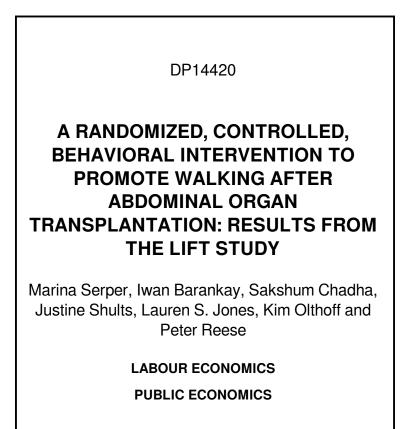
DISCUSSION PAPER SERIES





A RANDOMIZED, CONTROLLED, BEHAVIORAL INTERVENTION TO PROMOTE WALKING AFTER ABDOMINAL ORGAN TRANSPLANTATION: RESULTS FROM THE LIFT STUDY

Marina Serper, Iwan Barankay, Sakshum Chadha, Justine Shults, Lauren S. Jones, Kim Olthoff and Peter Reese

> Discussion Paper DP14420 Published 18 February 2020 Submitted 13 February 2020

Centre for Economic Policy Research 33 Great Sutton Street, London EC1V 0DX, UK Tel: +44 (0)20 7183 8801 www.cepr.org

This Discussion Paper is issued under the auspices of the Centre's research programmes:

- Labour Economics
- Public Economics

Any opinions expressed here are those of the author(s) and not those of the Centre for Economic Policy Research. Research disseminated by CEPR may include views on policy, but the Centre itself takes no institutional policy positions.

The Centre for Economic Policy Research was established in 1983 as an educational charity, to promote independent analysis and public discussion of open economies and the relations among them. It is pluralist and non-partisan, bringing economic research to bear on the analysis of medium- and long-run policy questions.

These Discussion Papers often represent preliminary or incomplete work, circulated to encourage discussion and comment. Citation and use of such a paper should take account of its provisional character.

Copyright: Marina Serper, Iwan Barankay, Sakshum Chadha, Justine Shults, Lauren S. Jones, Kim Olthoff and Peter Reese

A RANDOMIZED, CONTROLLED, BEHAVIORAL INTERVENTION TO PROMOTE WALKING AFTER ABDOMINAL ORGAN TRANSPLANTATION: RESULTS FROM THE LIFT STUDY

Abstract

Kidney transplant recipients (KTRs) and liver transplant recipients (LTRs) have significant posttransplant weight gain and low physical activity. We conducted a home-based, remotely-monitored intervention using wearable accelerometer devices to promote post-transplant physical activity. We randomized 61 KTRs and 66 LTRs within 24 months of transplant to: 1) control, 2) accelerometer, or 3) intervention: accelerometer paired with financial incentives and health engagement questions to increase steps by 15% from baseline every 2 weeks. The primary outcome was weight change. A co-primary outcome for the two accelerometer arms was steps. Participants were recruited at a median of 9.5 [3-17] months post-transplant. At 3 months, there were no significant differences in weight change across the 3 arms. The intervention arm was more likely to achieve \geq 7000 steps compared to control with device (OR 1.99, 95% CI:1.03-3.87); effect remained significant after adjusting for demographics, allograft, time from transplant, and baseline weight. Adherence to target step goals was 74% in the intervention arm, 84% of health engagement questions were answered correctly. A pilot study with financial incentives and health engagement questions was feasible and led KTRs and LTRs to walk more, but did not affect weight. A definitive trial is warranted. (ClinicalTrials.gov number: NCT03221465).

JEL Classification: N/A

Keywords: N/A

Marina Serper - marina.serper@uphs.upenn.edu Perelman School of Medicine, University of Pennsylvania; Leonard Davis Institute of Health Economics, University of Pennsylvania

Iwan Barankay - barankay@wharton.upenn.edu The Wharton School, University of Pennsylvania and CEPR

Sakshum Chadha - sakshumc@pennlaw.upenn.edu Perelman School of Medicine, University of Pennsylvania

Justine Shults - shultsj@email.chop.edu University of Pennsylvania

Lauren S. Jones - lauren.jones2@pennmedicine.upenn.edu

Perelman School of Medicine, University of Pennsylvania

Kim Olthoff - kim.olthoff@uphs.upenn.edu University of Pennsylvania

Peter Reese - peter.reese@uphs.upenn.edu Perelman School of Medicine, University of Pennsylvania **Title:** A Randomized, Controlled, Behavioral Intervention to Promote Walking after Abdominal Organ Transplantation: Results from the LIFT Study

Marina Serper, MD, MS^{1,2}, Iwan Barankay, PhD³, Sakshum Chadha, BS⁴, Justine Shults, PhD⁵, Lauren S. Jones, BS¹, Kim M. Olthoff, MD⁶, Peter P. Reese, MD, MSCE^{2,4,5} ¹Division of Gastroenterology, University of Pennsylvania Perelman School of Medicine,

Philadelphia PA

²Leonard Davis Institute of Health Economics, University of Pennsylvania, Philadelphia, PA

³The Wharton School, University of Pennsylvania, Philadelphia, PA

⁴Renal-Electrolyte and Hypertension Division, University of Pennsylvania Perelman School of Medicine

⁵Department of Biostatistics, Epidemiology and Informatics, University of Pennsylvania,

Philadelphia, PA

⁶Department of Surgery, Division of Transplant Surgery, University of Pennsylvania,

Philadelphia, PA

Authorship:

- MS study design, oversaw the study, statistical analysis, drafting of manuscript
- IB study design, oversaw the study, critical revisions of manuscript
- SC data collection, critical revisions of manuscript
- JS statistical analysis
- LJ data collection, critical revisions of manuscript
- KMO critical revisions of manuscript
- PPR study design, oversaw the study, critical revisions of manuscript

Funding sources:

This study was supported by a pilot grant from the Translational Medicine and Therapeutics (ITMAT) and the Leonard Davis Institute (LDI) Center for Health Incentives and Behavioral Economics (CHIBE) Pilot Grant at the University of Pennsylvania. Marina Serper is supported by the National Institute of Diabetes and Digestive and Kidney Diseases, award #1K23DK115897-01.

Corresponding author:

3400 Spruce St, 2 Dulles Philadelphia, PA, 19104 marina.serper@uphs.upenn.edu

Running Title:

The LIFT Study

Keywords:

Physical activity, behavior change, remote monitoring, self-care, behavioral economics, exercise

Abbreviations:

- BMI: body mass index
- CI: confidence interval
- IQR: interquartile range
- IS: immunosuppression
- KG: kilogram
- KT: kidney transplant
- LT: liver transplant

Conflicts of interest:

The authors of this manuscript have no conflicts of interest to disclose.

ABSTRACT

Kidney transplant recipients (KTRs) and liver transplant recipients (LTRs) have significant posttransplant weight gain and low physical activity. We conducted a home-based, remotelymonitored intervention using wearable accelerometer devices to promote post-transplant physical activity. We randomized 61 KTRs and 66 LTRs within 24 months of transplant to: 1) control, 2) accelerometer, or 3) intervention: accelerometer paired with financial incentives and health engagement questions to increase steps by 15% from baseline every 2 weeks. The primary outcome was weight change. A co-primary outcome for the two accelerometer arms was steps. Participants were recruited at a median of 9.5 [3-17] months post-transplant. At 3 months, there were no significant differences in weight change across the 3 arms. The intervention arm was more likely to achieve ≥7000 steps compared to control with device (OR 1.99, 95% CI:1.03-3.87); effect remained significant after adjusting for demographics, allograft, time from transplant, and baseline weight. Adherence to target step goals was 74% in the intervention arm, 84% of health engagement questions were answered correctly. A pilot study with financial incentives and health engagement guestions was feasible and led KTRs and LTRs to walk more, but did not affect weight. A definitive trial is warranted. (ClinicalTrials.gov number: NCT03221465).

INTRODUCTION

Post-transplant weight gain is highly prevalent and associated with adverse health outcomes among kidney transplant recipients (KTRs) and liver transplant recipients (LTRs) including a greater risk of graft loss, cardiovascular disease and new-onset diabetes after transplantation. The reasons for substantial weight gain stem from reduced physical activity after the development of end-stage organ disease that may further be impeded by the stresses of post-operative recovery. Additional contributors are increased post-transplant appetite as well as the obesity-promoting effects of calcineurin inhibitors and corticosteroids.(1-3) At one year post-transplant, KTRs and LTRs gain from 4-10 kg on average. Forty percent of LTRs with a normal body weight at transplantation become obese at one year.(4, 5) Among KTRs, weight gain doubles the risk of graft loss and is associated with reduced long-term survival.(5, 6) In LTRs, metabolic syndrome is twice as common as in the general population and is associated with cardiovascular events and new onset diabetes after transplantation.(7-10)

Despite the potential for positive behavior changes after the life-altering process of transplantation and close medical follow-up, weight gain and low physical activity have been the *status quo*. Intensive exercise interventions focused on aerobic and strength training have been studied, and, not surprisingly, improve muscle strength, exercise capacity, and health-related quality of life (11-17). However, despite the known benefits of physical activity after transplantation and guidelines recommending post-transplant exercise (18), durable behavior changes are difficult to maintain and intensive programs may be considered cost-prohibitive and not typically covered by healthcare plans.

From a behavioral economics standpoint, post-transplant weight gain and inactivity reflect a self-control burden on the patient who has to be adherent to medication as well as to diet,

exercise and weight management. (19) Two concepts that informed the design of this study are 1) hyperbolic discounting, whereby patients place a disproportionately low value on future health outcomes at the expense of the immediately more pleasing alternatives (e.g. overeating and sedentary behavior), and 2) cognitive load, the perceived inconvenience of thinking of and remembering to follow all prescribed clinical recommendations. The problem of hyperbolic discounting with sedentary behavior can be addressed by making healthy choices more beneficial in the present via financial incentives, which also serve to focus the patient on a health behavior like walking. The problem of cognitive load can be addressed by "retrieval practice", a structured process of training to recall and repeat health information with questions where correct answers are financially rewarded. This process induces a "testing effect" and leads to lasting retention of information. (20)

Despite the many challenges faced by transplant recipients, the post-transplant period whereby organ dysfunction is restored may be particularly salient in motivating individual behavior change. As substantial weight gain is expected in the post-transplant period, an intervention that succeeds in maintaining stable weight or preventing greater adiposity would be an improvement over typical outcomes. The objective of this randomized, controlled pilot study was to test the effectiveness of a home-based, low-impact exercise program using wearable devices, health engagement questions and financial incentives on post-transplant weight gain and walking among KTRs and LTRs. We hypothesized that a home-based physical activity program based on frequent feedback and financial incentives would mitigate post-transplant weight gain and increase walking.

PATIENTS AND METHODS

6

STUDY DESIGN

This was a block-randomized, controlled trial conducted for 18 weeks and consisted of a 2-week run-in period, a 12-week active intervention, and a 4-week follow-up. Patients were recruited at the Hospital of the University of Pennsylvania between March 2017 and January 2018. After confirming eligibility and obtaining informed consent, participants were randomized to one of three study arms. The three study arms were: Arm 1 – control, no device, Arm 2 – control with device only, and Arm 3 – intervention that included a device and an incentivized physical activity and health engagement program. This study was approved by the University of Pennsylvania Review Board (protocol # 825784; NCT03221465). The trial was initially planned to be conducted at 2 sites, however, due to rapid accrual, was conducted at a single site.

SETTING AND PARTICIPANTS

KTRs and LTRs were contacted by telephone by clinical research coordinators (CRCs) 1-2 weeks prior to their transplant clinic appointments to assess potential eligibility. Enrollment occurred in-person by the CRCs at transplant clinic appointments. The participants were followed remotely during the study through text, telephone calls, and email. At the end of the 12-week intervention period, participants were contacted and scheduled to complete an exit encounter.

Adults age 18or older who received KT, kidney/pancreas, LT or simultaneous liver kidney transplant (SLKT) from 2 - 24 months prior to screening were eligible for enrollment. The participants were included if they were English-speaking, able to provide informed consent,

owned a smartphone compatible with the wearable accelerometer (iOS or Android), and were willing to walk and sync the wearable accelerometer daily as well as provide an end-of-study weight. Participants were excluded if they already used a wearable accelerometer, had a severe vision, hearing, or mobility impairment precluding participation, or if they were enrolled in another financial incentive-based exercise program.

ENROLLMENT AND RANDOMIZATION

The study employed the University of Pennsylvania's Way to Health online platform (**Supplementary Appendix 1**) to facilitate enrollment, randomization, and subsequent tracking of step counts and bi-directional texting.(21, 22) Participants were told the investigators were studying the effects of a home-based walking program on their post-transplant health. Participants were randomized into one of three arms after consenting and completing the eligibility questionnaire. Block randomization was used with a block size of six, further stratified by organ (KT versus LT); patients who received SLKT were classified as LT as liver disease was the primary indication for transplant.

INTERVENTION

Participants in Arm 1 received standard instructions regarding healthy diet and physical activity that are provided after transplant and did not receive access to the online portal or health additional engagement questionsUpon enrollment, participants in Arms 2 and 3 received the same standard instructions as in Arm 1 and were also enrolled in a 2-week run-in period to get them accustomed to syncing the devices daily and to calculate baseline step counts. Participants in Arm 2 and 3 (those with wearable trackers) had access to an online portal with health information including answers to health engagement questions as well as links with

educational online resources regarding healthy diet and physical activity. In addition, Arm 3 received step goals and health engagement questions sent via text messages with financial incentives. We included a device-only Arm 2 to be able to distinguish between the device effect and the additional incentive effects in Arm 3.

Those randomized to Arm 3 (intervention) were enrolled in a physical activity program that consisted of individualized bi-weekly walking goals with the baseline determined using their mean steps during the 2-week run-in period. The decision to individualize step goals was based on lack of literature regarding typical physical activity levels in transplantation. Using participants' mean steps during the run-in as baseline, step goals were subsequently increased 15% every 2-weeks and were capped at a maximum goal 7,000 steps, which was chosen based on recommendations form the American College of Sports Medicine and exceeds the mean daily steps of about 5000 steps in the US population (23, 24).

Walking activity was promoted with financial incentives and rooted in the framework of behavioral economics, which recognizes that individuals often make inconsistent decisions over time about their health. Recent studies in non-transplant settings have effectively used financial incentives to make health benefits more salient and instant (21, 22, 25, 26). Financial incentives were "loss framed" since individuals tend to fear loss of rewards more than they value expected payouts of the same magnitude in the gain domain (27, 28). For this study, at the beginning of each 4-week study period, participants in Arm 3 were credited \$54 to a virtual account. For each day that a participant failed to meet their step goal, he or she was informed that \$3 was deducted from the virtual account balance.

Arm 3 participants were also financially incentivized to correctly answer two true/false transplant-specific health engagement questions each week during the intervention period (**Supplementary Appendix 2**). All participants in Arm 3 received paper and online copies of the questions and correct answers upon enrollment, since the objective was to test the retrieval practice effect rather than the effect of informing patients about specific recommendations. The questions were designed to give participants practice to more easily remember health information for when they make health-related decisions throughout the day. They included basic questions about exercise, healthful diet, and transplant food safety after transplantation (29, 30) Each participant was sent a true/false health engagement question twice a week; \$3 was deducted from the virtual account if the questions were not answered or answered incorrectly and they received prompt feedback about the accuracy of their answers and any possible changes in their balance. Balances were disbursed on a monthly basis.

After 12 weeks of intervention, Arm 2 and 3 participants were instructed to continue to use their devices, which they kept after the active intervention was over with no further feedback or text messaging.

OUTCOMES

The primary study outcome was change in patient weight from enrollment to the end of the 4month study period. End-of-study weight was obtained within a 5-week period of the completion of the active intervention (1 week before or 4 weeks after) and was obtained in-person by a research coordinator whenever possible (44/117, 38%) or by transplant clinic staff during a routine appointment (43/117, 37%). In 30 (26%) cases where exit encounters were conducted over the telephone for patient convenience, weight was obtained by documentation from an outside physician's office (14/117, 12%) or by having the participant text the study staff a photograph of their weight recorded while stepping on a scale (16/117, 14%). A secondary outcome was daily steps. Consistent with other studies, we analyzed the mean proportion of participant days that the target of 7000 steps was achieved, a previously studied goal in walking studies. (27) We also compared daily steps as a continuous outcome.

This was a single-blind study, where the participants and research staff could not be blinded. The investigators were blinded to study arm assignment and outcome measurement until all participants exited the study. After study completion, intervention fidelity in Arm 3 was assessed by measuring the percent adherence to step targets, the percent of health engagement questions answered via text message, and the percent of health engagement questions answered correctly.

STATISTICAL ANALYSES

All participants that were initially randomized were compared on baseline characteristics using one-way analysis of variance for continuous and chi-squared tests for categorical variables. Step data were analyzed for 76 participants in Arms 1 and 3 using an intention-to-treat approach. We fit a logistic regression model for the physical activity outcome of proportion of days with ≥7000 steps. We fit a linear regression model for the outcome of weight change at 3 months from baseline in kilograms; models were not fit for steps as a continuous outcome as the difference in average step counts was not statistically significant in unadjusted analysis. For both outcomes, secondary analyses were performed adjusting for baseline weight, age, sex, race/ethnicity, time from transplantation and allograft type (kidney versus liver). We used robust

standard errors for all models. For the physical activity outcome, additional sensitivity analyses were completed in which we: 1) excluded all days with less than 1000 steps; evidence from other studies suggests that this number of steps does not adequately reflect daily physical activity and may have resulted from device malfunction or misuse; 2) used multiple imputation to account for missing step counts assumed to be missing at random. The regression-based multiple imputation model (*mi impute* command in Stata) included age, gender, race, enrollment BMI, allograft type, time from transplant, participant, and study arm and included 20 imputations, which is considered more than sufficient to account for the 2% observed missing step data. Analyses were performed with Stata 15.0 (StataCorp, College Station, TX).

Sample size was constrained by the fact that this was a pilot study. Assuming 20% attrition and a sample size of 33 participants per arm (including Arms 2 and 3 with devices), the study had >90% power to detect a 6% difference in the proportion of days with \geq 7000 steps and had 90% power to detect a difference of 2000 steps between the control and intervention arms with a type 1 error of 0.05.

RESULTS

The study enrollment details are shown in **Figure 1**. A total of 513 participants who met initial criteria of being within 2-24 months from KT or LT were reviewed in the electronic health record and 425 were contacted by telephone. Among the 178 potentially eligible and interested patients, a total of 127 were randomized (n=41 to Arm 1: control, no device, n=44 to Arm 2: control with device, n=41 to Arm 3: intervention). The study retention rate was 117/127 participants (92.1%). Among the 117 retained in the study, a total of 103 (88.0%) provided end-of-study weight. Steps were analyzed among 76 participants in Arms 2 and 3; one participant in

Arm 2 died 10 days prior to study completion, which was unrelated to the study. No other studyrelated adverse events occurred.

Table 1 shows baseline characteristics by study arm. The mean age was 52 (SD 13) years, 64% were male, 64% were white and 27% were black. The median baseline body mass index (BMI) at enrollment was 28 kg/m² (IQR: 24,32). We did not observe clinically meaningful differences in participants at baseline across arms, except that participants in the intervention arm 3 were further from transplantation (median 13 months compared to 8.4 months in the control, no device arm and 6.5 months in the control with device arm). Participants in the intervention arm had a higher prevalence of new onset diabetes after transplant and higher estimated glomerular filtration rate (eGFR); these baseline differences were not statistically significant.

Table 2 provides the unadjusted weight and step data for 117 study participants with complete weight data after 18 weeks, which included the 2-week run-in period, 12 weeks of active intervention, and 4 weeks of passive observation. The median overall weight gain was 0.91 kg (IQR: -0.91, 3.9). The median unadjusted weight gain was 0.91 kg (IQR:-1.0, 5.4) in the control, no device arm and 2.4 kg (IQR:-.45, 5.4) in the control with device arm. By contrast, the intervention arm had a median weight loss of -.45 kg compared to control [(IQR:-0.14, 3.4); p=0.05 for comparison across all arms].

Among the 76 participants with step data, in univariable analysis, the overall proportion of participant-days achieving \geq 7000 steps was 0.53; this was 0.17 higher in the intervention group compared to control (0.45 control with device group versus 0.62 in the intervention group [p<0.001]). On average throughout the entire study period, participants in the intervention group walked 646 steps per day more than in the control group. The mean of the last 2-week study

period was 1195 steps higher in the intervention compared to the control group (p=0.19)
(Figure 2); mean absolute differences between step counts achieved and step count targets are shown in Figure 3. With regards to intervention fidelity, the mean adherence to step targets in the intervention group was 74% (Figure 4). Eighty-four percent of health engagement questions were answered, and among those, 95% were answered correctly (Supplementary Appendix 2).

In the primary model for the physical activity outcome (**Table 3**, Model 1), intervention arm 3 was associated with nearly twice the odds of achieving \geq 7000 steps compared to the control with device arm (OR 1.99, 95% CI: 1.03 - 3.87). Results were similar in multiple secondary analyses excluding days with less than 1000 steps, multiple imputation of missing steps, and after adjustment for baseline characteristics (**Table 3**, Models 2-4). Among patient characteristics, compared to KT recipients, LT recipient status was associated with lower likelihood of achieving \geq 7000 steps (OR 0.32, 95% CI :0.16-0.63).

For the outcome of change in weight from baseline (**Table 4**), no differences were noted by study arm. Older age and more time since transplant were associated with minimal, but statically significant weight loss from baseline with a 0.06 kg weight loss for every year increase in age (95% CI: 0.06 (-0.107 - 0.00) and a 0.24 kg weight loss with each additional month from transplant (95% CI: (-0.36 - -0.12).

In exploratory analyses, we investigated whether the proportion of days that ≥7000 steps were achieved at the participant level was associated with changes in weight from baseline. Among the 76 participants with step data, the mean percentage of days ≥7000 steps were reached during the study period was 52% (SD: 36%). Although not statistically significant, there was a

2.2 kg lesser change in weightfrom baseline among participants who reached \geq 7000 steps greater than 50% of the time compared to 50% or less (β = -2.2, 95% CI: - 4.50 - 0.09, p=0.06).

Exit survey data

In response to exit survey questions (**Supplementary Appendix 3**), most patients said they would be willing to participate in the study for greater than 9 months. A total of 89 (92%) enjoyed participating in the study. A total of 19 (56%) of patients in the control/no device arm strongly agreed/agreed that the study helped to increase their physical activity, versus 28 (78%) for the control with device arm and 18 (67)% for the incentives with device arm. A total of 38 (55%) of participants in the control or control with device arms strongly agreed/agreed that the study helped to 20 (71%) in the intervention arm. A total of 50 (79%)of patients enrolled in device arms felt that the study helped improve their health and 51 (82%) overall said they were committed to walking for exercise every day. A total of 22 (81%)of patients strongly agreed/agreed that text messages received as part of the active intervention were helpful.

Notably, open-ended feedback (**Supplementary Appendix 4**) included comments that patients gained more stamina by walking more and the study increased motivation to weigh themselves daily and increase physical activity. A few patients noted that because of the study, walking was "always at the top of my mind". A few patients in the control/no device arm were disappointed at their randomization assignment and either bought a wearable step tracker or started tracking steps on their phone. Participants made the following suggestions about improving the study: greater ease of technology use and accuracy of syncing; ability to track other types of exercise other than walking such as swimming or biking; and supplementary contacts by study staff to

make sure devices were working well. A few participants reported wanting more specific exercise goals and thresholds beyond steps as well as more specific dietary goals.

DISCUSSION

In this randomized, controlled pilot study, we noted that a home-based exercise program using wearable devices, health engagement questions and loss-framed financial incentives increased walking among KTRs and LTRs who were within 2-24 months of transplant. The program was feasible with rapid recruitment and greater than 90% retention, carried out with high fidelity, and was favorably received by patients. This study suggests that a home-based exercise program combined with health engagement questions has the potential to change patient behavior in transplantation (22, 28, 31). Our study incorporated several key principles of behavioral economics - the desired behavior (walking, in this case) was reinforced with immediate feedback and its practice was aided by the memory-enhancing effect of health questions with feedback and frequent financial incentives. These incentives were framed as loss incentives as it has been shown that individuals are more motivated by regret aversion that comes with avoiding a loss compared to anticipating a financial gain. (27, 32) Several features of this pilot study suggest future scalability. Deploying text-message communications in larger populations is simple and low-cost as most patients now own cell phones with text messaging plans while recent innovations in wireless-enabled wearable device technology allow for accurate measurement of physical activity.(31, 33)

We observed that a short-duration, relatively low touch and low-cost intervention delivered with an online portal (**Supplementary Appendix 1**), the percent of patients reaching a 7000-step daily target was 17% higher in the intervention compared to the device control group. The absolute difference in mean steps during the last 2 weeks of the active study period was 1195 higher in the intervention group and in adjusted models the odds of reaching the 7000 daily step threshold were 2.24 when comparing intervention to control and adjusting for baseline characteristics such as race/ethnicity, allograft type, time from transplant and baseline weight. Interestingly, we noted that LTRs were less likely to reach the 7000 steps targets. Although data are limited, it is possible that liver transplant recipients may be more debilitated prior to transplantation given the nature of end stage liver disease with more sarcopenia, physical frailty, and malnutrition. Future studies should further investigate: 1) whether liver versus kidney transplant recipients should have different physical activity targets, 2) how pre-transplant body mass composition and physical activity affect post-transplant recovery and response to physical activity interventions, and 3) how physical activity interventions affect body mass composition in addition to weight. Although in multivariable models, no significant association was found between study arm and weight changes, unadjusted analyses showed that participants in the intervention arm gained 0.5 kg less weight, compared to about 1-2 kg gain in the control no device or control with device arms. It is not altogether surprising that a study of 12-week duration had modest effects on weight loss. However, given these promising early data, a larger multicomponent behavioral intervention focused on diet and lifestyle interventions combined with physical activity should be conducted.

In addition to financial incentives, a novel component of the design of this trial was the addition of health engagement questions. These questions were based on the principle of "retrieval practice", which is rooted in educational psychology and assumes that memory improves with frequent testing making information more readily available. The health engagement questions in this trial (**Supplementary Appendix 2**) were designed to be simple and to keep the salience of both physical activity and healthful diet as "top of mind" for study participants; both behaviors are likely necessary to achieve positive changes in body composition. Although retrieval

practice has shown to improve test performance in a classroom setting, applications of this paradigm to healthcare have not been widely investigated and warrant future study (29, 30, 36).

Our study has several limitations. This was a single-center pilot study with a relatively small sample size. Patients who were not smartphone users accounted for approximately one third of those ineligible for the study, potentially limiting generalizability. The study was brief and likely underpowered to show changes in weight. Patients were included beyond the first posttransplant year, when weight gain be less common than in the first year. Weight change may also not capture important facets of body composition, such as the gain of muscle or loss of fat that could be measured using psoas muscle thickness or bioimpedance in future studies. The participants may have been too far out from transplant to measure weight gain prevention. The study design did not include follow-up to measure the sustainability of walking or health behavior changes after interventions concluded. Several participants in the control, no device arm commented in exit interviews that they began to use smart phones to track steps outside of the study protocol. The intervention was not specifically designed to address weight loss via calorie restriction and did not identify which recipients might be in need of weight loss interventions. Rather, patients were given standard diet instructions (Supplementary Appendix 5). Future studies should tailor dietary recommendations based on enrollment weight and body mass composition. We did not measure aerobic fitness of participants in this pilot study; this will need to be performed in larger trials. We excluded one patient on the basis of being non-English speaking; larger studies should adapt intervention materials to non-English speakers. Finally, the trial was not designed to compare the relative effectiveness of the intervention components of financial incentives, reminders, and health engagement questions.

4.1. Conclusions: A 12-week randomized, controlled pilot study of loss-framed financial incentives paired with frequent feedback and health engagement questions did not lead to weight loss but increased the proportion of days KTRs and LTRs walked ≥7000 daily steps. . The scalability and financing of monetary incentives to change behavior requires future study, however, models where employees and payers provide financial incentives for physical activity and biometric screening have been implemented (34, 35). It is, therefore, feasible to imagine such payer-based models to engage patients and promote healthy behaviors in the immediate post-transplant period. However, it will be important to consider the ethical implementation of these financial incentives prior to deploying them at a large scale. Future, larger, and longer studies should be conducted to test the effects of behavioral interventions pre- and post-transplant to promote physical activity, build strength, and minimize unhealthy weight gain.

Figure Legends

Figure 1. Study Flow Diagram

* 1 patient died 10 days prior to study completion, steps were included in analysis. Patients in the Control No Device arm did not have measured steps. The Control + Device arm included an accelerometer to measure daily steps. The Intervention arm included an accelerometer, daily step goal targets with loss-framed financial incentives, and biweekly text messages with health engagement questions.

Figure 2. Distribution of steps displayed by study arm for each 2-week interval (n=40 control+device, n=36 intervention+device)

Figure 3. Mean absolute differences between step counts achieved and step count targets (n=6) by 2-week period in the intervention (n=36)

Figure 4. Mean percent adherence to step targets for each 2-week study interval in the intervention arm

Description of Supporting Information

Supplementary Appendix 1. Description of Way to Health Portal used for study enrollment and

randomization

Supplementary Appendix 2. Health engagement questions and percent answered correctly in

the devices + incentives arm

Supplementary Appendix 3. Answers to exit survey questions by study arm

Supplementary Appendix 4. Summary of selected open-ended participant feedback about the study intervention.

Supplementary Appendix 5. Sample recommendations for post-transplant nutrition after liver transplant (instructions are similar after kidney transplant)

REFERENCES

1. Habedank D, Kung T, Karhausen T, von Haehling S, Doehner W, Schefold JC, et al. Exercise capacity and body composition in living-donor renal transplant recipients over time. Nephrol Dial Transplant. 2009;24(12):3854-60.

2. Han SS, Hwang JH, Oh YJ, Cha RH, Ahn C, Kim YS. Change in body compositions of Asian recipients after kidney transplantation. Journal of Korean medical science. 2012;27(10):1182-7.

3. Marchetti P. New-onset diabetes after liver transplantation: from pathogenesis to management. Liver transplantation : official publication of the American Association for the Study of Liver Diseases and the International Liver Transplantation Society. 2005;11(6):612-20.

4. Richards J, Gunson B, Johnson J, Neuberger J. Weight gain and obesity after liver transplantation. Transplant international : official journal of the European Society for Organ Transplantation. 2005;18(4):461-6.

5. Ducloux D, Kazory A, Simula-Faivre D, Chalopin JM. One-year post-transplant weight gain is a risk factor for graft loss. American journal of transplantation : official journal of the American Society of Transplantation and the American Society of Transplant Surgeons. 2005;5(12):2922-8.

6. el-Agroudy AE, Wafa EW, Gheith OE, Shehab el-Dein AB, Ghoneim MA. Weight gain after renal transplantation is a risk factor for patient and graft outcome. Transplantation. 2004;77(9):1381-5.

7. Laish I, Braun M, Mor E, Sulkes J, Harif Y, Ben Ari Z. Metabolic syndrome in liver transplant recipients: prevalence, risk factors, and association with cardiovascular events. Liver transplantation : official publication of the American Association for the Study of Liver Diseases and the International Liver Transplantation Society. 2011;17(1):15-22.

8. Nair S, Verma S, Thuluvath PJ. Obesity and its effect on survival in patients undergoing orthotopic liver transplantation in the United States. Hepatology. 2002;35(1):105-9.

9. Bodziak KA, Hricik DE. New-onset diabetes mellitus after solid organ transplantation. Transplant international : official journal of the European Society for Organ Transplantation. 2009;22(5):519-30.

10. Kuo HT, Lum E, Martin P, Bunnapradist S. Effect of diabetes and acute rejection on liver transplant outcomes, an analysis of the OPTN/UNOS database. Liver transplantation : official publication of the American Association for the Study of Liver Diseases and the International Liver Transplantation Society. 2016.

11. Galanti G, Stefani L, Mascherini G, Petri C, Corsani I, Francini L, et al. Short-term prospective study of prescribed physical activity in kidney transplant recipients. Intern Emerg Med. 2016;11(1):61-7.

12. Greenwood SA, Koufaki P, Mercer TH, Rush R, O'Connor E, Tuffnell R, et al. Aerobic or Resistance Training and Pulse Wave Velocity in Kidney Transplant Recipients: A 12-Week Pilot Randomized Controlled Trial (the Exercise in Renal Transplant [ExeRT] Trial). Am J Kidney Dis. 2015;66(4):689-98.

13. Lorenz EC, Amer H, Dean PG, Stegall MD, Cosio FG, Cheville AL. Adherence to a pedometerbased physical activity intervention following kidney transplant and impact on metabolic parameters. Clin Transplant. 2015;29(6):560-8.

14. Raymond J, Johnson ST, Diehl-Jones W, Vallance JK. Walking, Sedentary Time and Health-Related Quality Life Among Kidney Transplant Recipients: An Exploratory Study. Transplant Proc. 2016;48(1):59-64.

15. Garcia AM, Veneroso CE, Soares DD, Lima AS, Correia MI. Effect of a physical exercise program on the functional capacity of liver transplant patients. Transplant Proc. 2014;46(6):1807-8.

16. Painter P, Krasnoff J, Paul SM, Ascher NL. Physical activity and health-related quality of life in liver transplant recipients. Liver transplantation : official publication of the American Association for the Study of Liver Diseases and the International Liver Transplantation Society. 2001;7(3):213-9.

17. Takahashi A, Hu SL, Bostom A. Physical Activity in Kidney Transplant Recipients: A Review. Am J Kidney Dis. 2018;72(3):433-43.

Lentine KL, Kasiske BL, Levey AS, Adams PL, Alberu J, Bakr MA, et al. KDIGO Clinical Practice
 Guideline on the Evaluation and Care of Living Kidney Donors. Transplantation. 2017;101(8S Suppl 1):S1 S109.

19. Duckworth AL, Milkman KL, Laibson D. Beyond Willpower: Strategies for Reducing Failures of Self-Control. Psychol Sci Public Interest. 2018;19(3):102-29.

20. Karpicke JD, Blunt JR. Retrieval Practice Produces More Learning than Elaborative Studying with Concept Mapping. Science. 2011;331(6018):772-5.

21. Reese PP, Bloom RD, Trofe-Clark J, Mussell A, Leidy D, Levsky S, et al. Automated Reminders and Physician Notification to Promote Immunosuppression Adherence Among Kidney Transplant Recipients: A Randomized Trial. Am J Kidney Dis. 2017;69(3):400-9.

22. Patel MS, Asch DA, Rosin R, Small DS, Bellamy SL, Eberbach K, et al. Individual Versus Team-Based Financial Incentives to Increase Physical Activity: A Randomized, Controlled Trial. J Gen Intern Med. 2016;31(7):746-54.

23. Bassett DR, Jr., Wyatt HR, Thompson H, Peters JC, Hill JO. Pedometer-measured physical activity and health behaviors in U.S. adults. Med Sci Sports Exerc. 2010;42(10):1819-25.

24. Garber CE, Blissmer B, Deschenes MR, Franklin BA, Lamonte MJ, Lee IM, et al. American College of Sports Medicine position stand. Quantity and quality of exercise for developing and maintaining cardiorespiratory, musculoskeletal, and neuromotor fitness in apparently healthy adults: guidance for prescribing exercise. Med Sci Sports Exerc. 2011;43(7):1334-59.

25. Volpp KG, John LK, Troxel AB, Norton L, Fassbender J, Loewenstein G. Financial incentive-based approaches for weight loss: a randomized trial. JAMA. 2008;300(22):2631-7.

26. Halpern SD, French B, Small DS, Saulsgiver K, Harhay MO, Audrain-McGovern J, et al. Randomized trial of four financial-incentive programs for smoking cessation. N Engl J Med. 2015;372(22):2108-17. 27. Patel MS, Asch DA, Volpp KG. Framing Financial Incentives to Increase Physical Activity Among Overweight and Obese Adults. Ann Intern Med. 2016;165(8):600.

28. Chokshi NP, Adusumalli S, Small DS, Morris A, Feingold J, Ha YP, et al. Loss-Framed Financial Incentives and Personalized Goal-Setting to Increase Physical Activity Among Ischemic Heart Disease Patients Using Wearable Devices: The ACTIVE REWARD Randomized Trial. J Am Heart Assoc. 2018;7(12).

29. Karpicke JD, Roediger HL, 3rd. The critical importance of retrieval for learning. Science. 2008;319(5865):966-8.

30. Roediger HL, 3rd, Butler AC. The critical role of retrieval practice in long-term retention. Trends Cogn Sci. 2011;15(1):20-7.

31. Patel MS, Asch DA, Volpp KG. Use of wearable monitoring devices to change health behavior-reply. JAMA. 2015;313(18):1865-6.

32. Zeelenberg M, Pieters R. Consequences of regret aversion in real life: The case of the Dutch postcode lottery. Organ Behav Hum Dec. 2004;93(2):155-68.

33. Case MA, Burwick HA, Volpp KG, Patel MS. Accuracy of smartphone applications and wearable devices for tracking physical activity data. JAMA. 2015;313(6):625-6.

34. Medicaid Incentives for Prevention of Chronic Diseases.

https://downloads.cms.gov/files/cmmi/mipcd-finalevalrpt.pdf, Accessed July 19th, 2019.

35. Cleveland Clinic Employee Health Plan. <u>https://employeehealthplan.clevelandclinic.org/EHP-</u> Wellness-Program/Physical-Activity/Activity-Device-Program.aspx, Accessed July 19th, 2019.

36. McDaniel MA, Agarwal PK, Huelser BJ, McDermott KB, Roediger Iii HL. Test-enhanced learning in a middle school science classroom: The effects of quiz frequency and placement. Journal of Educational Psychology. 2011;103(2):399-414.

Participant	Total	Control	Control	Intervention	Р
Characteristics at the	n=127	No device	With Device	n=41	value
time of study		n=42	n=44		
enrollment					
Age, mean ± SD	52 ± 13	50 ± 15	53 ± 12	54 ± 13	0.42
Male, n (%)	81 (64)	27 (64)	30 (68)	24 (58)	0.65
Race, n (%)					0.97
White	81 (64)	28 (67)	28 (63)	25 (61)	
Black	34 (27)	10 (24)	11 (25)	13 (32)	
Hispanic/Asian/ Other/Unknown	12 (9)	4 (10)	5 (11)	3 (7)	
Months from transplant,	9.5 (3-17)	8.4 (3.7-16)	6.5 (3-13)	13 (4-19)	0.09
median (IQR)					
Organ, n (%)					0.73
Kidney	65 (51)	20 (48)	22 (50)	23 (56)	
Liver	62 (49)	22 (52)	22 (50)	18 (44)	
Pre-transplant diabetes, n (%)	35 (28)	14 (33)	10 (23)	11 (27)	0.54
NODAT, n (%)	28 (22)	7 (17)	7 (16)	14 (34)	0.08
eGFR , median (IQR)	64 (47-80)	57 (45-72)	65 (46-79)	68 (59-82)	0.08
Weight (kg), median (IQR)	84 (70-97)	84 (74-92)	82 (67-94)	83 (63-100)	0.72
Baseline BMI (kg/m²), median (IQR)	28 (24,32)	28 (25,31)	26 (23,33)	29 (25,32)	0.58
Baseline systolic blood	132 (119-143)	125 (116-139)	135 (121-143)	132 (121-147)	0.20
pressure (mm Hg), median (IQR)					
Baseline diastolic blood	75 (68-81)	72 (66-78)	76 (74-86)	77 (70-84)	<.01
pressure (mm Hg), median (IQR)					

Table 1. Characteristics of Study Participants Initially Randomized

SD=standard deviation, IQR=interquartile range, BMI=body mass index, NODAT=new onset diabetes after transplant

Table 2. Unadjusted weight and step data for study participants

Variable	Total n=117	Control No Device n=41	Control With Device n=40	Intervention n=36	P value
Baseline weight (kg), mean (SD)	84.5 (20.7)	84.8 (21.7)	82.5 (20.7)	86.3 (19.5)	0.54
End of study weight (kg), mean (SD)ª	86.2 (21.1)	86.0 (22.1)	85.5 (20.6)	87.1 (21.0)	0.84
Change in weight (kg), mean (SD) ^b	1.5 (4.5)	1.0 (3.9)	2.7 (5.3)	0.81 (4.0)	0.07
Change in weight (kg), Median [IQR] ^ь	0.91 [-0.91 to 3.9]	0.91 [-1.0 to 5.4]	2.4 [-0.45 to 5.4]	-0.45 [-1.4 to 3.4]	0.05
Variable	Total n=76	Control No Device 	Control With Device n=40	Intervention n=36	P value
Proportion of participant-days with \geq 7000 steps	0.5 <u>7</u> 3		0.4 <u>6</u> 5	0.6 <mark>82</mark>	<0.001
Proportion of days with ≥ 7000 steps at participant level mean (SD) Median [IQR]	0.51 (0.35) 0.51 [0.14-0.85]		0.43 (0.34) 0.36 (0.13-0.78)	0.60 (0.34) 0.72 [0.28-0.87]	<0.001
Daily steps throughout study period, mean (SD) Median [IQR]	7346-<u>7849</u> (3147<u>3887</u>) 6751-<u>7492</u> [4794<u>4982</u>- 9920<u>10214</u>]		7045-7346 (32964118) 6551-<u>6612</u> [4344<u>4194</u>- 65519802]	7691-<u>8368</u> (<u>3562</u>2978) 8150-<u>7908</u> [<u>53935972</u>- 1000010548]	0.30 <u><.0</u> 01
End of study steps, mean (SD) Median [IQR] ^c	8439 (3736) <u>7852</u> (4049)		7242_(<u>43494060</u>) 7121_6400 [4 <u>8534218</u> - 10012 <u>9474</u>]	8532 <u>8494</u> (39 <u>41</u> 07)	<u>0.19<.0</u> <u>01</u>

8455 <u>7527</u>		8754 <u>8058</u>	
55514948		60746560	
1001710212		1212010942	

Abbreviations: IQR=interquartile range, Kg=kilogram, SD=standard deviation ^aN=116 with baseline weight data, ^bN=103 with end of study weight data, ^c Steps reported for the last 2-week period of the intervention

Table 3. Unadjusted and adjusted results for the outcome of proportion of participant-days that ≥7000 were reached among 76 participants and 5,857 participant-days with step data.

	Model 1 (primary model) n=5,857		Model 2 (days with <1000 steps excluded ^a) n=5,549		Model 3 (with imputed step counts ^b) n=6,374		Model 4 (Model 1 + baseline characteristics) n=5,857	
Participant-days								
Variable	OR (95% CI)	P value	OR (95% CI)	P value	OR (95% CI)	P value	OR (95% CI)	P value
Intervention versus control with device	1.99 (1.03-3.87)	0.04	2.29 (1.56-4.52)	0.02	1.97 (1.78- 2.18)	<0.001	2.23 (1.06-4.71)	0.04
Age (years)							1.00 (0.98-1.03)	0.83
Race								0.57
White							Reference	
Black							0.60 (0.29-1.22)	
Hispanic							0.88 (0.31-2.41)	
Other							1.04 (0.18-5.90)	
Months from transplant							0.98 (0.93-1.03)	0.46
Allograft								
Kidney							Reference	
Liver/SLK							0.32 (0.16-0.63)	0.001
Baseline weight (kg)							1.00 (0.98-1.01)	0.89

^aA total of 308 participant-days achieved less than 1000 steps representing 5.3% of total participant-days. Abbreviations: kg=kilogram, OR=odds ratio, CI=confidence interval, SLK=simultaneous liver/kidney.

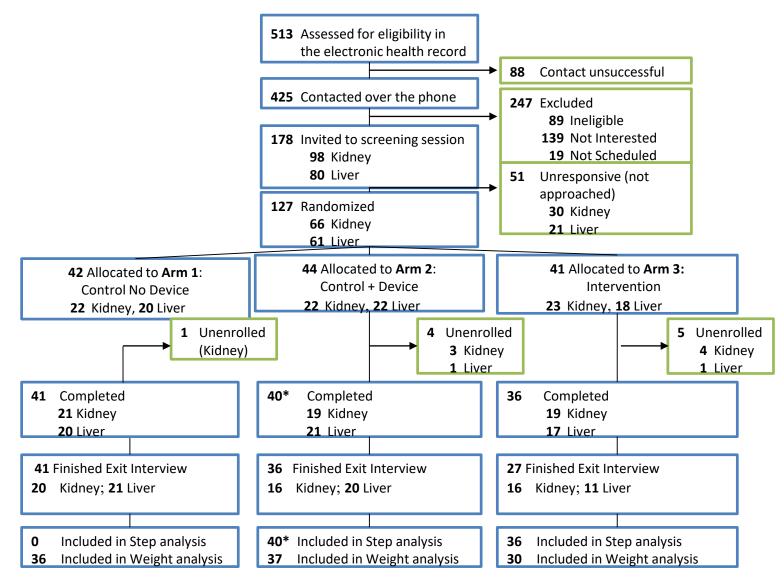
	Model 1		Model 2			
			(Model 1 + base characteristic			
Variable	β (95% Cl)	P value	β (95% CI)	P value		
Study arm		0.18		0.35		
Usual care control	Reference		Reference			
Control with device	1.70 (-0.35 - 3.75)		1.38 (-0.51 - 3.27)			
Intervention	-0.17 (-1.97 - 1.63)		0.58 (-1.20 - 2.36)			
Age (years)			-0.06 (-0.107 - 0.00)	0.03		
Race				0.24		
White			Reference			
Black			1.06 (-1.00 - 3.13)			
Hispanic			- 1.88 (-4.39 - 0.62)			
Other			0.50 (-1.99 - 2.98)			
Months from transplant			-0.24 (-0.360.12)	<0.01		
Allograft						
Kidney			Reference			
Liver transplant			1.39 (-0.20 - 2.98)	0.09		
Baseline weight (kg)			0.001 (-0.031 - 0.034)	0.12		

 Table 4. Unadjusted and adjusted results for the outcome of change in weight (kg) among 117

 participants with complete weight data

Interactions between study arm and organ and study arm and time from transplant were tested and were not significant. Model 1 is the primary pre-specified model. Model 2 is additionally adjusted for baseline weight, age race, organ, and months from transplant. Abbreviations: kg=kilogram, Cl=confidence interval, Simultaneous liver/kidney transplant was evaluated as liver transplant

Figure 1. Study flow diagram



* 1 patient died 10 days prior to study completion, steps were included in analysis. Patients in the Control No Device arm did not have measured steps. The Control + Device arm included an accelerometer to measure daily steps. The Intervention arm included an accelerometer, daily step goal targets with loss-framed financial incentives, and biweekly text messages with health engagement questions. **Figure 2.** Unadjusted distribution of step counts displayed by study arm for each 2-week study interval (n=40 control+device, n=36 intervention+device)

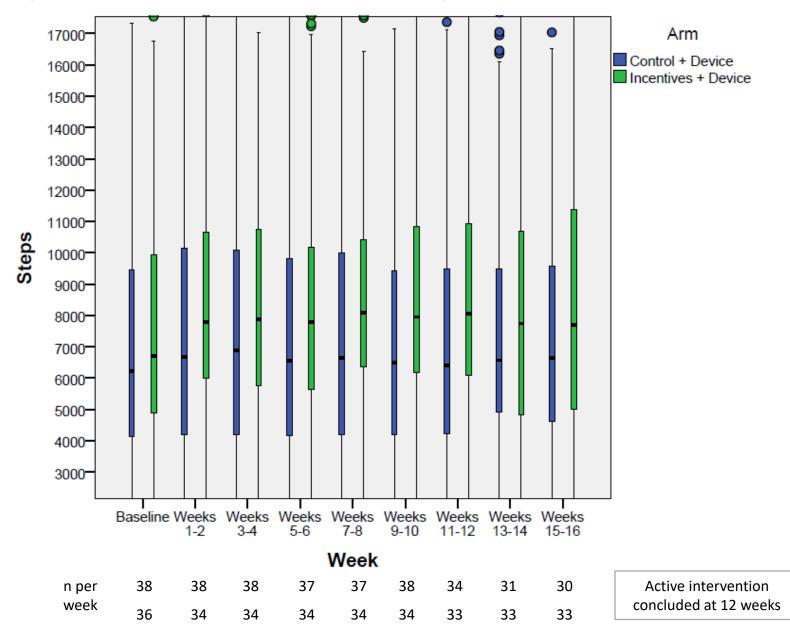


Figure 3: Mean absolute differences between step counts achieved and step count targets (n=6) by 2-week period in the intervention (n=36)

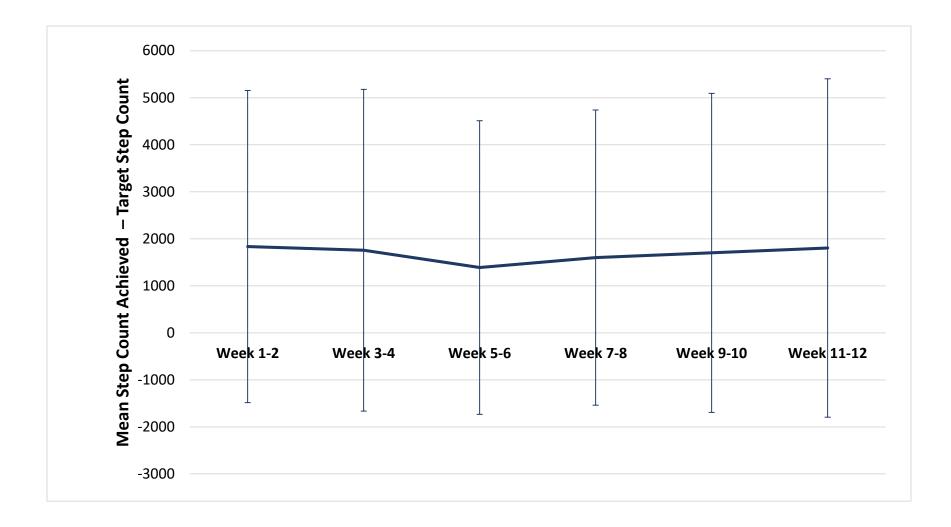
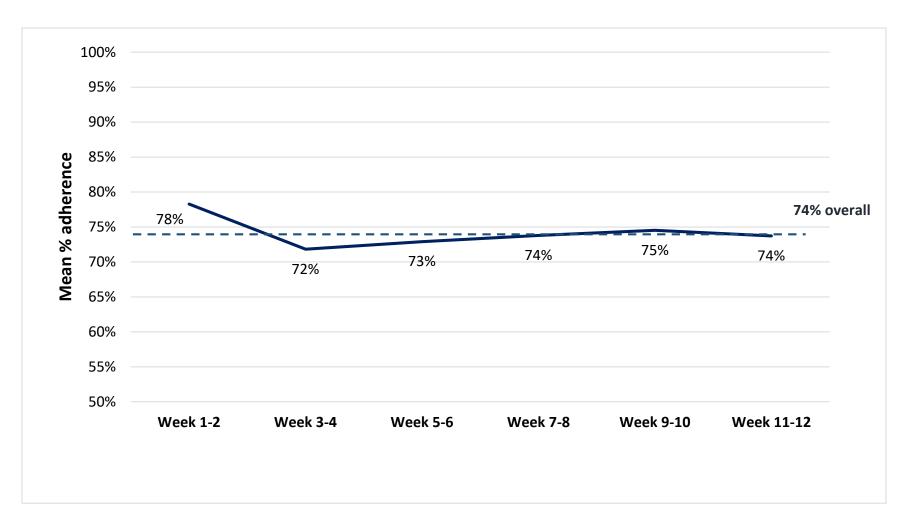


Figure 4. Mean percent adherence to step targets for each 2-week study interval in the incentives + device arm



The dashed line represents the mean percent adherence to step targets throughout the study period. The solid line represents the mean adherence to step targets within each 2-week interval.



Supplementary Appendix 1: Description of Way to Health Portal

Way to Health Summary of Data Protections

Introduction and Purpose

This document outlines how Protected Health Information is stored, secured and accessed on the Way to Health platform. For a complete list of data protections and associated policies and procedures, please visit <u>https://policy.waytohealth.org</u>.

What is Way to Health?

Way to Health (W2H) is a software platform developed by the Penn Center for Health Incentives and Behavioral Economics (CHIBE) and is currently operated through a partnership between CHIBE and the Penn Medicine Center for Health Care Innovation. W2H is an integrated, cloud-based platform that blends behavioral science with scalable digital technology to improve clinical outcomes. W2H automates many research functions necessary for conducting randomized controlled trials of healthy behavior interventions. The platform facilitates online and mobile participant enrollment; survey administration; integrated biomedical device data transmissions; automated randomization in a variety of schemes; automated communication with participants/patients via voice, text and email; delivery of financial and social incentives; utilization of gamification strategies and much more. More details are available at <u>https://waytohealth.org</u>.

Protected Health Information (PHI) Stored on the Platform

Way to Health can collect multiple pieces of data from patients and participants per the study requirements. This can include personally identifiable information (PII) such as name and date of birth and health information such as diagnosis or medications. This information can be requested and collected via secure customized surveys or direct integration with electronic health record systems (EHRs).

Access Controls

W2H uses a role-based access control (RBAC) approach to assure that participant confidentially and study integrity is preserved. Access and visibility is primary governed by the role of the individual accessing the system. Access is granted by invitation only and can be revoked at any time. More details are available here - <u>https://policy.waytohealth.org/#7-system-access-policy</u>.



Research Personnel: This includes roles such as principal investigators, project managers, research coordinators and statisticians. Staff such as principle investigators and statisticians are restricted using RBAC, with a role that provides them access to de-identified data sets only. Other staff such as project managers and research coordinators require access to identifiable data in order to conduct normal study operations such as follow up study visits, monitoring enrollment statuses, and updating contact information. These roles can toggle between identified and de-identified views as needed. Prior to receiving access to the platform, the study's project manager must confirm that the staff person has been added to the IRB and has completed their CITI Protection of Human Subjects Research Training – ORA. Research staff users must read and sign the W2H Data Security Agreement upon initial login to the platform. They cannot access PHI or any other data on the platform until that agreement has been reviewed and signed.

Way to Health Personnel: The W2H Team supports all research studies run on the platform. Default views within the platform for all W2H staff display de-identified participant data. As a part of support and troubleshooting, the W2H Team is trained to use only these de-identified views. In rare cases where the issue involves viewing identifiable participant data, the W2H team may need to view this data to assist the study team.

The W2H Team are employees of the University of Pennsylvania and Penn Medicine. All W2H team members have completed HIPAA Security training and CITI Protection of Human Subjects Research Training - ORA.

Access to the backend database is restricted and only available to a select group of developers. The database is accessible only via a secure VPN (Virtual Private Network) and cannot be accessed from the public internet at all, i.e. authorized users can only access the databases from within Penn's network and over a secure VPN channel.

Data Integrity Controls

To maximize security, W2H assumes that **all** data in the system is electronic protected health information (ePHI). Details of controls in place are available at https://policy.waytohealth.org/#17-data-integrity-policy and are summarized below.

Server Environments

All W2H servers are managed by Penn Medicine Academic Compute Services (PMACS).

Center for Health Care Innovation Penn Medicine 423 Guardian Drive Philadelphia, PA 19104



Encyption At-Rest

All data at-rest is stored on encrypted disks using encryption keys managed by W2H. Encrypted disks use AES encryption with a minimum of 256-bit keys, or keys and ciphers of equivalent or higher cryptographic strength. User passwords are never stored in clear text; they are "salted" and "hashed" to eliminate data leakage.

Encyption In-Transit

All data transmission is encrypted end to end using encryption keys managed by W2H. Transmission encryption keys use a minimum of 2048-bit RSA keys, or keys and ciphers of equivalent or higher cryptographic strength (e.g., 256-bit AES session keys in the case of IPsec encryption).

Data downloads are generally prohibited by policy. Where appropriate, most datasets are blinded of all personally identifiable information when exported for analysis. A limited number of exports including identifiers exist to assist research staff with recruitment tracking and study management efforts. These datasets are only accessible to certain user roles. These user roles are required to sign and adhere to a W2H Security Agreement as described above

Audit Logging and Monitoring

To monitor ongoing usage of the system and identify unauthorized usage of the system, all access to the application and the database are logged automatically. These logs are reviewed as described in the W2H policies.

Data Loss Prevention Controls

The intent here is to minimize data loss. This is done through the policies and procedures detailed here – Data Management Policy (<u>https://policy.waytohealth.org/#6-data-management-policy</u>), Disaster Recovery Policy (<u>https://policy.waytohealth.org/#13-disaster-recovery-policy</u>), Intrusion Detection Policy (<u>https://policy.waytohealth.org/#15-ids-policy</u>), and Vulnerability Scanning Policy (<u>https://policy.waytohealth.org/#16-vulnerability-scanning-policy</u>). This is summarized below.

Backups

W2H has automated procedures to create and maintain retrievable exact copies of ePHI utilizing our Backup Service. These backup procedures are run on a daily basis and stored in a



different location. Backups are encrypted. Backups are retained for a rolling 14 day period. Recovery from backups is also tested on a quarterly basis.

Disaster Recovery

W2H has policies and procedures in place for system recovery following a disruption resulting from a disaster (such as extended outages).

Security Scanning

Security is a paramount concern at W2H. We perform regular (at least monthly) vulnerability scans of our systems to identify and patch any known vulnerabilities in our systems. We also run Intrusion Detection Systems (IDS) to identify unauthorized system access.

Communication with human subjects

Individuals are asked to provide their name, an email address (personal or work), and phone number for the duration of the study. Participants are given the choice to receive automated study notifications and alerts via email, text message, phone or any combination of the above.

Way to Health Links to External Applications

Use of W2H includes access to an ecosystem of devices and web applications. This enables study teams to collect data such as steps, weight, blood pressure and patient reported outcomes. This data is paired with frequent behavioral feedback provided to the participant. For example, in a weight loss study the research team might establish daily or weekly weight goals for a participant, interface with an Internet-connected scale, and award the participant 10 points each day they weigh in and 100 points if they meet their weekly weight loss goal.

W2H has integrations with a variety of biometric and other devices (e.g. pedometers, scales, electronic pill bottles), communication services for sending/receiving SMS/MMS/IVR, communication services for sending email, Qualtrics for surveying, and Penn Medicine's Electronic Health Record (EHR) Epic.

Data Flows

There are three primary data flows we use for device integrations: 1.) consumer-authenticated devices, 2.) researcher-managed devices with API querying, and 3.) researcher-managed devices with data push. All three flows involve the physical devices connected to and communicating with a vendor-managed server. The mechanism for how the data gets from the



vendor server to Way to Health, and the authentication mechanism used for that connection, differ between the three flows.

Consumer-authenticated Device

Examples: Fitbit, Withings

For a consumer-authenticated device, the participant will create an account with the device vendor, link their device to the account (frequently setting up the device via Bluetooth), and then authorize Way to Health to access their data using a mechanism such as OAuth. For a research study, devices will frequently be purchased by the study and provided to the participants, but the account on the vendor system will belong to the participant rather than to the research team.

Once the participant's account is authenticated to Way to Health, we have an hourly background job that queries the vendor API for activity since the last data point that was downloaded, using an API endpoint like "show all activity since Y/m/d".

Researcher-managed Device with API Queries

Examples: Adheretech, Wisepill

In the researcher-managed device flows, the participant does not interact with or create an account on the vendor portal. Instead, the researcher has an account where they can view devices purchased, possibly register or set up devices, and see activity from the devices. Typically, these devices communicate with the vendor portal through a cellular connection (sometimes through an intermediate hub), rather than through a participant's smartphone and Bluetooth.

Once the device is configured on the vendor portal the researcher will enter a device ID (e.g. a serial number, MAC address, or other ID) into the participant's profile in Way to Health. Way to Health will then do an hourly query for activity since the last downloaded data point.

Researcher-managed Device with Data Push

Example: Qualcomm 2net SP

In this flow, similar to the previous researcher-managed device flow, the device is configured by the research team in the vendor portal. However, rather than an hourly process where Way to Health pulls data from the vendor server, instead the vendor server pushes data to Way to Health as it is processed from the device or hub.

Qualtrics



Prior to having our own survey builder, study teams exclusively used our Qualtrics integration to manage survey administration. This feature is only being used for studies started on the platform before March 2018. Survey answers are stored on the Qualtrics server before we retrieve them and save them on the platform. All interactions between a participant and the Qualtrics server are deidentified. Study staff members review the survey content to ensure that no questions in any of the surveys ask for patient identifiers. To ensure no patient identifiable data is stored by Qualtrics we use randomly generated 64 bit identifiers to link responses in Qualtrics to study events in our system. No PHI will ever be stored by our application in Qualtrics.

Communication Vendors

Most studies built on the platform employ some form of notifying participants and research coordinators either by text message, IVR or email. For text messaging and IVR, W2H uses Twilio Cloud Communications (http://twilio.com). While Twilio logs the content of each message that passes through its system along with the phone number, W2H automatically deletes the content of the messages from Twilio continuously. This allows W2H to collect health information such as a patient reported blood pressure readings.

We use Sendgrid (<u>https://sendgrid.com/</u>) for all email communications. W2H fully recognizes that emails are not a secure communication channel. Thus, emails auto-generated by W2H do not contain ePHI. This is also communicated to study leads and project managers.

Electronic Health Record

W2H is integrated with Penn Medicine's EHR Epic. W2H can link a participant profile with a patient's chart in Epic using the patient's MRN. W2H allows the user to configure additional fields for validation such as name, address and phone number.

Using this integration, W2H can retrieve study relevant data from Epic, primarily appointment data. Appointment dates can be used to trigger actions in the W2H intervention such as starting a participant after surgery or sending a reminder of an upcoming appointment. W2H also has the capability to send data sets collected on the platform into Epic flowsheets. These data sets are reviewed and pushed over by clinicians who have access to W2H.

Supplementary Appendix 2. Health engagement questions and percent answered correctly in the devices + incentives arm (n=36)

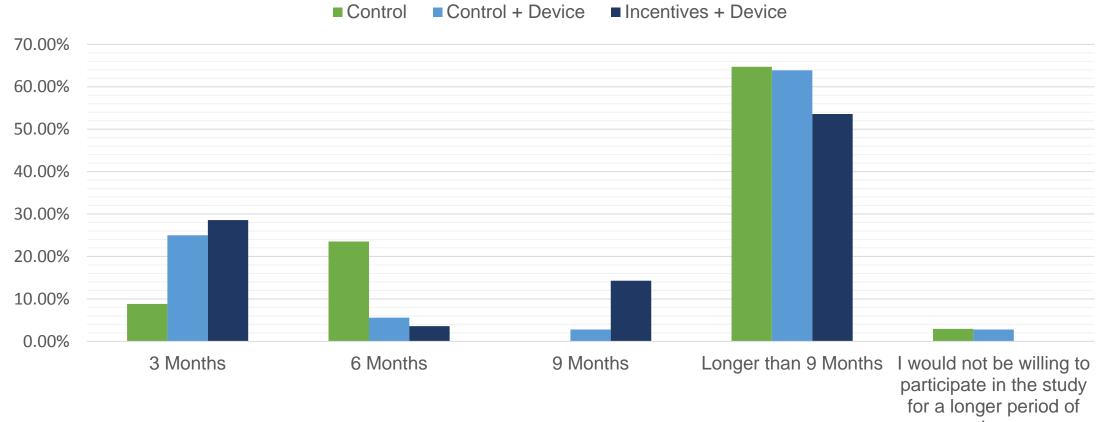
Question	Percent	Percent
	Questions Answered	Correct
1. It is okay to use the same cutting board for all food items without cleaning it with soapy water in		
between.	31 (86.1%)	30 (96.8%)
2. When buying milk, cheese, and other dairy	22 (04 70()	20 (00 00()
products buy only pasteurized products.3. You need to make sure you are receiving at least	33 (91.7%)	30 (90.9%)
1000 mg of calcium per day after transplant.	30 (83.3%)	24 (80.0%)
4. Half of my plate at a meal should contain fruit and vegetables.	26 (72.2%)	24 (92.3%)
5. Avoiding soda or juice and drinking calorie-free drinks (water, unsweetened tea or coffee, diet soda) can help in weight loss.		27 (93.1%)
6. Eating fish 2 or 3 times a week can give you heart health benefits from Omega-3 fatty acids.	31 (86.1%)	30 (96.8%)
7. Yogurt as a snack is a good source of protein.	31 (86.1%)	31 (100.0%)
8. Half of the grains (breads, cereals, pasta) you consume should be whole grains (such as whole wheat, oats).	22 (88 00/)	21 (06 0% 0
 Gookies, crackers, and bagels are a good source of protein. 	32 (88.9%) 27 (75.0%)	31 (96.9%0 27 (100.0%)
 Cooking at home instead of eating out can help you keep track of your calories better. 		31 (100.0%)
11. Fruits have less sugar than vegetables.	20 (83.3%)	19 (95.0)%
12. Sausages, hot dogs, and bacon have a lot of saturated fat and can raise your cholesterol.	31 (86.1%)	31 (100.0%)
13. 2.5 hours of exercise each week lowers the risk of heart disease, stroke, high blood pressure, diabetes, and can make your mood better.	27 (75.0%)	27 (100.0%)
14. Spreading physical activity across at least 3 days a week can help keep you from getting injured and feeling tired.	30 (83.3%)	29 (96.7%)
15. Gardening or carrying in groceries count as exercise.	28 (77.8%)	24 (85.7%)
16. It is not important to warm up or cool down before and after exercise.	33 (91.7%)	31 (93.9%)
17. Lifting weights increases bone strength and muscle fitness.	33 (91.7%)	32 (97.0%)
18. Taking stairs instead of using the elevator is good exercise.	26 (80.6%)	26 (100.0%)
19. One hour of exercise per week is enough.	26 (80.6%)	25 (96.6%)
20. Making time for a brisk walk just 10 minutes per day can help you stay in shape.	25 (69.4%)	23 (92.0%)

21. Transplant medications like tacrolimus/Prograf will cause weight loss.	31 (86.1%)	28 (90.3%)
22. Walking for 30 minutes every day at a moderate pace is enough exercise to keep you healthy.	32 (88.9%)	26 (81.3%)
23. Adults should do strength exercises like lifting weights, sit ups or push-ups at least 2 days per week.	30 (83.3%)	29 (96.7%)
24. Walking in place while watching TV can help you increase your activity levels.	33 (91.7%)	33 (100.0%)
On average 84% of questions were answered 85% were and	worod correctly	· · ·

On average, 84% of questions were answered, 95% were answered correctly

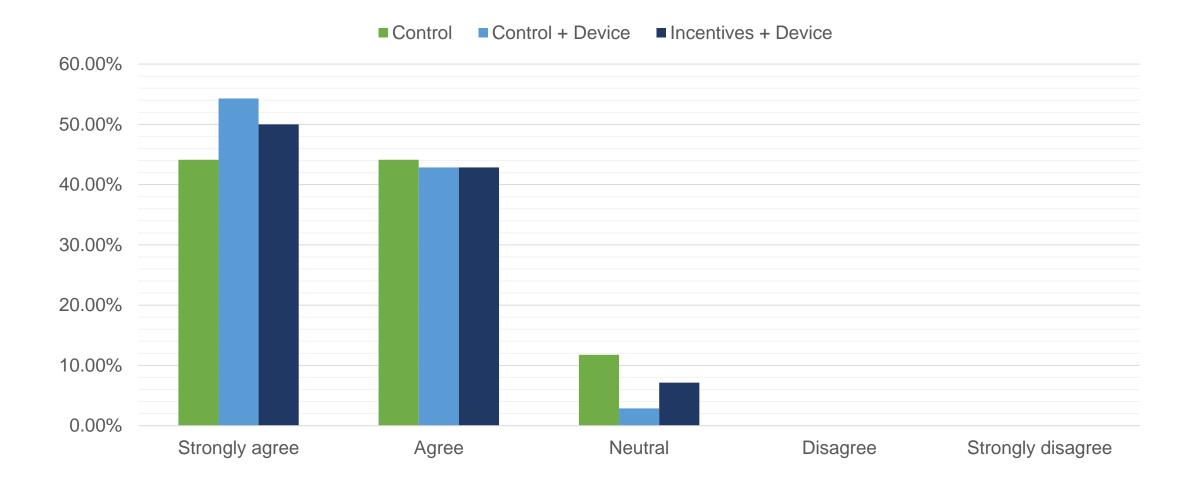
Supplementary Appendix 3 – Answers to Exit Survey Questions by Study Arm

How much longer would you be willing to participate in the study if given the opportunity?

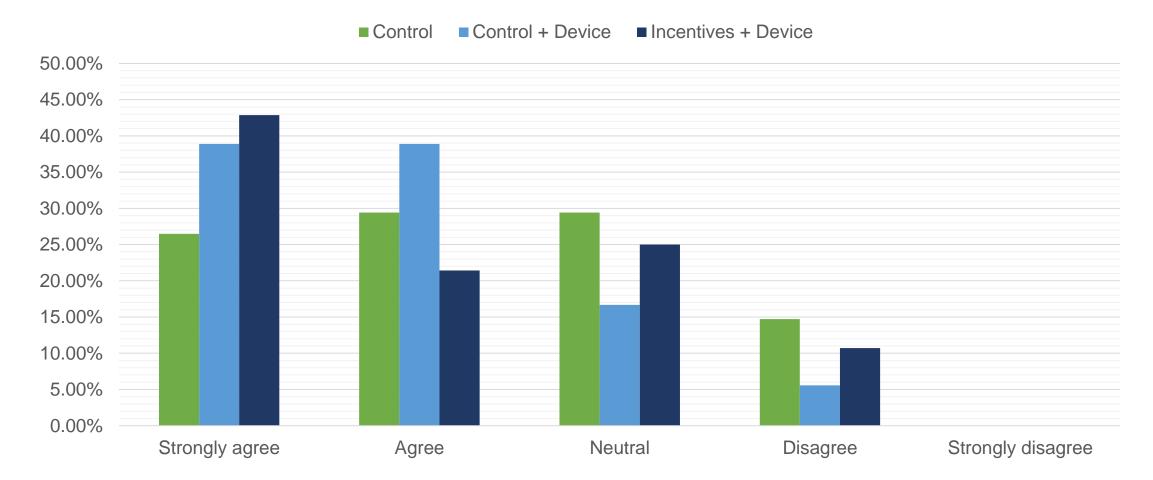


time

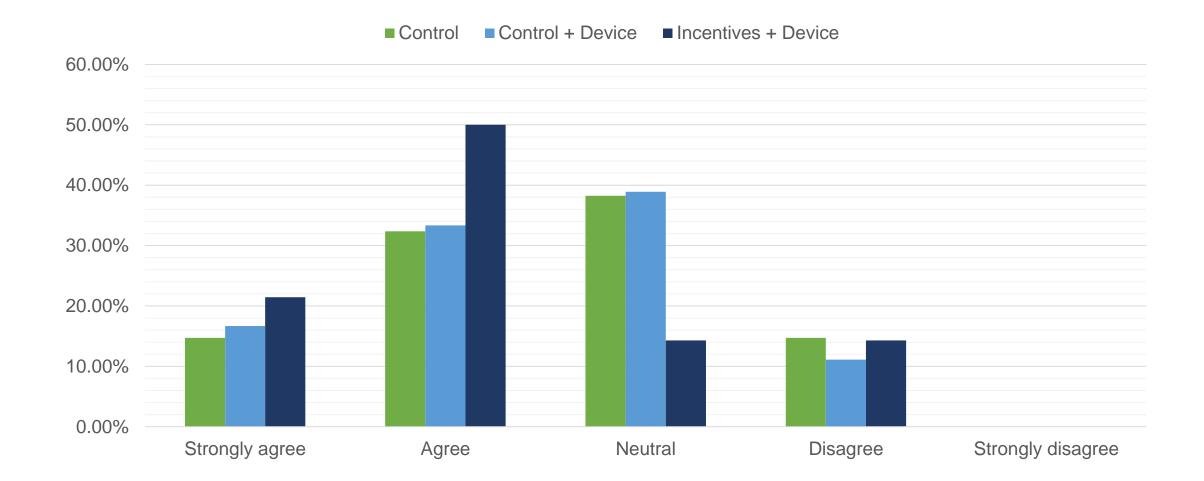
I enjoyed participating in this study



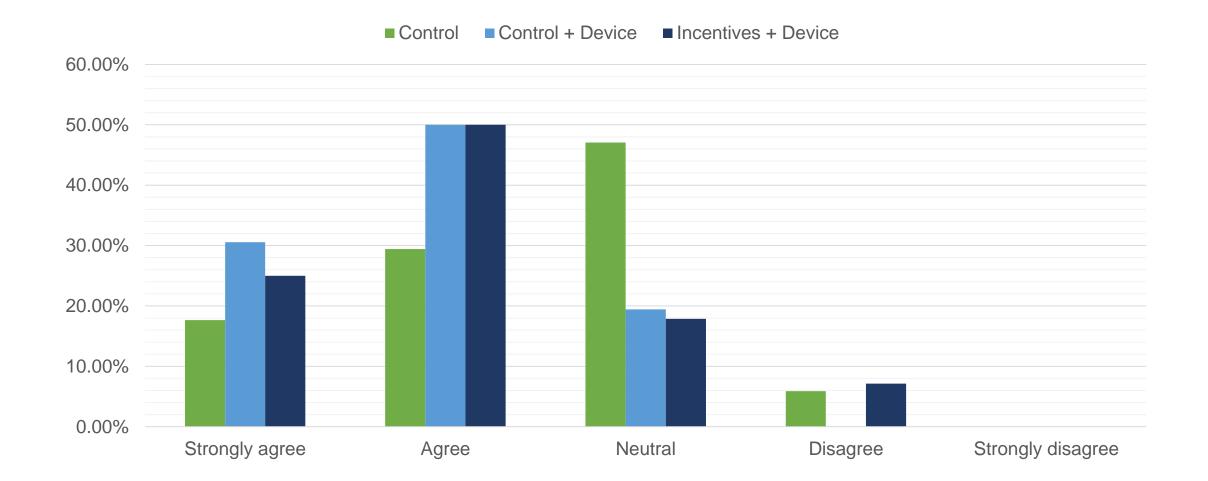
This study has helped to increase my physical activity



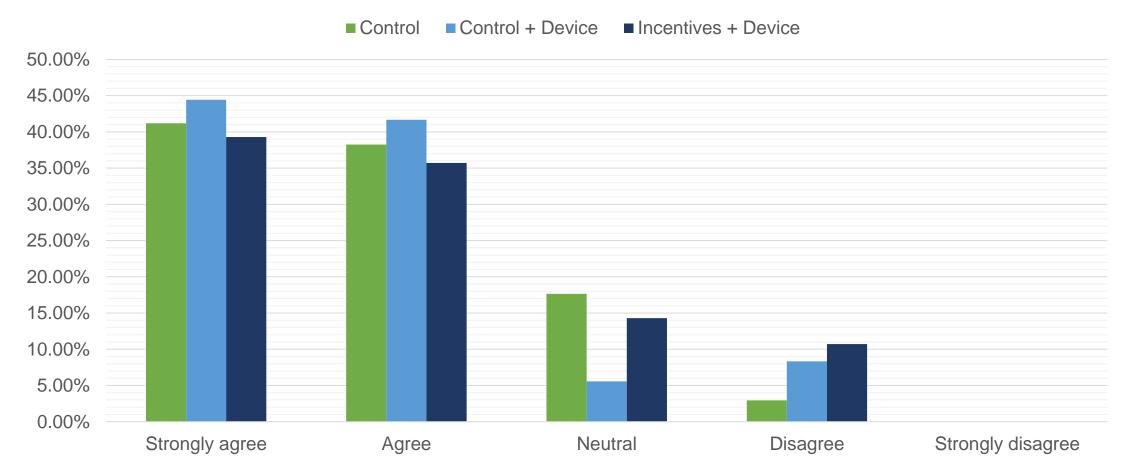
This study helped me keep a healthy diet



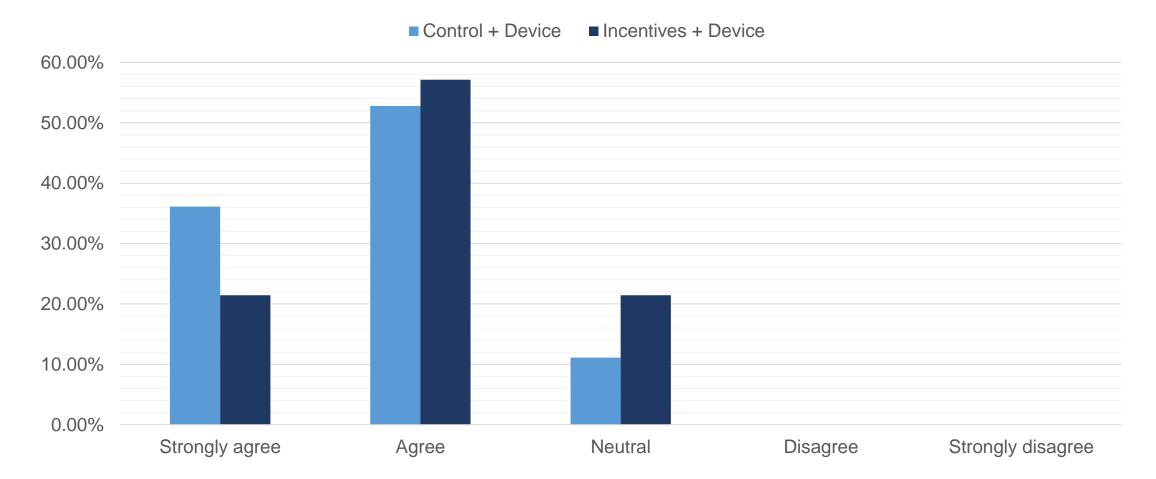
This study has helped to improve my health



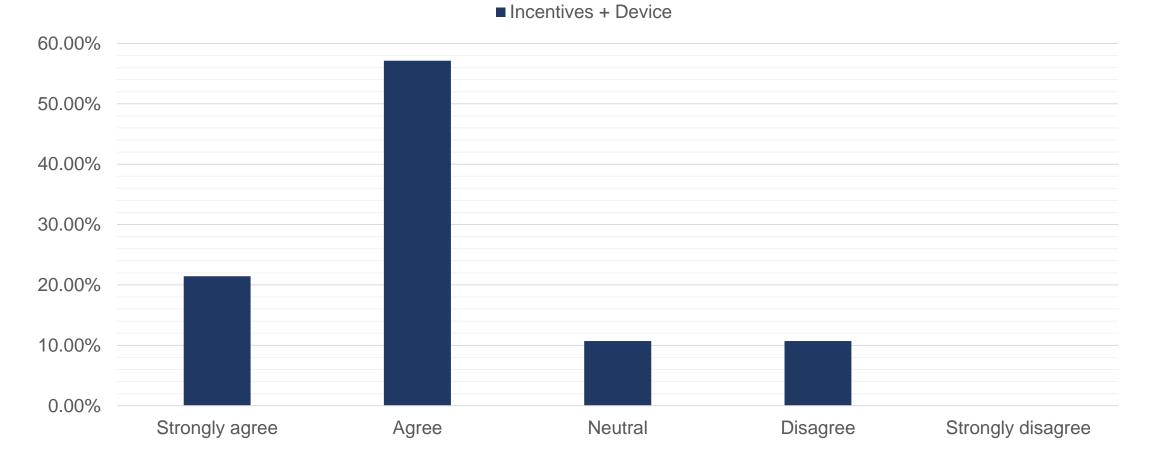
I am committed to walking for exercise every day



The device helped me improve my health (device arms only)



The text messages with questions that I received as part of this study were helpful to me (incentives + device arm only))



Supplementary Appendix 4. Summary of selected open-ended participant feedback about the study intervention.

Positive Feedback from Participants:		
Arm 1 - no device control		
Enrollment was a good motivator to improve health and walking	(n=9)	
Better awareness of weight and/or activity	(n=5)	
More accountable about health/activity	(n=2)	
Arm 2 - control with device		
Monitoring via device and knowledge of steps kept participant accountable	(n=20)	
Better awareness of weight and/or diet	(n=2)	
Arm 3 - intervention		
Daily texts were helpful	(n=2)	
Study monitoring via device and daily goal were motivating	(n=22)	
Motivated better diet	(n=4)	
Incentives were motivating	(n=1)	
Goals early in recovery were helpful	(n=2)	
Health questions were informative	(n=3)	
Ways study could be improved:		
Technical difficulties with Device/Battery Issues	(n=13)	
Way to log food/Nutrition Plan	(n=2)	
Credit/Tracking of other exercise	(n=3)	
More interaction with study team	(n=2)	
Activity in bad weather was hard	(n=2)	
Health questions not helpful	(n=3)	
Wearing device on wrist all the time not ideal	(n=2)	
Lack of Bilingual Texts	(n=1)	



Nutrition and Liver Transplant

It is important to eat a healthy diet after transplant. Good nutrition is important for you and for the health of your newly transplanted liver. Healthy food choices can help you:

- 1. Maintain normal blood sugar, helping to prevent diabetes.
- 2. Maintain a healthy weight.
- 3. Maintain normal blood pressure through salt control.
- 4. Keep blood fats like cholesterol in normal range.

CALORIES

Carbohydrates, proteins and fats provide calories. Eat enough calories to maintain a healthy weight. Excess calories will lead to weight gain. **Healthy food choices** will help you maintain a **healthy weight**. Limit high calorie, fatty foods and sugars.

CARBOHYDRATES AND BLOOD SUGAR

Some of the medications you must take to prevent rejection of your newly transplanted liver can lead to high blood sugars. Your blood sugar might be high even if you have never been a diabetic. The transplant team might instruct you to check your blood sugar at home. Juice, soda, desserts and candy can raise your blood sugar. Carbohydrates (carbs) in foods like bread, pasta, rice and potato, also turn into "sugar" in the blood. The healthiest carbs are whole grains like whole wheat bread, whole grain cereals, whole-wheat pasta and brown rice.

Clinical Nutrition Support Services Hospital of the University of Pennsylvania

[©] Copyright 2015 by the Trustees of the University of Pennsylvania. All rights reserved. No part of this publication may be reproduced without permission in writing from the Trustees of the University of Pennsylvania

PROTEIN

You need more protein to help with healing after transplant surgery. Healing usually takes between 6-8 weeks. Good sources of protein include fish, poultry, egg whites, egg substitutes, lean meat, and low fat dairy (milk, yogurt and cottage cheese). If your appetite is poor, we may recommend a supplement like Glucerna® or Ensure Plus®. To insure you are eating enough protein, include a protein food at breakfast, lunch and dinner. Milk on cereal at breakfast, tuna salad sandwich at lunch, grilled chicken breast at dinner and a yogurt at bedtime are examples of how to achieve this goal. Once you have healed, you should resume a more moderate protein.

FATS

Fats provide more than double the calories of protein and carbs. Choose lean proteins like fish and poultry. Purchase lean meats and trim the visible fat. Choose reduced or no fat milk and yogurt. Limit added fats, like butter and sour cream on baked potatoes. Limit fried foods, instead broil, roast or grill. Store bought cookies, crackers and snack foods are usually high in fat. They often are a source of trans- fats. Trans- fats can increase your cholesterol. Use canola oil, olive oil and cooking sprays.

<u>SODIUM</u>

The 2010 Dietary Guidelines for Americans recommend using less than 2300 milligrams of sodium per day. Seventy-five percent of our sodium intake comes from processed convenience and prepared foods. Canned soups, deli meats and cheeses, and many snack foods like chips and crackers are usually high in sodium. Remember that sea salt has the same amount of salt as regular table salt. If you have any questions, ask the dietitian to review this diet with you. Restaurant foods contain lots of sodium. Order grilled, baked, or roasted, chicken, fish or lean meat. Ask that they be prepared without additional salt. Request that sauces be served on the side. Many restaurants have a web site where you can check sodium information before you go. Better yet, limit how often you eat out.

FLUID

Water and other no calorie beverages are the best choice. Too much juice and soda adds sugar calories.

Clinical Nutrition Support Services Hospital of the University of Pennsylvania

© Copyright 2015 by the Trustees of the University of Pennsylvania. All rights reserved. No part of this publication may be reproduced without permission in writing from the Trustees of the University of Pennsylvania

POTASSIUM

Certain immunosuppressant medications may cause elevated blood potassium. This is often temporary and may change with medication adjustments. If you need a low potassium diet, the dietitian will provide you with a list of foods to help guide your choices. High potassium foods include oranges, orange juice, banana, cantaloupe, honeydew, baked potato, yams, spinach, tomato sauce, spaghetti sauce and tomato juice. It is not mandatory to list potassium on the nutrition label. The absence of potassium on the label does not mean there is no potassium in the food.

A healthy diet along with a healthy life style will provide the best environment for your liver. Healthy lifestyle choices include physical activity. Try to include some form of physical activity every day. Walking is easy and free. Walk the dog. Walk with a friend. Walk whenever you can. Be certain to wear comfortable shoes and clothes. Health experts recommend that we take 10,000 steps a day. Other activities include biking, dancing, swimming etc. Just think about moving your body. Always check with your doctor before beginning an exercise program.

See <u>www.choosemyplate.gov</u> for further details on choosing a healthy diet.

Updated: 11/10/2015 KED

Clinical Nutrition Support Services Hospital of the University of Pennsylvania

© Copyright 2015 by the Trustees of the University of Pennsylvania. All rights reserved. No part of this publication may be reproduced without permission in writing from the Trustees of the University of Pennsylvania