Supplementary Online Content

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This supplementary material has been provided by the authors to give readers additional information about their work.

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eMethods 1: Outcome ascertainment

The schema displays data collection for the primary outcome of LDL, the secondary adherence outcome and the spillover analyses.

**Primary outcome of LDL-c:** The primary outcome was change in LDL-c ($\Delta_{LDL}$), from baseline to a target date of 12 months, defined as 360 days ($+28/-14$ days). These LDL-c measurements were ordered by study personnel through affiliated labs or a national laboratory vendor, per participant preferences. Where available, study staff also collected LDL-c values measured through routine care and recorded in the electronic medical record (EMR).

An acceptable 12-month LDL outcome was defined as: an LDL measured using a study ordered lab or a lab obtained in clinical care on or after day 346 after the index date (date of randomization) and on or before 388 days after the index date. We provided a 42-day outcome measurement window in order to allow time for multiple reminders to participants to visit the lab for cholesterol measurement.

**Secondary pre-specified outcome of adherence:** A secondary outcome was statin adherence measured through pill bottle opening. Each day the pill bottle was opened, it electronically transmitted a signal to Way To Health. A participant could also be recorded as adherent in the database if he or she reported pill bottle malfunction and indicated that adherence data were not properly collected. In this case, staff promptly diagnosed and corrected the problem. Adherence was pre-defined as the number of daily pill bottle openings during the 12-month intervention.

**Pre-specified exploratory outcome of Hemoglobin A1c (HbA1c):** An exploratory outcome among patients with a diabetes diagnosis and recruited from Penn Medicine was Hemoglobin A1c. Using the electronic medical record, we collected usual care HgbA1c measurements in the baseline period (up to 6 months prior to and including the trial randomization date) and then within a 3 month window around 12 months post-randomization (i.e., between 9 and 15 months after randomization). Only individuals with at least one measurement in both periods were included. Within each period, if participants had multiple HgbA1c measurements, we used their median value. For each arm, we examined the distribution of HgbA1c in baseline period and the change from baseline to 12 months.

**Pre-specified exploratory outcome of systolic blood pressure:** Exploratory outcomes among patients with a hypertension diagnosis and recruited from Penn Medicine were systolic and diastolic blood pressures. Only systolic blood pressure (SBP) values are reported in the manuscript. Using the electronic medical record, we collected usual care SBP measurements in the baseline period (up to 6 months prior to and including the trial randomization date) and then within a 3 month window around 12 months post-randomization (i.e., between 9 and 15 months after randomization). Only individuals with at least one measurement in both periods were included. Within each period, if participants had multiple SBP measurements, we used their median value. For each arm, we examined the distribution of SBP in baseline period and the change from baseline to 12 months.
### eMethods 2: Inclusion and exclusion criteria

#### A) Eligibility criteria related to LDL cholesterol*

| Eligibility Criterion | Diagnosis or Risk Criterion | Population* |
|-----------------------|-----------------------------|-------------|
| LDL cholesterol       | Any$^1$ >190 mg/dl$^2$       | >190 mg/dl$^2$ |
|                        | Diabetes$^1$ Initially >130; revised to >100 mg/dl$^2$ | >100 mg/dl$^2$ |
|                        | Diagnosis of clinical ASCVD$^1$ Initially >130; revised to >100 mg/dl$^2$ | >100 mg/dl$^2$ |
|                        | ASCVD 10-year Risk >7.5%$^1$ >100 mg/dl$^2$ | >100 mg/dl$^2$ |

$^1$ Participants were >=18 years, except for participants with a diagnosis of diabetes who were 40 to 75 years of age

$^2$ Recorded as part of usual care

Abbreviations: LDL – low density lipoprotein cholesterol; ASCVD - Atherosclerotic Cardiovascular Disease

* Participants enrolled through Penn Medicine from January 2015 until March 2017. Participants enrolled from Lancaster General Health from April 2016 until March 2017.

#### B) Eligibility related to statin use

All participants attested to an active prescription to any statin medication. Patients also had to demonstrate evidence of nonadherence to the statin, which was ascertained using the 8-item Morisky Medication Adherence Questionnaire (MMAS-8). The MMAS includes 8 items that ask about medication adherence in different ways, such as asking about forgetting, skipping, and problems with adherence during travelling. Any response indicating adherence adds a point to the score. The score ranges from 0 to 8. Imperfect adherence was defined as a score less than 8 on the MMAS assessed during enrollment. A patient had to indicate with ≥1 response that they had less than perfect adherence to their statin.

1. Morisky DE, Green LW, Levine DM. Concurrent and predictive validity of a self-reported measure of medication adherence. Med Care. 1986 Jan;24(1):67-74. PMID: 3945130.
2. Morisky DE, Ang A, Krousel-Wood M, Ward HJ. Predictive validity of a medication adherence measure in an outpatient setting. J Clin Hypertens. 2008 May;10(5):348-54. PMCID: PMC2562622.
**eFigure 1. Prerandomization Invitation, Screening, and Exclusion**

Invited based on medical record from Penn Medicine Health System (n=6131)

- Not interested/Lost to follow up (n = 4582)
- Screened (n = 1549)

Invited based on medical record from Lancaster General Hospital (LGH) (n = 1275)

- Not interested/Lost to follow up (n = 1105)
- Screened (n = 170)

Excluded (n = 889)

| Reason | n |
|--------|---|
| Perfect Adherence | 680 |
| Declined Consent | 59 |
| No eligible statin Rx | 47 |
| Statin allergy (self-reported) | 31 |
| Missing or ineligible LDL at baseline | 30 |
| Did not complete screening survey | 26 |
| Disqualifying medical condition(s) | 19 |
| Did not provide SSN | 15 |
| Participating in similar study | 8 |
| No cellular service for pill bottle use | 0 |

*participants may be ineligible for multiple reasons

Eligible & sent electronic pill bottle (n = 660)

- Did not activate device (n = 4)
- Randomized (n = 656)

Excluded (n = 62)

| Reason | n |
|--------|---|
| Missing or ineligible LDL at baseline | 21 |
| Did not complete screening survey | 20 |
| Perfect Adherence | 17 |
| Did not provide SSN | 3 |
| No cellular service for pill bottle use | 1 |
| Declined Consent | 0 |
| No eligible statin Rx | 0 |
| Statin allergy (self-reported) | 0 |
| Disqualifying medical condition(s) | 0 |
| Participating in similar study | 0 |

Eligible & sent electronic pill bottle (n = 108)

- Randomized (n = 106)
- Did not activate device (n = 0)

Total Randomized (n = 764)
### eMethods 3: List of baseline assessments

| Measure                          | Description                                                                 | Timepoint(s) of Administration |
|---------------------------------|-----------------------------------------------------------------------------|---------------------------------|
| Exclusion Questionnaire         | 9-item survey confirming eligibility                                         | Baseline                        |
| Demographic Questionnaire       | 5-item survey                                                               | Baseline                        |
| Patience                        | 1 question on self-rated patience                                          | Baseline                        |
| Life Satisfaction               | 1 question on self-rated life satisfaction                                  | Baseline                        |
| Statistical Questionnaire (SNS) | 8-item survey measuring comfort with fractions, percentages, and mathematical scenarios | Baseline                        |
| Risk                            | 1 question on self-rated risk-tasking                                      | Baseline/12 month               |
| Stages of Change                | 1 question which measures health behavioral change tailored to adherence    | Baseline/6/12/18 month          |
| Financial Decision-Making (Slack) | 6-item survey measuring perception of disposable income                     | Baseline/6/12/18 month          |
| Incentive Questionnaire         | 2-item survey measuring perception of the effects of financial incentives on adherence | Baseline/6/12/18 month          |

1. Fagerlin, A., Zikmund-Fisher, B.J., Ubel, P.A., Jankovic, A., Derry, H.A., & Smith, D.M. Measuring numeracy without a math test: Development of the Subjective Numeracy Scale (SNS). Medical Decision Making, 2007: 27: 672-680.
2. Nigg, C.R., Burbank, P., Padula, C., Dufresne, R., Rossi, J. S., Velicer, W. F., Laforge, R. G. & Prochaska, J. O. (1999). “Stages of change across ten health risk behaviors for older adults.” The Gerontologist, 39, 473-482
3. Zauberman, G. & Lynch, J.G. (2005) Resource Slack and Propensity to Discount Delayed Investments of Time Versus Money. Journal of Experimental Psychology: General, 134, 23-37.
eMethods 4: Smart pill bottles used in the trial

Prior to randomization, every trial participant received a smart pill bottle, which used a cellular network to transmit a record of the bottle opening to the Way to Health platform. Over the course of the trial, we sequentially provided three different bottles from different manufacturers to participants. Model 1 was removed from service with the phasing out of a cellphone network standard; the bottle was incompatible with the new standard. Model 2 was initially chosen to replace Model 1, but the manufacturer was unable to supply a sufficient quantity of devices in a timely fashion and feedback about the devices indicated some dissatisfaction among participants. The majority of our study was conducted using Model 3. A total of 589 (77%) participants used only Model 3. Including the additional 117 participants who were ultimately switched to Model 3, a total of 696 (91%) participants used Model 3 during most if not all of the study.

| Pill Bottle Model | Started: N (% of Total) | Switched: N (% of Subjects Started) |
|-------------------|------------------------|-------------------------------------|
| 1                 | 123 (16.1%)            | 83 (67.5%)                          |
| 2                 | 52 (6.8%)              | 49 (94.2%)                          |
| 3                 | 589 (77.1%)            | 0 (0.0%)                            |
| Total             | 764 (100.0%)           | 132 (17.2%)                         |

^a 15 switched to Model 2 only; 59 switched to Model 3 only; 9 switched to model 2 and subsequently to model 3
^b all 49 switched to Model 3
eMethods 5: Methods related to administration of financial incentives

Over a 12-month period, individuals in the three intervention arms were eligible for financial incentives based on their daily statin adherence (Process arm), LDL-C value every 3 months (Outcomes arm), or both (Process plus Outcomes arm). We delivered statin adherence incentives as a sweepstakes to invoke people’s tendency to overestimate small probabilities. One daily bottle opening made the Process and Process plus Outcomes participants eligible for that day’s incentive. For the Process and Process plus Outcomes arms, each participant was assigned a 2-digit number. Every day, a random 2-digit number was generated by the Way To Health platform and compared to eligible participants’ assigned numbers to determine the size of the financial incentives. Participants in these arms were informed about their earnings the following day. For the Process arm, and the Process plus Outcomes arm, we invoked loss aversion through messages to non-adherent participants about the reward that they might have missed. Incentives for LDL-c reduction in the Outcomes and Process plus Outcomes arms were delivered without a sweepstakes.

**Process Arm:** If both digits matched (1 in 100 probability), an adherent participant received $50. If 1 digit matched (18 in 100 probability), an adherent participant received $5. A fully adherent participant in a financial incentives arm could earn on average $1.40/day.

**Outcomes Arm:** Participants in the Outcomes arms received $126 each time their LDL had decreased at least 10 mg/dl in the 3 months since the last visit. Over a year, these payments were equivalent to the expected value of the process arm. A participant who achieved an LDL-c reduction >20 mg/dl during one quarter and maintained that reduction the next quarter would receive the outcome incentive at the end of both quarters, even if no further reduction in LDL-c took place during the second quarter.

**Process plus Outcomes Arm:** Participants were eligible for daily sweepstake rewards, but with half the expected monetary value of the Process Arm, and for 3-monthly LDL-c rewards at half the value of the Outcomes arm. The payment for the Process with Outcomes Incentive arm were half this value, or $63 and the sweepstakes winnings were $2.50 for a one-digit match and $25 for a two-digit match.

Notably, participants in all three intervention arms had the opportunity to earn $504 if they met all adherence and/or LDL reduction targets for their assigned arm.
eMethods 6: Methods related to secondary and sensitivity analyses

The linear model for the primary outcome was refit using the same covariates and outcome of $\Delta_{LDL}$ from baseline to 18 months, 6-months after the conclusion of the interventions, to assess durability of response.

We assessed differences in mean $\Delta_{LDL}$ from baseline across the four visits of the intervention period using a mixed effects model. We contrasted the control arm with each of the intervention arms using a linear combination of the 3, 6, 9 and 12-month visits. We repeated these analyses by pre-specified subgroups; no test of an interaction was used as the sample lacked statistical power to detect meaningful differences.

Using a simple linear model, we reported measured adherence for both the 12-month intervention period, and differences between any intervention arms and control.

Sensitivity analyses included (1) a complete case analysis and (2) a model adjusted for gender, education, income, and race.

As a post-hoc analysis, we assessed differences in mean $\Delta_{LDL}$ from 3-months to 6, 9, and 12-months. Models were adjusted for LDL-c at baseline and stratified by site, using multiply imputed data.
**eTable 1: Adherence scores for participants enrolled in the trial, by study group**

| Variable                                      | Total (n=764) | Control (n=190) | Process (n=194) | Outcomes (n=187) | Process and Outcomes (n=187) |
|-----------------------------------------------|---------------|-----------------|-----------------|------------------|-----------------------------|
| Morisky Medication Adherence Questionnaire Level, n (%) |               |                 |                 |                  |                             |
| Medium Adherence                              | 385 (50.4)    | 97 (51.1)       | 106 (54.6)      | 94 (50.3)        | 88 (45.6)                   |
| Low Adherence                                 | 379 (49.6)    | 93 (48.9)       | 88 (45.4)       | 93 (49.7)        | 105 (54.4)                  |
| Morisky Medication Adherence Questionnaire Score, mean (SD) | 5.7 (1.4)     | 5.6 (1.4)       | 5.7 (1.4)       | 5.8 (1.2)        | 5.6 (1.4)                   |

*Score 6-7 is medium adherence; < 6 is low adherence.*
**eTable 2: Baseline characteristics of participants enrolled at Penn Medicine sites versus Lancaster General Hospital sites**

| Characteristic                              | Total (n=764) | Penn Medicine (n=656) | LGH (n=108) | P-value<sup>a</sup> |
|---------------------------------------------|---------------|-----------------------|-------------|---------------------|
| Age, mean (SD)                             | 62.4 (10.0)   | 62.0 (10.0)           | 65.1 (9.5)  | 0.003               |
| Sex<sup>b</sup>, n (%)                      |               |                       |             | 0.011               |
| Female                                      | 390 (51.2)    | 347 (53.1)            | 43 (39.8)   |                     |
| Male                                        | 372 (48.8)    | 307 (46.9)            | 65 (60.2)   |                     |
| Race<sup>b</sup>, n (%)                     |               |                       |             | <.001               |
| White                                       | 440 (58.0)    | 341 (52.4)            | 99 (91.7)   |                     |
| Black                                       | 271 (35.7)    | 268 (41.2)            | 3 (2.8)     |                     |
| Other                                       | 48 (6.3)      | 42 (6.5)              | 6 (5.6)     |                     |
| Ethnicity<sup>b</sup>, n (%)                |               |                       |             | 0.836               |
| Hispanic or Latino                          | 19 (2.5)      | 16 (2.5)              | 3 (2.8)     |                     |
| Not Hispanic or Latino                      | 737 (97.5)    | 633 (97.5)            | 104 (97.2)  |                     |
| Education<sup>b</sup>, n (%)                |               |                       |             | <.001               |
| High school or less                         | 224 (29.4)    | 174 (26.6)            | 50 (46.3)   |                     |
| Some college                                | 208 (27.3)    | 185 (28.3)            | 23 (21.3)   |                     |
| College degree                              | 330 (43.3)    | 295 (45.1)            | 35 (32.4)   |                     |
| Income before taxes, n (%)                  |               |                       |             | <.001               |
| Below $50,000                               | 303 (39.7)    | 293 (44.7)            | 10 (9.3)    |                     |
| Above $50,000                               | 338 (44.2)    | 329 (50.2)            | 9 (8.3)     |                     |
| Do not wish to answer<sup>c</sup>           | 123 (16.1)    | 34 (5.2)              | 89 (82.4)   |                     |
| Marital Status<sup>b</sup>, n (%)           |               |                       |             | 0.016               |
| Single                                      | 184 (24.1)    | 167 (25.5)            | 17 (15.7)   |                     |
| Married/Unmarried partners                  | 413 (54.2)    | 341 (52.1)            | 72 (66.7)   |                     |
| Divorced/Widowed                            | 165 (21.7)    | 146 (22.3)            | 19 (17.6)   |                     |
| Smoke more than 5 cigarettes per day, n (%) | 62 (8.1)      | 55 (8.4)              | 7 (6.5)     | 0.502               |
| Household size<sup>b</sup>, mean (SD)       | 2.3 (1.2)     | 2.3 (1.2)             | 2.3 (1.1)   | 0.842               |
| Diagnosed with Diabetes, n (%)              | 310 (40.6)    | 289 (44.1)            | 21 (19.4)   | <.001               |
| Diagnosed with ASCVD, n (%)                 | 298 (39.0)    | 252 (38.4)            | 46 (42.6)   | 0.410               |
| LDL-c Calculated, mean (SD)                 | 138.8 (37.6)  | 140.4 (38.2)          | 128.8 (32.4)| 0.003               |

Values are number of participants (%) or means and standard deviations (SD).

<sup>a</sup> Analysis of Variance (ANOVA) for continuous data and Pearson Chi-squared for categorical data

<sup>b</sup> Values may not sum to the total number of subjects due to missing data

<sup>c</sup> Subjects were asked to give their annual pre-tax household income in $10,000 intervals. Those who did not wish to answer the question were asked if they were willing to share whether their income was greater or less than $50,000.
eTable 3: Characteristics of participants who did and did not complete the 12-month LDL-c measurement

| Characteristic                          | Total (n=764) | Completed 12-month lab (n=644) | Missed 12-month lab (n=120) | P-value of difference completed vs missed |
|-----------------------------------------|---------------|---------------------------------|-----------------------------|--------------------------------------------|
| Age, mean (SD)                          | 62.4 (10.0)   | 63.2 (9.5)                      | 58.2 (11.4)                 | <.01                                       |
| Study group, n (%)                      |               |                                 |                             | .11                                        |
| Control                                 | 190 (24.9)    | 159 (24.7)                      | 31 (25.8)                   |                                            |
| Process                                 | 194 (25.4)    | 174 (27.0)                      | 20 (16.7)                   |                                            |
| Outcome                                 | 187 (24.5)    | 152 (23.6)                      | 35 (29.2)                   |                                            |
| P & O                                   | 193 (25.3)    | 159 (24.7)                      | 34 (28.3)                   |                                            |
| Site, n (%)                             |               |                                 |                             | .58                                        |
| Penn Medicine                           | 656 (85.9)    | 551 (85.6)                      | 105 (87.5)                  |                                            |
| Lancaster General                       | 108 (14.1)    | 93 (14.4)                       | 15 (12.5)                   |                                            |
| Gender, n (%)                           |               |                                 |                             | .20                                        |
| Female                                  | 390 (51.2)    | 335 (52.2)                      | 55 (45.8)                   |                                            |
| Male                                    | 372 (48.8)    | 307 (47.8)                      | 65 (54.2)                   |                                            |
| Missing                                 | 2 (0.3)       | 2 (0.3)                         | 0 (0.0)                     |                                            |
| Race, n (%)                             |               |                                 |                             | .12                                        |
| White                                   | 440 (58.0)    | 378 (59.2)                      | 62 (51.7)                   |                                            |
| Black                                   | 271 (35.7)    | 225 (35.2)                      | 46 (38.3)                   |                                            |
| Other                                   | 48 (6.3)      | 36 (5.6)                        | 12 (10.0)                   |                                            |
| Missing                                 | 5 (0.7)       | 5 (0.8)                         | 0 (0.0)                     |                                            |
| Education, n (%)                        |               |                                 |                             | .49                                        |
| High school or less                     | 224 (29.4)    | 190 (29.6)                      | 34 (28.3)                   |                                            |
| Some college                            | 208 (27.3)    | 170 (26.5)                      | 38 (31.7)                   |                                            |
| College degree                          | 330 (43.3)    | 282 (43.9)                      | 48 (40.0)                   |                                            |
| Missing                                 | 2 (0.3)       | 2 (0.3)                         | 0 (0.0)                     |                                            |
| Income, n (%)                           |               |                                 |                             | .20                                        |
| Marital Status, n (%) | Below $50,000 | Above $50,000 | Missing |
|-----------------------|---------------|---------------|---------|
| Single                | 184 (24.1)    | 147 (22.9)    | 37 (30.8) |
| Married/Unmarried partners | 413 (54.2)    | 356 (55.5)    | 57 (47.5) |
| Divorced/Widowed      | 165 (21.7)    | 139 (21.7)    | 26 (21.7) |
| Missing               | 2 (0.3)       | 2 (0.3)       | 0 (0.0)  |
| Household size, mean (SD) | 2.3 (1.2)     | 2.3 (1.2)     | 2.5 (1.3) |
| Missing               | 6 (0.8)       | 6 (0.9)       | 0 (0.0)  |
| Statin adherence score, mean (SD) | 5.7 (1.4)    | 5.7 (1.4)     | 5.5 (1.3) |
| Baseline LDL-c mg/dl, mean (SD) | 138.8 (37.6)  | 137.4 (37.9)  | 146.1 (35.4) |
### eTable 4: Secondary outcome of change in LDL-c from baseline to 18 months (mg/dL)\(^a\)

| Visit (months) | Outcome  | Control arm | Process arm | Outcomes arm | Process plus Outcomes arm |
|---------------|----------|-------------|-------------|--------------|---------------------------|
| 18            | \(\Delta_{\text{LDL}}\)\(^b\) | -34.9 \((-40.0, -29.9)\) | -39.6 \((-44.9, -34.3)\) | -35.9 \((-41.3, -30.5)\) | -38.5 \((-43.8, -33.3)\) |
|               | Difference in change versus control\(^b\) | -4.7 \((-11.9, 2.6)\) | -0.9 \((-8.2, 6.3)\) | -3.6 \((-10.4, 3.2)\) |
|               | P-value \(^c\) | 0.206 | 0.799 | 0.299 |

\(^a\) Secondary outcome. The 18-month timepoint was 6 months post-intervention.

\(^b\) Mean (95% CI) change from baseline from a linear model adjusted for baseline LDL-c and site. Results are reported for Penn Medicine at mean baseline LDL-c. Mean LDL-c at 18 months for LGH participants was 5.9 mg/dL higher than Penn Medicine participants. Multiple imputation was used to adjust for incomplete data.

\(^c\) No adjustment for multiple comparisons.
eFigure 2A-F: Subgroup analyses of the primary outcome of change in LDL-C (mg/dL) from baseline to 12 months using a linear mixed-effects model

Methods: Mean change in LDL-c was estimated by a linear mixed effects model within each subgroup using arm, visit, interaction of arm and visit, and baseline LDL-c as covariates with a random intercept term. We tested the null hypothesis that the linear combination of LDL-c change from baseline across the 3, 6, 9 and 12-month visits was identical for the control and each intervention group. Complete data were used in the analysis. Results are considered exploratory and no adjustment for multiple comparisons was made.

Forest Plots: Squares are the mean reduction in LDL-c from baseline at each timepoint, and after adjustment for the mean baseline value across all arms. Error bars are 95% confidence intervals (CI). Negative values indicate reduction in LDL-c versus baseline. Dashed line is the overall mean for the LDL-c reduction for control in the subgroup.
**eFigure 2A: Recruitment site.** For participants recruited at Penn Medicine (n=625), the results of the hypothesis test of each intervention arm versus control is Process (p=.047), Outcomes (p=.202), Process plus Outcomes (p=.063). For participants recruited at LGH (n=106) the results of the hypothesis test of each intervention arm versus control is Process (p=.362), Outcomes (p=.415), Process plus Outcomes (p=.919).
**Baseline LDL-c**

**eFigure 2B: Baseline LDL-c.** For those with LDL-c > 160 (n=150), the results of the hypothesis test of each intervention arm versus control is Process (p=.441), Outcomes (p=.297), Process plus Outcomes (p=.002). For those with LDL-c ≤ 160 (n=581) the results of the hypothesis test of each intervention arm versus control is Process (p=.379), Outcomes (p=.729), Process plus Outcomes (p=.772).
eFigure 2C: CVD diagnosis. For those with CVD (n=281) the results of the hypothesis test of each intervention arm versus control is Process (p=.026), Outcomes (p=.330), Process plus Outcomes (p=.020). For those without CVD (n=450) the results of the hypothesis test of each intervention arm versus control is Process (p=.957), Outcomes (p=.804), Process plus Outcomes (p=.583).
**Race**

**Black (n=258)**

| Visit (mo) | Arm       | Average of Control | Change [95% CI]          |
|------------|-----------|--------------------|--------------------------|
| 3          | Control   |                    | -3.19 [-3.89, -2.50]     |
| 6          |           |                    | -3.15 [-3.84, -2.46]     |
| 9          |           |                    | -3.21 [-3.89, -2.53]     |
| 12         |           |                    | -3.09 [-3.78, -2.40]     |
| 3          | Process   |                    | -4.38 [-5.12, -3.64]     |
| 6          |           |                    | -4.54 [-5.26, -3.82]     |
| 9          |           |                    | -4.01 [-4.73, -3.29]     |
| 12         |           |                    | -3.70 [-4.52, -3.08]     |
| 3          | Outcomes  |                    | -4.17 [-4.98, -3.37]     |
| 6          |           |                    | -4.11 [-4.89, -3.34]     |
| 9          |           |                    | -3.90 [-4.59, -3.01]     |
| 12         |           |                    | -3.87 [-4.51, -3.23]     |
| 3          | Process plus |               | -4.54 [-5.31, -3.77]     |
| 6          |           |                    | -4.77 [-5.54, -3.99]     |
| 9          |           |                    | -4.82 [-5.56, -4.05]     |
| 12         |           |                    | -4.43 [-5.20, -3.66]     |

**White (n=424)**

| Visit (mo) | Arm       | Average of Control | Change [95% CI]          |
|------------|-----------|--------------------|--------------------------|
| 3          | Control   |                    | -4.32 [-4.95, -3.69]     |
| 6          |           |                    | -4.29 [-4.92, -3.65]     |
| 9          |           |                    | -4.48 [-5.12, -3.85]     |
| 12         |           |                    | -4.31 [-4.95, -3.67]     |
| 3          | Process   |                    | -4.16 [-4.75, -3.57]     |
| 6          |           |                    | -4.11 [-4.70, -3.53]     |
| 9          |           |                    | -4.30 [-4.88, -3.72]     |
| 12         |           |                    | -4.26 [-4.83, -3.68]     |
| 3          | Outcomes  |                    | -3.50 [-4.10, -2.90]     |
| 6          |           |                    | -3.75 [-4.35, -3.15]     |
| 9          |           |                    | -3.73 [-4.34, -3.12]     |
| 12         |           |                    | -3.76 [-4.36, -3.14]     |
| 3          | Process plus |               | -3.56 [-4.16, -2.96]     |
| 6          |           |                    | -4.25 [-4.85, -3.65]     |
| 9          |           |                    | -4.09 [-4.88, -3.30]     |
| 12         |           |                    | -4.22 [-4.82, -3.63]     |

**eFigure 2D: Race:** Due to small sample size, participants of race category ‘Other’ or ‘do not wish to disclose’ (n=49) were excluded from this analysis. For those of Black race (n=258), the results of the hypothesis test of each intervention arm versus control is Process (p=.023), Outcomes (p=.033), Process plus Outcomes (p=.001). For those of White race (n=424) the results of the hypothesis test of each intervention arm versus control is Process (p=.720), Outcomes (p=.111), Process plus Outcomes (p=.650).
**eFigure 2E: Income.** Income category based on a baseline survey question asking pre-tax household income levels in $10,000 intervals with a follow-up question for subjects who did not wish to answer of: “Are you willing to share if your income is above or below $50,000?”. The 121 participants who did not wish to disclose their income in response to either question are excluded from this analysis. For those with income>US $50,000 (n=324), the results of the hypothesis test of each intervention arm versus control is Process (p=.367), Outcomes (p=.869), Process plus Outcomes (p=.941). For those of income <US $50,000 (n=286) the results of the hypothesis test of each intervention arm versus control is Process (p=.097), Outcomes (p=.047), Process plus Outcomes (p=.006).
**Sex**

**Female (n=375)**

| Visit (mo) | Arm      | Average of Control | Change [95% CI]          |
|------------|----------|--------------------|--------------------------|
| 3          | Control  | -37.3 [-43.3, -30.7]|
| 6          | Control  | -31.3 [-37.3, -24.3]|
| 9          | Control  | -34.4 [-40.4, -28.4]|
| 12         | Control  | -34.0 [-40.0, -27.4]|
| 3          | Process  | -44.5 [-51.5, -37.5]|
| 6          | Process  | -42.0 [-48.0, -35.0]|
| 9          | Process  | -41.0 [-47.0, -34.0]|
| 12         | Process  | -35.7 [-42.7, -29.7]|
| 3          | Outcomes | -37.7 [-44.7, -31.7]|
| 6          | Outcomes | -35.6 [-42.6, -29.6]|
| 9          | Outcomes | -36.6 [-43.6, -29.6]|
| 12         | Outcomes | -38.8 [-45.8, -32.8]|
| 3          | Process plus | -30.1 [-37.1, -23.1]|
| 6          | Process plus | -42.2 [-49.2, -35.2]|
| 9          | Process plus | -42.1 [-49.1, -35.1]|
| 12         | Process plus | -45.0 [-52.0, -38.0]|

**Male (n=354)**

| Visit (mo) | Arm      | Average of Control | Change [95% CI]          |
|------------|----------|--------------------|--------------------------|
| 3          | Control  | -41.0 [-47.0, -34.0]|
| 6          | Control  | -45.0 [-51.0, -38.0]|
| 9          | Control  | -42.4 [-48.4, -35.4]|
| 12         | Control  | -40.5 [-46.5, -33.5]|
| 3          | Process  | -39.1 [-45.1, -32.1]|
| 6          | Process  | -42.5 [-48.2, -35.2]|
| 9          | Process  | -42.4 [-48.3, -35.3]|
| 12         | Process  | -46.0 [-52.0, -39.0]|
| 3          | Outcomes | -39.2 [-45.2, -32.2]|
| 6          | Outcomes | -45.3 [-51.3, -38.3]|
| 9          | Outcomes | -41.1 [-47.1, -34.1]|
| 12         | Outcomes | -42.5 [-49.5, -36.5]|
| 3          | Process plus | -37.0 [-44.0, -30.0]|
| 6          | Process plus | -43.8 [-50.8, -37.8]|
| 9          | Process plus | -42.5 [-48.5, -35.5]|
| 12         | Process plus | -43.8 [-50.8, -37.8]|

**eFigure 2F: Sex.** The 2 participants who did not wish to disclose their sex are excluded from this analysis. For females (n=375), the results of the hypothesis test of each intervention arm versus control is Process (p=.115), Outcomes (p=.351), Process plus Outcomes (p=.043). For males (n=354) the results of the hypothesis test of each intervention arm versus control is Process (p=.794), Outcomes (p=.930), Process plus Outcomes (p=.858).
eTable 5: Secondary complete case analysis for outcome of change in LDL-c (mg/dL) from baseline to 12 months using the same model as reported for the primary analysis\textsuperscript{a}

| Visit (months) | Outcome | Control arm | Process arm | Outcomes arm | Process plus Outcomes arm |
|----------------|---------|-------------|-------------|--------------|----------------------------|
| 12             | $\Delta_{LDL}$ | -36.9 (-41.7, -32.1) | -40.0 (-44.6, -35.5) | -41.5 (-46.4, -36.7) | -42.9 (-47.7, -38.1) |
|                | Difference in change versus control | -3.1 (-9.6, 3.3) | -4.6 (-11.3, 2.1) | -6.0 (-12.6, 0.6) |
|                | P-value | 0.342 | 0.175 | 0.075 |

\textsuperscript{a} Mean (95% CI) change from baseline from a linear model adjusted for baseline LDL-c and site. Results are reported for Penn Medicine at mean baseline LDL-c. Mean LDL-c at 12 months for LGH participants was 0.4 mg/dL lower than Penn Medicine participants.
eFigure 3: Secondary analysis of data from all visits during the intervention (3, 6, 9 and 12 months)

Methods: Mean change in LDL-c was estimated by a linear mixed effects model using arm, visit, interaction of arm and visit, and baseline LDL-c as covariates, and a random intercept term. We tested the null hypothesis that the linear combination of LDL-c change from baseline across the 3, 6, 9 and 12 month visits was identical for the control and each intervention group. Complete data were used in the analysis (n=731). No adjustment for multiple comparisons was made.

| Visit (mo) | Arm          | Average of Control | Change [95% CI]          |
|-----------|--------------|--------------------|--------------------------|
| 3         | Control      |                    | -38.9 [-43.5, -34.4]     |
| 6         | Process      |                    | -37.7 [-42.3, -33.1]     |
| 9         | Outcomes     |                    | -38.2 [-42.7, -33.6]     |
| 12        | Process plus |                    | -37.0 [-41.6, -32.4]     |
| 3         | Process      |                    | -41.9 [-46.5, -37.4]     |
| 6         | Outcomes     |                    | -42.2 [-46.7, -37.7]     |
| 9         |              |                    | -41.7 [-46.1, -37.2]     |
| 12        |              |                    | -40.6 [-45.0, -36.1]     |
| 3         |              |                    | -38.4 [-43.0, -33.8]     |
| 6         |              |                    | -40.3 [-44.9, -35.7]     |
| 9         |              |                    | -38.8 [-43.4, -34.2]     |
| 12        |              |                    | -40.6 [-45.3, -36.0]     |
| 3         |              |                    | -38.4 [-43.0, -33.7]     |
| 6         |              |                    | -43.1 [-47.7, -38.5]     |
| 9         |              |                    | -42.4 [-47.0, -37.8]     |
| 12        |              |                    | -41.8 [-46.4, -37.2]     |

Figure: Forest plots of LDL-c for the intervention period. Squares are the mean change in LDL-c at each timepoint. Error bars are 95% confidence intervals (CI) based on the mixed effects model. Bold squares are the primary outcome at 12 months. Dashed line at the overall mean of the LDL-c reduction for control.

The results of the hypothesis test of each intervention arm versus control are Process (p=.166), Outcomes (p=.416), Process plus Outcomes (p=.088). P-values are unadjusted for multiple comparisons.
# eTable 6: Sensitivity of primary results to different models; Change in LDL-c (mg/dL) from baseline to 12 months using a linear model with adjustment for different baseline covariates

| Model Adjustment a | Metric | Control arm | Process arm | Outcomes arm | Process plus Outcomes arm |
|--------------------|--------|-------------|-------------|--------------|--------------------------|
| None b             | $\Delta_{LDL}$ | -35.2 (-41.9, -28.6) | -42.0 (48.3, -35.7) | -40.0 (-46.4, -33.6) | -43.6 (-50.0, -37.3) |
| Difference versus control | P-value | 0.149 | 0.310 | 0.069 |
| Baseline LDL-c only c | $\Delta_{LDL}$ | -36.8 (-41.8, -31.9) | -39.9 (-44.4, -35.4) | -41.5 (-46.0, -37.0) | -42.7 (-47.2, -38.1) |
| Difference versus control | P-value | 0.147 | 0.310 | 0.069 |
| Site only d | $\Delta_{LDL}$ | -35.2 (-41.9, -28.6) | -42.1 (-48.4, -35.8) | -39.9 (-46.3, -33.5) | -43.6 (-50.0, -37.3) |
| Difference versus control | P-value | 0.147 | 0.310 | 0.069 |
| Baseline LDL-c, sex, race, income, education e | $\Delta_{LDL}$ | -37.1 (-42.0, -32.2) | -39.8 (-44.3, -35.2) | -41.5 (-46.0, -37.0) | -42.6 (-47.1, -38.0) |
| Difference versus control | P-value | 0.441 | 0.197 | 0.102 |

a Analyses used imputed data

b Linear model including terms for intervention arm (no adjustment for site or baseline LDL-c). Mean (95% CI) change from baseline to 12 months. Values for change from baseline LDL-c ($\Delta_{LDL}$) are across all subjects.

c Linear model including terms for intervention arm and baseline LDL-c only. Values for change from baseline LDL-c ($\Delta_{LDL}$) are across baseline LDL-c.

d Linear model including terms for intervention arm and site (Penn Medicine versus LGH) but no adjustment for baseline LDL-c. Values for change from baseline LDL-c ($\Delta_{LDL}$) are across site.

e Linear model including terms for intervention arm, baseline LDL-c, sex, race, income, education. Values for change from baseline LDL-c ($\Delta_{LDL}$) are across all terms in the model.
eTable 7: Change in LDL-c (mg/dL) from 3-month visit to 12-month visit

| Timeframe | Group            | Mean (95% CI) | Difference from control, mean (95% CI) |
|-----------|------------------|---------------|--------------------------------------|
| **3-6 months** |                  |               |                                      |
|            | Control          | 2.9 (-2.5, 8.3) | -                                    |
|            | Process          | -0.3 (-5.9, 5.3) | -3.2 (-11.0, 4.6)                   |
|            | Outcomes         | -2.3 (-7.5, 2.9) | -5.2 (-12.3, 1.9)                   |
|            | Process & Outcomes | -5.6 (-11.3, 0.1) | -8.5 (-16.3, -0.7)              |
| **3-9 months** |                  |               |                                      |
|            | Control          | 1.8 (-3.5, 7.2) | -                                    |
|            | Process          | 0.0 (-5.5, 5.5) | -1.8 (-9.4, 5.8)                   |
|            | Outcomes         | 0.7 (-4.9, 6.4) | -1.1 (-8.5, 6.3)                   |
|            | Process & Outcomes | -4.1 (-9.6, 1.3) | -6.0 (-13.7, 1.8)              |
| **3-12 months** |                  |               |                                      |
|            | Control          | 3.8 (-2.0, 9.5) | -                                    |
|            | Process          | 1.8 (-3.6, 7.2) | -2.0 (-10.0, 6.0)                  |
|            | Outcomes         | -2.2 (-7.5, 3.1) | -6.0 (-13.9, 1.9)                  |
|            | Process & Outcomes | -4.9 (-10.2, 0.4) | -8.7 (-16.2, -1.2)              |

*All analyses were adjusted for LDL-c at baseline and stratified by site, using multiply imputed data. Results are presented for Penn Medicine site participants.
eFigure 4: Secondary outcome of mean weekly measured statin adherence, by intervention arm

Adherence measured through smart pill bottle. Values are weekly mean adherence for each intervention arm over the 12-month intervention period. The Process and the Process plus Outcomes arms received financial incentives to encourage statin adherence.
eTable 8: Secondary outcome of mean weekly measured statin adherence, by intervention arm$^a$

| Window          | Metric     | Control arm | Process arm | Outcomes arm | Process plus Outcomes arm |
|-----------------|------------|-------------|-------------|--------------|----------------------------|
|                 |            | 0.70 (0.66, 0.74) | 0.83 (0.79, 0.87) | 0.70 (0.66, 0.74) | 0.80 (0.76, 0.84) |
| 0-12 months     | Adherence  |            |             |              |                            |
|                 | Difference vs. control | 0.13 (0.08, 0.19) | 0.00 (-0.05, 0.06) | 0.10 (0.04, 0.15) |                            |
|                 | P-value    | <.001       | 0.924       | <.001        |                            |
| Final 30 days   | Adherence  | 0.62 (0.57, 0.67) | 0.80 (0.75, 0.85) | 0.60 (0.55, 0.65) | 0.77 (0.72, 0.82) |
|                 | Difference vs. control | 0.18 (0.11, 0.25) | -0.02 (-0.09, 0.05) | 0.15 (0.08, 0.22) |                            |
|                 | P-value    | <.001       | 0.601       | <.001        |                            |

$^a$ Adherence measured through smart pill bottle. Mean proportion of days adherent by study arm across 12 month or in the final 30 days of the intervention. Hypothesis tests from a linear model with adherence as the outcome compared each arm to control and are unadjusted for multiple comparisons.
Data on adverse events were assessed at 3, 6, 9, 12 and 18-month study encounters and could also be reported spontaneously at other time points by participants to investigators.

| Arm | Adverse Event                                           | Action                  | Outcome (at last follow-up)                                      |
|-----|--------------------------------------------------------|-------------------------|-----------------------------------------------------------------|
| D   | Subject reported serious adverse reactions to statins  | Dose modification        | Recovered with minor sequelae                                   |
| D   | Chest pain                                             | Hospitalization         | Resolved                                                         |
| A   | Muscle, weakness, and pain in knees, fingers and joints| None                     | Condition still present and under treatment                     |
| A   | Muscle pain and weakness in thighs                     | Dose modification        | Condition still present and under treatment                     |
| C   | Skin rash on legs, neck, chest                         | Dose modification        | Resolved                                                         |
| C   | Reaction to statin                                     | Dose modification        | Condition still present and under treatment                     |
| A   | Aches and pains in arms/legs                           | Dose modification        | Resolved                                                         |
| A   | Reaction to statin                                     | Dose modification        | Recovered with minor sequelae                                   |
| B   | Hives                                                  | Dose modification        | Resolved                                                         |
| B   | Muscle pain and weakness in left thighs                | Medical/Surgical         | Resolved                                                         |
| D   | Cardio myopathy worsened                              | Dose modification        | Resolved                                                         |
| D   | Elevated liver function tests                         | Dose modification        | Condition still present and under treatment                     |
| B   | Muscle pain and cramps bilateral lower extremities     | Dose modification        | Resolved                                                         |
| C   | Radiating pain bilateral upper extremities            | Drug permanently         | Condition continues to worsen                                    |
| Column | Condition | Intervention | Status |
|--------|-----------|--------------|--------|
| B      | Muscle pain and weakness | Drug permanently discontinued | Condition still present and under treatment |
| C      | Muscle pain/cramps bilateral legs | Dose modification | Condition still present and under treatment |
| A      | Chest pain | Hospitalization | Condition still present and under treatment |
| D      | Pain in right thigh | None | Condition still present and under treatment |
| D      | Muscle pain and weakness | Other | Condition still present and under treatment |
| C      | Leg muscle cramps | None | Condition still present and under treatment |
| C      | Joint pain | Drug permanently discontinued | Condition still present and under treatment |
| C      | Muscle pain and weakness | Drug permanently discontinued | Condition still present and under treatment |
| C      | Muscle pain and weakness bilateral arms and shoulder | Drug permanently discontinued | Condition still present and under treatment |
| B      | Muscle pain and cramps bilateral lower extremities | None | Condition still present and under treatment |
| D      | Muscle pain over lumbar back and bilateral knees | Dose modification | Condition still present and under treatment |
| D      | ALT & AST increase | None | Condition still present and under treatment |
| A      | Weakness over bilateral lower and upper extremities | None | Condition still present and under treatment |
|   | Condition | Management | Status                  |
|---|-----------|------------|-------------------------|
| D | Muscle pain and weakness over upper left arm | None | Condition still present and under treatment |
| D | Muscle pain and weakness | Drug permanently discontinued | Condition continues to worsen |
| A | Muscle pain and weakness | None | Condition still present and under treatment |
| A | Muscle pain and weakness | None | Condition still present and under treatment |
| B | Increased liver enzyme activity | Drug permanently discontinued | Recovered with major sequelae |
| B | Muscle cramping and weakness | Dose modification | Resolved |
| C | Muscle pain and weakness | None | Resolved |
| C | Intense Pains | Drug permanently discontinued | Resolved |
| B | Memory/Concentration issues | Dose modification | Resolved |
| D | Muscle pain in leg | None | Resolved |
| D | Muscle/joint pain in lower back and shoulders | None | Resolved |
|   |        |                     |                     |
|---|--------|---------------------|---------------------|
| B | Muscle pain and weakness | Dose modification | Resolved            |
| A | Muscle pain and weakness | Dose modification | Resolved            |
| B | Memory/Concentration issues | Dose modification | Resolved            |
| A | Unable to determine | None | Resolved            |
| B | Headaches | Dose modification | Resolved            |
| B | Unhealthy liver enzyme activity | Other | Resolved            |
| D | Shoulder pain | None | Condition still present and under treatment |
| A | Memory/Concentration issues | None | Resolved            |
| A | Muscle cramps and light headedness | Dose modification | Resolved            |
| B | Muscle spasms in legs | None | Resolved            |
| D | Muscle pains | Dose modification | Resolved            |
| D | Muscle pain and twitching | None | Resolved            |
| Group | Event Description                          | Intervention       | Outcome      |
|-------|-------------------------------------------|--------------------|-------------|
| B     | Headaches                                 | Dose modification  | Resolved    |
| B     | Muscle pain and cramps                    | Dose modification  | Resolved    |
| B     | Weakening in legs                         | Dose modification  | Resolved    |
| A     | Leg and foot cramps                       | Dose modification  | Resolved    |
| C     | High glucose                              | Hospitalization    | Resolved    |
| A     | Muscle and joint pain                     | Dose modification  | Resolved    |
| B     | Muscle pain                               | Dose modification  | Resolved    |
| A     | Muscle pain                               | Dose modification  | Resolved    |
| C     | Muscle pain                               | Dose modification  | Resolved    |
| B     | Dose modification                          | Dose modification  | Resolved    |
| D     | Muscle pain and weakness                  | Dose modification  | Resolved    |

*Adverse events were reviewed and assessed by the Principal Investigators on a monthly basis, and then presented using descriptive statistics to the DSMB and IRB yearly.*
eFigure 5: Spillover analysis flowchart of Penn Medicine patients with hypertension and diabetes plus usual care data for hemoglobin A1c and systolic blood pressure, respectively, in the pre-randomization period (up to 6 months prior) and later period (9 – 15 months post-randomization)

Participants at Penn Medicine
N=656

Hypertensive participants
N=525 (80.0%)

(Analytical sample) Participants having BP measures in the pre-randomization period and later period
N=459 (87.4%)

Participants at Penn Medicine
N=656

Diabetic participants
N=261 (39.8%)

(Analytical sample) Participants having HbA1c measures in the pre-randomization period and later period
N=177 (67.8%)