Original Article
CLINICAL TRIALS AND INVESTIGATIONS

Obesity

A Factorial Experiment to Optimize Remotely Delivered Behavioral Treatment for Obesity: Results of the Opt-IN Study

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Objective: Intensive behavioral obesity treatments face scalability challenges, but evidence is lacking about which treatment components could be cut back without reducing weight loss. The Optimization of Remotely Delivered Intensive Lifestyle Treatment for Obesity (Opt-IN) study applied the Multiphase Optimization Strategy to develop an entirely remotely delivered, technology-supported weight-loss package to maximize the amount of weight loss attainable for ≤$500.

Methods: Six-month weight loss was examined among adults ($N = 562$) with BMI ≥ 25 who were randomly assigned to conditions in a factorial experiment crossing five dichotomous treatment components set to either low/high (12 vs. 24 coaching calls) or off/on (primary care provider reports, text messaging, meal replacements, and buddy training).

Results: About 84.3% of participants completed the final assessment. The treatment package yielding maximum weight loss for ≤$500 included 12 coaching calls, buddy training, and primary care provider progress reports; produced average weight loss of 6.1 kg, with 57.1% losing ≥5% and 51.8% losing ≥7%; and cost $427 per person. The most expensive candidate-treatment component (24 vs. 12 coaching calls) was screened out of the optimized treatment package because it did not increase weight loss.

Conclusions: Systematically testing each treatment component's effect on weight loss made it possible to eliminate more expensive but less impactful components, yielding an optimized, resource-efficient obesity treatment for evaluation in a randomized controlled trial.

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Study Importance

What is already known?

- Effective behavioral treatment packages for obesity impose a burden and cost that impede scalability, but evidence is lacking about which components could be reduced or eliminated without losing effectiveness

What does this study add?

- A factorial optimization trial was conducted using the Multiphase Optimization Strategy to identify a set of intervention components that cost-efficiently enhanced weight loss. When added to a core intervention involving an app, goals, and online lessons, an optimized treatment package consisting of 12 health-coaching calls, progress reports sent to a primary care physician, and training a support buddy maximized weight loss at a cost of $427 per person. More expensive components (e.g., 24 vs. 12 coaching calls) were omitted because they proved cost-inefficient.

How might these results change the focus of clinical practice?

- Applying an optimization strategy allows data to be used systematically to guide decisions about which treatment components are essential and which can be reduced or eliminated to reduce cost and burden. This makes it possible to assemble a treatment package that provides a desired balance of effectiveness and economy.

Introduction

Practice guidelines advise clinicians to offer or refer adults with obesity to intensive, multicomponent, behavioral weight-loss treatment (1). The Diabetes Prevention Program (DPP), the gold-standard behavioral weight-loss treatment program, and similar

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interventions have effectively produced clinically meaningful weight loss and improved health in adults with overweight and obesity (2-5). However, these programs are expensive to deliver (exceeding $1,000 in the first year), largely due to the personnel costs for at least 14 professionally led treatment sessions during the first 6 months (6). Reducing treatment intensity and implementing the DPP in community or primary care settings lowers the annual program cost to an average of $653 per participant, which is still out of reach for many and decreases intervention effectiveness (7).

The challenge of increasing the population impact of obesity interventions can be framed as an optimization problem: that is, the challenge is to systematically identify the set of intervention components that delivers meaningful weight loss while remaining scalable. However, because behavioral weight-loss interventions have traditionally been deployed as bundled "treatment packages," an evidence base is lacking to guide decisions about which intervention components at which intensity should be included in this set.

The Multiphase Optimization Strategy (MOST) (8,9) framework offers a toolbox of experimental designs that can be used to optimize interventions systematically so they efficiently achieve a stated optimization criterion without resource overuse (e.g., they achieve the best clinical outcome possible without exceeding a specified per-participant cost). One design, the factorial experiment, can be conducted to examine effects of individual treatment components and their interactions to determine which components and component levels, singly or combined, make important contributions to the desired outcome. That information, with data on cost, then guides decision-making about assembling an optimized treatment package that best achieves target outcomes within resource constraints. Factorial experiments are often more economical than alternative approaches (e.g., multiple sequential randomized controlled trials) because they test multiple component effects simultaneously, requiring fewer participants to achieve the same statistical power (10).

Despite many calls to understand which treatment components are essential to produce meaningful weight loss (6,11-13), few studies have systematically examined this question. The Optimization of Remotely Delivered Intensive Lifestyle Treatment for Obesity (Opt-IN) study (12) aimed to develop an optimized, scalable version of a remotely delivered, technology-supported weight-loss intervention by determining which of 5 treatment components contributed most meaningfully and cost-efficiently to weight loss over a 6-month period.

On the basis of social cognitive theory (14,15) and prior mobile-health obesity-intervention trials (16-19), we posited a need for multilevel intervention, testing two components aiming to enhance the individual's weight-regulation skills and attitudes and testing three components addressing environmental facilitators and barriers to weight-loss success (20). The two individually targeted components, coaching and text messaging, aimed to enhance the person's self-regulation abilities and self-efficacy regarding managing diet and physical activity (PA) (14). Buddy training and primary care provider (PCP) reporting aimed to foster a facilitating environment for weight loss by prompting others in the participant's interpersonal network to convey social support and accountability for weight management (15). The third environmentally targeted component, meal replacements (MRs), aimed to overcome a weight-regulation barrier by simplifying portion control (15).

The primary aim of Opt-IN was to determine which intervention components maximize weight loss. The secondary aim was to integrate these findings with cost data to build a treatment package producing the greatest weight loss attainable for ≤$500 (selected because the Centers for Disease Control and Prevention and commercial insurers consider this a reasonable cost to deliver the DPP to an individual) (21). To our knowledge, this was the first study using the MOST framework to optimize adult obesity treatment.

Methods

Opt-IN involved a factorial experiment that randomly assigned 562 participants to 1 of 32 experimental conditions representing all possible combinations of 5 treatment components. The purpose of the experiment was to estimate the effect of each component and any component interactions. The primary outcome was weight loss at the end of the 6-month intervention. The study protocol, design, and a corrigendum were published previously (12,22). Participants were recruited throughout the Chicagoland area between 2013 and 2017 through flyers, public-transit advertisements, research registries, and word-of-mouth. Randomization at the rate of approximately 168 participants per year occurred over 40 months.

Procedure

Eligible participants (12) were required to be 18 to 60 years old, have a BMI between 25 and 40 kg/m^2 (i.e., have overweight or obesity), be weight stable, and be neither enrolled in a formal weight-loss program nor taking medications known to cause weight loss or gain. They were also required to own an iPhone or Android smartphone, have a PCP, and be able to enlist a weight-loss support "buddy" from their existing social network who was at least 18 years old and had internet access. Participants were excluded if they had an unstable medical condition (e.g., uncontrolled hypertension); had contraindications to engaging in moderate-to-vigorous PA (MVPA); used insulin; had Crohn disease or obstructive sleep apnea; had physician-diagnosed plantar fasciitis; used an assistive device (e.g., cane) for mobility; had been hospitalized recently for psychiatric reasons or expressed current suicidality; were pregnant, lactating, or trying to conceive; met criteria for an eating disorder; endorsed substance abuse or dependence (per *Diagnostic and Statistical Manual of Mental Disorders* [Fourth Edition] criteria); or followed a strict dietary regimen incompatible with study goals. To reduce contamination, participants were also excluded if they lived with another study participant or had already participated in the study as a buddy.

Participants were screened for eligibility through a multistep process that included an online web screener, phone screener, and in-person group orientation and equipoise induction session, during which study candidates discussed the advantages and disadvantages of different treatment conditions to equalize their desirability prior to randomization (23). At orientation, participants underwent a written-informed-consent process and provided contact information and their PCP's medical approval to participate. Next, an in-person baseline assessment involved additional screening (e.g., depression and BMI) and demographic information (e.g., age, race, ethnicity, gender, and socioeconomic status). Socioeconomic status was self-reported on a scale that ranged from 1 (poor) through 5 (middle class) to 9 (wealthy). Eligible candidates were scheduled for in-person randomization (12) and 3-month and 6-month follow-up assessments, during which a blinded assessor measured weight using a calibrated balance-beam scale. Participants received an honorarium of $20 for each follow-up assessment.

A Consolidated Standards of Reporting Trials (CONSORT) diagram showing participant flow through the study appears in Figure 1.

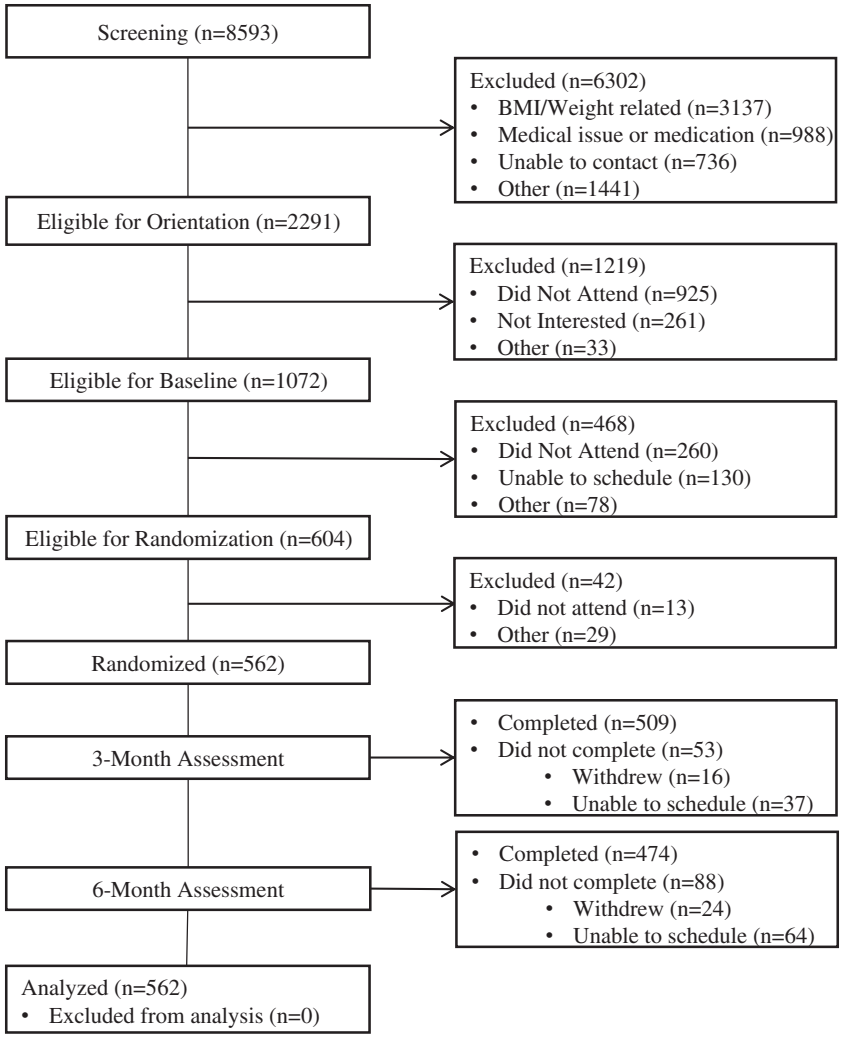

Figure 1 Consolidated Standards of Reporting Trials (CONSORT) diagram depicting participant flow through the 6-month study.

Data were collected and maintained using Research Electronic Data Capture (24,25), hosted by Northwestern University (Evanston, Illinois). All study protocols were approved by the Northwestern University Institutional Review Board.

Randomization

Participants were recruited in two cohorts. Cohort 1 ($n=289$) was randomly assigned to conditions 1 to 16; cohort 2 ($n=273$) was randomly assigned to conditions 17 to 32 (12,22). Randomization was stratified by gender and performed in randomly permuted blocks. Interventionists and participants were informed of the randomized assignment. Outcome assessors were blinded to participants' assigned treatment condition, behavioral adherence, and weight-loss trajectory.

Intervention

Each of the 32 experimental conditions (shown in Table 1) included delivery of up to 5 behavioral components, per the factorial design. Regardless of their randomized condition, all participants also received the core intervention described below.

The core intervention involved a smartphone app showing personalized goals for diet, PA, and weight (Supporting Information Figure S1) and online lessons (Supporting Information Figure S2). The core intervention invoked three behavior-change techniques (goal-setting, self-monitoring, and feedback) that Control Theory identifies as enhancing self-regulation (26,27). Participants downloaded a custom-designed Opt-IN app for self-monitoring all food and drink intake and PA throughout the day and for recording weight daily. They were given a 6-month weight-loss goal of 7% of initial body weight, daily calorie and fat-gram intake goals based on the DPP (2), and a weekly PA goal that increased gradually from 100 to 300 minutes of MVPA over the course of the intervention. The app displayed feedback about calorie and fat intakes, MVPA, and weight relative to goals; these data were transmitted to a coach dashboard (Supporting Information Figure S3). Participants received access

TABLE 1 Opt-IN factorial design with 32 conditions

Intervention target	Individual		Environment		
Combination	Coaching calls	Texts	Meal replacement	PCP reports	Buddy training
1	12	No	No	Yes	No
2	12	No	Yes	Yes	Yes
3	12	Yes	No	Yes	Yes
4	12	Yes	Yes	Yes	No
5	12	No	No	No	Yes
6	12	No	Yes	No	No
7	12	Yes	No	No	No
8	12	Yes	Yes	No	Yes
9	24	No	No	Yes	No
10	24	No	Yes	Yes	Yes
11	24	Yes	No	Yes	Yes
12	24	Yes	Yes	Yes	No
13	24	No	No	No	Yes
14	24	No	Yes	No	No
15	24	Yes	No	No	No
16	24	Yes	Yes	No	Yes
17	12	No	No	No	No
18	12	No	Yes	No	Yes
19	12	Yes	No	No	Yes
20	12	Yes	Yes	No	No
21	12	No	No	Yes	Yes
22	12	No	Yes	Yes	No
23	12	Yes	No	Yes	No
24	12	Yes	Yes	Yes	Yes
25	24	No	No	No	No
26	24	No	Yes	No	Yes
27	24	Yes	No	No	Yes
28	24	Yes	Yes	No	No
29	24	No	No	Yes	Yes
30	24	No	Yes	Yes	No
31	24	Yes	No	Yes	No
32	24	Yes	Yes	Yes	Yes

Adapted with permission from Pellegrini et al. (12).
PCP, primary care provider.

to online lessons about weight-related topics adapted from the DPP (e.g., basic nutritional information, barriers to PA, and setting specific, measurable, achievable, relevant, and time-bound goals) that they discussed with their coach.

Behavioral intervention components (factors)

Five behavioral intervention components functioned as dichotomous factors set to one of two levels (either low/high or off/on) to which participants were randomly assigned.

Coaching calls. Participants received either 12 biweekly or 24 weekly 10- to 15-minute calls from a health coach, during which the coach discussed core lessons and reviewed data transmitted from the participant's app to the coach dashboard to address self-monitoring adherence, progress toward goals, and motivation to change. Participants retained the same coach throughout the study, except in cases of staff absence or transition.

Progress report to PCP. Participants were randomly assigned to have reports about their weight-loss progress sent to their PCP or not. Those assigned to PCP report "on" were reminded on every call that their PCP would be mailed a tailored progress report after their 3- and 6-month assessments. The report showed participants' weight trajectory from baseline onward and provided topical recommendations for PCP-patient discussion.

Text messages. Participants were randomly assigned to receive text messages throughout the study or not. Messages were sent as automated push notifications on a schedule determined by (1) the participant's stated preferences and (2) the times when the participant was detected

to be engaging with the app. Those assigned to receive texts received seven messages dispersed throughout each week. They could also opt to receive two "bonus" messages conveying general weight-loss information. Messages addressed prespecified daily topics and were tailored on the basis of participants' self-monitored progress toward goals. On the basis of social cognitive theory (14,15), message framing conveyed either supportive accountability (e.g., "Awesome job meeting the physical activity goal" and "Remember to log your foods to stay on track") or facilitation (e.g., "Keeping sliced veggies in your fridge can steer you toward a low-cal snack").

MR recommendations. At randomization, those assigned to MR were given a week's supply of prepackaged shakes and bars and asked to consume these daily to supply part of their calorie and nutrient intakes. After the initial week, those assigned to MR "on" were asked to purchase their own MR supplies because providing MR supplies continually was considered unscalable. On coaching calls, they were advised to continue using MR products.

Buddy training. All participants entered the study with a buddy of their own choosing to provide support. Participants were randomly assigned either to have their buddy undergo training about how to behave supportively or not to undergo this training. Buddies assigned to receive training were asked to complete one individual coaching phone call and up to four online group-training webinars. During webinars, a facilitator conveyed skill-building lessons and led peer problem-solving about how to provide effective weight-loss support. Buddies earned $5 for each webinar attended, plus a $20 bonus if they attended three of the four webinars.

Treatment fidelity

Treatment fidelity was assessed quarterly using a checklist to score a random sampling of 15% of each coach's telephone-coaching calls. The scoring system added points for required treatment elements the coach delivered correctly and subtracted points for contaminating treatment elements the coach delivered from an unassigned condition. If the average fidelity for any coach fell below 90%, retraining occurred.

Average treatment fidelity across all coaches was 99.3% throughout the 5-year study, indicating that treatment components were delivered as intended. None of the nine coaches required retraining. Coaches assured text-messaging receipt by querying about message delivery and detecting and fixing any technical difficulties. Coaching-call receipt was verified by audiotape; almost twice as many calls were delivered in the 24-call coaching condition compared with the 12-call coaching condition, and total call duration was substantially longer ($P<0.001$) (Table 2). Calls were approximately 2 minutes shorter in the 24-session condition than in the 12-session condition ($P<0.001$).

Outcomes

Because the primary aim of the Opt-IN study was to determine which intervention components maximize weight loss, the primary outcome was weight loss from baseline to 6 months. As an optimization trial to identify promising components for inclusion in an optimized treatment package (8), Opt-IN's criterion to consider an effect important was set liberally at $P<0.10$ to decrease the type 2 error rate (8). Hence, for any 1-*df* test in the factorial design (essentially any main effect or two-way or three-way interaction in a design in which all factors have just two levels), the detectable effect size (with power = 0.8 and alpha = 0.10, given a sample size of 562) is an $f=0.105$ or a $d=0.21$. Note that this effect size, detectable with alpha = 0.10, is comparable, albeit slightly smaller than the $d=0.25$ effect size detectable with alpha = 0.05, for which the trial was powered.

TABLE 2 Coaching-call receipt for 12- versus 24-call coaching conditions

	12-call condition	24-call condition
Calls completed, mean (SD)	10.43 (2.65)	19.10 (6.13)***
Total call minutes, mean (SD)	159.60 (71.31)	240.13 (121.04)***
Minutes per call, mean (SD)	15.40 (5.61)	12.50 (4.55)***

***$P<0.001$.

TABLE 3 Cost per person of lower and higher level of intervention components

	Lower level	Higher level
Core intervention	$174	$174
Telephone-coaching calls	$150	$276
PCP reports	$0	$13
Text messages	$0	$26
Meal replacement	$0	$33
Buddy training	$0	$90
Total	$324	$612

PCP, primary care provider.

The secondary aim was to apply these results, together with cost data, to build the treatment package producing the greatest weight loss attainable for $500 or less. First we estimated the costs of each component and component level (Table 3) from the perspective of an organization that would implement Opt-IN. We used study records to estimate staff time, including supervision and training, to deliver the core intervention, telephone-coaching calls, and buddy training, and to prepare text messages and PCP reports. Staff salaries plus 25% fringe benefits were calculated on the basis of median salaries for each of the three bachelors-level staff categories (research assistant assessor, project coordinator/coach, and programmer) plus the doctorate-level clinical supervisor. Equipment and subscription costs included fees to access the study's web server and the webinar service used to deliver buddy training. Supplies, including printing, paper, and postage for PCP reports, as well as MR shakes and bars, were estimated on the basis of actual 2016 prices. The cost of the telephone-coaching calls was calculated separately for the 12-call and 24-call conditions. Cost estimates were adjusted from previously published values (12) to reflect real costs to deliver the intervention to 168 participants per year.

Statistical analysis

Data, analyzed on an intent-to-treat basis using mixed models, allowed for a full unstructured variance-covariance matrix for the repeated measures and used SPSS Mixed (64-bit version 26.0.0.0; IBM Corp.,

TABLE 4 Baseline participant demographics by component level[a]

	Sex		Race			Ethnicity			Age,
	Male	Female	White	Black	Other	Not Hispanic	Hispanic	Other	mean (SD),
Factor level	(*n* = 103)	(*n* = 459)	(*n* = 417)	(*n* = 87)	(*n* = 58)	(*n* = 489)	(*n* = 53)	(*n* = 20)	38.9 (10.9)
Coaching									
12	51 (49.5)	229 (49.9)	206 (49.4)	40 (46.0)	34 (58.6)	232 (47.4)	33 (62.3)	15 (75.0)	38.8 (11.1)
24	52 (50.5)	230 (50.1)	211 (50.6)	47 (54.0)	24 (41.4)	257 (52.6)	20 (37.7)	5 (25.0)	39.1 (10.8)
PCP									
No	51 (49.5)	229 (49.9)	211 (50.6)	40 (46.0)	29 (50.0)	244 (49.9)	26 (49.1)	10 (50.0)	38.1 (11.0)
Yes	52 (50.5)	230 (50.1)	206 (49.4)	47 (54.0)	29 (50.0)	245 (50.1)	27 (50.9)	10 (50.0)	39.7 (10.8)
Texts									
No	50 (48.5)	231 (50.3)	213 (51.1)	38 (43.7)	30 (51.7)	243 (49.7)	32 (60.4)	6 (30.0)	39.0 (10.4)
Yes	53 (51.5)	228 (49.7)	204 (48.9)	49 (56.3)	28 (48.3)	246 (50.3)	21 (39.6)	14 (70.0)	38.9 (11.4)
Meal									
No	51 (49.5)	231 (50.3)	205 (49.2)	46 (52.9)	28 (53.4)	240 (49.1)	32 (60.4)	10 (50.0)	38.5 (10.6)
Yes	52 (50.5)	228 (49.7)	212 (50.8)	41 (47.1)	31 (46.6)	249 (50.9)	21 (39.6)	10 (50.0)	39.4 (11.2)
Buddy									
No	50 (48.5)	230 (50.1)	206 (49.4)	39 (44.8)	35 (60.3)	239 (48.9)	30 (56.6)	11 (55.0)	39.0 (10.7)
Yes	53 (51.5)	229 (49.9)	211 (50.6)	48 (55.2)	23 (39.7)	250 (51.1)	23 (43.4)	9 (45.0)	38.9 (11.1)
Test (*P*)	$x^2 = 0.22$ (*P* = 0.999)	$x^2 = 8.82$ (*P* = 0.549)	$x^2 = 19.31$ (*P* = 0.037)	F = .697 (*P* = 0.626)	—	—	—	—	—

[a]Sex/race/ethnicity: count (% by factor level); age: M (SD). Omnibus tests of distribution across levels of all factors (gender: logistic regression; race/ethnicity: nominal regression; age: ANOVA).

TABLE 5 Abbreviated full mixed model examining effects on 6-month weight loss

Effect	Estimate	*t*	*P*	95% CI
Baseline				
Intercept	91.093	114.382	0.000	89.529 to 92.658
Cohort	−2.170	−1.899	0.058	−4.414 to 0.075
Coaching[a]	−0.106	−0.185	0.853	−1.227 to 1.016
PCP[a]	0.796	1.393	0.164	−0.326 to 1.917
Text[a]	0.242	0.423	0.672	−0.880 to 1.363
Meal[a]	−1.114	−1.951	0.052	−2.236 to 0.008
Buddy[a]	0.464	0.813	0.417	−0.658 to 1.586
3 months				
Time	−3.761	−25.237	0.000	−4.054 to −3.468
6 months				
Time	−4.841	−22.284	0.000	−5.268 to −4.415
Time × coaching	0.124	0.572	0.567	−0.303 to 0.551
Time × PCP	−0.023	−0.104	0.917	−0.449 to 0.404
Time × text	0.084	0.387	0.699	−0.343 to 0.511
Time × meal	0.108	0.498	0.619	−0.319 to 0.535
Time × buddy	**−0.435**	**−2.003**	**0.046**	**−0.862 to −0.008**
Time × coaching × PCP	−0.130	−0.601	0.548	−0.556 to 0.296
Time × coaching × text	−0.179	−0.824	0.411	−0.604 to 0.247
Time × coaching × meal	−0.096	−0.444	0.657	−0.522 to 0.330
Time × coaching × buddy	−0.085	−0.394	0.694	−0.511 to 0.341
Time × PCP × text	−0.211	−0.974	0.331	−0.637 to 0.215
Time × PCP × meal	0.093	0.429	0.668	−0.333 to 0.519
Time × PCP × buddy	−0.276	−1.273	0.204	−0.702 to 0.150
Time × text × meal	0.101	0.465	0.642	−0.325 to 0.527
Time × text × buddy	0.217	1.003	0.316	−0.208 to 0.643
Time × meal × buddy	0.041	0.188	0.851	−0.385 to 0.467
Time × coaching × PCP × text	−0.074	−0.342	0.733	−0.500 to 0.352
Time × coaching × PCP × meal	**0.362**	**1.6700**	**0.096**	**−0.064 to 0.788**
Time × coaching × PCP × buddy	0.090	0.413	0.680	−0.336 to 0.515
Time × coaching × text × meal	−0.062	−0.286	0.775	−0.488 to 0.364
Time × coaching × text × buddy	0.068	0.313	0.755	−0.358 to 0.494
Time × coaching × meal × buddy	0.008	0.035	0.972	−0.418 to 0.434
Time × PCP × text × meal	−0.165	−0.760	0.448	−0.591 to 0.261
Time × PCP × text × buddy	**0.424**	**1.956**	**0.051**	**−0.002 to 0.850**
Time × PCP × meal × buddy	0.112	0.517	0.606	−0.314 to 0.538
Time × text × meal × buddy	−0.186	−0.856	0.392	−0.612 to 0.240
Time × coaching × PCP × text × meal	0.204	0.941	0.347	−0.222 to 0.630
Time × coaching × PCP × text × buddy	**−0.383**	**−1.769**	**0.078**	**−0.809 to 0.042**
Time × coaching × PCP × meal × buddy	**−0.376**	**−1.736**	**0.083**	**−0.802 to 0.050**
Time × coaching × text × meal × buddy	−0.171	−0.790	0.430	−0.597 to 0.255
Time × PCP × text × meal × buddy	−0.027	−0.123	0.902	−0.454 to 0.400
Time × coaching × PCP × text × meal × buddy	−0.164	−0.755	0.451	−0.590 to 0.262

[a]Main effects from *coaching* to *buddy* represent component effects at baseline (time zero) and therefore do not test the hypotheses of interest.
Effects that meet the criterion of importance (interacting with *time* or with a screened-in component and $P<0.10$ at 6 months) are designated in bold. The full analytic model from which these estimates are derived also contains effects and interactions at time 3 months, corresponding to the 6-month effects that are of primary interest and shown here. For brevity, 3-month outcomes have been omitted from this table but are presented in Supporting Information Table S1.
PCP, primary care provider.

Armonk, New York) with restricted maximum-likelihood estimation to estimate the model parameters. Effect coding was used; off/low component levels were coded as −1, on/high component levels were coded as 1. Cohort was entered into the model as a covariate. Dummy variables for time were included to represent the change relative to baseline at the 3- and 6-month follow-ups.

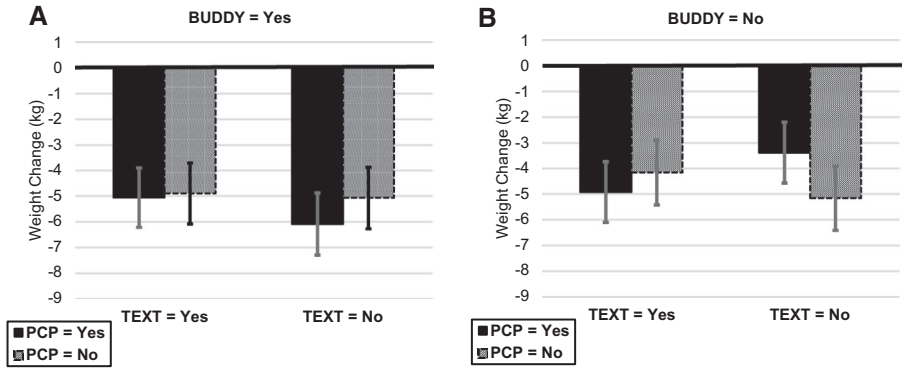

Figure 2 Effect of *buddy* × *PCP* × *text* interaction on weight change (kilograms) at 6 months. (**A**) Weight gain or loss among those who received buddy training, with text messaging and PCP reports turned on or off. (**B**) Weight change among those who received no buddy training with text messaging and PCP report either on or off. Error bars depict the 95% CI of each estimated mean. BUDDY, buddy training; PCP, progress report sent to primary care provider; text, text messaging.

Decision-making proceeded as follows (8,28). First, all two-way interactions between a component and time were examined. (In our longitudinal mixed model, this is conceptually equivalent to a component main effect on weight change.) Components that showed important interactions with time at the 6-month primary study endpoint ($P<0.10$) were tentatively selected. Next, all interactions, from lower to higher order, that included important component-by-time interactions were examined. Tentative decisions made about component inclusion were reconsidered on the basis of important synergistic or antagonistic interaction effects involving initially selected components. Components identified in this manner formed the screened-in set.

With the screened-in set of components identified, decision-making began for the secondary aim. Treatment effect estimates and costs of all possible treatment packages involving these components were examined. Estimated weight loss was calculated on the basis of a parsimonious regression model that included as predictors only the screened-in components, interactions that led to their selection, and corresponding lower-order terms. A version of this parsimonious model (excluding interactions with time) was used to estimate the proportion of participants achieving ≥5% and ≥7% 6-month weight loss.

Accounting for attrition led to a sample size estimate of 560 to yield 80% power to detect an effect size of 0.25 (Cohen *d*) under a two-tailed hypothesis test. Assuming an estimated SD of 4 kg (29), this translates to a 1-kg difference in weight loss from baseline to 6 months.

Results

Opt-IN participants were mostly female (81.5%), white (74.1%), and middle class (M=5 [SD=1.4]), and they self-identified as non-Hispanic/Latinx (86.8%). Mean (SD) BMI at baseline was 32.3 (3.6) kg/m^2. There were no significant differences in sex, race, or age as a function of the component levels to which participants were assigned (Table 4). However, component level and ethnicity interacted ($P=0.037$), such that fewer self-identified Hispanic/Latinx participants and fewer participants who identified with other ethnicities were randomly assigned to receive 24 rather than 12 sessions of coaching compared with nonminorities ($P=0.007$).

Of the full sample of 562 individuals who began the study, 474 (84.3%) completed the 6-month endpoint, 64 (11.4%) were lost to follow-up, and 24 (4.3%) formally withdrew. None of these showed a differential effect of treatment component level.

Table 5 shows abbreviated results of the full model testing all main effects and effects of interactions of treatment components on the primary 6-month weight-loss outcome. Effects on 3-month outcomes are omitted for brevity, but all effects from the full model appear in Supporting Information Table S1. Supporting Information Table S2 shows 6-month weight loss for both levels of each intervention component. Mixed model results (*buddy* × *time* interaction) showed that buddy training was the only component whose inclusion significantly increased 6-month weight loss beyond the effect of the core intervention. Therefore, we tentatively included buddy training in the screened-in set of components and excluded the other four components. Next, we reconsidered these decisions in the light of important interaction effects. We particularly examined interactions with *buddy* to determine whether any of the four omitted components should be included in the screened-in set, even though they did not show two-way interactions with time because they boosted or reduced the effect of buddy training.

No other two- or three-way interactions were identified as important; however, two four-way and two five-way interactions met the $P<0.10$ criteria for importance. The four-way interaction of *time* × *coaching* × *PCP* × *meal* was not considered further because it did not involve *buddy*. The interaction of *time* × *PCP* × *text* × *buddy* was identified as important, so we examined a plot of the interaction (Figure 2) to determine whether components were synergistic with or antagonistic to *buddy*. As shown, the greatest weight loss occurred when *text* was off and both *buddy* and *PCP* were on. Therefore, we preliminarily considered including both buddy training and PCP reports in

TABLE 6 Predicted 6-month weight change and cost of candidate component combinations (i.e., intervention packages)

No.	Calls	Text message	Meal replacement	PCP report	Buddy training	Estimated effects			
						6-month weight change (kg)	Achieving 5% weight loss (%)	Achieving 7% weight loss (%)	Cost
21	12	No	No	Yes	Yes	−6.1112	57.13	51.77	$427
1	12	No	No	Yes	No	−3.3966	34.48	25.86	$337
5	12	No	No	No	Yes	−5.0540	46.56	31.02	$414
17	12	No	No	No	No	−5.2389	52.95	41.17	$324

our screened-in set. The two remaining important effects were five-way interactions involving *time* × *PCP* × *buddy* × *coaching* × *meal* and *time* × *PCP* × *buddy* × *coaching* × *text*. Examination of the first interaction (Supporting Information Figure S4) showed a reduced effect of *meal* when *buddy* and *PCP* were included components, so we continued to screen out MR recommendations. Examination of the second of these interactions (Supporting Information Figure S5) continued to support the decision to leave PCP reports in and text messages out of the screened-in set. Neither plot showed an advantage for the higher level of coaching calls when *buddy* was turned on, so we left coaching at its lower, less expensive level.

For our secondary aim of identifying the combination of components that produces the maximum expected weight loss attainable for <$500 (i.e., the optimized intervention), we computed the average expected weight loss and expected proportion achieving 5% and 7% weight loss for each combination of components in the screened-in set on the basis of parsimonious regression models. These quantities and estimated cost appear in Table 6. Combination 21, which costs $427, adds the synergistic effect of PCP report to buddy training, achieving an estimated average 6-month weight loss of 6.1 kg, with an expected 57.1% of the sample losing 5% and 51.8% losing 7% of their initial body weight.

Discussion

The Opt-IN study addressed barriers to the institutional uptake of remotely delivered intensive lifestyle interventions for obesity by applying the MOST framework. We performed a factorial optimization trial designed to determine which of 5 components of a remotely delivered, technology-supported obesity intervention contributed importantly to 6-month weight loss in a sample of adults with obesity. That information, combined with data on cost, was then used to explore which combinations of components and component levels best met our prespecified optimization criterion by producing the maximum weight loss attainable for ≤$500 per person. The results suggested that the combination of the core intervention (i.e., app, goals, and online lessons), 12 coaching calls, buddy training, and PCP reports best met our optimization criterion.

It is important to note that the optimization criterion we applied (i.e., maximum weight loss for ≤$500) is not the only one that might be considered. Our criterion gave highest priority to maximizing weight loss, in part because we were able to assume access to resources of at least $500 per treated person, supplied by either insurance or the individual. A different context characterized by greater resource constraints might call for a different optimization criterion. For example, a program for low-income, uninsured adults might prioritize maximizing population reach: that is, achieving allocation of scarce financial resources to treat the maximum possible number of people who need obesity intervention (30). Here, decision-makers might find it an acceptable tradeoff to achieve somewhat lower weight loss so that funds could be stretched to benefit a larger population, leading to selection of combination 17 in Table 6. Combination 17, which leaves all components off or to the lowest level, is the least expensive treatment package ($324, vs. $427 for combination 21), while still achieving an estimated 5.2-kg average weight loss, or at least 5% weight loss for more than 50% of participants. Hence, combination 17 offers better value ($61.8 per kilogram lost) than combination

21 ($69.9 per kilogram lost), although it results in somewhat lower weight loss.

Of the treatment components we tested, only training the participant's buddy to be supportive increased average 6-month weight loss, a benefit marginally augmented by adding PCP reports. There was no evidence to suggest that increasing the number of coaching calls from 12 to 24 or adding MR recommendations, text messages, or PCP progress reports increased weight loss on its own. The absence of a dosage effect due to doubling the number of coaching calls was unexpected, as prior research has suggested that a greater number of treatment sessions is associated with greater weight loss (31-33). Our analyses of call receipt show that the lack of a dosage effect cannot be attributed to failure of treatment implementation. At least one prior study also found that offering moderate-intensity obesity treatment with sessions every other week yielded weight-loss results comparable to higher-intensity, more-frequent treatment and was more cost-effective (34).

The failure to find an increasing weight-loss benefit as a result of adding more intensive or expensive treatment components is good news for public health. Findings suggest that the average adult who seeks treatment for obesity can lose weight with a relatively low-cost intervention (8,17,35,36). As noted, our results indicate that several different treatment packages produced meaningful weight loss for <$500. The one yielding the greatest weight loss added buddy training plus PCP reports to 12 connected coaching sessions plus the core intervention. We interpret this finding to mean that the 12 individually targeted coaching sessions saturated participants' skill-building needs but that environmentally targeted components addressed otherwise unmet needs.

Conceivably, an even lower-cost intervention involving the core intervention alone might produce weight loss because the app and online lessons incorporate well-studied behavior-change techniques (goal-setting, self-monitoring, and feedback) that have been shown in some (37) but not all (38) systematic reviews to improve diet, PA, and weight loss. Although we cannot presently determine how much of the weight loss produced by the optimized treatment package was attributable to the core intervention versus the added intervention components, we are conducting a trial that, in part, compares the impact on weight loss of obesity treatment that uses the app alone versus using the app plus coaching (39).

This research has limitations, including that it did not test all possible intervention components, evaluated a diluted version of MR for the sake of scalability, and examined weight-loss initiation but not maintenance. Very importantly, the weight-loss and cost figures we report for different combinations of components are estimates. Further, the developed intervention packages were optimized for adults with obesity who enrolled in a remotely delivered treatment program and were predominately non-Hispanic, middle-class, white women. Results may not generalize to other subpopulations. Definitive demonstration of the effectiveness of a developed, optimized treatment package requires a test against a comparator in a randomized controlled trial. If an optimized obesity treatment package demonstrates effectiveness, it can be considered an evidence-based practice (or empirically supported treatment) that has good odds of producing meaningful weight loss for an average adult (40). Per precision behavioral medicine, however, individual and temporal variability in the response to any single treatment are likely. To address those issues, the MOST research design toolkit includes methods to develop treatment algorithms that can adapt and guide the evidence-based practice process in a resource-efficient manner (8,9,39-42).

Conclusion

The Opt-IN study demonstrates how a factorial experiment can be used to gather data about which components of an intensive, behavioral obesity treatment program contribute meaningfully to weight loss, and at what cost. When 5 components were evaluated for effects on 6-month weight loss in a remotely delivered, technology-supported obesity treatment, training participants' buddies to be supportive augmented weight loss, a benefit enhanced by providing progress reports to the PCP. Providing 24 rather than 12 coaching calls, MR recommendations, and text messaging produced no additional weight loss. The resulting data were used systematically to guide decisions about which components were essential to achieve meaningful weight loss, which could be reduced or eliminated to reduce cost and burden, and which provided a desired balance of effectiveness and economy. Results suggest an optimally cost-efficient obesity treatment package to maximize weight loss and an alternative to consider when the context requires reducing treatment cost to extend treatment to a greater number of people.

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