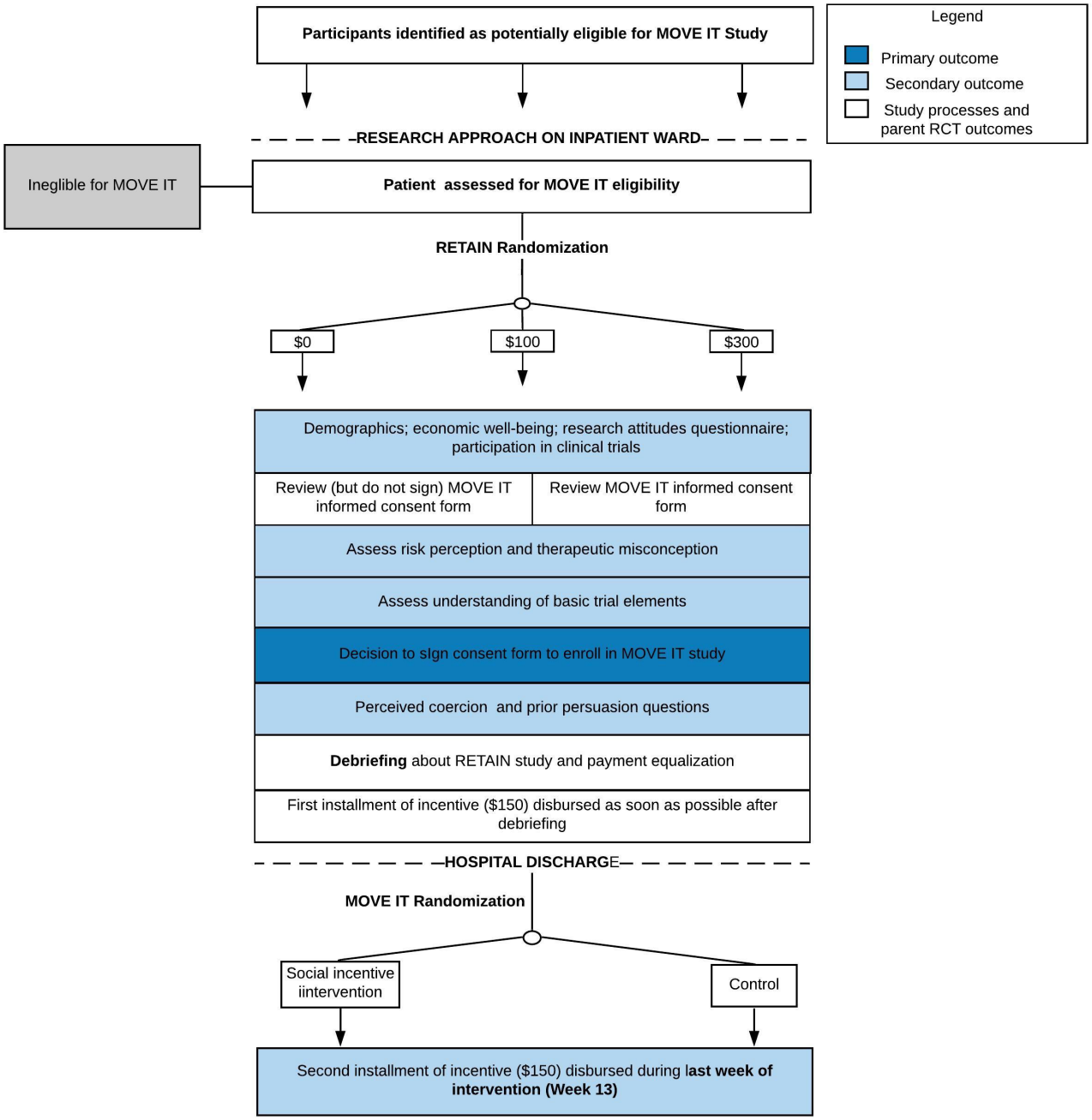
a. RTOG 1308 Schema



b. BASC Schema



c. MOVE IT Schema



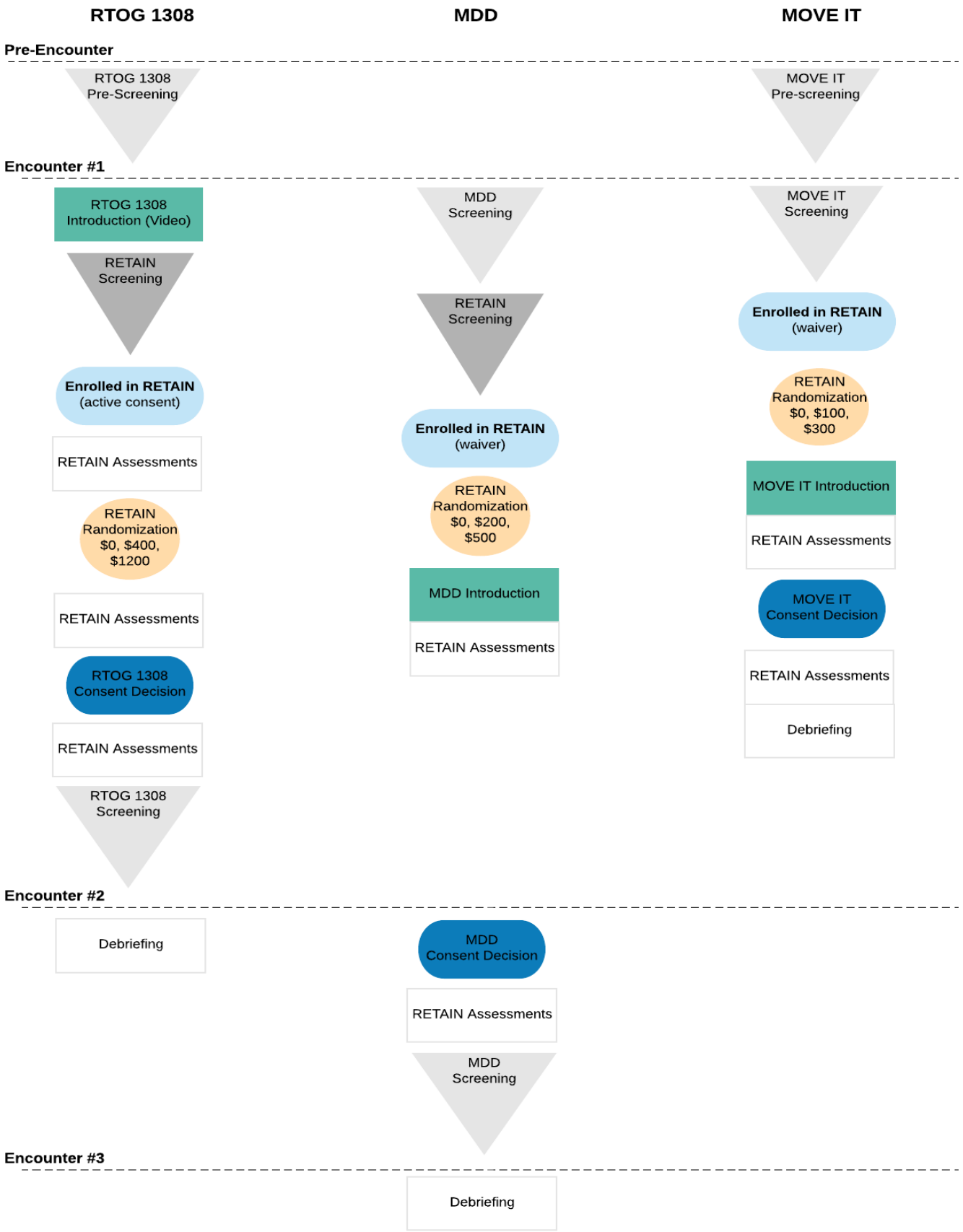
d. Key Study Design Elements across Parent Trials

Key elements in study design across the three parent trials are highlighted in the table and figure below.

	RTOG 1308	BASC	MOVE IT
Is there a separate step to screen for RETAIN-specific eligibility? Please see Section 8.b. Eligibility.	**Yes** Patients will be probed for prior knowledge of incentive randomization, equalization, or the maximum amount offered under RETAIN.	**Yes** Patients will be probed for prior knowledge of incentive randomization, equalization, or the maximum amount offered under RETAIN.	**No**
Do patients actively consent to the RETAIN trial? Please see Sections 8.d. and 8.e. Informed Consent.	**Yes** Research staff first solicit consent for a "research attitudes study" (RETAIN consent) and then solicit consent for the parent study.	**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 decline the Research Attitudes consent or screen ineligible specifically for RETAIN.	**Yes**, if they screen ineligible specifically for RETAIN	**No**
Incentive for parent trial subjects not enrolled in RETAIN Please see Section 6.d. Subject Remuneration.	**$0**	**$200**	**Not applicable**
Incentive levels Please see Section 7. Randomization.	Low: **$0** Middle: **$400** High: **$1,200**	Low: **$0** Middle: **$200** High: **$500**	Low: **$0** Middle: **$100** High: **$300**
Debriefing Plan Please see Section 8.h. 8.i. and 8.j. Debriefing.	**In-person**, before or on the same day as the first day of treatment on the parent trial.	**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 Please see Section 6.d. Subject Remuneration.	**$1,200 in two $600 installments**	**$300 in two $150 installments, plus up to $200 from individual session/travel payments.**[1]	**$300 in two $150 installments**

[1] The 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 the RETAIN study, 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 by the parent trial research staff.


RTOG 1308
MDD
MOVE IT
Pre-Encounter
RTOG 1308 Pre-Screening
MOVE IT Pre-screening
Encounter #1
RTOG 1308 Introduction (Video)
RETAIN Screening
Enrolled in RETAIN (active consent)
RETAIN Assessments
RETAIN Randomization $0, $400, $1200
RETAIN Assessments
RTOG 1308 Consent Decision
RETAIN Assessments
RTOG 1308 Screening
MDD Screening
RETAIN Screening
Enrolled in RETAIN (waiver)
RETAIN Randomization $0, $200, $500
MDD Introduction
RETAIN Assessments
MOVE IT Screening
Enrolled in RETAIN (waiver)
RETAIN Randomization $0, $100, $300
MOVE IT Introduction
RETAIN Assessments
MOVE IT Consent Decision
RETAIN Assessments
Debriefing
Encounter #2
Debriefing
MDD Consent Decision
RETAIN Assessments
MDD Screening
Encounter #3
Debriefing

e. Duration

Patient recruitment began in August 2016. The trial is slated to conclude June 30, 2020, following the development of a manuscript and dissemination of our findings.

i. RTOG 1308

RETAIN procedures will be conducted over one to three visits across one day to two weeks, depending on the sequence of eligibility determination and treatment planning conducted by RTOG 1308 research staff at each site. Study participants will be asked to spend approximately 30-75 minutes of their time to complete the questionnaires and consent processes for both the RETAIN trial and the parent trial (see Section 8.f. Administration of Survey Instruments). Following consent, participants will be debriefed and compensation will be arranged at the next in-person appointment. We anticipate that the debriefing and payment process will take approximately 20-25 minutes. In total, we do not expect the length of a subject's participation time in the study will exceed two hours.

ii. BASC

RETAIN procedures will be conducted over two phone calls and one in-person visit across one day to three weeks, depending on the intake scheduling capacity of the Penn and Northwestern clinics. RETAIN procedures will commence during the initial pre-screening eligibility assessment for BASC participants, which takes place before participants' first in-person or "intake" visit with BASC research staff. This phone assessment, which reduces the likelihood that BASC participants will attend an intake session only to learn that they are ineligible, is a pre-screening encounter during which participants first learn basic details of the BASC trial. If eligible for RETAIN, they will be randomized and complete the first set of RETAIN assessments over the phone. RETAIN assessments will take 10 additional minutes during the initial phone eligibility call (see Section 8.f. Administration of Survey Instruments).

Participants who pass the BASC pre-screening on the phone will schedule a baseline intake visit. During the baseline intake visit, RETAIN assessments, including the BASC consent process, will constitute 20-30 additional minutes of the encounter. Next, for all consenting BASC participants who have been randomized and enrolled to RETAIN, research staff will place a reminder call immediately prior to their first visit once enrolled on the study; during this call, all RETAIN-randomized, BASC-consented patients will be debriefed and learn of the payment procedures. The debriefing process will take 10-15 minutes during the reminder call. In total, we do not expect the length of a subject's participation time in the study will exceed two hours.

iii. MOVE IT

RETAIN procedures will commence during clinical research coordinators' initial encounter with patients

on the hospital ward. The clinical research coordinator will administer all RETAIN assessments in one encounter (see Section 8.f. Administration of Survey Instruments). Study participants will spend approximately 30-75 minutes of their time to complete the questionnaires and the MOVE IT consent process. Following consent, participants will be debriefed and compensation will be arranged during the same encounter. We anticipate that the debriefing and payment process will take approximately 20-25 minutes. In total, we do not expect the length of a subject's participation time in the study will exceed two hours.

6. Subject Recruitment

Recruitment for the RETAIN study is intricately linked to recruitment for the parent RCTs. No recruitment efforts outside the parent trials' efforts will occur. Specific measures will be taken to ensure that patients who are exposed to RETAIN procedures by word-of-mouth (RTOG 1308 and BASC) or during their inpatient stay (MOVE IT) are screened out or not approached for the RETAIN study.

a. Accrual

During the 44-month period of the trial, 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 roughly 1,778 patients in RETAIN overall, but RETAIN data associated with each of the 3 parent trials will be analyzed separately. Within each parent trial, we anticipate that 50% of RETAIN patients (288 of 576) will choose to enroll in the parent trial. However, we recognize that the total sample sizes and consent rates may vary across the 3 parent trials associated with RETAIN.

b. Key inclusion criteria

The eligibility criteria are:

1) Eligible for parent trial
2) 18 years or older
3) Speaks English

c. Key exclusion criteria

In the RTOG 1308 and BASC partnerships, prior knowledge of the incentive randomization or payment equalization used for this trial, which will be assessed with open-ended prompts during the first encounter, is an exclusion criterion.

We will not assess for prior knowledge in the inpatient MOVE IT study population. However, only one patient per room will be approached for the MOVE IT study to protect against contamination.

d. Subject remuneration

i. RTOG 1308

Participants who only consent to participate in RETAIN study (see Section 8.d. Informed Consent for RETAIN in RTOG 1308) will not receive any payment. Participants who consent to participate in the RETAIN study and the parent trial RTOG 1308 will receive a two-installment payment amounting to a total of $1,200 after they have started their participation in the parent trial. They will receive the first payment ($600) as soon as possible after debriefing. They will receive the second payment ($600) during their final week of treatment therapy for the RTOG 1308 trial. Patients who are taken off the RTOG 1308 study for medical reasons will receive full compensation. If patients withdraw from the study for personal reasons, they will not receive the second payment.

ii. BASC

Prospective participants who are not eligible, randomized, and enrolled in RETAIN but consent to the BASC parent trial receive $200 in time, effort, and travel payments. Participants who are eligible, randomized, and enrolled in RETAIN and consent to the BASC parent trial will receive a total of $500 (see Section 8.e. Informed Consent for RETAIN in BASC and MOVE IT and Section 8.g. Parent Trial Informed Consent); $300 of this payment derives from the RETAIN incentive payment, while $200 derives from the non-RETAIN BASC time, effort, and travel payment. Participants will receive the incentives payment in two installments. They will receive the first payment ($150) as soon as possible after debriefing, during their first in-person visit on trial (Pre-Quit 1). They will receive the second payment ($150) during their final week of treatment for the BASC trial (Week 27). Participants who are taken off the BASC study for medical reasons will receive full compensation. If participants withdraw from the study for personal reasons, they will not receive the second payment.

iii. MOVE IT

Patients who are not eligible for MOVE IT will not be paid. Participants who are eligible for MOVE IT, enrolled in RETAIN, and consent to the study will receive the payment in two installments (see Section 8.e. Informed Consent for RETAIN in BASC and MOVE IT). They will receive the first payment ($150) as soon as possible after debriefing; they will receive the second payment ($150) during their final week of participation (week 13). Participants who are taken off the MOVE IT study for medical reasons will receive full compensation. If patients withdraw from the study for personal reasons, they will not receive the second payment.

e. Payment Equalization

During the debriefing session, the parent trial staff will explain that all RETAIN- and parent trial-enrolled participants will receive the full high-level incentive payment ($1,200 in RTOG 1308, $300 in BASC (see

Section 6.d.iii), and $300 in MOVE IT) in two installments. Such payment equalization is necessary because it promotes fairness by rewarding people equally for making equal contributions to the parent RCTs.

7. Randomization

a. Groups

Subjects enrolled in RETAIN will be randomized into three groups. Depending on which group they've been assigned, subjects will be presented with one of three parent trial consent forms in both electronic and paper formats (see Section 8 Study Procedures). The parent trial consent forms will display three different incentive amounts (low-, middle-, or high-level incentive). Consent 1 (low-level incentive arm) will include a paragraph on the first page that will briefly state what the study is about and indicate to patients that participation in the study is voluntary and patients will not be paid if they choose to participate. The consent form will indicate that participants will not be paid under the standard section, "Will I be paid for taking part in this study?" Consents 2 (middle-level incentive arm) and 3 (high-level incentive arm) will include a paragraph on the first page that will briefly state what the study is about and indicate that participation is voluntary and patients will be paid the incentive (middle- or high-level) if they choose to participate. The consent form will also include payment information under the standard section, "Will I be paid for taking part in this study?" that describes the level. Consents 2 and 3 will also include information regarding the impact on compensation if patients stop taking part in the study under the standard section (RTOG 1308 and BASC trials). During debriefing, all participants enrolled in RETAIN and their respective parent trials will learn of their assignment to one of three groups.

b. Assignment

Participants will be randomized to the 3 experimental arms (low-, middle-, and high-level incentive) in equal, 33.3% probabilities. A Penn analyst will implement block randomization stratified by providers across the four sites in the RTOG 1308 parent trial; stratified by site in the BASC parent trial; and stratified by clinical research coordinator in the MOVE IT trial. The trial's primary statistician on the Penn research staff will provide a block randomization scheme for each provider (RTOG 1308) or clinical research coordinator (MOVE IT) and will upload a CSV file to the REDCap randomization module. He/she will also provide a block randomization scheme for each site for the Access Data Management System (BASC) (see Section 10. Data Management – BASC). The parent trial research staff will enter the provider (RTOG 1308) or clinical research coordinator (MOVE IT) information into the REDCap software through an initialization step and will immediately receive the randomization assignment for that participant. This will allow them to message to the participant the appropriate incentive level for participation in the parent trial, and present the correct paper consent based on their arm assignment (see Sections 8.g. Parent Trial Informed Consent).

i. RTOG 1308

Randomization and group assignment occurs after the economic well-being, demographic, and attitudes towards biomedical research, prior experience with research studies questions are assessed (see Section 8.f.1 Administration of Survey Instruments – RTOG 1308). Therefore, the parent trial research staff will not know group assignment when patients are approached and completing initial assessments. Once randomization occurs, by necessity, the research nurse/staff will know group assignment so that the correct electronic RTOG parent trial consent form ($0, $400, $1,200) can be viewed.

ii. BASC

Randomization and group assignment occurs after pre-screening data are collected and RETAIN eligibility probes are administered on the eligibility pre-screening call for the BASC parent trial (see Section 8.f.2 Administration of Survey Instruments – BASC). Research staff will know group assignment when patients are first introduced to the BASC trial on the phone in order to message the assigned payment ($0, $200, $500) for the participant. Participants who are deemed preliminarily eligible will schedule an intake session, where they will view the electronic BASC parent trial consent form ($0, $200, or $500) and receive a paper copy of the form with respective incentive information.

iii. MOVE IT

Randomization and group assignment occur after MOVE IT screening steps (see Section 8.f.3 Administration of Survey Instruments – MOVE IT) following clinical research coordinators' brief introduction to the study upon entering patients' hospital room. Clinical research coordinators will randomize patients and know the group assignment as they complete the recruitment script and assess patients' interest in learning about the MOVE IT trial. Assignment occurs prior to registering the patient in the Way to Health platform used for survey administration.

8. Study Procedures

a. Screening

In the RTOG 1308 trial, patients will be screened for parent trial eligibility by the parent trial research staff at the participating sites. To the extent possible, determination of parent trial eligibility may take place before the patient arrives for his/her radiation oncology consultation, or within several days following the consultation. Patients will be screened for RETAIN eligibility immediately after watch the RTOG 1308 patient education video.

In the BASC study, final determination of parent trial eligibility may not take place until labs are conducted at the baseline intake session, following participants' signature of the parent trial consent form. However, initial eligibility screening on the pre- screen eligibility call will enable the BASC research team to determine which participants may be assessed for RETAIN eligibility.

In the MOVE IT study, clinical research coordinators will pre- screen participants for parent trial eligibility prior to the initial approach on the inpatient wards. However, final eligibility determination will take place immediately after coordinators' initial approach once smartphone ownership and patients' participation status in other physical activity trials is ascertained.

b. Eligibility

Using methods employed by PI Halpern in several prior studies,[29,30,64] parent trial research staff will use prompts to assess participants' prior knowledge about the RETAIN study in the RTOG 1308 and BASC studies. Prompts will not be used in the MOVE IT study, as we do not anticipate contamination among patients on the general medicine and oncology wards of the hospital; no two patients will be approached in the same room at once; and readmitted patients will not be re-approached.

c. Inclusion of Women and Minorities

No participants will be excluded from study participation based on gender, race, or ethnicity. We expect that enrollment of participants from The University of Pennsylvania Perelman Center for Advanced Medicine, Northwestern University, the University of Texas MD Anderson Cancer Center, Washington University and Massachusetts General Hospital out-patient clinics and the Hospital of the University of Pennsylvania inpatient clinics will result in study populations that closely reflect the underlying outpatient populations at these facilities in terms of gender, race, and ethnicity. These populations are also reflective of the broader populations of the Philadelphia, Chicago, Houston, St. Louis, and Boston metropolitan areas.

d. Informed Consent for RETAIN in RTOG 1308

In the RTOG 1308 study, all RETAIN-related procedures and processes for the RETAIN study will be covered in an initial consent process except patients will not be informed that they will be randomly assigned to different incentives ($0, $400, $1,200) for participating in the parent RCT. This is necessary because it would be impossible to test the effect of different incentives on study participation if participants were aware of this randomization. Please see the Sections 8.h -8.j Debriefing for details on

how this omission will be handled.

For all patients without prior knowledge of the incentives of any size or payment equalization (see Section 8.b. Eligibility), the parent trial research staff will solicit consent to participate in a "study of attitudes about research on different forms of radiation for non-small cell lung cancer." By signing this first consent for the RETAIN study, patients will authorize the use of basic demographic data and agree to complete questionnaires that measure the secondary outcomes of the incentives trial.

Of note, patients who decline participation in this study will be given an opportunity to consent in the parent trial, RTOG 1308.

e. Informed Consent for RETAIN in BASC and MOVE IT

The sole informed consent processes used in both BASC and MOVE IT will be for the parent trials (see Section 8.g. Parent Trial Informed Consent). Randomization and enrollment to RETAIN in the BASC and MOVE IT studies will be carried out under a Waiver of Informed Consent, approved by the University of Pennsylvania Review Board. Thus, research staff will not present a "study of research attitudes" prior to randomization. BASC participants deemed eligible for BASC via phone pre-screening and RETAIN MOVE IT participants will be randomized immediately after eligibility screening in their hospital rooms.

All participants who are randomized and enrolled in RETAIN and consent to the BASC and MOVE IT will be debriefed on the randomization of incentives and the purpose of the RETAIN study will be explained (see Sections 8.i. and 8.j. Debriefing in BASC and MOVE IT).

f. Administration of Survey Instruments

i. RTOG 1308

Consenting participants will then complete a series of questionnaires (demographic characteristics, income and economic well-being, attitudes towards biomedical research, and prior experience with research studies questions) with the parent trial research staff via REDCap using a tablet device.

Once these measures have been completed, participants will be randomized to receive one of three different versions of the informed consent form for the parent trial, RTOG 1308, each indicating different financial incentive amounts ($0, $400, or $1,200). Once the parent trial research staff has received the appropriate randomization, he or she will briefly introduce the informed consent form and note whether patients are being offered either $0, $400, or $1,200, depending on randomization, to participate in the parent trial. Participants will be presented with their assigned consent forms electronically for review on their own. Participants will NOT be alerted to their assigned parent trial arm (conventional radiotherapy or proton-beam therapy) at this stage. This step will occur at or before their simulation appointment.

Once the consent forms have been reviewed, but not signed, participants will be asked to complete the Compared Riskiness and Therapeutic Misconception tool as well as the trial elements quiz. The parent trial research nurse/staff will review the answers to the trial elements quiz. Patients' advancement through the consent process will not be contingent on their responses to the quiz; however, following completion of the quiz, the parent trial research nurse/staff will review the questions that patients missed and discuss these portions of the consent until the participant understands the entire consent and its detailed procedures. The participant will be encouraged to ask questions about portions they do not understand.

ii. BASC

Procedures for this study will commence during initial pre-screening eligibility assessment via phone for the BASC trial. During this call, all study candidates will complete an initial eligibility assessment with research staff members from the clinical site from which they are being recruited (Northwestern or Penn). Research staff will begin with the BASC eligibility screen survey, which includes basic demographic questions, as well as questions related to participants' endorsement of symptoms of clinical depression. Once a patient is determined to be preliminarily eligible for BASC, the research staff will ask the RETAIN eligibility prompt to assess for prior knowledge of the specific incentives or randomization used for RETAIN. Participants who do not have prior knowledge of the RETAIN incentives or randomization will be randomized by the research staff via the BASC trial's Data Management System (DMS) (see Section 10.a.3. Data Collection and Data Confidentiality – BASC). Prospective participants will then be introduced to BASC study basics and risks and informed that if they are determined to be eligible for the BASC study and participate in the BASC trial, they will receive $0, $200, or $500 for participation.

Prospective participants who have prior knowledge of the incentives or randomization used for RETAIN will not be randomized, enrolled, or receive RETAIN-related messaging on the phone call. They will receive the standard study information regarding session and travel compensation for the BASC trial without RETAIN messaging. For information on remuneration in the BASC trial, see Section 6.d.. These participants will not be debriefed or paid the RETAIN incentives.

Before research staff finalize logistical details on the BASC study and schedule intakes for tentatively eligible patients, they will administer several RETAIN-related questionnaires to assess 1) demographics and personal financial well-being, 2) attitudes towards biomedical research, 3) prior experience in research, and 4) perceptions of research risk. The screener will administer these surveys via phone using CRF forms adopted for the RETAIN trial that will later be scanned into the BASC trial's DMS.

Participants who pass the BASC pre-screening will be scheduled to attend a 2-3½ hour Intake session for the BASC trial. During the intake session, BASC research staff at Penn and Northwestern will read a pre-BASC consent script before presenting an electronic image of the BASC informed consent/ HIPAA forms with additional information regarding the RETAIN incentive randomization condition; this electronic

image will be presented via tablet or desktop. By presenting the BASC consent with randomized compensation information electronically, we will assess the amount of time participants spend reading each part of the main trial consent form. Each section (e.g., Study Introduction, Procedures by Visit, Possible Risks and Discomforts, etc.) will be presented as a survey in REDCap. Time-stamp data collected for this REDCap module will be linked by the study ID generated in the BASC Data Management System during candidates' telephone pre-screen call (see Section 10.a.3 Data Collection and Data Confidentiality - BASC).

Once participants finish reading and before signing a paper version of the BASC trial consent, they will complete brief assessments of perceptions of research risk (administered over the telephone pre-screen and again at intake – see Section 9.b. BASC Study Calendar). They will also complete assessments on perceptions of the difference between research and individualized patient care and understanding of the smoking cessation study via a trial elements quiz. All of these measures will be administered via the CRF paper and pencil processes currently used in the BASC trial. The responses to the quiz will be reviewed with participants, during which participants' questions will be answered.

iii. MOVE IT

Clinical research coordinators will identify patients through electronic health record-based screening for the MOVE IT study and preliminarily eligible patients will be approached for recruitment in their hospital rooms.

Using a recruitment script in REDCap, clinical research coordinators will describe a study that aims to help patients improve their mobility and prevent them from needing to return to the hospital. The REDCap-hosted MOVE IT recruitment script will prompt the clinical research coordinator to assess for patient's eligibility in the MOVE IT study through two screening questions. Eligible patients will be randomized in real time to one of three incentives for participation ($0, $100, or $300). The clinical research coordinator will finish reading the recruitment script, indicating the amount participants will be paid for the MOVE IT Trial. Ineligible patients will not be randomized or enrolled on the RETAIN trial.

For patients who are interested in learning more about the MOVE IT study, the MOVE IT clinical research coordinators will proceed to register the participant in the Way to Health platform and administer the tools in Way to Health via tablet (see Section 10.a.3. Data Management- MOVE IT). The patient will be asked to complete several short questionnaires: 1) demographics, 2) personal financial well-being, 2) attitudes towards biomedical research, and 3) prior experience in research.

Once the patient has completed aforementioned tools in Way to Health, the clinical research coordinator will return to the REDCap database and read a pre-consent introduction script before presenting the an electronic image of the MOVE IT informed consent/ HIPAA forms with additional information regarding the RETAIN incentive randomization condition. By presenting the MOVE IT consent with randomized compensation information electronically, we will assess the amount of time

participants spend reading each part of the main trial consent form. Each section will be presented as a survey in REDCap. Time-stamp data collected for this REDCap module will be linked by the study ID generated in Way to Health.

Once participants finish reading and before signing a paper version of the MOVE IT trial paper consent, they will complete brief assessments of perceptions of research risk. They will also complete assessments on perceptions of the difference between research and individualized patient care and understanding of the MOVE IT via a trial elements quiz. All of these measures will be administered via the Way to Health platform on a tablet. The responses to the quiz will be reviewed with participants, during which participants' questions will be answered.

g. Parent Trial Informed Consent (RTOG 1308, BASC, and MOVE IT)

Parent trial research staff will present the paper consent in conjunction with their review of any questions generated by the participant during their review of the electronic, REDCap-hosted images of the consent form. Next, prospective participants will be asked to either provide consent or decline participation in the parent trials. The research staff will then facilitate participants' completion of the final two surveys (perceived coercion and prior persuasion questions). All participants – no matter their decision – will be asked to complete these two post-consent surveys.

In the RTOG 1308, participants who decline consent will proceed with their treatment under the guidance and assistance from their MD outside of the context of this trial.

In the BASC and MOVE IT studies, participants who decline consent may seek participation in other trials for smoking cessation or physical activity, respectively.

h. Debriefing in RTOG 1308

At the participants' simulation, or dry run/set-up appointment, patients will be informed of their treatment randomization. During this appointment, or at the first possible time to debrief in-person following this appointment (i.e. first treatment visit), the parent trial research staff will read the debriefing script, which will inform the participant of the trial deception and purpose. The parent trial research staff will explain that the incentives were randomly assigned. Such 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. Using the attached script, the parent trial research staff will inform patients that: (1) recruitment for the parent RTOG trial included a study of the effects of incentives on enrollment and decision making; (2) patients were randomly assigned to receive incentives of $0, $400,

or $1,200; (3) patients were not informed about the incentives study to avoid bias; (4) patients should not disclose their incentives to others to prevent biasing future patients' enrollment decisions; and (5) no further data will be collected as part of the incentives study after the incentives are disbursed. They will also learn about the payment equalization and informed that they will earn the full $1200 in two installments for their participation. Any questions they have will be answered. In order to receive their payment, patients will be asked to complete a W-9 Tax form.

i. Debriefing in BASC

Participants will be debriefed following their intake eligibility visit once they have signed consent, and they are determined to be fully eligible for the BASC trial. Debriefing will take place on the reminder call before participants' first scheduled visit on trial, called "Pre-Quit 1." The same processes described in Section 8.h. will be used to inform patients of the RETAIN study procedures and process payment per institutional standard.

j. Debriefing in MOVE IT

Participants will be debriefed during the same encounter in which they are approached. The same processes described in Section 8.h. will be used to inform patients of the RETAIN study procedures and process payment per institutional standard.

k. Deception

We believe debriefing remains an essential element of this RCT in which information regarding the random allocation of incentive levels is necessarily withheld during the consent processes. The following justifications support the research team's use of incomplete disclosure in the RETAIN trial:

<u>The use of incomplete disclosure in this study is grounded in the trial's status as minimal risk.</u>

The RETAIN study involves no more than minimal risk to participants for 5 reasons: (1) incentives in the amounts we are proposing are given to patient subjects as part of many ongoing or completed trials;[35] (2) the evidence available to date suggests that the ethical concerns identified with incentives may not arise, (3) we have established robust procedures for monitoring whether those ethical concerns do in fact arise and for stopping the incentives study if so, (4) the patients would be approached to participate in the parent RCTs without the incentive study, and (5) their participation in the RETAIN study will not affect which treatment they receive in the parent RCTs.

<u>To the extent that it is avoidable, the use of deception will have no adverse effects on welfare, and all adverse effects will be minimized.</u>

Adverse events from the incomplete disclosure of the randomization of participants to different levels of incentives will be minimized through the debriefing process. Patients will be debriefed following their decision to enroll in the parent trial during the very next appointment at the radiation oncology clinic (RTOG 1308); immediately before their first treatment visit (BASC); and within the same session as the initial approach (MOVE IT). This debriefing will therefore happen within a few days (at maximum) of the deception, and will provide participants with full disclosure of the research and with an opportunity to withdraw their participation or their data. Patients who decline to participate in the parent trials will not be debriefed. The Principal Investigator will be directly responsible for identifying and reporting adverse events to the IRB of record and respective IRBs at the four sites and the DSMB.

Additional oversight will be provided by the following: (1) a DSMB that will have the flexibility to adjudicate trial continuation or cessation based on a compendium of outcomes data; (2) two advisory boards comprised of experts in relevant disciplines including research ethics and regulations that will assist the investigators in addressing any unforeseen ethical and scientific issues during the trial's conduct.

<u>The value of the study is sufficient to warrant waiving some aspects of the requirement for full disclosure in the informed consent process.</u>

While our study does not provide participants with untrue information and thus does not technically qualify as deception research, it remains necessary for parent trial research staff to withhold information regarding the random assignment of incentive levels during the incentives trial consent process. This RCT will provide important information about the impact of financial incentives on enrollment in a research study with therapeutic benefit. Because it is taking place within the context of a real RCT and the incentives will be randomly assigned, this will be the first every study to explore how financial incentives impact actual decisions made by patients contemplating participation in a real trial. It will inform the practice of paying human research subjects to participate in studies by providing a new standard by which to adjudicate the process. Specifically, the study is designed to inform the conduct of future human research subjects by providing evidence about how the presence and magnitude of incentives influence enrollment and recruitment efficiency, and whether reasonable but uncertain ethical concerns arise when offering different levels of incentives. In short, the present variability in IRB practices regarding incentive use means, by definition, that either (a) incentives are being underutilized, creating inefficiencies, potentially sacrificing study completion, and thereby curtailing the ability of investigators to fulfill their commitments to research participants; or (b) incentives are being over-utilized, creating threats to autonomous choice or targeting a "research underclass". The current trial is necessary to improve upon this worrisome status quo, and hence has the potential to make the entire practice of clinical trials more ethical.

<u>There is no alternative to address the scientific question in a valid manner but to use deception/incomplete disclosure.</u>

It would not be feasible to address the aims of the study in the context of a real RCT (RTOG 1308, BASC, and MOVE IT) without the incomplete disclosure related to the random assignment of financial incentives. Indeed, any disclosure about the random assignment of incentives would thwart the ability to measure either the intended or the potential unintended consequences of research incentives. To definitively address the ethics, effectiveness, and cost effectiveness of incentives for research participation, high-quality evidence is needed, and to date, studies of incentives to participate in hypothetical RCTs of common interventions, as well as small studies in non-generalizable cohorts, do not fully answer whether the ethical concerns of financial incentives actually manifest.

Subjects cannot be informed prospectively of the use of deception/incomplete disclosure and consent to its use.

Prospectively informing patients in even a general way would sabotage the goals of the research because it would create a cognitive state (decision-making context) that is fundamentally different from that which future patients encountering future incentives would have at corresponding times. Because this trial is fundamentally about choices made by prospective research participants, and how risks and incentives might modify those choices, any extraneous factors that could also modify decisions or choices must be avoided. Following the debriefing, all eligible patients will be given the opportunity to ask any questions regarding the incentives study. The parent trial nurse/staff will then explain that all participants actually will receive the full $1,200 payment and he or she will detail the plans for disbursement.

9. Study Calendars

The following calendar reflects the procedures as they are described in Section 8.

a. RTOG 1308 Study Calendar

Study calendar for RETAIN and Phase III Randomized Trial Comparing Overall Survival After Photon Versus Proton Chemoradiotherapy for Inoperable Stage II-IIIB Non-Small Cell Lung Cancer.

Week	**0[c]**	**0-1[C]**	**7-8[C/M]**
Screening and Eligibility (RTOG 1308)	X	X	
1308 Video	X		
RETAIN Eligibility Prompts	X		
Informed Consent for Research Attitudes Study (RETAIN Study Consent)	X		
Demographics	X		
Economic Well-Being	X		
Research Attitudes Questionnaire	X		
Prior Research Experience	X		

Informed Consent Administration (RTOG 1308 Parent Trial)	X		
Compared Riskiness Scale	X		
Therapeutic Misconceptions			
Trial Elements Quiz	X		
Review answers + Patient Q &A	X		
Informed Consent Signing (RTOG 1308 Parent Trial)	X		
Perceived Coercion and Prior Persuasion Questions	X		
Debriefing		X [At simulation or next in-person appointment]	
Payment		X [First Installment Disbursed as soon as possible after debriefing]	X [Second Installment Disbursed during Final Week of Treatment]
	C=clinic visit (in-person session) M= no visit or call		

b. BASC Study Calendar

Study calendar for RETAIN and Behavioral Activation and Varenicline for Smoking Cessation in Depressed Smokers.

Week	**0^P**	**0^c**	**0^p**	**1^c**	**27^P**
Screening and Eligibility (BASC)	X	X			
RETAIN Eligibility Prompts					
Demographics	X				
Economic Well-Being	X				
Research Attitudes Questionnaire	X				
Prior Research Experience	X				
Compared Riskiness Scale	X				
Informed Consent Administration (BASC Trial)		X			
Compared Riskiness Scale		X			
Therapeutic Misconceptions		X			
Trial Elements Quiz		X			
Review answers + Patient Q &A		X			
Informed Consent Signing (BASC Trial consent)		X			
Perceived Coercion and Prior Persuasion Question		X			
Debriefing			X		
Payment				X	X

				[First Installment of 150 disbursed as soon as possible after debriefing]	[Second Installment of 150 disbursed during final week of treatment]
	P= phone C=clinic visit (in-person session)				

c. MOVE IT Study Calendar

Study calendar for RETAIN and Mobility, Outcomes, and Validated Experiences Incentive Trial (MOVE IT).

Week	**0[c]**	**1[c]**	**13[M]**
Screening and Eligibility	X		
Demographics	X		
Economic Well-Being	X		
Research Attitudes Questionnaire	X		
Previous Research Experience	X		
Informed Consent Administration (MOVE IT Trial)	X		
Compared Riskiness Scale	X		
Therapeutic Misconceptions	X		
Trial Elements Quiz	X		
Review answers + Patient Q &A	X		
Informed Consent Signing (MOVE IT Trial consent)	X		
Perceived Coercion and Prior Persuasion Question	X		
Debriefing	X		
Payment		X [First Installment of 150 disbursed as soon as possible after debriefing]	X [Second Installment of 150 disbursed during final week of intervention]

	P= phone C=clinic visit (in-person session) M=Mail – no visit or call

10. Data Management

a. Data Collection and Data Confidentiality

Prudent steps will be taken to ensure that all information will be kept confidential and secure, including medical and survey data as well as social security numbers. Unique patient identifiers will be assigned to each subject locally.

i. RTOG 1308

Survey data will be collected on-site by parent trial research staff and entered into REDCap (Research Electronic Data Capture), hosted at the University of Pennsylvania, for the RTOG 1308 trial. REDCap provides multi-site access, enabling staff from the parent trial sites to use the database, and it supports secure data integration, as well as several features that minimize data entry error. The Penn Project Manager will maintain the database with oversight from the key study personnel.

The parent trial recruitment teams at each site will maintain their own patient screening databases to track information such as when eligible patients will be in clinic; date of biopsy; when they completed study measures; when they might be returning to clinic, dates of consent; as well as when payments are disbursed. Data from the screening process specifically for patients who become RETAIN subjects will be entered into REDCap to enable its inclusion in data extracts. All other information about the combined screening process will be provided to the RETAIN project manager as aggregate numbers only.

All datasets and computer files and study ID numbers will be further secured as follows. We will implement multiple, redundant protective measures to guarantee the security of participant data. All data for this project will be stored on the secure and firewalled servers of the Center for Clinical Epidemiology and Biostatistics (CCEB). These data servers are maintained in a guarded facility behind several locked doors, with very limited physical access rights. Electronic access rights are carefully controlled by Penn system managers. We will use highly secure methods of data encryption for all transactions involving participants' financial information, such as W-9 forms, using a level of security comparable to what is used in commercial financial transactions. This multi-layer system of data security, identical to the system protecting the University of Pennsylvania Health System's medical records, greatly minimizes privacy risks.

Only authorized personnel will have access to the data. All of these personnel will have completed research and confidentiality training (specifically, CITI training). Through REDCap, each study subject will

be given a unique study identification number (ID). By default, all direct identifiers will be omitted from data extracts, and the study ID will be used exclusively in all analytical files.

Records containing subjects' social security numbers will be maintained, used, and destroyed according to Penn's social security number policy. Any paper records collected for regulatory purposes or as backup for direct electronic data entry will be kept in locked filing cabinets at the site where they were collected. All data will be destroyed after 7 years.

ii. BASC

Survey data will be collected via phone and in-person using a Case Report Form format for the RETAIN-BASC partnership. The BASC Penn database manager will oversee the database management system (DMS) for this trial. The DMS is an MS Access database that permits real-time data entry, storage, and QA by secured network remote access and scannable forms, which increase standardization across personnel.

The DMS generates database tables in a NIH-compliant format, constructs semantic constraints on fields, and is used for data entry, storage, retrieval, and security. The DMS uses session dates to describe procedures and measures to be ascertained. The DMS mimics the appearance of CRFs completed at sessions. Daily backups occur to protect against accidental corruption or deletion. The Penn BASC research staff will compare 100% of hard copy to computer data. Protection of participant privacy is accomplished by minimizing use of identifying information, use of ID numbers rather than participant names, keeping all data in locked files, and strictly limiting access to the dataset that links participant names with ID numbers.

Every touchpoint with participants is “milestoned” (e.g., attended, missed, scheduled) in the trial database to ensure subject tracking through the trial. The RETAIN team will work with the BASC study team to ensure all RETAIN-relevant screening outcomes are adequately milestoned within the DMS.

For measures of time spent reading the BASC parent trial consent form, BASC research staff will use REDCap at the eligibility intake session. The same procedures described in Section 10.a.2 will be used to manage these data. BASC research staff will enter the subject and contact database IDs into REDCap to enable linking between databases.

iii. MOVE IT

Survey data will be collected via Qualtrics on the Way to Health platform for the MOVE IT partnership. Penn Medicine Academic Computing Services (PMACS) supports the computing infrastructure that will be used for the MOVE IT study, including the Way to Health web portal. PMACS is a joint effort of the University of Pennsylvania's Abramson Cancer Center, the Cardiovascular Institute, the Department of Pathology, and the Leonard Davis Institute. PMACS provides a secure computing environment for a

large volume of highly sensitive data, including clinical, genetic, socioeconomic, and financial information. PMACS requires all users of data or applications on PMACS servers to complete a PMACS-hosted cybersecurity awareness course annually, which stresses federal data security policies under data use agreements with the university. The curriculum includes Health Insurance Portability and Accountability Act (HIPAA) training and covers secure data transfer, passwords, computer security habits and knowledge of what constitutes misuse or inappropriate use of the server. All investigators and research staff with direct access to the identifiable data will be required to undergo annual responsible conduct of research, cybersecurity, and HIPAA certification in accordance with University of Pennsylvania regulations.

All data will be stored and analyzed on institutionally managed and secured servers with access privileges limited to those with a need to know via the use of single-user access passwords and usernames. All study personnel that will use this data are listed on the IRB application and have completed training in HIPAA standards and human subjects research. Whenever possible, direct identifiers will be removed from analysis files.

Screening data, as well as the RETAIN randomization step, scripts, and data collection for time spent reading the MOVE IT parent trial consent form, will be integrated into a REDCap database. The same procedures described in Section 10.a.2 will be used to manage these data. MOVE IT research staff will enter Way to Health Study IDs into REDCap to enable linkage between subject records across different data extracts.

b. Subject Confidentiality

RETAIN data hosted on the REDCap application for this study will use account-based authentication and permission systems to protect confidentiality. An investigator or statistician who logs in will be able to download only de- identified data. Parent trial research staff at the different sites will not be able to access information from other sites; we will put in place data user groups in the REDCap system. Only parent trial research staff responsible for contacting participants for follow-up meetings or responding to questions about the study will be able to view participant names and contact information. This personal information will be used to contact participants if there is an issue with their account, payments, or they contact us with a problem. We will implement multiple, redundant protective measures to guarantee the privacy and security of the participant data. All study data will be stored on the secure/firewalled servers at the University of Pennsylvania. These data servers are maintained in a guarded facility behind several locked doors, with very limited physical access rights. They are also cyber-protected by extensive firewalls and multiple layers of communication encryption. Electronic access rights are carefully controlled by UPenn system managers. We believe this multi-layer system of data security, identical to the system protecting the University of Pennsylvania Health Systems medical records, greatly minimizes the risk of loss of privacy.

c. Subject Privacy

We will collect subjects' names, addresses, phone numbers, and data required for the completion of W-9 forms for subject compensation. All of these data will be stored in a HIPAA-compliant database that conforms to applicable data security standards. Access to all such data will be limited to specifically designated researchers who are responsible for contacting participants for responding to questions and concerns from participants. Subjects will complete study surveys in a secure, private locations at each center with research staff. Social security numbers for all persons to whom incentives are sent will be transmitted in encrypted format to Accounts Payable, which will store the data for W-9 forms. After the social security numbers are no longer needed, they will be deleted from our system.

11. Data and Safety Monitoring

a. Monitoring Plan

The data and safety monitoring plan will have several parts. First, we will develop and implement methods of verifying entered data and of quality control among parent trial research staff who will be directly entering data into the REDCap system. Second, the PI will be directly responsible for identifying and reporting all serious adverse events, protocol deviations/violations and unanticipated events to the IRBs and funding agency promptly, as appropriate. The PI will also report all adverse events, accrual rates, retention rates, and all other logistical issues to the DSMB at least biannually (if there are serious adverse events occur at any time that the investigators feel ought to be brought to the attention of the DSMB sooner, the DSMB can also meet on an ad hoc basis). Third, there will be a DSMB responsible for monitoring the trial, convening for the first time in December 2015 to inform the RETAIN trial planning process.

b. Data and Safety Monitoring Board Members

The Data and Safety Monitoring Board includes the following members:

Jennifer S. Blumenthal-Barby, PhD (Chair): expertise in ethical contexts of human judgment and decision-making in human research.

Salma Jabbour, MD: expertise in radiation oncology with a subspecialty in lung cancer.

Brenda F. Kurland, PhD: expertise in biostatistics with research emphasis on longitudinal and other correlated data.

Jeffrey M. Peppercorn, MD, MPH: expertise in medical oncology with research emphasis on bioethics and health policy, as well as cancer survivorship.

Kim Vernick: member of the University of Pennsylvania's Proton Patient Alumni Program, Patient and

Family Advisory Council, and a cancer survivor.

The PI (Scott Halpern), assisted by the project manager, will be responsible for maintaining communication between the DSMB and the individual project staff. The DSMB will be responsible for monitoring the trial and making decisions about the termination of individual study arms or the study itself. The DSMB will review and approve the research protocol. They will also assess the progress of the trial, including the assessment of data quality, participant recruitment, accrual and retention, participant risk versus benefit, and study outcomes. Corresponding recommendations will be issued at all subsequent meetings. These recommendations will be based on the results and discussion of interim analyses, conducted at one-half, and three-fourths of the target same size. DSMB recommendations may be guided by statistical monitoring guidelines. The DSMB may recommend permanent suspension of enrollment, or temporary suspension pending protocol modification. Following each meeting, and the provision of recommendations and the response from the research team, the Principal Investigator and Project Manager will prepare progress reports to be submitted to the University of Pennsylvania Institutional Review Board and any other IRBs participating in the trial. Prior to submission to these IRBs, the progress reports will be approved by the DSMB chair.

c. Stopping Rules

The PI, in consultation with Co-Investigator and Faculty Statistician Dr. Alisa Stephens-Shields, has identified TWO trial stopping rules. The DSMB approved these stopping rules as grounds to terminate the trial:

1. Early evidence of undue inducement that distorts voluntary informed consent. To detect whether incentives represent undue inducement, the research team will test the statistical interaction between incentive size and risk perception on the outcome of enrollment in the parent RCTs. A statistically significant interaction, in the direction that risk perception is less strongly associated with enrollment in higher-payment arms, would be grounds for terminating the trial or suspending a trial arm.

2. Early evidence of unjust inducement by preferentially encouraging participation among participants with either (a) lower income, or (b) reduced financial well-being. Two interaction terms will be evaluated in separate models to avoid collinearity. Unjust inducement will be defined as a statistically significant interaction between (a) incentive size and annual household income, or (b) between incentive size and economic well-being, each on the outcome of trial enrollment. One or both of these interactions, if statistically significant in the direction that lower-income persons or persons with reduced economic well-being are more strongly motivated to participate by increasingly large payments, will be considered grounds for terminating the trial or suspending a trial arm.

Analyses of these interaction terms will be structured as tests of non-inferiority, enabling the research team to exclude the presence of undue or unjust inducements if the interactions do not manifest. Specifically, the research team will use one-sided alpha levels of 0.05 to exclude, with 95% confidence, the possibility that any of these interaction odds ratios are >2.0. The interim tests will use 1-sided significance levels of 0.0055 and 0.0219. The DSMB will be empowered to stop the trial early if the confidence bound

exceeds the non-inferiority bound of 2.0, thus protecting against undue or unjust inducement. Interim analyses will be conducted at one-half, and three-fourths of the target sample size.

The DSMB may also wish to consider increased rates of therapeutic misconception as grounds for early termination of the trial. The research team will compare responses to the trial's measure of the construct of therapeutic misconception across the three trial arms. While no pre-specified statistical monitoring guidelines are proposed for this measure, DSMB members may consult with Dr. Scott Kim, with whom the therapeutic misconception tool for the trial has been developed, for guidance on interpretation of the data provided in the open statistical report. Dr. Kim is Senior Investigator in the Department of Bioethics at the NIH, and a member of the trial's External Advisory Board. He is an expert in the use of these measures and can provide independent guidance on their interpretation.

d. Adverse Events

As this is a minimal risk study, we do not anticipate adverse events; however, we will report all adverse events to the Data and Safety Monitoring Board.

e. Clinicaltrials.gov

The RETAIN trial has been registered on clinicaltrials.gov (NCT02697799). The study profile will be regularly updated on the website and summary results uploaded to make information about the study publicly available and promote transparency.

12. Human Subjects Protection

a. Potential Study Risks

A primary risk to this study is that financial incentives either unfairly induce participants to participate in a trial that they would not otherwise participate in. This is a primary question of this trial. We will convene a data and safety monitoring board (DSMB) in conjunction with NIH to monitor any indication that this is occurring. Our hypothesis is that no population will be unfairly manipulated into participating in a trial that they would not otherwise, and that financial incentives could lead to participants examining the potential risks of a study more closely than they would have otherwise.

<u>Supporting Research</u>

A study led by PI Halpern and Co-I Karlawish assessed 126 hypertensive patients' willingness to participate in RCTs of experimental antihypertensive drugs.[7] We used a 3 x 3 within-subjects factorial design in which hypertensive patients were administered, in random sequence, 9 hypothetical RCTs which differed in their risk level (10%, 20%, or 30% chance of drug-related adverse events) and payment ($100, $1,000, or $2,000 for a 10-week trial). We found that increasing payments motivated greater RCT

participation, and that increasing risk levels reduced participation levels ($p < 0.001$ for each). Importantly, patients' participation rates declined equivalently with increasing risk levels across all payment levels studied, and the statistical interaction between risk and payment was not statistically significant (p=0.30). This shows that patients were equally sensitive to risk despite very different payment amounts, suggesting that research incentives are not undue inducements.

Furthermore, this study of payments for RCT enrollment,[7] as well as another study by PI Halpern of payments for living kidney donation,[51] counter the notion that payments are unjust inducements. Specifically, in both studies, increasing payment levels were similarly motivating among patients with higher and lower incomes. Indeed, in the RCT participation study,[7] there was an indication that larger payments may preferentially motivate wealthier people to participate (payment-by-income interaction p=0.09). The validity of these results is enhanced by the income diversity among the study samples and the substantial statistical power to identify such income-by-payment interactions if they existed.

Co-I Volpp and colleagues asked participants to rate the riskiness of a new technology (transcranial magnetic stimulation) being tested in RCTs after being told they would receive $25 or $1,000 for trial participation.[8] Participants assigned to review the trials offering $1,000 spent more time reading about study risks and other research aspects (mean = 3.7 minutes) than did patients assigned to trials offering $25 (mean = 1.0 minutes) ($p < 0.01$). Larger incentives also decreased the odds that participants would skip the page of the informed consent form that described study contraindications ($p < 0.05$). These findings suggest that payments alert people to the possibility of risk, and encourage them to learn more about the study.[8] Thus, rather than contravening the goals of informed consent, incentives may actually promote informed decision-making.

Another potential risk is breach of confidentiality and privacy for completion of study surveys. No identifiable data will be reported to anyone outside of the research staff. Due to the compensation in this study, we will be collecting personal information needed for completion of W-9 forms, including social security numbers, for participants receiving incentives. Accidental disclosure of social security numbers could lead to identity theft. Social security numbers will be deleted once they are no longer needed. Names and addresses will be stored in encrypted databases. These data will be viewable only by the parent trial research staff. All other researchers will be able to view only participant ID numbers. Intervention arms will be identified by code letters until both the statistician and PI agree that interim analysis is complete.

b. Potential Study Benefits

There is no direct benefit to patients for participating in the RETAIN trial. Patients may perceive the money as a benefit, but remuneration for research participation is not traditionally considered a benefit justifying human subjects research.[3] Patients may benefit from participation in the parent RCTs. The RETAIN study will provide important information about the impact of incentives on enrollment and decision making, which can inform the conduct of human subjects research more generally. The participants will be debriefed about the purpose of this study and the knowledge to be gained from it.

c. Risk/Benefit Analysis

In light of the tremendous benefits to public health and individuals developing more effective programs, as well as our efforts, outlined above, to mitigate all risks associated with this study, we believe that this study presents a highly favorable risk-benefit ratio for participation.

d. Protective Measures

The first safeguard for protection of human subjects includes an experienced and well-trained study team. Dr. Scott Halpern (PI) is Associate Professor of Medicine, Epidemiology, and Medical Ethics & Health Policy at Penn, Director of the Palliative and Advanced Illness Research (PAIR Center, and Deputy Director of the Center for Health Incentives and Behavioral Economics (CHIBE) at the Leonard Davis Institute of Health Economics. He has considerable expertise in the design, ethics, and recruitment barriers of clinical trials, in leading RCTs of financial incentives to modify health behaviors, and in the ethics of using behavioral economic approaches, including incentives, to modify health-related decisions.

i. RTOG 1308

Drs. Sam Swisher-McClure, Zhongxing Liao, Noah Choi, and Jeffrey Bradley are the site Principal Investigators for the parent trial, RTOG 1308. Dr. Liao also serves as the overall Chair of this trial. These Co-I's are among the nation's leading clinical researchers in radiation oncology, and have considerable influence on related policy. The RETAIN trial will also harness the support from key research staff from the Department of Radiation Oncology at the University of Pennsylvania's Perelman Center for Advanced Medicine (PCAM).

In conjunction with the planning and implementation support provided by the team at in Penn's Radiation Oncology Group, Dr. Halpern and the University of Pennsylvania research team will also work closely with leadership at NRG Oncology, the NCI cooperative group with oversight of the parent trial RTOG 1308. NRG Oncology will provide ongoing guidance to ensure that the goals of the RETAIN study align with the goals of the parent trial protocol with respect for human research protection.

RTOG 1308 study supports research nurses/staff at the four sites participating in the incentives trial. In advance of the January 2016 launch of the incentives trial, key study personnel from the University of Pennsylvania will engage with the parent trial nurses/staff, who have been pre-selected by the RTOG 1308 site PIs as the key points of contact for the incentives trial, in the planning and implementation process. All RTOG 1308 parent trial research staff will receive training from the University of Pennsylvania research team on the incentives trial protocol in February 2016.

ii. BASC

Northwestern University PI Brian Hitsman, PhD, along with Site PI Robert Schnoll, PhD, of the BASC study, will support the implementation of the RETAIN trial at both participating sites. Dr. Hitsman leads the Nicotine Dependence and Treatment Lab at Northwestern. The lab frequently recruits from high burden populations, including cancer patients. Dr. Hitsman's current collaborations with Penn include the Abramson Cancer Center- sponsored Extended Duration Varenicline for Smoking Among Cancer Patients (NCT02378714) and the NCI-sponsored project described in this report, Behavioral Activation and Varenicline for Smoking Cessation in Depressed Smokers (NCT02378714) – both of which involve Penn colleague Dr. Schnoll, who has also successfully collaborated with the RETAIN PI previously. Both Drs. Hitsman and Schnoll have experience layering social behavioral manipulations onto existing smoking cessation studies to address recruitment challenges, as well as research focuses that are geared toward the recruitment of vulnerable patients.

iii. MOVE IT

Ryan Greysen, MD, MHS, MA, Section Chief of Hospital Medicine, will co-lead the implementation of the MOVE IT study at Penn, in collaboration with Drs. Patel (Co-I) and Halpern. Dr. Greysen's expertise in patient-oriented research targeting vulnerable older adults with multiple comordities-- with particular focus on improving both hospital and transition care--will be leveraged to integrate RETAIN procedures in a way that is at once sensitive to the inpatient care environment and scientifically sound. Dr. Greysen will lead the MOVE IT study protocol with Site PI Mitesh Patel, MD, MBA, MS. An expert in digital health initiatives to improve health outcomes and change health behaviors, Dr. Patel is well-equipped to operationalize the integration of the RETAIN trial into the mobility study at the Hospital of the University of Pennsylvania, having significant content expertise in the use of incentives within a hospital setting.

e. Additional Protective Measures

To guide the ethical and scientific conduct of this study, and to help position the results so that they may have maximal impact on future research efficiency and regulation, we have assembled an External Advisory Board (EAB) and an Internal Advisory Board (IAB). The External Advisory Board includes: Christine Grady, MSN, PhD, Chief of the NIH Clinical Center's Department of Bioethics and Head of the Section on Human Subjects; Scott Kim, MD, PhD, Senior Investigator in the NIH Department of Bioethics; Leslie Wolf, JD, MPH, Professor at the Georgia State School of Law's Center for Law Health and Society; Timothy Coetzee, PhD, Chief Advocacy and Research Officer for the National MS Foundation; and Barbara Langloss, Patient Advocate and an alumna of Penn's Proton Therapy Program. Our Internal Advisory Board includes: Steven Joffe, MD, MPH, pediatric oncologist and Vice Chair of the Department of Medical Ethics and Health Policy at Penn; Ezekiel Emanuel, MD, PhD, Chair of the Department of Medical Ethics and Health Policy at Penn; and David Festinger, PhD, Adjunct Assistant Professor of Psychiatry at Penn and Direct of the Treatment Research Institute's Section on Law and Ethics Research.

Finally, the debriefing process, delivered by parent trial research staff, is an important element of human subject protection and will ensure that patients (1) understand the recruitment for the parent trial included a study on the effects of incentives on study enrollment; (2) understand they were randomized to receive one of three study incentives (3) understand they were not informed about the RETAIN study to avoid biasing the study results; and (4) understand no further data are to be collected as part of the RETAIN study and the study will complete as soon as the incentives are disbursed.

Additional layers of protection for human subjects include the robust informed consent process (Sections 8.d.-8.e.), exceptional data security (Section 10), and the empowered Data Safety and Monitoring Board (Sections 11.a and 11.b), all described in detail in this protocol.

13. References

1. Halpern SD. Financial Incentives for Research Participation: Empirical Questions, Available Answers and the Burden of Further Proof. *American Journal of the Medical Sciences.* Oct 2011;342(4):290-293.
2. National Institutes of Health Office of Human Subjects Research. *Guidelines for remuneration of research subjects in the intramural research program and registration in the clinical research volunteer program database. Accessed December 3, 2011 at http://ohsr.od.nih.gov/info/pdf/InfoSheet20.pdf.*
3. Macklin R. 'Due' and 'undue' inducements: On paying money to research subjects. *IRB: a review of human subjects research.* 1981;3(5):1-6.
4. McGee G. Subject to payment? *JAMA.* 1997;278:199-200.
5. McNeil P. Paying people to participate in research: why not? *Bioethics.* 1997;11:390-396.
6. Bentley JP, Thacker PG. The influence of risk and monetary payment on the research participation decision making process. *J Med Ethics.* June 1, 2004 2004;30(3):293-298.
7. Halpern SD, Karlawish JHT, Casarett D, Berlin JA, Asch DA. Empirical assessment of whether moderate payments are undue or unjust inducements for participation in clinical trials. *Archives of Internal Medicine.* 2004;164:801-803.
8. Cryder C, London AJ, Volpp KG, Loewenstein G. Informative Inducement: Study Payment as a Signal of Risk. *Social Science & Medicine.* 2010;70(3):455-464.
9. Altman DG. Statistics and ethics in medical research III: How large a sample? *Br Med J.* 1980;281:1336-1338.
10. Drazen JM, Koski G. To protect those who serve. *New England Journal of Medicine.* 2000;343:1643-1645.
11. Ellenberg SS. Randomization designs in comparative clinical trials. *N Engl J Med.* 1984;310(21):1404-1408.
12. Freiman JA, Chalmers TC, Smith H, Jr, Kuebler RR. The importance of beta, the type II error and sample size in the design and interpretation of the randomized controlled trial: survey of 71 "negative" trials. *N Engl J Med.* 1978;299:690-694.
13. Meinert CL. *Clinical trials: Design, conduct, and analysis.* New York: Oxford University Press; 1986.
14. Nass SJ, Moses HL, Mendelsohn J. *A national cancer clinical trials system for the 21st century: Reinvigorating the NCI Cooperative Group Program.* Washington, D.C.: The National Academies Press; 2010.

15. Freedman B. Scientific value and validity as ethical requirements for research: A proposed explication. *IRB: Rev Hum Subjects Res.* 1987;9(6)):7-10.
16. Halpern SD, Karlawish JHT, Berlin JA. The continuing unethical conduct of underpowered clinical trials. *JAMA.* 2002;288:358-362.
17. Kramer MS, Shapiro SH. Scientific challenges in the application of randomized trials. *JAMA.* 1984;252(19):2739-2745.
18. Nathan RA. How important is patient recruitment in performing clinical trials? *Journal of Asthma.* 1999;36(3):213-216.
19. Hunningshake DB, Darby CA, Probstfield JL. Recruitment experience in clinical trials: Literature summary and annotated bibliography. *Controlled Clinical Trials.* 1987;8:6S-30S.
20. Probstfield JL, Wittes JT, Hunningshake DB. Recruitment in the NHLBI population-based studies and randomized clinical trials: data analysis and survey results. *Controlled Clinical Trials.* 1987;8:141S-149S.
21. Vollmer VM, Osborn ML, Hertert S, et al. Recruiting hard-to-reach subjects: Is it worth the effort? *Controlled Clinical Trials.* 1994;15:154-159.
22. Emanuel EJ, Schnipper LE, Kamin DY, Levinson J, Lichter AS. The costs of conducting clinical research. *J Clin Oncol.* Nov 15 2003;21(22):4145-4150.
23. Caldwell PH, Hamilton S, Tan A, Craig JC. Strategies for increasing recruitment to randomised controlled trials: systematic review. *PLoS Med.* 2010;7(11):e1000368.
24. Donovan J, Mills N, Smith M, et al. Quality improvement report: Improving design and conduct of randomised trials by embedding them in qualitative research: ProtecT (prostate testing for cancer and treatment) study. *BMJ.* October 5, 2002 2002;325(7367):766-770.
25. Sugarman J, Kass NE, Goodman SN, Perentesis P, Fernandes P, Faden RR. What patients say about medical research. *IRB: A review of human subjects research.* 1998;20(4):1-7.
26. Wendler D, Krohmal B, Emanuel EJ, Grady C, Grp E. Why patients continue to participate in clinical research. *Archives of Internal Medicine.* Jun 23 2008;168(12):1294-1299.
27. Halpern SD. Prospective preference assessment: A method to enhance the ethics and efficiency of randomized controlled trials. *Controlled Clinical Trials.* 2002;23:274-288.
28. Shah A, Efstathiou JA, Paly JJ, et al. Prospective preference assessment of patients' willingness to participate in a randomized controlled trial of intensity-modulated radiotherapy versus proton therapy for localized prostate cancer. *International Journal of Radiation Oncology*Biology*Physics.* 2012;83:E13-E19.
29. Carroll R, Antigua J, Taichman DB, et al. Pulmonary arterial hypertension patients' willingness to participate in randomized clinical trials of novel therapies. *Clinical Trials.* 2010;9:348-357.
30. Halpern SD, Karlawish JHT, Casarett D, Berlin JA, Townsend RR, Asch DA. Hypertensive patients' willingness to participate in placebo-controlled trials: Implications for recruitment efficiency. *American Heart Journal.* 2003;146:985-992.
31. Slomka J, McCurdy S, Ratliff EA, Timpson S, Williams ML. Perceptions of financial payment for research participation among african-american drug users in HIV studies. *Journal of General Internal Medicine.* Oct 2007;22(10):1403-1409.
32. Stunkel L, Grady C. More than the money: A review of the literature examining healthy volunteer motivations. *Contemporary Clinical Trials.* May 2011;32(3):342-352.
33. Dunn LB, Kim DS, Fellows IE, Palmer BW. Worth the risk? Relationship of incentives to risk and benefit perceptions and willingness to participate in schizophrenia research. *Schizophr Bull.* Jul 2009;35(4):730-737.
34. Dickert N, Emmanuel E, Grady C. Paying research subjects: An analysis of current policies. *Annals of Internal Medicine.* 2002;136:368-373.

35. Grady C, Dickert N, Jawetz T, Gensler G, Emanuel E. An analysis of U.S. practices of paying research participants. *Contemp Clin Trials.* 2005;26:365-375.
36. Emanuel EJ. Ending concerns about undue inducement. *Journal of Law Medicine & Ethics.* Spr 2004;32(1):100-105.
37. Emanuel EJ. Undue inducement: Nonsense on stilts? *American Journal of Bioethics.* Sep-Oct 2005;5(5):9-13.
38. Emanuel EJ, Currie XE, Herman A. Undue inducement in clinical research in developing countries: is it a worry? *The Lancet.* 2005;366(9482):336-340.
39. Hyun I. Fair payment or undue inducement? *Nature.* 2006;442(7103):629-630.
40. Martin R. Undue inducement in clinical research. *Lancet.* 2005;366(9482):275-276.
41. Casarett D, Karlawish JHT, Asch DA. Paying hypertension research subjects. *Journal of General Internal Medicine.* 2002;17:650-652.
42. Wilkinson M, Moore A. Inducement in research. *Bioethics.* 1999;11:373-389.
43. Elliott C, Abadie R. Exploiting a research underclass in phase 1 clinical trials. *New England Journal of Medicine* 2008;358:2316-2317.
44. Denny CC, Grady C. Clinical research with economically disadvantaged populations. *Journal of Medical Ethics.* July 1, 2007 2007;33(7):382-385.
45. Viens AM. Socio-economic status and inducement to participate. *American Journal of Bioethics.* 2001;1(2).
46. Wertheimer A. Should we worry about money? *Rethinking the ethics of clinical research*. New York: Oxford University Press; 2011:117-190.
47. Bernstein M. Payment of research subjects involved in clinical trials is unethical. *Journal of Neuro-Oncology.* Jul 2003;63(3):223-224.
48. Burt RA. On gnats, camels, and payment to research subjects: A comment. *Journal of Medicine and Law.* 2005;9:25-30.
49. Grant RW, Sugarman J. Ethics in human subjects research: Do incentives matter? *Journal of Medicine and Philosophy.* Dec 2004;29(6):717-738.
50. 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.
51. Halpern SD, Raz A, Kohn R, Rey M, Asch DA, Reese P. Regulated payments for living kidney donation: an empirical assessment of the ethical concerns. *Ann Intern Med.* Mar 16 2010;152(6):358-365.
52. Kim S, Kim H, McCallum C, Tariot P. What do people at risk for Alzheimer disease think about surrogate consent for research? *Neurology.* 2005;65:1395–1401.
53. Karlawish J, Rubright J, Casarett D, Cary M, TenHave T, P S. Older adults' attitudes toward non-competent subjects participating in Alzheimer's research. *American Journal of Psychiatry.* 2009;166(2):182-188.
54. Muroff J, Hoerauf S, Kim S. Is psychiatric research stigmatized? An experimental survey of the public. *Schizophrenia Bulletin.* 2006;32:129-136.
55. Henderson GE. Is Informed Consent Broken? *American Journal of the Medical Sciences.* Oct 2011;342(4):267-272.
56. Bialkova S, van Trijp HCM. An efficient methodology for assessing attention to and effect of nutrition information displayed front-of-pack. *Food Quality and Preference.* 2011;22:592–601.
57. Pieters R, Warlop L. Visual attention during brand choice: The impact of time pressure and task motivation. *International Journal of Research in Marketing.* 1999;16:1-16.

58. Munafò MR, Roberts N, Bauld L, Leonards U. Plain packaging increases visual attention to health warnings on cigarette packs in non-smokers and weekly smokers but not daily smokers. *Addiction.* 2011;106(8):1505–1510.
59. Kim SH WR, De Vries R, Kim H, Holloway R, Kieburtz K. Could the High Prevalence of Therapeutic Misconception Partly Be a Measurement Problem? *IRB: Ethics & Human Research* 2015;37(4):11.
60. Kim SH SL, Wilson RM, Frank SA, Holloway RG, Keiburtz K, De Vries RG. An Approach to Evaluating the Therapeutic Misconception. *IRB: Ethics & Human Research.* 2009;31(5):7-14.
61. Pentz RD, White M, Harvey RD, et al. Therapeutic misconception, misestimation and optimism in subjects enrolled in phase I trials. *Cancer.* 2012;18(118):4571-4578.
62. Gardner W, Hoge SK, Bennett N, et al. Two scales for measuring patients' perceptions for coercion during mental hospital admission. *Behavioral Sciences and the Law* 1993;11:307-321.
63. Shea JA, Micco E, Dean L, McMurphy S, Schwartz SJ, Armstrong K. Development of a revised health care system distrust scale. *Journal of General Internal Medicine.* 2008;6(23):727-732.
64. Israni AK, Halpern SD, McFadden C, et al. Willingness of dialysis patients to participate in a randomized controlled trial of daily dialysis. *Kidney International.* Mar 2004;65(3):990-998.
65. Shea JA ME, Dean LT, McMurphy S, Schwartz JS, Armstrong K. . Development of a Revised Health Care System Distrust Scale. *Journal of General Internal Medicine.* 2008;26(6):727-732.

II. Changes to Protocol

1. Approved August 21, 2017

a. Phase I – Removal of the University of Pennsylvania as a Recruiting Site

Due to staff turnover, lack of departmental resources, and the slow accrual of RTOG 1308 at the Penn site, the Penn was removed from the Phase I collaboration. At this junction the team decided to continue recruiting patients at MD Anderson, Washington University, St. Louis, and MGH, where accrual for RTOG 1308 and personnel resources were better positioned for success.

b. Phase II – Modification to BASC recruitment script

The addition of an eligibility probe in the recruitment script to ensure that patients with prior knowledge of the maximum incentive of $500 used for RETAIN, or the randomization to one of three incentives, are screened out on the pre-screen call and provided the opportunity to participate in the BASC trial without RETAIN procedures.

2. Approved August 30, 2017

a. Phase I – Removal of the Healthcare System Distrust Scale

We removed the Healthcare System Distrust Scale from Phase I, the partnership with the lung cancer study (RTOG 1308), as this tool was never intended to be used in the study (it was not proposed in the NCI-funded protocol), but rather was added as a condition of participation following review by the Penn Radiation Oncology Protocol Committee's (ROPC) review of this trial. Once Penn was no longer a Phase I site, the study team determined that it would be optimal to remove the tool to reduce assessment burden for lung cancer patients who consent to both RETAIN and RTOG 1308. Of note, the Healthcare System Distrust Scale was never proposed for use in Phases II and III of the study.

b. Phase II – Modification to BASC screening procedures

The Northwestern and Penn teams adjusted the patient flow such that the phone-based eligibility assessment for the smoking cessation study (BASC) happened before BASC screeners randomized the participants and revealed the RETAIN-associated financial incentives amount on screening calls. This allowed the study team to avoid biases in RETAIN that would result from post-RETAIN randomization losses. Subsequent to this change, all BASC-eligible participants were assessed for RETAIN eligibility via the standard eligibility probe assessing for prior knowledge of RETAIN procedures.

We also removed the RETAIN verbal consent question about "research attitudes questions" and eliminated the practice of placing patients on the RETAIN or non-RETAIN pathway depending on their response to the eligibility probe. This approach is consistent to the Phase III MOVE-IT study protocol and ensured uniform approaches across the two minimal risk studies, while also optimizing practicability of the research for the BASC team.

c. Phases II and III - Modification to the BASC and MOVE-IT debriefing scripts

We removed the question, "When you agreed to participate in the [MOVE IT or smoking cessation study], did you know that all participants would receive up to [maximum RETAIN incentive amount] in the end?" from Phase II (BASC) and Phase III (MOVE IT) debriefing scripts. After speaking with the RETAIN study's biostatistician, we determined that these data would not be useful for analyses, nor effective at ascertaining post-hoc contamination in these companion studies.

3. Approved September 26, 2017

a. Phases II and III - Modifications to the Compared Riskiness Scale

It was determined by the trial's faculty statistician and data manager that the items in the 9-item Compared Riskiness Scale should contain activities that are more aligned in risk-level and the probability, as well as nature, of consequences of participation in trials like the BASC and MOVE IT, as opposed to the lung cancer trial RTOG 1308. Several items were replaced to better align these risky activities and enable a range of responses from participants, including "taking 3 times the recommended dose of pain killers;" "receiving stitches;" "riding a motorcycle with no helmet;" "getting a body piercing;" and "bungee jumping."

4. Approved October 25, 2017

a. Phases II and III – Clarification of Payment Procedures

Debriefing scripts, recruitment procedures, and FAQs for both BASC and MOVE-IT trials were modified to clarify the procedures and timing for subject compensation.

Compensation information available to BASC subjects (if requested) during recruitment:

"When do I get compensated (if randomized to the $200/$500)?"

- For $500 subjects: You will receive up to $500 for completing this study. This includes $150 at the beginning of the study, $150 at the end of the study, and the remaining $200 will be disbursed for attending scheduled visits and completing tasks.

- For $200 subjects: You will receive session completion payments up to $200. These are disbursed based on your attendance at specific visits."

Compensation information provided to BASC subjects during debriefing:

You will be paid a total of $300 in two installments of $150: You will receive the first installment of $150 now, and the second installment of $150 during the final week of follow-up for the study. The payment will be issued on a card that can be used like cash. If you withdraw from the study, you will not receive the second payment.

Compensation information provided to MOVE-IT subjects during enrollment:

If you withdraw from the study at any point prior to enrollment and completion of today's questionnaires, you will not receive the first payment. If you withdraw for personal reasons or discontinue the use of the study's wearable before the completion of study-related tasks at 3 months post-discharge, you will not receive the second payment. I'll ask that you fill out an electronic W9 form so that we can ensure the payment is properly processed."

5. Approved November 20, 2017

a. Phase II – Revision of BASC Debriefing Script

At the request of the BASC study team, we abbreviated the RETAIN debriefing script during the Reminder Call (between "intake" and "Pre-Quit 1") during which participants are informed of the payment scheme and goals of the RETAIN study. All participants who sign consent at intake and are confirmed eligible by the BASC team are read the debriefing script. The BASC study team expressed that the information being conveyed on the call is dense; participants may not fully appreciate the nuances in payment structure between RETAIN and BASC, as well as key elements of the study's purpose. Subjects will hear the abbreviated script on the Reminder Call and then the full, IRB-approved script at their Pre-Quit 1 visit.

b. Phase II - BASC Waiver of HIPPA Authorization

A request for Waiver of HIPAA Authorization was submitted as data captured on RETAIN-randomized subjects who do not consent to the BASC trial would need to be analyzed in order to assess the primary and secondary outcomes of the RETAIN trial. The MOVE-IT trial already had a Waiver of HIPAA Authorization in place for the purpose.

c. Phase II – Revision to Compared Riskiness Scale for BASC study

The team made a minor modification to the introduction of items on the Compared Riskiness Scale for the BASC study. Instead of research coordinators introducing the scale by saying, "Does participating in this

study, versus not participating, seem…" they will say, "Does participating in this study seem more risky than" and go through respective activities, item by item to elicit a Yes/No response.

6. Approved January 3, 2018

a. Phase I – Termination of RTOG 1308 Collaboration

The RETAIN trial was originally launched at the University of Pennsylvania, University of Texas MD Anderson Cancer Center, Massachusetts General Hospital, and the Washington University, St. Louis in collaboration with a lung cancer parent trial, RTOG 1308, the Phase III Randomized Trial Comparing Overall Survival After Photon Versus Proton Chemoradiotherapy for Inoperable Stage II-IIIB NSCLC. This parent trial faced accrual challenges from its outset, due largely to insurance denial of proton therapy, which precludes eligibility for 1308. Despite making every effort possible to surmount this barrier to the 1308 collaboration, accrual to 1308 had only worsened through 2018. A total of 5 patients across all sites had been enrolled in RETAIN through the 1308 collaboration, and none had been enrolled in the previous 4 months. Indeed, accrual to 1308 had been so challenging that the 1308 investigators changed their primary outcome so as to enable a reduction in the target sample size for the 1308 trial from 576 to 350. This reduction in the parent trial's target sample size made it impossible for the RETAIN-1308 collaboration to yield an adequately powered embedded trial, even if the insurance denials had been overcome.

As a result of both the successes of the Phase II and Phase III collaborations, and the shortcomings of the Phase I 1308 collaboration, the RETAIN team decided to end our collaboration with 1308 and focus all resources squarely on the Phase II and Phase III collaborations. This decision was discussed with the 1308 investigators on November 27 and the RETAIN team received approval to move forward exclusively focused on Phases II and II from the sponsor, the Nation Cancer Institute, on November 30, 2017.

As a result of this change, the team removed RTOG 1308-relevant language from the IRB protocol and ended Penn's oversight of the RETAIN trial at MDACC, a relying institution. The MGH and Washington University research teams closed out the RETAIN study at their respective sites.

7. Approved January 25, 2018

a. Phase II – Modification to BASC screening procedures

The study teams for BASC and RETAIN implemented a RETAIN-related change to the phone screen script being used at Northwestern and Penn. For patients randomized to RETAIN, the team stopped asking, "Does this sound like something that you are interested in?" before administering the RETAIN surveys. They simply transitioned from introducing the study basics to administering the RETAIN questions by saying, "Now we ask that you answer a few more questions before finalizing the details of your intake visit."

The goal of this change was to provide an opportunity to capture RETAIN baseline data that was not being collected systematically due to early withdraws from the phone screen call.

b. Phases II and III - Revisions to the Compared Riskiness Scale

The study team examined the phrasing for the Compared Riskiness scale in an Amazon mechanical Turk study aimed at countering floor effects in our measure of risk perception. As a result of this investigation we made several changes to the phrasing of the questions in the scale. We did not add new items to the scale.

8. Approved February 21, 2018

a. Phase II – Modification to MOVE IT recruitment procedures

This modification was submitted in tandem with our colleagues on the Mobility, Outcomes, and Validated Experiences Incentive Trial (MOVE IT) study (IRB # 823491). With this change MOVE IT eligibility was assessed earlier in the enrollment process order to randomize and announce the incentives earlier to patients. We also added a note to patients randomized to the $100 and $300 arms that they can receive the first installment of their payment the day they decide to participate. We modified the modality of payments such that the first payment would be administered via ClinCard to ensure that all patients who enroll can go get the first installment in a non-check format. These changes were reflected in the updated debriefing and consent forms.

b. Phases II and III – Modifications to the Compared Riskiness Scale

We also updated the Compared Riskiness scale once more in an effort to counter early floor effects.

9. Approved April 23, 2018

a. Phase III – Modification to data collection and administration of surveys

In our modification approved February 21, 2018, we moved the randomization to 1 of 3 incentives to earlier in the clinical research coordinators' recruitment script to optimize the research team's ability to augment enrollment in the MOVE IT study. Patients who are randomized in this model become RETAIN subjects, and we had a way to capture demographic information on RETAIN subjects who decline participation in MOVE IT. However, we did not have a means of capturing risk perception data on patients who declined early, before reading the consent form for MOVE IT. To mitigate the issue of data missingness among these patients and to ensure we were able to execute the study successfully, we decided to include the Compared Riskiness survey in the baseline set of surveys, as well as include a minimal description of risks and benefits early in the enrollment script. This modification and change in data collection allowed us to test the interaction between incentive size and risk perception on the outcome of enrollment – and detect undue inducement, a key outcome of the study and criterion for the Data Safety and Monitoring Board to consider stopping the trial.

10. Approved January 25, 2019

a. Phase III – Addition of Qualitative Evaluation of Patient Decision-Making

We developed a new qualitative study to explore participants' motivations for enrolling or not enrolling in the MOVE IT study. The qualitative study consists of 1) data collection during the enrollment encounter for the purposes of conducting a discourse analysis and 2) semi-structured interviews among participants who decline MOVE IT (in-person) and enroll in MOVE IT (2 weeks after discharge from the hospital by phone). For the latter, the MOVE IT team has added additional questions pertaining to the intervention and patients' transitions from hospital to home. We engaged Penn's Mixed Methods Research Lab to support data collection, transcription, coding, and analysis; key personnel were added to the IRB application. The MOVE IT research coordinator also supported in-person data collection. The addition of this study had no impact on the RETAIN study itself, but the two were linked for regulatory/oversight purposes.

III. Final Protocol

1. Abstract

The most common and conceptually sound[1,2] ethical concerns with incentives for research participation are that they may (1) represent undue inducements by blunting peoples' perceptions of research risks, thereby preventing fully informed consent[3-5]; or (2) represent unjust inducements by encouraging enrollment preferentially among the poor. Neither of these concerns has been shown to manifest in studies using hypothetical incentives for participating in hypothetical RCTs.[6-8] But without evidence of how real incentives influence decision-making for real RCTs, practice variability remains.

We will conduct a randomized trial of 3 real incentives to participate in two parent randomized clinical trials (RCTs). Following clinicians' and research staff's preliminary determination of patients' eligibility in the parent RCT, we will assess patients' research attitudes, demographic characteristics, perceived research risks, time spent reviewing informed consent documents, ability to distinguish research from individualized 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 participating in trials, and the relative influence of incentives on those choices.

After patients make a decision about parent trial enrollment, we will debrief patients consenting to the parent trial about the random assignment of the incentives. The study will have adequate power to rule out between incentive size and risk perception (i.e., undue inducement) and between incentive size and income or economic well-being (i.e., unjust inducement) , using formal "non-inferiority" tests, interactions. We also will explore potential benefits of incentives, such as the possibilities that incentives improve informed consent by making people attend more thoroughly to research risks, and that they expedite recruitment enough to be cost-saving on balance.

2. Background and Significance

Recruitment problems often cause randomized clinical trials (RCTs) to fail or accrue excess costs

The concomitant problems of under-enrollment and selective enrollment in randomized clinical trials have long plagued efforts to evaluate new and existing medical interventions. [9-13] For example, a recent Institute of Medicine report found that 40% of cancer RCTs are never completed and published.[14] Under-enrollment occurs when too few research participants are enrolled to provide adequate statistical power to answer the study's primary research question. Because under-enrollment yields unacceptably high probabilities for type II (false negative) errors, these problems reduce the RCT's ability to answer the

research question, thereby degrading the trial's scientific value and hence, ethics.[15,16] Selective enrollment occurs when certain subgroups within the target population enroll in proportions greater or less than their representation in that population. By limiting the generalizability of the trial's results, this problem also curtails scientific value. [17]

These problems typically arise due to unexpected impediments to participant recruitment, which has been called "the most difficult and challenging aspect of clinical trials.[18]" Even when investigators enroll an adequate number of participants, they rarely do so on schedule,[13,19,20] or in a manner that attracts the full range of eligible participants.[17,21] 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.[22]

Financial Incentives may augment the precision, generalizability, and efficiency of RCTs

Given the growing gap between the supply of and demand for clinical research participants, 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.[23-27] Among the 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[28-30] and volunteers.[31,32] 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.[6,7,33]

If financial incentives do indeed increase the enrollment fraction – the number of patients enrolled among all patients recruited – they could enhance considerably the scientific value and validity of the research by augmenting the precision (i.e., statistical power) of RCTs. Further, because prior studies by our team[7,8,28] suggest that payments may influence participation decisions across socioeconomic and racial groups, it is possible that incentives could combat selective enrollment, augmenting the generalizability of RCT results. Despite these conceptual merits of incentives for research participation, and the fact that they are commonly provided, [34,35] the practice is controversial due to legitimate concerns regarding their unintended consequences.

There are two primary ethical concerns with providing incentives for research participation

Perhaps the most often-cited concern with paying people to participate in research is that incentives represent undue inducements – that is, they might alter peoples' perceptions of the risks associated with research participation, thereby preventing fully informed consent. [3-5,36-42] In the face of monetary offers, particularly those that are large and immediate, people may overlook or underestimate a study's risks, and hence consent to participate against their own better judgment. Importantly, an inducement is not undue if it merely encourages people to do things they would not do for free.[36,37,39,42]

A second common concern with incentives is that they may represent unjust inducements – that is, incentives could encourage enrollment preferentially among less-wealthy persons. Such differences in the effects of payments may be unjust if they create a system in which the burdens of research participants are borne preferentially by the poor, whereas the knowledge gained from the research would benefit all

(or worse, benefit the rich preferentially).[43-45] These concerns persist despite observations that less-advantaged persons commonly incur risks for the benefit of others (e.g., military service, coal mining), [1,44,46]and that larger payments – rather than none – may be needed to counter concerns regarding exploitation.[44] Thus, to address this controversial matter requires definitive evidence of whether or how payments differentially motivate participation among persons with different incomes or financial needs.

These ethical concerns with research incentives have yielded variable policies and practices

Views that research incentives are invariably wrong [3,4,47] have largely been replaced by arguments that payment for research participation can be ethical.[1,36,37,42,46,48,49] Indeed, some scholars have changed the core question from whether participants should be paid to how much is fair.[50] Yet the 2 core concerns noted above continue to engender inconsistent policies for regulating incentives by institutional review boards (IRBs) and funding agencies.[2,34] Indeed, a review of research protocols approved by 11 IRBs revealed marked and unexplained variability in the size of payments used across similar studies, and even across sites within the same study.[35] Such variability is unsurprising given concerns regarding the unintended consequences of research incentives, minimal regulatory guidance on incentive use, and considerable uncertainty regarding what incentive sizes may be cost effective in expediting enrollment.[35] 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.

3. Objectives

a. Aims

Aim I: The primary aim of the RETAIN trial is to determine if the ethical concerns with incentives for research participation actually manifest.

By randomly assigning patients considering participation in two RCTs (see Section 4. Study Organization) to low-, middle-, and high-level incentives for enrolling, and using our established methods for measuring the unintended consequences of incentives for participation[1,7,8,51], we will conclusively determine how incentives influence perceptions of research risks, and the proportion of economically disadvantaged patients who enroll.

Aim II: The secondary aim of the RETAIN trial is to assess the possible scientific and ethical benefits of financial incentives for RCT participation.

The potential benefits of incentives also are grounded more in theory than in evidence. We will empirically examine 3 potential benefits, testing whether incentives (1) increase the enrollment rate, thereby improving the parent trial's efficiency; (2) increase participants' attention to risk information and their understanding of the research study, thereby improving the quality of informed consent; and (3) reduce the rate of "therapeutic misconceptions," defined as patients' failures to appreciate how the goals

and processes of research differ from those of clinical care.

Aim III: The third aim of the RETAIN trial is to evaluate the cost-effectiveness of using financial incentives to increase RCT enrollment rates.

To inform the use or nonuse of incentives requires not only that we understand their scientific and ethical pros and cons, but also their economic costs. To further guide investigators' and funders' decisions regarding incentive use, we will assess the incremental costs relative to the incremental time saved if an otherwise identical RCT was conducted with versus without financial incentives.

b. Primary Outcome Variable

The primary outcome is the proportion of people assigned to each incentive amount that consent to participate in two parent RCTs (see Section 4. Study Organization).

c. Secondary Outcome Variables

1. Attitudes towards research: Attitudes towards research will be measured using the Research Attitudes Questionnaire-7 (RAQ-7).[52] The RAQ has high internal consistency and factorial validity.[53,54] We will measure the RAQ prior to disclosure of incentives in order to 1) assess patients' broad reasons to participate in research or not without being biased by prior discussions of payment 2) assess whether the hypothesized relationship between RAQ score and the odds of enrolling is modified by incentives. The presence of such effect modification would suggest that incentives represent undue inducements.
2. Attention to the informed consent document: Attending more carefully to informed consent documents may promote informed choice. [55] Visual focus has been established as a measure of attention in several settings, and has been associated with peoples' choices[56,57]and subsequent recall. [58] We will assess 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 will include the time – to the second – at which the participant moved to another section through a timestamp. The primary measure of this assessment will be time spent on the risk section; the secondary measure will be total time spent on the consent form.
3. Perceived risks of the research: Perceived risks of the research will be measured by a modified 9-item "compared riskiness" scale, which assesses perceptions of research risk.[8]
4. Incidence of therapeutic misconceptions: It has been hypothesized that the use of financial incentives could reduce therapeutic misconceptions, 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 will test the hypothesized benefit of research incentives by measuring the incidence of therapeutic

misconceptions in each incentive arm. We will assess this outcome with a 4-item therapeutic misconceptions tool, developed by External Advisory Board member, Dr. Scott Kim. [59-61]

5. Understanding of the trial: In preliminary work, we have shown that research incentives may encourage potential participants to spend more time learning about study elements.[7,27] To assess whether increased attention translates into improved understanding of the trial, we will use a 6-item Trial Elements Quiz, featuring core elements of the parent trial's consent form.

6. Perceptions of influence or coercion: To measure general perception of coercion and voluntariness of research participation, we will use the five-item Perceived Coercion Scale of the MacArthur Admission Experience Survey[62]. 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.

7. Retention through the end of treatment sessions: To assess the impact of incentives on retention status in the protocol, we will disburse payment in two installments- one as soon as possible after debriefing and one during the patient's last week of treatment therapy or study intervention. The denominator for analyses of this outcome will be all those who received the first payment. We will assess whether patients completed their treatment, and if not, reasons for non-completion.

Please see Section 8.f. Administration of Survey Instruments and for additional information on the Study Instruments used to measure outcomes for the RETAIN trial.

4. Study Organization

a. RETAIN Infrastructure

The RETAIN study infrastructure is supported by two individual parent trials among two different patient populations:

4) The Behavioral Activation and Varenicline for Smoking Cessation in Depressed Smokers Study, or **BASC**, which tests two behavioral interventions in combination with Chantix in a population of daily smokers with current or lifetime major depressive disorder (BASC). The primary outcome of this trial is point-prevalence abstinence post target quit date (NCT 02378714).

5) The Mobility, Outcomes, and Validated Experiences Incentive Trial, or **MOVE IT**, which targets adults admitted for inpatient care on medicine or oncology floors on 6 wards of the Hospital of the University of Pennsylvania. The study aims to examine the impact of a hospital-implemented mobility protocol for general medical and cancer patients using wearable technology. The primary outcome is the change in mean daily step count from the baseline period (week 1 post-discharge) to the intervention period (weeks 2-13 post-discharge)

(NCT03321279).

RETAIN procedures have been layered on each study to maximize practicability for parent trial research staff and to align with the scientific goals of each parent trial. Key differences between the RETAIN study design in the context of the three parent trials are further described in Section 5. Study Design.

b. Research Team

The University of Pennsylvania research team includes investigators with expertise in research ethics, clinical trials, biostatistics, health economics, and in the use of financial incentives to motivate a variety of health-related behaviors.

Dr. Scott Halpern (PI) is Professor of Medicine, Epidemiology, and Medical Ethics & Health Policy at Penn, Director of the Palliative and Advanced Illness Research (PAIR) Center, and a member of the Steering Committee for the Center for Health Incentives and Behavioral Economics (CHIBE) at the Leonard Davis Institute of Health Economics. He has considerable expertise in the design, ethics, and recruitment barriers of clinical trials, in leading RCTs of financial incentives to modify health behaviors, and in the ethics of using behavioral economic approaches, including incentives, to modify health-related decisions.

Dr. Kevin Volpp (Co-I) is Director of the CHIBE and PENN-CMU Roybal P30 Center on Behavioral Economics and Health. He has successfully completed numerous NIH-funded RCTs of financial incentives to modify health-related behaviors.

Dr. Jason Karlawish (Co-I), Professor of Medicine and Medical Ethics & Health Policy, is one of the nation's leading scholars on patient capacity to consent to research and decisions to enroll in trials. He has extensive experience using many of the instruments to be employed in this study, and is an expert in interpreting the data they produce.

Dr. Frances Barg (Co-I) is Associate Professor of Family Medicine and Co-Director of Penn's Mixed Methods Research Lab. She has great expertise in the use of qualitative methods in medical research and will work closely with Dr. Halpern to oversee the conduct of semi-structured interviews, once implemented, to assess patients' motivations for participating in the RCT.

Dr. Daniel Polsky (Co-I) is Professor of Medicine and Executive Director of the Leonard Davis Institute of Health Economics. He is a leading authority on economic analyses within RCTs, and will guide our analysis of the cost-effectiveness of incentives for RCT enrollment.

Dr. Alisa Stephens-Shields (Co-I), Assistant Professor of Biostatistics in Biostatistics and Epidemiology at the University of Pennsylvania, will be the principal biostatistician for this RCT. She has significant expertise in clinical trials and longitudinal data analysis.

<u>Site Principal Investigators</u>

<u>BASC</u>

Dr. Brian Hitsman (Co-I), Associate Professor of Preventive Medicine and Psychiatry and Behavioral Sciences at Northwestern University, is the Principal Investigator for the NCI-funded parent study Behavioral

Activation and Varenicline for Smoking Cessation in Depressed Smokers Study (BASC). Dr. HItsman will lead BASC parent trial research staff at the Northwestern site in RETAIN recruitment efforts.

Dr. Robert Schnoll (Co-I), Associate Professor of Psychology in Psychiatry at the University of Pennsylvania is Site Principal Investigator for the NCI-funded parent study Behavioral Activation and Varenicline for Smoking Cessation in Depressed Smokers Study (BASC). Dr. Schnoll will lead BASC parent trial research staff at the Penn site in RETAIN recruitment efforts. Together with Co-I Hitsman, Dr. Schnoll will work with Dr. Halpern to address any issues that arise with recruitment, study execution, or data monitoring.

MOVE IT

Dr. Ryan Greysen (Co-I), Chief of the Section of Hospital Medicine in the Division of General Internal Medicine and an Assistant Professor of Medicine at the Perelman School of Medicine at the University of Pennsylvania, is the Principal Investigator for the Mobility, Outcomes, and Validated Experiences Incentive Trial, or MOVE IT. Dr. Greysen will oversee recruitment in the inpatient hospital wards for the MOVE IT-RETAIN partnership, in collaboration with Drs. Patel (Co-I) and Halpern.

Dr. Mitesh Patel (Co-I) is an Assistant Professor of Medicine and Health Care Management at the Perelman School of Medicine and The Wharton School at the University of Pennsylvania is the Co-Investigator for the Mobility, Outcomes, and Validated Experiences Incentive Trial, or MOVE IT.

c. Participating Parent Trial Sites

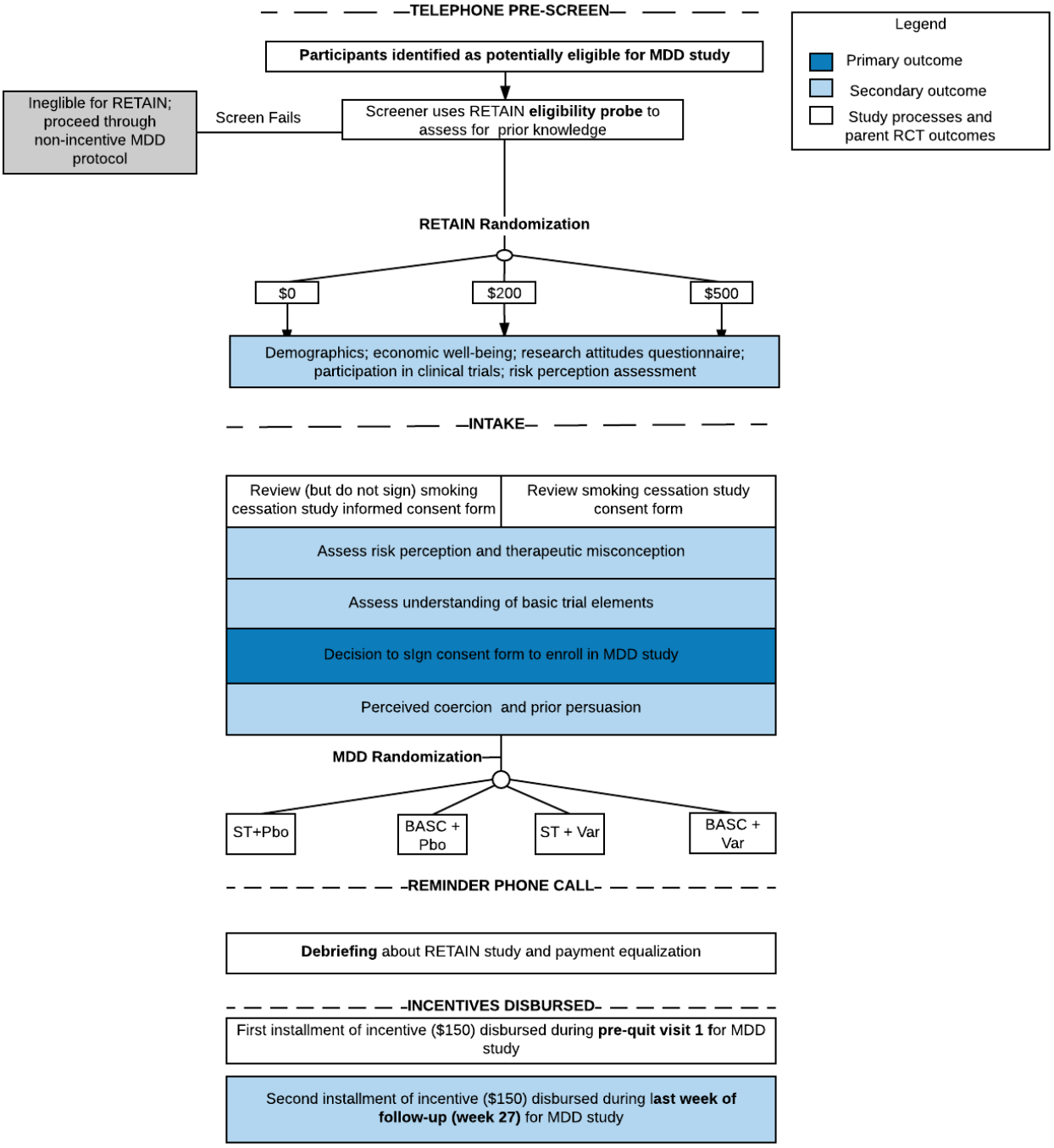
Parent Trial	Site Name	Location
BASC	Northwestern University	Chicago, IL 60611
	The University of Pennsylvania	Philadelphia, PA 19104
MOVE IT	The Hospital of the University of Pennsylvania	Philadelphia, PA 19104

The RETAIN trial will be conducted at two sites participating in the BASC parent trial, Northwestern University and the University of Pennsylvania; and one site participation in the MOVE IT parent trial, the Hospital of the University of Pennsylvania. These institutions are imbued with substantial research infrastructures and offer close proximity of site PIs to the clinics from which patients will be recruited. Each parent trial supports research staff; in collaboration with the Site PIs, the parent trial research staff will carry out the protocol at their respective institutions.

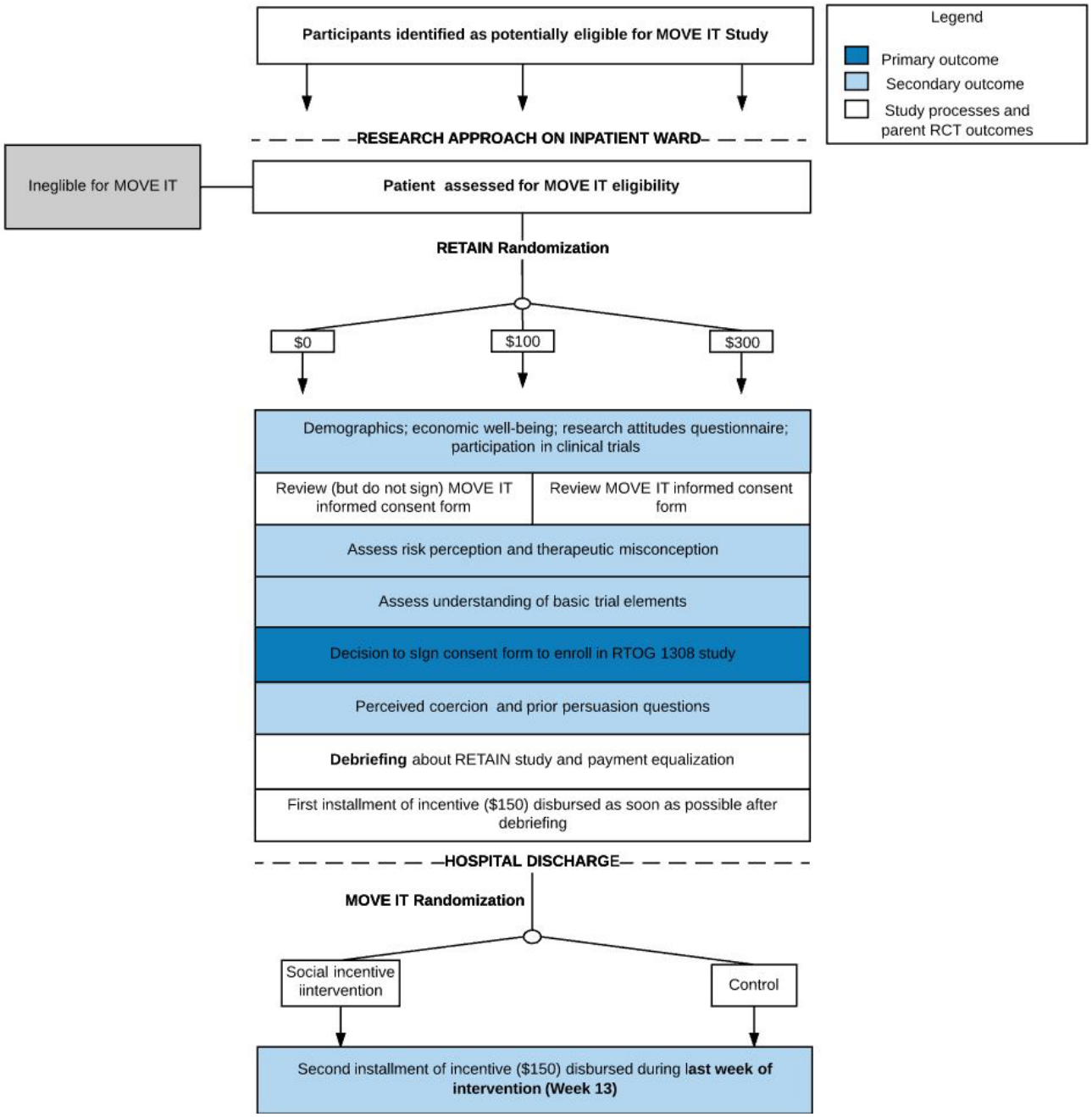
5. Study Design

This study is a prospective randomized controlled trial nested within two randomized controlled trials.

a. BASC Schema



b. MOVE IT Schema



c. Key Study Design Elements across Parent Trials

Key elements in study design across thetwo parent trials are highlighted in the table and figure below.

	BASC	MOVE IT
Is there a separate step to screen for RETAIN-specific eligibility? Please see Section 8.b. Eligibility.	**Yes** Patients will be probed for prior knowledge of incentive randomization, equalization, or the maximum amount offered under RETAIN.	**No**
Do patients actively consent to the RETAIN trial? Please see Section 8.d.	**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 Please see Section 6.d. Subject Remuneration.	**$200**	**Not applicable**
Incentive levels Please see Section 7. Randomization.	Low: **$0** Middle: **$200** High: **$500**	Low: **$0** Middle: **$100** High: **$300**
Debriefing Plan Please see Section 8.h.	**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 Please see Section 6.d Subject Remuneration.	**$300 in two $150 installments, plus up to**	**$300 in two $150 installments**

	$200 from individual session/travel payments.[2]	

d. Duration

Patient recruitment began in August 2016. The trial is slated to conclude June 30, 2020, following the development of a manuscript and dissemination of our findings.

i. BASC

RETAIN procedures will be conducted over two phone calls and one in-person visit across one day to three weeks, depending on the intake scheduling capacity of the Penn and Northwestern clinics. RETAIN procedures will commence during the initial pre-screening eligibility assessment for BASC participants, which takes place before participants' first in-person or "intake" visit with BASC research staff. This phone assessment, which reduces the likelihood that BASC participants will attend an intake session only to learn that they are ineligible, is a pre-screening encounter during which participants first learn basic details of the BASC trial. If eligible for RETAIN, they will be randomized and complete the first set of RETAIN assessments over the phone. RETAIN assessments will take 10 additional minutes during the initial phone eligibility call (see Section 8.f. Administration of Survey Instruments).

Participants who pass the BASC pre-screening on the phone will schedule a baseline intake visit. During the baseline intake visit, RETAIN assessments, including the BASC consent process, will constitute 20-30 additional minutes of the encounter. Next, for all consenting BASC participants who have been randomized and enrolled to RETAIN, research staff will place a reminder call immediately prior to their first visit once enrolled on the study; during this call, all RETAIN-randomized, BASC-consented patients will be debriefed and learn of the payment procedures. The debriefing process will take 10-15 minutes during the reminder call. In total, we do not expect the length of a subject's participation time in the study will exceed two hours.

ii. MOVE IT

RETAIN procedures will commence during clinical research coordinators' initial encounter with patients on the hospital ward. The clinical research coordinator will administer all RETAIN assessments in one encounter (see Section 8.f. Administration of Survey Instruments). Study participants will spend approximately 30-75 minutes of their time to complete the questionnaires and the MOVE IT consent process. Following consent, participants will be debriefed and compensation will be arranged during the same encounter. We anticipate that the debriefing and payment process will take approximately 20-25

[2] The 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 the RETAIN study, 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 by the parent trial research staff.

minutes. In total, we do not expect the length of a subject's participation time in the study will exceed two hours.

6. Subject Recruitment

Recruitment for the RETAIN study is intricately linked to recruitment for the parent RCTs. No recruitment efforts outside the parent trials' efforts will occur. Specific measures will be taken to ensure that patients who are exposed to RETAIN procedures by word-of-mouth (and BASC) or during their inpatient stay (MOVE IT) are screened out or not approached for the RETAIN study.

a. Accrual

During the 44-month period of the trial, 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 roughly 1,778 patients in RETAIN overall, but RETAIN data associated with each of the 2 parent trials will be analyzed separately. Within each parent trial, we anticipate that 50% of RETAIN patients (288 of 576) will choose to enroll in the parent trial. However, we recognize that the total sample sizes and consent rates may vary across the 2 parent trials associated with RETAIN.

b. Key inclusion criteria

The eligibility criteria are:

1) Eligible for parent trial
2) 18 years or older
3) Speaks English

c. Key exclusion criteria

In the BASC partnership, prior knowledge of the incentive randomization or payment equalization used for this trial, which will be assessed with open-ended prompts during the first encounter, is an exclusion criterion.

We will not assess for prior knowledge in the inpatient MOVE IT study population. However, only one patient per room will be approached for the MOVE IT study to protect against contamination.

d. Subject remuneration

i. BASC

Prospective participants who are not eligible, randomized, and enrolled in RETAIN but consent to the BASC parent trial receive $200 in time, effort, and travel payments. Participants who are eligible,

randomized, and enrolled in RETAIN and consent to the BASC parent trial will receive a total of $500 (see Section 8.d. Informed Consent for RETAIN in BASC and MOVE IT and Section 8.g. Parent Trial Informed Consent); $300 of this payment derives from the RETAIN incentive payment, while $200 derives from the non-RETAIN BASC time, effort, and travel payment. Participants will receive the incentives payment in two installments. They will receive the first payment ($150) as soon as possible after debriefing, during their first in-person visit on trial (Pre-Quit 1). They will receive the second payment ($150) during their final week of treatment for the BASC trial (Week 27). Participants who are taken off the BASC study for medical reasons will receive full compensation. If participants withdraw from the study for personal reasons, they will not receive the second payment.

ii. MOVE IT

Patients who are not eligible for MOVE IT will not be paid. Participants who are eligible for MOVE IT, enrolled in RETAIN, and consent to the study will receive the payment in two installments (see Section 8.d. Informed Consent for RETAIN in BASC and MOVE IT). They will receive the first payment ($150) as soon as possible after debriefing; they will receive the second payment ($150) during their final week of participation (week 13). Participants who are taken off the MOVE IT study for medical reasons will receive full compensation. If patients withdraw from the study for personal reasons, they will not receive the second payment.

e. Payment Equalization

During the debriefing session, the parent trial staff will explain that all RETAIN- and parent trial-enrolled participants will receive the full high-level incentive payment ($300 in BASC (see Section 6.d.), and $300 in MOVE IT) in two installments. Such payment equalization is necessary because it promotes fairness by rewarding people equally for making equal contributions to the parent RCTs.

7. Randomization

a. Groups

Subjects enrolled in RETAIN will be randomized into three groups. Depending on which group they've been assigned, subjects will be presented with one of three parent trial consent forms in both electronic and paper formats (see Section 8 Study Procedures). The parent trial consent forms will display three different incentive amounts (low-, middle-, or high-level incentive). Consent 1 (low-level incentive arm) will include a paragraph on the first page that will briefly state what the study is about and indicate to patients that participation in the study is voluntary and patients will not be paid if they choose to participate. The consent form will indicate that participants will not be paid under the standard section, "Will I be paid for taking part in this study?" Consents 2 (middle-level incentive arm) and 3 (high-level incentive arm) will include a paragraph on the first page that will briefly state what the study is about and indicate that participation is voluntary and patients will be paid the incentive (middle- or high-level) if they choose to participate. The consent form will also include payment information under the

standard section, “Will I be paid for taking part in this study?” that describes the level. Consents 2 and 3 will also include information regarding the impact on compensation if patients stop taking part in the study under the standard section (BASC). During debriefing, all participants enrolled in RETAIN and their respective parent trials will learn of their assignment to one of three groups.

b. Assignment

Participants will be randomized to the 3 experimental arms (low-, middle-, and high-level incentive) in equal, 33.3% probabilities. A Penn analyst will implement block randomization stratified by site in the BASC parent trial and stratified by clinical research coordinator in the MOVE IT trial. The trial’s primary statistician on the Penn research staff will provide a block randomization scheme for each clinical research coordinator (MOVE IT) and will upload a CSV file to the REDCap randomization module. He/she will also provide a block randomization scheme for each site for the Access Data Management System (BASC) (see Section 10.a.1. Data Management – BASC). The parent trial research staff will respond to initial eligibility prompts n the REDCap software through an initialization step and will immediately receive the randomization assignment for that participant. Randomization will take place in the DMS for the BASC trial. This will allow them to message to the participant the appropriate incentive level for participation in the parent trial, and present the correct paper consent based on their arm assignment (see Sections 8.g. Parent Trial Informed Consent).

i. BASC

Randomization and group assignment occurs after pre-screening data are collected and RETAIN eligibility probes are administered on the eligibility pre-screening call for the BASC parent trial (see Section 8.e.2 Administration of Survey Instruments – BASC). Research staff will know group assignment when patients are first introduced to the BASC trial on the phone in order to message the assigned payment ($0, $200, $500) for the participant. Participants who are deemed preliminarily eligible will schedule an intake session, where they will view the electronic BASC parent trial consent form ($0, $200, or $500) and receive a paper copy of the form with respective incentive information.

ii. MOVE IT

Randomization and group assignment occur after MOVE IT screening steps (see Section 8.e.3 Administration of Survey Instruments – MOVE IT) following clinical research coordinators’ brief introduction to the study upon entering patients’ hospital room. Clinical research coordinators will randomize patients and know the group assignment as they complete the recruitment script and assess patients’ interest in learning about the MOVE IT trial. Assignment occurs prior to registering the patient in the Way to Health platform used for survey administration.

8. Study Procedures

a. Screening

In the BASC study, final determination of parent trial eligibility may not take place until labs are conducted at the baseline intake session, following participants' signature of the parent trial consent form. However, initial eligibility screening on the pre- screen eligibility call will enable the BASC research team to determine which participants may be assessed for RETAIN eligibility.

In the MOVE IT study, clinical research coordinators will pre- screen participants for parent trial eligibility prior to the initial approach on the inpatient wards. However, final eligibility determination will take place immediately after coordinators' initial approach once smartphone ownership and patients' participation status in other physical activity trials is ascertained.

a. Eligibility

Using methods employed by PI Halpern in several prior studies,[29,30,64] parent trial research staff will use prompts to assess participants' prior knowledge about the RETAIN study in the BASC study. Prompts will not be used in the MOVE IT study, as we do not anticipate contamination among patients on the general medicine and oncology wards of the hospital; no two patients will be approached in the same room at once; and readmitted patients will not be re-approached.

b. Inclusion of Women and Minorities

No participants will be excluded from study participation based on gender, race, or ethnicity. We expect that enrollment of participants from The University of Pennsylvania Perelman Center for Advanced Medicine, Northwestern University out-patient clinics and the Hospital of the University of Pennsylvania inpatient clinics will result in study populations that closely reflect the underlying outpatient populations at these facilities in terms of gender, race, and ethnicity. These populations are also reflective of the broader populations of the Philadelphia, Chicago, Houston, St. Louis, and Boston metropolitan areas.

c. Informed Consent for RETAIN in BASC and MOVE IT

The sole informed consent processes used in both BASC and MOVE IT will be for the parent trials (see Section 8.f Parent Trial Informed Consent). Randomization and enrollment to RETAIN in the BASC and

MOVE IT studies will be carried out under a Waiver of Informed Consent, approved by the University of Pennsylvania Review Board. BASC participants deemed eligible for BASC via phone pre-screening and RETAIN. MOVE IT participants will be randomized immediately after eligibility screening in their hospital rooms.

All participants who are randomized and enrolled in RETAIN and consent to the BASC and MOVE IT will be debriefed on the randomization of incentives and the purpose of the RETAIN study will be explained (see Sections 8.g. and 8.h. Debriefing in BASC and MOVE IT, respectively).

d. Administration of Survey Instruments

i. BASC

Procedures for this study will commence during initial pre-screening eligibility assessment via phone for the BASC trial. During this call, all study candidates will complete an initial eligibility assessment with research staff members from the clinical site from which they are being recruited (Northwestern or Penn). Research staff will begin with the BASC eligibility screen survey, which includes basic demographic questions, as well as questions related to participants' endorsement of symptoms of clinical depression. Once a patient is determined to be preliminarily eligible for BASC, the research staff will ask the RETAIN eligibility prompt to assess for prior knowledge of the specific incentives or randomization used for RETAIN. Participants who do not have prior knowledge of the RETAIN incentives or randomization will be randomized by the research staff via the BASC trial's Data Management System (DMS) (see Section 10.a.1 Data Collection and Data Confidentiality – BASC). Prospective participants will then be introduced to BASC study basics and risks and informed that if they are determined to be eligible for the BASC study and participate in the BASC trial, they will receive $0, $200, or $500 for participation.

Prospective participants who have prior knowledge of the incentives or randomization used for RETAIN will not be randomized, enrolled, or receive RETAIN-related messaging on the phone call. They will receive the standard study information regarding session and travel compensation for the BASC trial without RETAIN messaging. For information on remuneration in the BASC trial, see Section 6.d. These participants will not be debriefed or paid the RETAIN incentives.

Before research staff finalize logistical details on the BASC study and schedule intakes for tentatively eligible patients, they will administer several RETAIN-related questionnaires to assess 1) demographics and personal financial well-being, 2) attitudes towards biomedical research, 3) prior experience in research, and 4) perceptions of research risk. The screener will administer these surveys via phone using CRF forms adopted for the RETAIN trial that will later be scanned into the BASC trial's DMS.

Participants who pass the BASC pre-screening will be scheduled to attend a 2-3½ hour Intake session for the BASC trial. During the intake session, BASC research staff at Penn and Northwestern will read a pre-BASC consent script before presenting an electronic image of the BASC informed consent/ HIPAA forms with additional information regarding the RETAIN incentive randomization condition; this electronic

image will be presented via tablet or desktop. By presenting the BASC consent with randomized compensation information electronically, we will assess the amount of time participants spend reading each part of the main trial consent form. Each section (e.g., Study Introduction, Procedures by Visit, Possible Risks and Discomforts, etc.) will be presented as a survey in REDCap. Time-stamp data collected for this REDCap module will be linked by the study ID generated in the BASC Data Management System during candidates' telephone pre-screen call (see Section 10.a.1. Data Collection and Data Confidentiality - BASC).

Once participants finish reading and before signing a paper version of the BASC trial consent, they will complete brief assessments of perceptions of research risk (administered over the telephone pre-screen and again at intake – see Section 9.a. BASC Study Calendar). They will also complete assessments on perceptions of the difference between research and individualized patient care and understanding of the smoking cessation study via a trial elements quiz. All of these measures will be administered via the CRF paper and pencil processes currently used in the BASC trial. The responses to the quiz will be reviewed with participants, during which participants' questions will be answered.

ii. MOVE IT

Clinical research coordinators will identify patients through electronic health record-based screening for the MOVE IT study and preliminarily eligible patients will be approached for recruitment in their hospital rooms.

Using a recruitment script in REDCap, clinical research coordinators will describe a study that aims to help patients improve their mobility and prevent them from needing to return to the hospital. The REDCap-hosted MOVE IT recruitment script will prompt the clinical research coordinator to assess for patient's eligibility in the MOVE IT study through two screening questions. Eligible patients will be randomized in real time to one of three incentives for participation ($0, $100, or $300). The clinical research coordinator will finish reading the recruitment script, indicating the amount participants will be paid for the MOVE IT Trial. Ineligible patients will not be randomized or enrolled on the RETAIN trial.

For patients who are interested in learning more about the MOVE IT study, the MOVE IT clinical research coordinators will proceed to register the participant in the Way to Health platform and administer the tools in Way to Health via tablet (see Section 10.a.3. Data Management- MOVE IT). The patient will be asked to complete several short questionnaires: 1) demographics, 2) personal financial well-being, 2) attitudes towards biomedical research, and 3) prior experience in research.

Once the patient has completed aforementioned tools in Way to Health, the clinical research coordinator will return to the REDCap database and read a pre-consent introduction script before presenting the an electronic image of the MOVE IT informed consent/ HIPAA forms with additional information regarding the RETAIN incentive randomization condition. By presenting the MOVE IT consent with randomized compensation information electronically, we will assess the amount of time

participants spend reading each part of the main trial consent form. Each section will be presented as a survey in REDCap. Time-stamp data collected for this REDCap module will be linked by the study ID generated in Way to Health.

Once participants finish reading and before signing a paper version of the MOVE IT trial paper consent, they will complete brief assessments of perceptions of research risk. They will also complete assessments on perceptions of the difference between research and individualized patient care and understanding of the MOVE IT via a trial elements quiz. All of these measures will be administered via the Way to Health platform on a tablet. The responses to the quiz will be reviewed with participants, during which participants' questions will be answered.

e. Parent Trial Informed Consent (BASC, and MOVE IT)

Parent trial research staff will present the paper consent in conjunction with their review of any questions generated by the participant during their review of the electronic, REDCap-hosted images of the consent form. Next, prospective participants will be asked to either provide consent or decline participation in the parent trials. The research staff will then facilitate participants' completion of the final two surveys (perceived coercion and prior persuasion questions). All participants – no matter their decision – will be asked to complete these two post-consent surveys.

In the BASC and MOVE IT studies, participants who decline consent may seek participation in other trials for smoking cessation or physical activity, respectively.

f. Debriefing in BASC

Participants will be debriefed following their intake eligibility visit once they have signed consent, and they are determined to be fully eligible for the BASC trial. Debriefing will take place on the reminder call before participants' first scheduled visit on trial, called "Pre-Quit 1." The same processes described in Section 8.g. will be used to inform patients of the RETAIN study procedures and process payment per institutional standard. Debriefing in MOVE IT

Participants will be debriefed during the same encounter in which they are approached. The same processes described in Section 8.g. will be used to inform patients of the RETAIN study procedures and process payment per institutional standard.

g. Deception

We believe debriefing remains an essential element of this RCT in which information regarding the random allocation of incentive levels is necessarily withheld during the consent processes. The following justifications support the research team's use of incomplete disclosure in the RETAIN trial:

<u>The use of incomplete disclosure in this study is grounded in the trial's status as minimal risk.</u>

The RETAIN study involves no more than minimal risk to participants for 5 reasons: (1) incentives in the amounts we are proposing are given to patient subjects as part of many ongoing or completed trials;[35] (2) the evidence available to date suggests that the ethical concerns identified with incentives may not arise, (3) we have established robust procedures for monitoring whether those ethical concerns do in fact arise and for stopping the incentives study if so, (4) the patients would be approached to participate in the parent RCTs without the incentive study, and (5) their participation in the RETAIN study will not affect which treatment they receive in the parent RCTs.

<u>To the extent that it is avoidable, the use of deception will have no adverse effects on welfare, and all adverse effects will be minimized.</u>

Adverse events from the incomplete disclosure of the randomization of participants to different levels of incentives will be minimized through the debriefing process. Patients will be debriefed following their decision to enroll in the parent trial immediately before their first treatment visit (BASC)and within the same session as the initial approach (MOVE IT). This debriefing will therefore happen within a few days (at maximum) of the deception, and will provide participants with full disclosure of the research and with an opportunity to withdraw their participation or their data. Patients who decline to participate in the parent trials will not be debriefed. The Principal Investigator will be directly responsible for identifying and reporting adverse events to the IRB of record and respective IRBs at the four sites and the DSMB.

Additional oversight will be provided by the following: (1) a DSMB that will have the flexibility to adjudicate trial continuation or cessation based on a compendium of outcomes data; (2) two advisory boards comprised of experts in relevant disciplines including research ethics and regulations that will assist the investigators in addressing any unforeseen ethical and scientific issues during the trial's conduct.

<u>The value of the study is sufficient to warrant waiving some aspects of the requirement for full disclosure in the informed consent process.</u>

While our study does not provide participants with untrue information and thus does not technically qualify as deception research, it remains necessary for parent trial research staff to withhold information regarding the random assignment of incentive levels during the incentives trial consent process. This RCT will provide important information about the impact of financial incentives on

enrollment in a research study with therapeutic benefit. Because it is taking place within the context of a real RCT and the incentives will be randomly assigned, this will be the first every study to explore how financial incentives impact actual decisions made by patients contemplating participation in a real trial. It will inform the practice of paying human research subjects to participate in studies by providing a new standard by which to adjudicate the process. Specifically, the study is designed to inform the conduct of future human research subjects by providing evidence about how the presence and magnitude of incentives influence enrollment and recruitment efficiency, and whether reasonable but uncertain ethical concerns arise when offering different levels of incentives. In short, the present variability in IRB practices regarding incentive use means, by definition, that either (a) incentives are being underutilized, creating inefficiencies, potentially sacrificing study completion, and thereby curtailing the ability of investigators to fulfill their commitments to research participants; or (b) incentives are being over-utilized, creating threats to autonomous choice or targeting a "research underclass". The current trial is necessary to improve upon this worrisome status quo, and hence has the potential to make the entire practice of clinical trials more ethical.

<u>There is no alternative to address the scientific question in a valid manner but to use deception/incomplete disclosure.</u>

It would not be feasible to address the aims of the study in the context of a real RCT (BASC, and MOVE IT) without the incomplete disclosure related to the random assignment of financial incentives. Indeed, any disclosure about the random assignment of incentives would thwart the ability to measure either the intended or the potential unintended consequences of research incentives. To definitively address the ethics, effectiveness, and cost effectiveness of incentives for research participation, high-quality evidence is needed, and to date, studies of incentives to participate in hypothetical RCTs of common interventions, as well as small studies in non-generalizable cohorts, do not fully answer whether the ethical concerns of financial incentives actually manifest.

<u>Subjects cannot be informed prospectively of the use of deception/incomplete disclosure and consent to its use.</u>

Prospectively informing patients in even a general way would sabotage the goals of the research because it would create a cognitive state (decision-making context) that is fundamentally different from that which future patients encountering future incentives would have at corresponding times. Because this trial is fundamentally about choices made by prospective research participants, and how risks and incentives might modify those choices, any extraneous factors that could also modify decisions or choices must be avoided. Following the debriefing, all eligible patients will be given the opportunity to ask any questions regarding the incentives study. The parent trial nurse/staff will then explain that all participants actually will receive the full $1,200 payment and he or she will detail the plans for disbursement.

9. Study Calendars

The following calendar reflects the procedures as they are described in Section 8.

i. BASC Study Calendar

Study calendar for RETAIN and Behavioral Activation and Varenicline for Smoking Cessation in Depressed Smokers.

Week	**0^{P}**	**0^{C}**	**0^{P}**	**1^{C}**	**27^{P}**
Screening and Eligibility (BASC)	X	X			
RETAIN Eligibility Prompts					
Demographics	X				
Economic Well-Being	X				
Research Attitudes Questionnaire	X				
Prior Research Experience	X				
Compared Riskiness Scale	X				
Informed Consent Administration (BASC Trial)		X			
Compared Riskiness Scale		X			
Therapeutic Misconceptions		X			
Trial Elements Quiz		X			
Review answers + Patient Q &A		X			
Informed Consent Signing (BASC Trial consent)		X			
Perceived Coercion and Prior Persuasion Question		X			
Debriefing			X		
Payment				X [First Installment of 150 disbursed as soon as possible after debriefing]	X [Second Installment of 150 disbursed during final week of treatment]
	P= phone C=clinic visit (in-person session)				

ii. MOVE IT Study Calendar

Study calendar for RETAIN and Mobility, Outcomes, and Validated Experiences Incentive Trial (MOVE IT).

Week	**0^{C}**	**1^{C}**	**13^{M}**
Screening and Eligibility	X		
Demographics	X		

Economic Well-Being	X		
Research Attitudes Questionnaire	X		
Previous Research Experience	X		
Informed Consent Administration (MOVE IT Trial)	X		
Compared Riskiness Scale	X		
Therapeutic Misconceptions	X		
Trial Elements Quiz	X		
Review answers + Patient Q &A	X		
Informed Consent Signing (MOVE IT Trial consent)	X		
Perceived Coercion and Prior Persuasion Question	X		
Debriefing	X		
Payment		X [First Installment of 150 disbursed as soon as possible after debriefing]	X [Second Installment of 150 disbursed during final week of intervention]
	P= phone C=clinic visit (in-person session) M=Mail – no visit or call		

10. Data Management

a. Data Collection and Data Confidentiality

Prudent steps will be taken to ensure that all information will be kept confidential and secure, including medical and survey data as well as social security numbers. Unique patient identifiers will be assigned to each subject locally.

i. BASC

Survey data will be collected via phone and in-person using a Case Report Form format for the RETAIN-BASC partnership. The BASC Penn database manager will oversee the database management system (DMS) for this trial. The DMS is an MS Access database that permits real-time data entry, storage, and QA by secured network remote access and scannable forms, which increase standardization across

personnel.

The DMS generates database tables in a NIH-compliant format, constructs semantic constraints on fields, and is used for data entry, storage, retrieval, and security. The DMS uses session dates to describe procedures and measures to be ascertained. The DMS mimics the appearance of CRFs completed at sessions. Daily backups occur to protect against accidental corruption or deletion. The Penn BASC research staff will compare 100% of hard copy to computer data. Protection of participant privacy is accomplished by minimizing use of identifying information, use of ID numbers rather than participant names, keeping all data in locked files, and strictly limiting access to the dataset that links participant names with ID numbers.

Every touchpoint with participants is "milestoned" (e.g., attended, missed, scheduled) in the trial database to ensure subject tracking through the trial. The RETAIN team will work with the BASC study team to ensure all RETAIN-relevant screening outcomes are adequately milestoned within the DMS.

For measures of time spent reading the BASC parent trial consent form, BASC research staff will use REDCap at the eligibility intake session. BASC research staff will enter the subject and contact database IDs into REDCap to enable linking between databases.

ii. MOVE IT

Survey data will be collected via Qualtrics on the Way to Health platform for the MOVE IT partnership. Penn Medicine Academic Computing Services (PMACS) supports the computing infrastructure that will be used for the MOVE IT study, including the Way to Health web portal. PMACS is a joint effort of the University of Pennsylvania's Abramson Cancer Center, the Cardiovascular Institute, the Department of Pathology, and the Leonard Davis Institute. PMACS provides a secure computing environment for a large volume of highly sensitive data, including clinical, genetic, socioeconomic, and financial information. PMACS requires all users of data or applications on PMACS servers to complete a PMACS-hosted cybersecurity awareness course annually, which stresses federal data security policies under data use agreements with the university. The curriculum includes Health Insurance Portability and Accountability Act (HIPAA) training and covers secure data transfer, passwords, computer security habits and knowledge of what constitutes misuse or inappropriate use of the server. All investigators and research staff with direct access to the identifiable data will be required to undergo annual responsible conduct of research, cybersecurity, and HIPAA certification in accordance with University of Pennsylvania regulations.

All data will be stored and analyzed on institutionally managed and secured servers with access privileges limited to those with a need to know via the use of single-user access passwords and usernames. All study personnel that will use this data are listed on the IRB application and have completed training in HIPAA standards and human subjects research. Whenever possible, direct identifiers will be removed from analysis files.

Screening data, as well as the RETAIN randomization step, scripts, and data collection for time spent reading the MOVE IT parent trial consent form, will be integrated into a REDCap database. The same procedures described in Section 10.a.2 will be used to manage these data. MOVE IT research staff will enter Way to Health Study IDs into REDCap to enable linkage between subject records across different data extracts.

b. Subject Confidentiality

RETAIN data hosted on the REDCap application for this study will use account-based authentication and permission systems to protect confidentiality. An investigator or statistician who logs in will be able to download only de- identified data. Parent trial research staff at the different sites will not be able to access information from other sites; we will put in place data user groups in the REDCap system. Only parent trial research staff responsible for contacting participants for follow-up meetings or responding to questions about the study will be able to view participant names and contact information. This personal information will be used to contact participants if there is an issue with their account, payments, or they contact us with a problem. We will implement multiple, redundant protective measures to guarantee the privacy and security of the participant data. All study data will be stored on the secure/firewalled servers at the University of Pennsylvania. These data servers are maintained in a guarded facility behind several locked doors, with very limited physical access rights. They are also cyber-protected by extensive firewalls and multiple layers of communication encryption. Electronic access rights are carefully controlled by UPenn system managers. We believe this multi-layer system of data security, identical to the system protecting the University of Pennsylvania Health Systems medical records, greatly minimizes the risk of loss of privacy.

c. Subject Privacy

We will collect subjects' names, addresses, phone numbers, and data required for the completion of W-9 forms for subject compensation. All of these data will be stored in a HIPAA-compliant database that conforms to applicable data security standards. Access to all such data will be limited to specifically designated researchers who are responsible for contacting participants for responding to questions and concerns from participants. Subjects will complete study surveys in a secure, private locations at each center with research staff. Social security numbers for all persons to whom incentives are sent will be transmitted in encrypted format to Accounts Payable, which will store the data for W-9 forms. After the social security numbers are no longer needed, they will be deleted from our system.

11.Data and Safety Monitoring

a. Monitoring Plan

The data and safety monitoring plan will have several parts. First, we will develop and implement methods of verifying entered data and of quality control among parent trial research staff who will be directly entering data into the REDCap system. Second, the PI will be directly responsible for identifying and reporting all serious adverse events, protocol deviations/violations and unanticipated events to the IRBs and funding agency promptly, as appropriate. The PI will also report all adverse events, accrual rates, retention rates, and all other logistical issues to the DSMB at least biannually (if there are serious adverse events occur at any time that the investigators feel ought to be brought to the attention of the DSMB sooner, the DSMB can also meet on an ad hoc basis). Third, there will be a DSMB responsible for monitoring the trial, convening for the first time in December 2015 to inform the RETAIN trial planning process.

b. Data and Safety Monitoring Board Members

The Data and Safety Monitoring Board includes the following members:

Jennifer S. Blumenthal-Barby, PhD (Chair): expertise in ethical contexts of human judgment and decision-making in human research.

Salma Jabbour, MD: expertise in radiation oncology with a subspecialty in lung cancer.

Brenda F. Kurland, PhD: expertise in biostatistics with research emphasis on longitudinal and other correlated data.

Jeffrey M. Peppercorn, MD, MPH: expertise in medical oncology with research emphasis on bioethics and health policy, as well as cancer survivorship.

Kim Vernick: member of the University of Pennsylvania's Proton Patient Alumni Program, Patient and Family Advisory Council, and a cancer survivor.

The PI (Scott Halpern), assisted by the project manager, will be responsible for maintaining communication between the DSMB and the individual project staff. The DSMB will be responsible for monitoring the trial and making decisions about the termination of individual study arms or the study itself. The DSMB will review and approve the research protocol. They will also assess the progress of the trial, including the assessment of data quality, participant recruitment, accrual and retention, participant risk versus benefit, and study outcomes. Corresponding recommendations will be issued at all subsequent meetings. These recommendations will be based on the results and discussion of interim analyses, conducted at one-half, and three-fourths of the target same size. DSMB recommendations may be guided by statistical monitoring guidelines. The DSMB may recommend permanent suspension of enrollment, or temporary suspension pending protocol modification. Following each meeting, and the provision of recommendations and the response from the research team, the Principal Investigator and Project Manager will prepare progress reports to be submitted to the University of Pennsylvania Institutional Review Board and any other IRBs participating in the trial. Prior to submission to these IRBs, the progress reports will be approved by the DSMB chair.

c. Stopping Rules

The PI, in consultation with Co-Investigator and Faculty Statistician Dr. Alisa Stephens-Shields, has identified TWO trial stopping rules. The DSMB approved these stopping rules as grounds to terminate the trial:

1. Early evidence of undue inducement that distorts voluntary informed consent. To detect whether incentives represent undue inducement, the research team will test the statistical interaction between incentive size and risk perception on the outcome of enrollment in the parent RCT. A statistically significant interaction, in the direction that risk perception is less strongly associated with enrollment in higher-payment arms, would be grounds for terminating the trial or suspending a trial arm.

2. Early evidence of unjust inducement by preferentially encouraging participation among participants with either (a) lower income, or (b) reduced financial well-being. Two interaction terms will be evaluated in separate models to avoid collinearity. Unjust inducement will be defined as a statistically significant interaction between (a) incentive size and annual household income, or (b) between incentive size and economic well-being, each on the outcome of trial enrollment. One or both of these interactions, if statistically significant in the direction that lower-income persons or persons with reduced economic well-being are more strongly motivated to participate by increasingly large payments, will be considered grounds for terminating the trial or suspending a trial arm.

During the trial we will conduct two interim tests of these interactions to evaluate evidence of undue or unjust inducement. In contrast to the final analyses, which will be structured as tests of non-inferiority, 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. The interim tests will be conducted after 50% and 75% of the data have accrued within both BASC and MOVE IT and use 1-sided significance levels of 0.0055, and 0.0219. The DSMB is empowered to stop the trial early if the lower confidence bound exceeds 2.0, thus protecting against undue or unjust inducement.

The DSMB may also wish to consider increased rates of therapeutic misconception as grounds for early termination of the trial. The research team will compare responses to the trial's measure of the construct of therapeutic misconception across the three trial arms. While no pre-specified statistical monitoring guidelines are proposed for this measure, DSMB members may consult with Dr. Scott Kim, with whom the therapeutic misconception tool for the trial has been developed, for guidance on interpretation of the data provided in the open statistical report.

d. Adverse Events

As this is a minimal risk study, we do not anticipate adverse events; however, we will report all adverse events to the Data and Safety Monitoring Board.

e. Clinicaltrials.gov

The RETAIN trial has been registered on clinicaltrials.gov (NCT02697799). The study profile will be regularly updated on the website and summary results uploaded to make information about the study publicly available and promote transparency.

12.Human Subjects Protection

a. Potential Study Risks

A primary risk to this study is that financial incentives either unfairly induce participants to participate in a trial that they would not otherwise participate in. This is a primary question of this trial. We will convene a data and safety monitoring board (DSMB) in conjunction with NIH to monitor any indication that this is occurring. Our hypothesis is that no population will be unfairly manipulated into participating in a trial that they would not otherwise, and that financial incentives could lead to participants examining the potential risks of a study more closely than they would have otherwise.

Supporting Research

A study led by PI Halpern and Co-I Karlawish assessed 126 hypertensive patients' willingness to participate in RCTs of experimental antihypertensive drugs.[7] We used a 3 x 3 within-subjects factorial design in which hypertensive patients were administered, in random sequence, 9 hypothetical RCTs which differed in their risk level (10%, 20%, or 30% chance of drug-related adverse events) and payment ($100, $1,000, or $2,000 for a 10-week trial). We found that increasing payments motivated greater RCT participation, and that increasing risk levels reduced participation levels ($p < 0.001$ for each). Importantly, patients' participation rates declined equivalently with increasing risk levels across all payment levels studied, and the statistical interaction between risk and payment was not statistically significant ($p=0.30$). This shows that patients were equally sensitive to risk despite very different payment amounts, suggesting that research incentives are not undue inducements.

Furthermore, this study of payments for RCT enrollment,[7] as well as another study by PI Halpern of payments for living kidney donation,[51] counter the notion that payments are unjust inducements. Specifically, in both studies, increasing payment levels were similarly motivating among patients with higher and lower incomes. Indeed, in the RCT participation study,[7] there was an indication that larger payments may preferentially motivate wealthier people to participate (payment-by-income interaction $p=0.09$). The validity of these results is enhanced by the income diversity among the study samples and the substantial statistical power to identify such income-by-payment interactions if they existed.

Co-I Volpp and colleagues asked participants to rate the riskiness of a new technology (transcranial magnetic stimulation) being tested in RCTs after being told they would receive $25 or $1,000 for trial

participation.[8] Participants assigned to review the trials offering $1,000 spent more time reading about study risks and other research aspects (mean = 3.7 minutes) than did patients assigned to trials offering $25 (mean = 1.0 minutes) ($p < 0.01$). Larger incentives also decreased the odds that participants would skip the page of the informed consent form that described study contraindications ($p < 0.05$). These findings suggest that payments alert people to the possibility of risk, and encourage them to learn more about the study.[8] Thus, rather than contravening the goals of informed consent, incentives may actually promote informed decision-making.

Another potential risk is breach of confidentiality and privacy for completion of study surveys. No identifiable data will be reported to anyone outside of the research staff. Due to the compensation in this study, we will be collecting personal information needed for completion of W-9 forms, including social security numbers, for participants receiving incentives. Accidental disclosure of social security numbers could lead to identity theft. Social security numbers will be deleted once they are no longer needed. Names and addresses will be stored in encrypted databases. These data will be viewable only by the parent trial research staff. All other researchers will be able to view only participant ID numbers. Intervention arms will be identified by code letters until both the statistician and PI agree that interim analysis is complete.

b. Potential Study Benefits

There is no direct benefit to patients for participating in the RETAIN trial. Patients may perceive the money as a benefit, but remuneration for research participation is not traditionally considered a benefit justifying human subjects research.[3] Patients may benefit from participation in the parent RCTs. The RETAIN study will provide important information about the impact of incentives on enrollment and decision making, which can inform the conduct of human subjects research more generally. The participants will be debriefed about the purpose of this study and the knowledge to be gained from it.

c. Risk/Benefit Analysis

In light of the tremendous benefits to public health and individuals developing more effective programs, as well as our efforts, outlined above, to mitigate all risks associated with this study, we believe that this study presents a highly favorable risk-benefit ratio for participation.

d. Protective Measures

The first safeguard for protection of human subjects includes an experienced and well-trained study team. Dr. Scott Halpern (PI) is Associate Professor of Medicine, Epidemiology, and Medical Ethics & Health Policy at Penn, Director of the Palliative and Advanced Illness Research (PAIR Center, and Deputy Director of the Center for Health Incentives and Behavioral Economics (CHIBE) at the Leonard Davis Institute of Health Economics. He has considerable expertise in the design, ethics, and recruitment barriers of clinical trials, in leading RCTs of financial incentives to modify health behaviors, and in the

ethics of using behavioral economic approaches, including incentives, to modify health-related decisions.

i. BASC

Northwestern University PI Brian Hitsman, PhD, along with Site PI Robert Schnoll, PhD, of the BASC study, will support the implementation of the RETAIN trial at both participating sites. Dr. Hitsman leads the Nicotine Dependence and Treatment Lab at Northwestern. The lab frequently recruits from high burden populations, including cancer patients. Dr. Hitsman's current collaborations with Penn include the Abramson Cancer Center- sponsored Extended Duration Varenicline for Smoking Among Cancer Patients (NCT02378714) and the NCI-sponsored project described in this report, Behavioral Activation and Varenicline for Smoking Cessation in Depressed Smokers (NCT02378714) – both of which involve Penn colleague Dr. Schnoll, who has also successfully collaborated with the RETAIN PI previously. Both Drs. Hitsman and Schnoll have experience layering social behavioral manipulations onto existing smoking cessation studies to address recruitment challenges, as well as research focuses that are geared toward the recruitment of vulnerable patients.

ii. MOVE IT

Ryan Greysen, MD, MHS, MA, Section Chief of Hospital Medicine, will co-lead the implementation of the MOVE IT study at Penn, in collaboration with Drs. Patel (Co-I) and Halpern. Dr. Greysen's expertise in patient-oriented research targeting vulnerable older adults with multiple comordities-- with particular focus on improving both hospital and transition care--will be leveraged to integrate RETAIN procedures in a way that is at once sensitive to the inpatient care environment and scientifically sound. Dr. Greysen will lead the MOVE IT study protocol with Site PI Mitesh Patel, MD, MBA, MS. An expert in digital health initiatives to improve health outcomes and change health behaviors, Dr. Patel is well-equipped to operationalize the integration of the RETAIN trial into the mobility study at the Hospital of the University of Pennsylvania, having significant content expertise in the use of incentives within a hospital setting.

e. Additional Protective Measures

To guide the ethical and scientific conduct of this study, and to help position the results so that they may have maximal impact on future research efficiency and regulation, we have assembled an External Advisory Board (EAB) and an Internal Advisory Board (IAB). The External Advisory Board includes: Christine Grady, MSN, PhD, Chief of the NIH Clinical Center's Department of Bioethics and Head of the Section on Human Subjects; Scott Kim, MD, PhD, Senior Investigator in the NIH Department of Bioethics; Leslie Wolf, JD, MPH, Professor at the Georgia State School of Law's Center for Law Health and Society; Timothy Coetzee, PhD, Chief Advocacy and Research Officer for the National MS Foundation; and Barbara Langloss, Patient Advocate and an alumna of Penn's Proton Therapy Program. Our Internal Advisory Board includes: Steven Joffe, MD, MPH, pediatric oncologist and Vice Chair of the

Department of Medical Ethics and Health Policy at Penn; Ezekiel Emanuel, MD, PhD, Chair of the Department of Medical Ethics and Health Policy at Penn; and David Festinger, PhD, Adjunct Assistant Professor of Psychiatry at Penn and Direct of the Treatment Research Institute's Section on Law and Ethics Research.

Finally, the debriefing process, delivered by parent trial research staff, is an important element of human subject protection and will ensure that patients (1) understand the recruitment for the parent trial included a study on the effects of incentives on study enrollment; (2) understand they were randomized to receive one of three study incentives (3) understand they were not informed about the RETAIN study to avoid biasing the study results; and (4) understand no further data are to be collected as part of the RETAIN study and the study will complete as soon as the incentives are disbursed.

Additional layers of protection for human subjects include the robust informed consent process (Section 8.d.), exceptional data security (Section 10), and the empowered Data Safety and Monitoring Board (Section 11) all described in detail in this protocol.

13. References

1. Halpern SD. Financial Incentives for Research Participation: Empirical Questions, Available Answers and the Burden of Further Proof. *American Journal of the Medical Sciences.* Oct 2011;342(4):290-293.
2. National Institutes of Health Office of Human Subjects Research. *Guidelines for remuneration of research subjects in the intramural research program and registration in the clinical research volunteer program database. Accessed December 3, 2011 at* http://ohsr.od.nih.gov/info/pdf/InfoSheet20.pdf.
3. Macklin R. 'Due' and 'undue' inducements: On paying money to research subjects. *IRB: a review of human subjects research.* 1981;3(5):1-6.
4. McGee G. Subject to payment? *JAMA.* 1997;278:199-200.
5. McNeil P. Paying people to participate in research: why not? *Bioethics.* 1997;11:390-396.
6. Bentley JP, Thacker PG. The influence of risk and monetary payment on the research participation decision making process. *J Med Ethics.* June 1, 2004 2004;30(3):293-298.
7. Halpern SD, Karlawish JHT, Casarett D, Berlin JA, Asch DA. Empirical assessment of whether moderate payments are undue or unjust inducements for participation in clinical trials. *Archives of Internal Medicine.* 2004;164:801-803.
8. Cryder C, London AJ, Volpp KG, Loewenstein G. Informative Inducement: Study Payment as a Signal of Risk. *Social Science & Medicine.* 2010;70(3):455-464.
9. Altman DG. Statistics and ethics in medical research III: How large a sample? *Br Med J.* 1980;281:1336-1338.
10. Drazen JM, Koski G. To protect those who serve. *New England Journal of Medicine.* 2000;343:1643-1645.
11. Ellenberg SS. Randomization designs in comparative clinical trials. *N Engl J Med.* 1984;310(21):1404-1408.
12. Freiman JA, Chalmers TC, Smith H, Jr, Kuebler RR. The importance of beta, the type II error and sample size in the design and interpretation of the randomized controlled trial: survey of 71 "negative" trials. *N Engl J Med.* 1978;299:690-694.
13. Meinert CL. *Clinical trials: Design, conduct, and analysis.* New York: Oxford University Press; 1986.

14. Nass SJ, Moses HL, Mendelsohn J. *A national cancer clinical trials system for the 21st century: Reinvigorating the NCI Cooperative Group Program.* Washington, D.C.: The National Academies Press; 2010.

15. Freedman B. Scientific value and validity as ethical requirements for research: A proposed explication. *IRB: Rev Hum Subjects Res.* 1987;9(6)):7-10.

16. Halpern SD, Karlawish JHT, Berlin JA. The continuing unethical conduct of underpowered clinical trials. *JAMA.* 2002;288:358-362.

17. Kramer MS, Shapiro SH. Scientific challenges in the application of randomized trials. *JAMA.* 1984;252(19):2739-2745.

18. Nathan RA. How important is patient recruitment in performing clinical trials? *Journal of Asthma.* 1999;36(3):213-216.

19. Hunningshake DB, Darby CA, Probstfield JL. Recruitment experience in clinical trials: Literature summary and annotated bibliography. *Controlled Clinical Trials.* 1987;8:6S-30S.

20. Probstfield JL, Wittes JT, Hunningshake DB. Recruitment in the NHLBI population-based studies and randomized clinical trials: data analysis and survey results. *Controlled Clinical Trials.* 1987;8:141S-149S.

21. Vollmer VM, Osborn ML, Hertert S, et al. Recruiting hard-to-reach subjects: Is it worth the effort? *Controlled Clinical Trials.* 1994;15:154-159.

22. Emanuel EJ, Schnipper LE, Kamin DY, Levinson J, Lichter AS. The costs of conducting clinical research. *J Clin Oncol.* Nov 15 2003;21(22):4145-4150.

23. Caldwell PH, Hamilton S, Tan A, Craig JC. Strategies for increasing recruitment to randomised controlled trials: systematic review. *PLoS Med.* 2010;7(11):e1000368.

24. Donovan J, Mills N, Smith M, et al. Quality improvement report: Improving design and conduct of randomised trials by embedding them in qualitative research: ProtecT (prostate testing for cancer and treatment) study. *BMJ.* October 5, 2002 2002;325(7367):766-770.

25. Sugarman J, Kass NE, Goodman SN, Perentesis P, Fernandes P, Faden RR. What patients say about medical research. *IRB: A review of human subjects research.* 1998;20(4):1-7.

26. Wendler D, Krohmal B, Emanuel EJ, Grady C, Grp E. Why patients continue to participate in clinical research. *Archives of Internal Medicine.* Jun 23 2008;168(12):1294-1299.

27. Halpern SD. Prospective preference assessment: A method to enhance the ethics and efficiency of randomized controlled trials. *Controlled Clinical Trials.* 2002;23:274-288.

28. Shah A, Efstathiou JA, Paly JJ, et al. Prospective preference assessment of patients' willingness to participate in a randomized controlled trial of intensity-modulated radiotherapy versus proton therapy for localized prostate cancer. *International Journal of Radiation Oncology*Biology*Physics.* 2012;83:E13-E19.

29. Carroll R, Antigua J, Taichman DB, et al. Pulmonary arterial hypertension patients' willingness to participate in randomized clinical trials of novel therapies. *Clinical Trials.* 2010;9:348-357.

30. Halpern SD, Karlawish JHT, Casarett D, Berlin JA, Townsend RR, Asch DA. Hypertensive patients' willingness to participate in placebo-controlled trials: Implications for recruitment efficiency. *American Heart Journal.* 2003;146:985-992.

31. Slomka J, McCurdy S, Ratliff EA, Timpson S, Williams ML. Perceptions of financial payment for research participation among african-american drug users in HIV studies. *Journal of General Internal Medicine.* Oct 2007;22(10):1403-1409.

32. Stunkel L, Grady C. More than the money: A review of the literature examining healthy volunteer motivations. *Contemporary Clinical Trials.* May 2011;32(3):342-352.

33. Dunn LB, Kim DS, Fellows IE, Palmer BW. Worth the risk? Relationship of incentives to risk and benefit perceptions and willingness to participate in schizophrenia research. *Schizophr Bull.* Jul 2009;35(4):730-737.

34. Dickert N, Emmanuel E, Grady C. Paying research subjects: An analysis of current policies. *Annals of Internal Medicine.* 2002;136:368-373.

35. Grady C, Dickert N, Jawetz T, Gensler G, Emanuel E. An analysis of U.S. practices of paying research participants. *Contemp Clin Trials.* 2005;26:365-375.

36. Emanuel EJ. Ending concerns about undue inducement. *Journal of Law Medicine & Ethics.* Spr 2004;32(1):100-105.

37. Emanuel EJ. Undue inducement: Nonsense on stilts? *American Journal of Bioethics.* Sep-Oct 2005;5(5):9-13.

38. Emanuel EJ, Currie XE, Herman A. Undue inducement in clinical research in developing countries: is it a worry? *The Lancet.* 2005;366(9482):336-340.

39. Hyun I. Fair payment or undue inducement? *Nature.* 2006;442(7103):629-630.

40. Martin R. Undue inducement in clinical research. *Lancet.* 2005;366(9482):275-276.

41. Casarett D, Karlawish JHT, Asch DA. Paying hypertension research subjects. *Journal of General Internal Medicine.* 2002;17:650-652.

42. Wilkinson M, Moore A. Inducement in research. *Bioethics.* 1999;11:373-389.

43. Elliott C, Abadie R. Exploiting a research underclass in phase 1 clinical trials. *New England Journal of Medicine* 2008;358:2316-2317.

44. Denny CC, Grady C. Clinical research with economically disadvantaged populations. *Journal of Medical Ethics.* July 1, 2007 2007;33(7):382-385.

45. Viens AM. Socio-economic status and inducement to participate. *American Journal of Bioethics.* 2001;1(2).

46. Wertheimer A. Should we worry about money? *Rethinking the ethics of clinical research*. New York: Oxford University Press; 2011:117-190.

47. Bernstein M. Payment of research subjects involved in clinical trials is unethical. *Journal of Neuro-Oncology.* Jul 2003;63(3):223-224.

48. Burt RA. On gnats, camels, and payment to research subjects: A comment. *Journal of Medicine and Law.* 2005;9:25-30.

49. Grant RW, Sugarman J. Ethics in human subjects research: Do incentives matter? *Journal of Medicine and Philosophy.* Dec 2004;29(6):717-738.

50. 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.

51. Halpern SD, Raz A, Kohn R, Rey M, Asch DA, Reese P. Regulated payments for living kidney donation: an empirical assessment of the ethical concerns. *Ann Intern Med.* Mar 16 2010;152(6):358-365.

52. Kim S, Kim H, McCallum C, Tariot P. What do people at risk for Alzheimer disease think about surrogate consent for research? *Neurology.* 2005;65:1395–1401.

53. Karlawish J, Rubright J, Casarett D, Cary M, TenHave T, P S. Older adults' attitudes toward non-competent subjects participating in Alzheimer's research. *American Journal of Psychiatry.* 2009;166(2):182-188.

54. Muroff J, Hoerauf S, Kim S. Is psychiatric research stigmatized? An experimental survey of the public. *Schizophrenia Bulletin.* 2006;32:129-136.

55. Henderson GE. Is Informed Consent Broken? *American Journal of the Medical Sciences.* Oct 2011;342(4):267-272.

56. Bialkova S, van Trijp HCM. An efficient methodology for assessing attention to and effect of nutrition information displayed front-of-pack. *Food Quality and Preference.* 2011;22:592–601.

57. Pieters R, Warlop L. Visual attention during brand choice: The impact of time pressure and task motivation. *International Journal of Research in Marketing.* 1999;16:1-16.

58. Munafò MR, Roberts N, Bauld L, Leonards U. Plain packaging increases visual attention to health warnings on cigarette packs in non-smokers and weekly smokers but not daily smokers. *Addiction.* 2011;106(8):1505–1510.
59. Kim SH WR, De Vries R, Kim H, Holloway R, Kieburtz K. Could the High Prevalence of Therapeutic Misconception Partly Be a Measurement Problem? *IRB: Ethics & Human Research* 2015;37(4):11.
60. Kim SH SL, Wilson RM, Frank SA, Holloway RG, Keiburtz K, De Vries RG. An Approach to Evaluating the Therapeutic Misconception. *IRB: Ethics & Human Research.* 2009;31(5):7-14.
61. Pentz RD, White M, Harvey RD, et al. Therapeutic misconception, misestimation and optimism in subjects enrolled in phase I trials. *Cancer.* 2012;18(118):4571-4578.
62. Gardner W, Hoge SK, Bennett N, et al. Two scales for measuring patients' perceptions for coercion during mental hospital admission. *Behavioral Sciences and the Law* 1993;11:307-321.
63. Shea JA, Micco E, Dean L, McMurphy S, Schwartz SJ, Armstrong K. Development of a revised health care system distrust scale. *Journal of General Internal Medicine.* 2008;6(23):727-732.
64. Israni AK, Halpern SD, McFadden C, et al. Willingness of dialysis patients to participate in a randomized controlled trial of daily dialysis. *Kidney International.* Mar 2004;65(3):990-998.
65. Shea JA ME, Dean LT, McMurphy S, Schwartz JS, Armstrong K. . Development of a Revised Health Care System Distrust Scale. *Journal of General Internal Medicine.* 2008;26(6):727-732.

IV. Original Statistical Analysis Plan

1. Background and rationale

This study is designed to provide the first-ever real-world tests of a broad range of intended and unintended consequences of financial incentives for research participation. It will do so through the conduct of two separate, but similarly designed, embedded randomized trials within actual parent clinical trials. This Original Statistical Analysis plan was finalized after the decision to remove the RETAIN collaboration with RTOG1308, but before the enrollment of participants in BASC or MOVE IT. It is our hope the findings from this study will inform research regulations and guide the use of incentives in future RCTs so as to expedite medical innovation and improve health.

2. Objectives and hypotheses

The aims of this study are to (1) determine if the ethical concerns with incentives for research participation actually manifest; and (2) assess the possible scientific and ethical benefits of financial incentives for RCT participation.

We hypothesize that research incentives will:

- Augment participants' perceptions of risk without disproportionately encouraging economically disadvantaged participants to enroll
- Demonstrate an increased enrollment fraction in the parent trials, thereby enhancing the scientific value and validity of the research by augmenting the precision of the studies

3. Design and randomization

RETAIN comprises two prospective randomized controlled trials, embedded within two parent trials conducted in parallel, each comparing three intervention arms. Arms vary by the amount of the financial incentives that are offered to potential participants. Amounts offered differ on a per trial basis determined by the relative time and effort being asked of the participant for each parent trial. Assignment to arms is determined by computerized random-number generation with block randomization using variable block sizes of 3 and 6. Participants in both embedded trials have a 33.3% probability of being assigned to each RETAIN arm.

a. BASC Trial

- The Behavioral Activation and Varenicline for Smoking Cessation in Depressed Smokers Study (BASC) (NCT 02378714)
- Tests two behavioral interventions in combination with Varenicline in a population of daily smokers with current or lifetime major depressive disorder
- Eligible patients are randomized to receive inform consent forms offering $0, $200, or $500 incentives for participation
- Patients are enrolled at The University of Pennsylvania and Northwestern University; randomization is stratified by site

b. MOVE IT Trial

- The Mobility and Outcomes for Validated Evidence – Incentive Trial (MOVE IT) (NCT 03321279)
- 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
- Eligible patients are randomized to receive inform consent forms offering $0, $100, or $300 incentives for participation
- Patients are enrolled at the Hospital of the University of Philadelphia by a team of clinical research coordinators; randomization is stratified by clinical research coordinator

By necessity, clinical research coordinators administering the consent process in both parent trials are unmasked to the incentive information being messaged to prospective participants. The introduction to the study and the informed consent process have been robustly scripted for research staff involved in both trials to ensure that messaging is consistent and biases are minimized.

4. Population

Eligibility for RETAIN is contingent on eligibility for the BASC and MOVE IT parent trials.

- Adults age 18 years or older who are daily smokers with current or lifetime major depressive disorder without psychotic features (BASC)
- Adults age 18 years or older who are admitted for inpatient care to the Hospital of the University of Pennsylvania (HUP) on medicine or oncology floors (MOVE IT)

Patients randomized to RETAIN must be:

- Eligible for parent RCT
- 18 years or older
- English-speaking

In the BASC trial, prior knowledge of the incentive randomization or payment equalization used for this study, which will be assessed with open-ended prompts during the first encounter, is an exclusion criterion. We will not assess for prior knowledge in the inpatient MOVE IT study population. However, only one patient per hospital room will be approached for the MOVE IT study to protect against contamination.

5. Primary outcome and analytic method

a. Primary outcome

The primary outcome is the proportion of participants assigned to each incentive amount that consent to enroll in each of the two parent RCTs.

b. Primary analytic sample

Intention-to-treat (ITT) approach such that the analytic sample will include all patients randomized in the RETAIN trial, even if ultimately deemed ineligibile for the parent trials.

c. Primary analysis

We will first assess bivariate relationships of incentives with the primary outcome using 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 Holm method.

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. To adjust for chance covariate imbalance among

arms, primary analyses will include covariates (see Table 1) in multivariable models if they are significantly associated with the intervention arm and predictive of enrollment in the parent trials in bivariate analyses. 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. In all analyses related to the BASC parent trial, 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.

Our analyses to rule out undue and unjust inducements entail three primary covariates: risk perception, annual household income, and economic well-being. All models will use enrollment in the parent trial as the outcome. To determine if 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. We will test two interactions, each in a separate model to avoid collinearity, to determine if incentives represent unjust inducements: that between incentive size and the primary covariate of annual household income, and that between incentive size and the primary covariate of economic well-being. All analyses will be stratified by parent study.

Analyses of interaction terms will be structured as tests of non-inferiority. The null hypothesis, for both trials, will be that the use of incentives meets criteria for undue or unjust inducement. We can 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). Said a different way, our analyses are designed to determine if we can exclude the possibility that incentives represent undue or unjust inducements if the resulting interaction terms are sufficiently small. Specifically, we will use one-sided alpha levels of 0.05 to exclude, with 95% confidence, the possibility that any of these interaction odds ratios are >2.0.

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 used in these studies, we will adjust for their influence by entering time as a covariate, modeled as a spline. We will evaluate potential effect modifiers (variables in Table 1) using stratified analyses. If differences among strata appear, we will formally test their corresponding interactions with the incentive amount.

TABLE 1 FACTORS FOR ADJUSTMENT AND EXPLORATION OF EFFECT MODIFICATION

Potential factors for adjustment	
Patient level covariates	***Variable coding or definition***
• Age	Continuous
• Gender	Binary
• Race	Categorical
• Marital status	Categorical
• Education	Categorical
• Income	Categorical
• Economic well-being	Categorical
• Prior research participation	Categorical
• Attitudes towards research:	Continuous, measured using the Research Attitudes Questionnaire-7 (RAQ-7).

6. Approach to missing data & sensitivity analyses

In addition to introducing several modifications to enrollment procedures to safeguard against missing data, some guidelines have been implemented to address missing data. The study team is particularly concerned about missingness of key RETAIN outcomes due to post-randomization ineligibility (i.e. a patient is discovered to be ineligible for the parent trial after randomization into RETAIN). If missingness due to parent trial ineligibility does not exceed 10%, the primary analysis will be limited to participants with complete data.

If missingness due to parent trial ineligibility is greater 10%, logistic models will be fit separately among observed data within each arm with the consent decision (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.

In the event that our primary analyses include imputed data, sensitivity analyses will evaluate the robustness of our conclusions. Specifically, sensitivity analyses will vary the intercept parameter in the models used to generate outcomes for post-randomization ineligibles so that they are more or less likely to consent than subjects with observed outcomes. We will assume, however, that covariate effects on consent are the same. The intercept parameter will be varied using a minimum of 5 different values per arm. These values will be chosen such that the average probability of consent within arm spans the

range (0,1) and gives sufficient information to informally assess which assumptions would influence the results of the primary analysis. For each combination of parameter values, estimates will be obtained using the same techniques as described above for the primary analysis.

We do not anticipate substantial missing data beyond that which is due to ineligibility, as most outcomes are assessed by parent trial research staff once determination of eligibility for the parent trial is finalized. Nonetheless, it is possible that participants may not complete certain portions of the instruments measuring the outcomes of interest. We will explore and potentially adjust for missing values using pattern-mixture methods and multiple imputation models in secondary analyses.

7. Secondary Outcomes

a. Outcome measures

Attention to the informed consent document: We will assess 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 will include the time – to the second – at which the participant moved to another section through a timestamp. The primary measure of this assessment will be time spent on the risk section; the secondary measure will be total time spent on the consent form.

Perceived risks of the research: Perceived risks of the research will be measured by a modified 9-item "compared riskiness" scale, which has been used in previous studies and refined for the RETAIN trial.

Incidence of therapeutic misconceptions: It has been hypothesized that the use of financial incentives could reduce therapeutic misconceptions, and thereby promote informed decision-making. Because patients are not accustomed to being paid for their clinical care, offering incentives could signal that research is different. We will test the hypothesized benefit of research incentives by measuring the incidence of therapeutic misconception in each incentive arm. We will assess this outcome with a 4-item therapeutic misconception tool, developed by External Advisory Board member, Dr. Scott Kim.

Understanding of the trial: To assess whether increased attention translates into improved understanding of the trial, we will use a 6-item Trial Elements Quiz, featuring core elements of the parent trials' consent forms.

Perceptions of influence or coercion: To measure general perception of coercion and voluntariness of research participation, we will use the five-item Perceived Coercion Scale of the MacArthur Admission

Experience Survey.

Retention through the end of treatment sessions: To assess the impact of incentives on retention status in the protocol, we will disburse payment in two installments- one as soon as possible after debriefing and one during the patient's last week of treatment therapy or study intervention. The denominator for analyses of this outcome will be all those who received the first payment. We will assess if patients completed their treatment, and if not, reasons for non-completion.

b. Analysis of secondary outcomes

We will first test the bivariate relationships between incentives and secondary 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 assess the outcomes with adjustments, we will use logistic, linear, or quantile regression, as appropriate based on outcome parameterizations and distributions. We will adjust significance levels for multiple comparisons using the Holm method.

8. Sample size and statistical power calculations

a. Sample size

We plan to enroll 576 patients who are approached for participation in each parent trial, such that the total RETAIN sample will include 1,152 patients. However, RETAIN data associated with each of the two parent trials will be analyzed separately in primary analyses.

b. Statistical power calculations

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. 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 the median level of risk perception who will be randomized to the highest incentive versus the lowest incentive. With an overall sample size of 576 participants in each parent study involved in the RETAIN trial, we assumed that 192 participants would be randomized to each of the 3 incentive arms. Assuming that randomization balances the incentives distribution within each risk-perception group, 96 participants will be assigned to each of the 3 incentives within both the high and low risk-perception groups. Among patients assigned to receive $0, we set the 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 or $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 ratios of 2.0 or greater. However, because we will actually analyze risk as a continuous variable and incentive size as a 3-level variable, our true power will be greater than the estimates reported here. Similar analyses suggest similar levels of power to rule out the unjust inducement interaction terms.

9. Data Safety & Monitoring Board (DSMB)

We have chartered a DSMB to monitor RETAIN, with purview over both embedded trials, for the expressed purpose of evaluating evidence of undue or unjust inducement. Any serious adverse events, protocol deviations/violations, and unanticipated events will be reported to the IRBs with oversight of recruiting

sites, the DSMB, and The National Cancer Institute.

10. Stopping Rules

Trial stopping rules were approved by the Data Safety and Monitoring Board for the following events:

I. Undue inducement

To detect if incentives represent undue inducement that could distort voluntary informed consent, the research team will test the statistical interaction between incentive size and risk perception on the outcome of enrollment in the parent RCT.

II. Unjust inducement

To assess the presence of unjust inducement, or preferential participation among participants with either (a) lower income, or (b) reduced financial well-being, two interaction terms will be evaluated in separate models to avoid collinearity. Unjust inducement will be defined as a statistically significant interaction between (a) incentive size and annual household income, or (b) between incentive size and economic well-being, each on the outcome of trial enrollment. One or both of these interactions, if statistically significant in the direction that lower-income persons or persons with reduced economic well-being are more strongly motivated to participate by increasingly large payments, will be considered grounds for terminating the trial or suspending a trial arm.

11. Timing of analysis and adjustment of significance level

Interim analyses will be conducted after 50% and 75% of the data have accrued within each the BASC and MOVE IT trials. In contrast to the final analyses, which will be structured as tests of non-inferiority, 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. We will use 1-sided significance levels of 0.0055, and 0.0219.

12. Personnel

Interim analyses will be performed by the trial's primary statistician who will conduct all analyses blinded to trial arm. Investigators, the project manager, and the DSMB will remain blinded to treatment arm through completion of analyses. The data manager and faculty statistician have been unblinded as was necessary to perform essential functions of their roles.

V. Changes to Statistical Analysis Plan

Date	Change	Reason for change
1/27/2020	We realized that because the incentive arm was to be treated as an ordered variable, per the chi-squared test, there was no role for 'Holm' adjustment for multiple testing as this was a single test.	The incentives are in increasing order and tests with an ordered variable have only a single contrast, obviating the need for adjustment.
1/27/2020	Use of Jonckheere-Terpstra test instead of Kruskal-Wallis.	To make comparisons across ordered incentive groups, the Jonckheere test is the appropriate statistic for non-parametric data, rather than the Kruskal Wallis.
1/27/2020	We implemented a diagnostic check to detect outlier and influential observations.	The compared riskiness data were observed to be very sparse in the higher-risk ranges, particularly in the Ambulation trial. This diagnostic was designed to ensure that inferences were not driven by a few influential observations.
1/27/2020	Given extremely limited RETAIN secondary outcome data among patients who do not consent to the parent trials, we will analyze secondary outcomes among consenting subjects only.	Very few patients who chose not to consent to the parent trial were willing to complete these post-consent instruments, so there was no basis for including non-consenting patients in tests of secondary outcomes. Instead, we limit our contrasts to those among incentive arms among the consenting patients.

1/27/2020	Secondary outcomes were analyzed 2 ways for both trials: Primary approach- Unweighted; Secondary approach – adjusted for response rate using propensity weights.	These outcomes are analyzed among the consented sample because of aforementioned limitations in capturing secondary outcomes. Participants who consented and didn't consent might be different and non-response might not be at random. To check if the inference is robust we planned for both analyses.
2/17/2020	Included secondary analysis of the risk score and incentives where risk score is treated as a binary variable (0 and >0).	During the interim analyses we gained meaningful insight into the risk score distributions. We found that in the Ambulation trial the risk score mostly (>85%) clumped on 0, and in the smoking trial the score is extremely right skewed. To better handle this sparsity of data we planned a secondary analysis in which we treat the risk scores as binary and compare the inferences.

VI. Final Statiscal Analysis Plan

1. Background and rationale

This study is designed to provide the first-ever real-world tests of a broad range of intended and unintended consequences of financial incentives for research participation. It will do so through the conduct of two separate, but similarly designed, embedded randomized trials within actual parent clinical trials. It is our hope the findings from this study will inform research regulations and guide the use of incentives in future RCTs so as to expedite medical innovation and improve health

2. Objectives and hypotheses

The aims of this study are to (1) determine if the ethical concerns with incentives for research participation actually manifest; and (2) assess the possible scientific and ethical benefits of financial incentives for RCT participation.

We hypothesize that research incentives will:

- Augment participants' perceptions of risk without disproportionately encouraging economically disadvantaged participants to enroll
- Demonstrate an increased enrollment fraction in the parent trials, thereby enhancing the scientific value and validity of the research by augmenting the precision of the studies

3. Design and randomization

RETAIN comprises two prospective randomized controlled trials, embedded within two parent trials conducted in parallel, each comparing three intervention arms. Arms vary by the amount of the financial incentives that are offered to potential participants. Amounts offered differ on a per trial basis determined by the relative time and effort being asked of the participant for each parent trial. Assignment to arms is determined by computerized random-number generation with block randomization using variable block sizes of 3 and 6. Participants in both embedded trials have a 33.3% probability of being assigned to each RETAIN arm.

a. BASC Trial

- The Behavioral Activation and Varenicline for Smoking Cessation in Depressed Smokers Study (BASC) (NCT 02378714)

- Tests two behavioral interventions in combination with Varenicline in a population of daily smokers with current or lifetime major depressive disorder
- Eligible patients are randomized to receive inform consent forms offering $0, $200, or $500 incentives for participation
- Patients are enrolled at The University of Pennsylvania and Northwestern University; randomization is stratified by site

b. MOVE IT Trial

- The Mobility and Outcomes for Validated Evidence – Incentive Trial (MOVE IT) (NCT 03321279)
- 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
- Eligible patients are randomized to receive inform consent forms offering $0, $100, or $300 incentives for participation
- Patients are enrolled at the Hospital of the University of Philadelphia by a team of clinical research coordinators; randomization is stratified by clinical research coordinator
- By necessity, clinical research coordinators administering the consent process in both parent trials are unmasked to the incentive information being messaged to prospective participants. The introduction to the study and the informed consent process have been robustly scripted for research staff involved in both trials to ensure that messaging is consistent and biases are minimized.

4. Population

Eligibility for RETAIN is contingent on eligibility for the BASC and MOVE IT parent trials.

- Adults age 18 years or older who are daily smokers with current or lifetime major depressive disorder without psychotic features (BASC)
- Adults age 18 years or older who are admitted for inpatient care to the Hospital of the University of Pennsylvania (HUP) on medicine or oncology floors (MOVE IT)

Patients randomized to RETAIN must be:

- Eligible for parent RCT
- 18 years or older
- English-speaking

In the BASC trial, prior knowledge of the incentive randomization or payment equalization used for this

study, which will be assessed with open-ended prompts during the first encounter, is an exclusion criterion. We will not assess for prior knowledge in the inpatient MOVE IT study population. However, only one patient per hospital room will be approached for the MOVE IT study to protect against contamination.

5. Primary outcome and analytic method

a. Primary outcome

The primary outcome is the proportion of participants assigned to each incentive amount that consent to enroll in each of the two parent RCTs.

b. Primary analytic sample

Intention-to-treat (ITT) approach such that the analytic sample will include all patients randomized in the RETAIN trial, even if ultimately deemed ineligible for the parent trials.

c. Primary analysis

We will first assess bivariate relationships of incentives with the primary outcome using 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. In the above analyses we treated incentive as an ordered variable. 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. To adjust for chance covariate imbalance among arms, primary analyses will include covariates (see Table 1) in multivariable models if they are significantly associated with the intervention arm and predictive of enrollment in the parent trials in bivariate analyses. 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. In all analyses related to the BASC parent trial, 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.

Our analyses to rule out undue and unjust inducements entail three primary covariates: risk perception, annual household income, and economic well-being. All models will use enrollment in the parent trial as the outcome. To determine if 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. We will test two interactions, each in a separate model to avoid collinearity, to determine if incentives represent unjust inducements: that between incentive size and the primary covariate of annual household income, and that between incentive size and the primary covariate of economic well-being. All analyses will be stratified by parent study.

Analyses of interaction terms will be structured as tests of non-inferiority. The null hypothesis, for both trials, will be that the use of incentives meets criteria for undue or unjust inducement. We can 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). Said a different way, our analyses are designed to determine if we can exclude the possibility that incentives represent undue or unjust inducements if the resulting interaction terms are sufficiently small. Specifically, we will use one-sided alpha levels of 0.05 to exclude, with 95% confidence, the possibility that any of these interaction odds ratios are >2.0.

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 used in these studies, we will adjust for their influence by entering time as a covariate, modeled as a spline. We will evaluate potential effect modifiers (variables in Table 1) using stratified analyses. If differences among strata appear, we will formally test their corresponding interactions with the incentive amount.

TABLE 1 FACTORS FOR ADJUSTMENT AND EXPLORATION OF EFFECT MODIFICATION

Potential factors for adjustment	
Patient level covariates	***Variable coding or definition***
• Age	Continuous
• Gender	Binary
• Race	Categorical
• Marital status	Categorical
• Education	Categorical
• Income	Categorical
• Economic well-being	Categorical
• Prior research participation	Categorical
• Attitudes towards research:	Continuous, measured using the Research Attitudes Questionnaire-7 (RAQ-7).

6. Secondary analysis

We will implement secondary interaction analyses of risk score with incentive arm. Risk score will be treated as binary variable with 0 and >0 categories and Incentive will be treated as ordinal factor. The analysis method will be same as described in section **c**. We plan to compare the inference of this analysis with the primary approach and report accordingly.

a. Approach to outliers and influential observations

We plan to perform diagnostic checks for influential and outlier observations in interaction analyses. The analyses will be done both ways including and then excluding influential observations if any is detected. To implement the diagnostic process we will use 'car' package from R.

b. Secondary outcome measures

Attention to the informed consent document: We will assess 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 will include the time – to the second – at which the participant moved to another section through a timestamp. The primary measure of this assessment will be time spent on the risk section; the secondary measure will be total time spent on the consent form.

Perceived risks of the research: Perceived risks of the research will be measured by a modified 9-item "compared riskiness" scale, which has been used in previous studies and refined for the RETAIN trial.

Incidence of therapeutic misconceptions: It has been hypothesized that the use of financial incentives could reduce therapeutic misconceptions, and thereby promote informed decision-making. Because patients are not accustomed to being paid for their clinical care, offering incentives could signal that research is different. We will test the hypothesized benefit of research incentives by measuring the incidence of therapeutic misconception in each incentive arm. We will assess this outcome with a 4-item therapeutic misconception tool, developed by External Advisory Board member, Dr. Scott Kim.

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c. Analysis of secondary outcomes

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Participants who consented and who didn't might be different meaning non response might not be random. To check if the inference is robust or not we plan to analyze the appropriate secondary outcomes 2 ways- unweighted and weighted. In survey weighted approach we plan to use propensity scores (inverse of probability of consent) as weights.

7. Sample size and statistical power calculations

a. Sample size

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parent trials will be analyzed separately in primary analyses.

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