

Incorporating Tailored Interactive Patient Solutions Using Interactive Voice Response Technology to Improve Statin Adherence: Results of a Randomized Clinical Trial in a Managed Care Setting

Jane N. Stacy, Pharm.D.,¹ Steven M. Schwartz, Ph.D.,²
Daniel Ershoff, Dr.P.H.,³ and Marilyn Standifer Shreve, Pharm.D.⁴

Abstract

The current study presents the impact of a behavior change program to increase statin adherence using interactive voice response (IVR) technology. Subjects were affiliated with a large health benefit company, were prescribed a statin (index) and had no lipid-lowering pharmacy claims in the previous 6 months, and were continuously enrolled in the plan for 12 months prior and 6 months post index statin.

Potential subjects (1219) were contacted by the IVR system; 497 gave informed consent. Subjects were asked to respond to 15 questions from the IVR that were guided by several behavior change theories. At the conclusion of the questions, subjects were randomly assigned to either a control group ($n=244$), who received generic feedback at the conclusion of the call and were then mailed a generic cholesterol guide, or an experimental group ($n=253$), who received tailored feedback based on their cholesterol-related knowledge, attitudes, beliefs, and perceived barriers to medication adherence, and were mailed a tailored guide that reinforced similar themes. Subjects in the experimental group had the opportunity to participate in 2 additional tailored IVR support calls.

The primary dependent variable was 6-month point prevalence, defined as claims evidence of a statin on days 121–180 post index statin. Subjects in the experimental group had a significantly higher 6-month point prevalence than the controls (70.4% vs. 60.7%, $P < 0.05$). Results of this study suggest that a behavioral support program using IVR technology can be a cost-effective modality to address the important public health problem of patient nonadherence with statin medication. (*Population Health Management* 2009;12:241–254)

Introduction

OVER 80 MILLION AMERICANS ARE DIAGNOSED WITH CARDIOVASCULAR DISEASE, the leading cause of morbidity and mortality in the United States, with an estimated total direct and indirect expenditure of \$448.5 billion for 2008. Coronary artery disease (CAD), with a prevalence of 16 million Americans, consumed an estimated \$156.4 billion dollars, and was associated with 1 of every 5 deaths in 2004.¹

Dyslipidemia is a well-recognized and prevalent risk factor for coronary heart disease (CHD), with an estimated 36 million Americans qualified as candidates for lipid-lowering therapy, a number that exceeds 50 million when optional treatment guidelines are utilized as the treatment criteria.^{2,3}

Further, multiple randomized clinical trials have demonstrated that statins lead to significant cardiovascular event risk reductions in both primary and secondary prevention trials.^{4–7} Data from clinical trials and observational studies support the clinical and economic value that these compounds can bring to managed care, which has historically underappreciated the evidence supporting statin treatment with regard to short-term clinical outcomes and concomitant financial savings.^{8,9}

The observed reductions in cardiovascular events associated with statin treatment within 1–2 year time frames, coupled with the declining treatment costs associated with generic entrants into the marketplace, suggest that appropriate use of statin therapy can yield a positive return on

¹Humana Inc., Louisville, Kentucky.

²HealthMedia, Inc., Ann Arbor, Michigan.

³AstraZeneca, Tarzana, California.

⁴Kentfield, California.

investment to managed care organizations, notwithstanding the well-recognized high membership turnover rate. However, the favorable outcomes from clinical trials of statins are often substantially reduced when compared to the impact of statin therapy in real-world settings.¹⁰ A significant factor contributing to suboptimal statin outcomes is the high rate of early discontinuation (persistence) and/or poor adherence (number of doses taken in proportion to the number of doses prescribed). One-year statin persistency/adherence rates found in studies conducted in managed care settings typically range from 50% to 66%, although rates as low as 33% have been reported.^{11–20}

Given the public health need for lipid-lowering risk reduction in the general population and the significant problem of poor persistence/adherence leading to suboptimal outcomes, there have been numerous attempts to develop and test interventions for statin persistence/adherence. The current literature has shown inconsistent results; therefore, most authors conclude that, based on the available evidence, no specific intervention aimed at improving adherence to lipid-lowering drugs can be recommended.^{21,22} Furthermore, in a systematic review of randomized clinical trials of medication adherence studies across therapeutic areas, the authors concluded that the academically-driven adherence research for chronic conditions were complex, labor intensive, expensive, and impractical to implement and sustain in usual practice settings.²³

Despite the equivocal literature, there are some promising findings worth noting. For example, trials employing intensified patient support (telephonic reminders coupled with written materials) achieved the most success.²⁴ These authors recommend that future interventions consider more than 1 or 2 behavioral factors associated with adherence (ie, knowledge, health beliefs, risk perception, memory, concerns about side effects, cost) as part of a comprehensive, patient-centered approach. A recent review of 79 adherence-enhancing interventions targeting hypertensive and dyslipidemic patients found greater adherence was a function of more intensive and tailored programs involving frequent interactions with health care professionals. The authors concluded that the results likely allowed the health care provider to adequately address patients' unique barriers to adherence.²⁵

Tailored communication and behavior change theory and technique appear to be 2 effective characteristics of adherence literature to date. Tailored health messaging differs from generic or even targeted communications in terms of the degree to which the content is personalized to the target (person receiving the communication). While generic information does not consider any of the unique characteristics of the intended recipient, targeted information either uses gross constructs such as name, sex, and age, or in some marketing applications, bases the communication on a broad market segment. Tailored health communications, on the other hand, employ a far more granular degree of specificity, and when that specificity is informed by evidence-based behavioral theory (eg, the health beliefs model, social learning theory, stage of change), such communications have been shown in many cases to be very effective. In fact there is a growing body of literature, the preponderance of which supports the notion that highly tailored health communications are more likely to be read, understood, and acted upon,

and can produce superior outcomes in a variety of areas including smoking cessation, mammography, nutrition, health risk appraisal feedback, asthma, exercise, chronic illness self-management, diabetes prevention, colorectal cancer screening, hypertension, and adherence (including to anti-hypertensives and lipid-lowering medications).^{26–44}

In a managed care setting, the need for an effective, scalable, and cost-effective intervention for statin persistence/adherence is imperative. As a potential solution, computerized interactive feedback systems that incorporate reminders, educational information, and self-management interventions intended to influence health via behavior change hold tremendous promise, but as yet have been minimally tested under rigorous methodological conditions that are highly generalizable (ie, retain real-world implementation potential). Advances in technology (eg, telephonic voice-activated technology [VAT], mobile messaging, Web-based) have the advantage of increased power to reach large populations at relatively low cost, and have the capacity to provide information in a highly tailored fashion.

Therefore, the opportunity exists to enhance persistence and adherence by effectively coupling 1 or more communications media with multiple and appropriate behavioral science theories and techniques delivered via a tailored and personalized communication. However, the challenge is how to use these technologies such that they draw from and utilize the best available evidence regarding behavior change and medication adherence, and deliver information in ways that patients perceive as personally relevant and capable of addressing their unique circumstances and challenges, and that provide meaningful and practical action steps. Therefore, the purpose of this study was to develop and test the impact of a tailored communications schema for increasing statin adherence/persistence delivered via a combination of print and telephonic VAT in an integrated system. The content of the message was based on a number of well-validated behavioral science theories and techniques such as the Transtheoretical Stages of Change,^{45,46} the Health Beliefs Model,^{47–49} the Chronic Care Model,⁵⁰ motivational interviewing,^{51,52} and reflective listening. The experimental compliance communications strategy used a combination of the behavioral change models mentioned and a tailoring technology in order to help statin users understand and overcome identifiable barriers to persistence and adherence, develop and maintain their motivation, and increase their self-confidence to manage this aspect of their medical regimen.

Methods

Overview

This prospective randomized clinical trial comprised subjects who recently filled a prescription for a hydroxymethyl glutaryl coenzyme A reductase inhibitor (statin) and who consented to participate in a study testing an innovative strategy that held the promise of improving their persistence and adherence with their prescribed cholesterol-lowering medication regimen. Consenting subjects were randomly assigned to either (a) an experimental group, who received up to 3 separate tailored behavioral support interactions delivered via an interactive voice recognition (IVR) system coupled with tailored print material received through

the mail (the tailored guide provided personalized intervention regarding verbal reinforcement, tips for overcoming barriers, habit formation, and working with their physician), or (b) an enhanced care control group, who received nontailored behavioral advice from a single IVR call, coupled with a nontailored, generic, self-help cholesterol management guide received through the mail. This guide provided educational material on cholesterol and lipid values, a brief knowledge quiz, and a nontailored action plan. Outcome measures were assessed from pharmacy claims data during a subsequent 180-day follow-up period. The study protocol and intervention materials were approved by an independent institutional review board.

Sample

Study subjects were affiliated with a large health benefits company as either health maintenance organization (HMO) or preferred provider (PPO) members. The initial subject pool consisted of members, derived from the health plan pharmacy claims database, who processed a pharmacy claim for a statin (termed *index statin*) during the study recruitment period between May and November 2005. Of note, the fact that a pharmacy claim was processed for the index statin does not necessarily imply that the prescription was ever actually dispensed to the member. For approximately 4% of study subjects, the index statin was "reversed" (the original index statin prescription was filled but never picked up, and was placed back in stock). Therefore, the medication may never have been dispensed to the study subject during the 180-day observation period, or the first actual dispensed statin could have been weeks, if not months, subsequent to the original index statin date.

Members with an index statin were eligible for the study if they met the following criteria: (a) continuously enrolled in the plan with a pharmacy benefit for a minimum of 12 months prior to the date of the index statin; (b) no pharmacy claims evidence of any lipid-lowering agent in the 6-month period prior to the index statin; (c) 21 years of age or older; and (d) a statin prescription with a 30-day supply. Approximately 95% of all statin prescriptions in this health plan at the time of the study were written for a 30-day supply and, given the relatively short 180-day observation period, an initial prescription exceeding a 30-day supply would greatly reduce the ability to detect differences in outcomes between experimental conditions.

Based on the criteria outlined, 6242 potential subjects were identified for inclusion in the study. The current report is based on the 5174 (82.9%) who remained continuously enrolled in the plan with a pharmacy benefit for a minimum of 6 months after the index statin date. The 6 months of continuous enrollment was necessary to calculate the primary and secondary outcome measures (to be described).

Procedure

On a weekly basis, the names and telephone numbers of potential subjects were forwarded to the IVR company (Eliza Corporation, Beverly, MA). The IVR company attempted 6 separate calls over the subsequent 10-day period. Successful contact with potential subjects was made within 7–14 days of the date of their index statin. Calls were made at various times, including nights and weekends, and all calls were

made in English. If an answering machine or another member of the household was reached, a Health Insurance Portability and Accountability Act-compliant message was left that encouraged the target subject to call back at a toll-free number. If the target patient was reached and the patient agreed to continue with the call, he or she was read a brief verbal informed consent statement.

Figure 1 displays the recruitment flow based on IVR call results. Of the 5174 potential participants, nearly three fourths (73.0%, $n = 3775$) were never contacted by the IVR system after 6 attempts, including: (a) 10.9% ($n = 566$) because of an incorrect telephone number; (b) 14.7% ($n = 758$) because of a busy signal/no answer; (c) 2.0% ($n = 103$) because a respondent prematurely discontinued the call prior to a final disposition; (d) 18.6% ($n = 964$) after a message was left with another member of the household; and (e) 26.7% ($n = 1384$) after a message was left on an answering machine. Of the remaining 1399 (27.0%), 3.5% ($n = 180$) failed to agree to continue with the call and 12.4% ($n = 641$) failed to provide verbal consent, leaving a final sample of 578 subjects (11.2% of the initial subject pool) who consented to participate in the study. At this juncture, the IVR system randomly assigned subjects to either the experimental or the enhanced care control group. Subjects who provided consent were nonetheless deemed ineligible for the study if they reported in the initial baseline assessment that they were not aware they had been prescribed a cholesterol-lowering agent ($n = 21$), or reported that they had no intention of picking up their prescription at the pharmacy within the next 7-day period ($n = 2$). Finally, 58 subjects were excluded from the study population because they failed to answer at least half of the 15 IVR baseline assessment items.^a Taking into consideration the aforementioned exclusions, the final sample size consisted of 497 subjects ($n = 253$ experimental subjects and $n = 244$ enhanced care controls subjects).

Measures

Background characteristics. The subject's age, sex, health plan affiliation (HMO or PPO), and enrollment status were obtained from the membership database. Data on the index statin were obtained from the pharmacy claims database, including the name of the medication, member co-payment amount, verification that the medication actually was dispensed on the date corresponding to the index statin, and whether 1 or more lipid-lowering agents had been prescribed in the 7–12 month period preceding the index statin.

Health status. Several surrogate measures of the subject's health status were derived from pharmacy and medical claims and administrative data. Subjects were classified as to whether they were enrolled in the cardiac disease

^aThe vast majority of these 58 subjects failed to answer any of the baseline items; therefore, although providing verbal consent to participate, they appeared to more closely approximate members who failed to consent to the study. From a practical standpoint, the lack of data from the baseline assessment for these subjects precluded the ability to provide experimental subjects with tailored behavioral feedback either at the conclusion of the initial call or in the printed tailored guide, which in turn would reduce the integrity of the implementation of the competing interventions and potentially lead to a biased impact. This is frequently referred to as a Type III error.⁵³

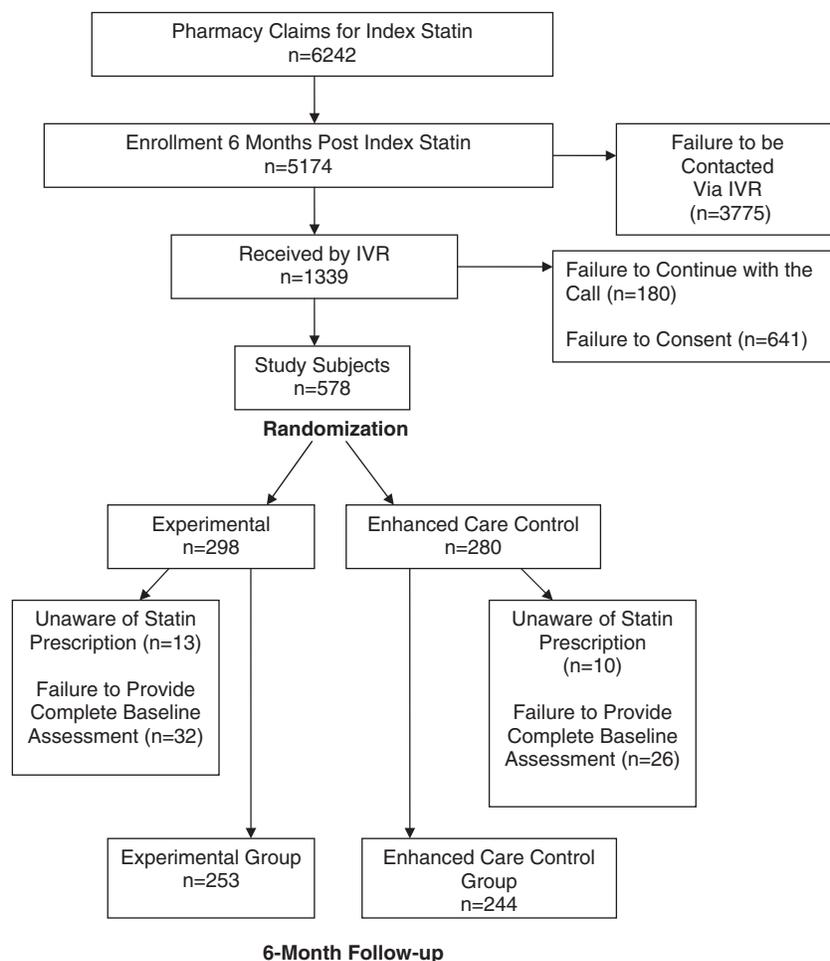


FIG. 1. Flowchart of participants. IVR, interactive voice response.

management program (an intervention targeted at individuals in the health benefits organization who were diagnosed with CAD) and, if enrolled, the timing of the enrollment relative to the date of the index statin. Utilizing pharmacy claims data during the 3-month period prior to the index statin, a count was made of the number of distinct medications that were indicative of the presence of a chronic condition (eg, an individual who had filled prescriptions for metformin and atenolol would be classified as having a chronic disease count of 2, with the medications presumably indicative of diabetes and hypertension). Chronic medications were determined based on the First Data Bank classification of maintenance medications. Finally, using inpatient and outpatient medical claims and pharmacy claims for the 12-month period prior to the index statin, each member was classified into the National Cholesterol Education Program (NCEP) Adult Treatment Panel III risk classification system.⁵⁴

Details of the classification scheme are provided elsewhere, but briefly, an individual was classified as "High Risk" (a low-density lipoprotein [LDL] treatment goal of <100 mg/dl) if he or she had CHD or a CHD risk equivalent based on *International Classification of Diseases, Ninth Revision, Clinical Modification* (ICD-9-CM) or procedural codes for myocardial infarction, ischemic heart disease, transient ischemic attacks, angioplasty, or other, or diabetes.⁵⁵ Individuals were classified as "Moderate Risk" (LDL treatment goal of <130 mg/dl)

if they had at least 2 of the following 3 risk factors identifiable from claims databases: hypertension (ICD-9-CM code or pharmacy claim for a blood pressure-lowering agent); age 45 years or older for men and 55 years or older for women; or a high-density lipoprotein (HDL) level below 40 mg/dl (an HDL of >0.60 is counted as a negative risk factor). Because the NCEP-defined CHD risk factors of smoking and a family history of premature CHD could not accurately be obtained from the claim databases, these factors were not included in the risk stratification typology. For this reason, individuals with 0 or 1 risk factor were classified as "No Risk Category Assigned" because of potential misclassification.

Medication-related beliefs and attitudes. In order to effectively tailor the content in the experimental group and as a point for between-groups comparisons, several baseline constructs derived from key behavioral theories associated with medication adherence (eg, Health Belief Model, Social Cognitive Theory, Self-Regulation Theory) were collected on both experimental and enhanced care control subjects as part of the initial IVR baseline assessment, including expectations regarding the ability of the statin to lower cholesterol, perceived barriers to adherence, level of motivation and confidence in the ability to take their medication, and expectations regarding length of time the subject expects to take the statin.

Medication utilization measures. Using data from the pharmacy claims database, data on prescriptions dispensed for statins were captured starting with the index statin date through the subsequent 179-day period, for a total of a 180-day follow-up observation period. For each prescription dispensed, data were obtained regarding the date the prescription was dispensed and the total number of days' supply associated with the prescription. For calculation of the primary and secondary outcome measures (outlined in the following section), it was permissible for a subject to fill a prescription for a statin other than the original agent observed for the index statin, including a switch to a combination product. However, subjects who discontinued filling prescriptions that included a statin and exclusively switched to other lipid-lowering agents (eg, fibrates, niacin, Zetia) were classified as not meeting the criteria for success.

The calculation of the statin persistency measures incorporated a 30-day grace or gap period. Specifically, a subject was classified as persistent if no more than 30 days elapsed from the date corresponding to the end date associated with a given dispensed statin as reflected in a pharmacy claim (ie, the date dispensed and its associated days' supply) and the date of the subsequent dispensed statin. The 30-day grace period applied to all dispensed statins, including the small number of 90-day supplies that were dispensed subsequent to the index statin. Stockpiling of statin medications did not affect the 30-day grace period decision rule (eg, a subject filling an index statin, followed by a subsequent statin prescription associated with a 30-day supply 20 days subsequent to the date of index statin, would need to fill a third prescription no more than 60 days subsequent to the date of the second prescription to maintain a designation of persistent).

Measures that incorporated adherence were based on a calculation of the Proportion of Days Covered (ie, the simple addition of days' supply associated with the total number of separate pharmacy claims) over the course of the 180-day follow-up observation period, which equates to a Medication Possession Ratio (MPR) given the standardized 180-day observation period for each subject. Pursuant to this calculation, the days' supply associated with pharmacy claims dispensed toward the end of the observation period were only included in the calculation of the total sum if the date associated with the days' supply did extend beyond the 180th day (eg, a subject with a statin prescription associated with a 30-day supply filled on observation day 175 would be credited with a total of only 6 pills in calculating the MPR value). For the medication possession measure, stockpiling of medication was permissible in deriving the total sum; however, the total sum of pills dispensed was truncated at a maximum of 180 days.

Outcome measures. The primary dependent measure of program success was termed 6-month point prevalence persistency, defined as a subject being in possession of a statin at the end of the 180-day observation period. Operationally, this was defined as a pharmacy claim associated with a 30-day supply dispensed between follow-up observation days 121–180. For prescriptions associated with a 90-day supply, a subject could be classified as being in possession of a statin at the end of the 180-day observation period if the prescription was filled between follow-up observation days

61–180. As suggested by Hudson et al., possession of a statin at a fixed point in time would provide a more accurate measurement of persistence, given that patients in real-world settings can be expected to have variations in timing of refills unrelated to issues of persistence (eg, abnormal lab results, adverse effects, drug interactions, dose titrations, acute care hospitalizations) and the fixed time point measure could help minimize classification errors associated with pill splitting.⁵⁶

A series of secondary outcome measures of program success were also calculated including continuous persistence (defined as having any statin prescription dispensed at least every 30 days after the end date of a previous prescription for a statin) for the duration of the 180-day observation period. An MPR was calculated for each subject; a subject was classified as adherent if he or she achieved a value of at least 80% (ie, a total of at least 144 pills dispensed during the 180-day follow-up observation period). The 80% threshold was based on an arbitrary threshold used in multiple research studies that examined statin adherence.^{57–62}

The final secondary measure incorporated a "hybrid model" that combined the continuous persistence measure outlined previously (based upon refill sequence data including permissible gaps) with the proportion of days covered (an MPR of at least 80%).⁶³

Description of interventions

Call #1: Baseline Behavioral Constructs. All randomized subjects were given a baseline assessment delivered by IVR. This assessment was developed based on constructs known to impact health behavior and medication adherence (ie, condition concern, knowledge of cholesterol and related risk, motives for risk modification including medication adherence, anticipated barriers to adherence, confidence in medication taking, intentions to persist).

Enhanced care control group. Subjects randomly assigned to this group received generic targeted feedback at the conclusion of the baseline call, were thanked for their participation, and notified to expect a nontailored cholesterol educational guide in the mail. The guide did not specifically address medication adherence. There was no further interaction with this group of subjects for the duration of the 6-month follow-up period.

Experimental Intervention. This group received up to 2 calls in addition to the baseline call. (Not all subjects in this group received all possible calls.) These calls were generated by a computerized VAT that provided highly tailored messages that specifically reinforced adherence/persistence with statin medication by using a combination of behavioral science theories and techniques in a personalized or tailored manner dependent on the subject's previous response characteristics. Therefore, each communication was potentially unique. Additionally, the subsequent calls referred respondents to the health plan Web site for additional information regarding dyslipidemia, risk reduction, and lipid-lowering medication. These calls were coupled with a print guide (mailed at the conclusion of the first call) that provided tailored messages designed to enhance commitment, improve

communication with the health care team, and address specific barriers to adherence. The goal of the intervention in total (ie, tailored letter and series of tailored VAT calls) was to enhance both intrinsic motivations for medication persistence of this asymptomatic condition, and to enhance self-management skills. Figure 2 presents a detailed description of the topics covered in the 3 calls.

Statistical analysis

Based on a previous study of statin utilization patterns of the health benefits organization membership, it was anticipated that enhanced care controls would have a 6-month

point prevalence rate of 65%, and that exposure to the experimental intervention would increase this rate to 75%.⁶⁴ With power set at 0.80 and alpha at <0.05 (1-sided test), it was necessary to impanel 260 subjects per group.⁶⁵ Given an anticipated member disenrollment rate of 10% over the 6-month follow-up period, we sought to enroll approximately 290 subjects per group. Unfortunately, due to a higher than anticipated proportion of subjects refusing the informed consent process, the disenrollment rate was higher than anticipated because it was necessary to recruit subjects who had their 6-month follow-up observation date extend beyond a single calendar year (ie, a high percentage of health plan members have the option of voluntarily changing health

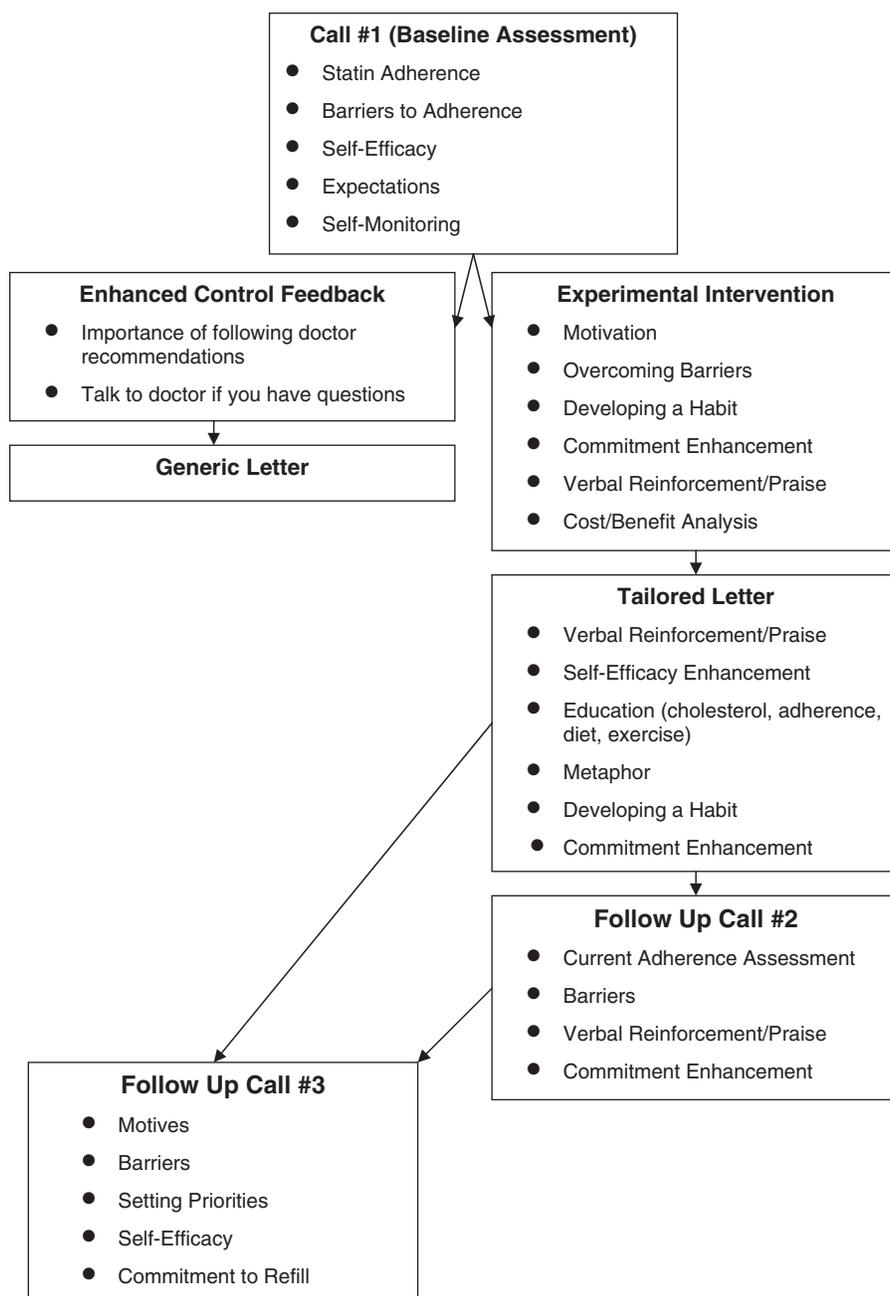


FIG. 2. Communication map.

plan coverage at the beginning of the year). As such, the final sample size available for analysis was slightly lower than the projected 260 subjects per group.

Baseline data contrasting the experimental and enhanced care control groups on baseline claims and psychosocial variables were evaluated using chi-square tests for categorical data and *t* tests for continuous measures, with a *P* value ≤0.10 considered statistically significant. Based on the published literature, it was hypothesized that exposure to the experimental intervention would only act to increase medication adherence/persistency, and thus a 1-tailed test was used, with statistical significance contrasting the experimental and enhanced care control group set at *P* ≤0.10. A logistic regression model with odd ratios and 90% confidence intervals was used to assess group differences with regard to the primary and secondary outcomes. Potential confounding covariates were entered in the logistic regression model to obtain adjusted odds ratios of the treatment effect where appropriate. Tests of differential effectiveness of exposure to the experimental group versus the enhanced care control

group within the context of varying strata of possible effect modifiers (ie, a treatment by covariate interaction) were assessed by entering interaction terms into the logistic regression model. Given the large number of post hoc comparisons, interaction terms were considered statistically significant at a *P* ≤0.05 level. All statistical analyses were carried out using SPSS, version 15.0 (SPSS Inc., Chicago, IL).

Results

Description of sample

Table 1 compares the enhanced care control and experimental groups on sociodemographic characteristics and pharmacy/medical claims-related measures. With the exception of the item assessing the number of chronic medications in the 3-month period prior to the index statin (subjects assigned to the experimental group had a lower number of concomitant medications), no statistically significant group differences were detected between the groups. Overall, the sample was approximately two-thirds female,

TABLE 1. SOCIODEMOGRAPHIC AND MEDICAL/PHARMACY CLAIMS-RELATED BACKGROUND CHARACTERISTICS BY EXPERIMENTAL CONDITION

	<i>Enhanced Care Control Group</i> (N = 244)	<i>Experimental Group</i> (N = 253)	<i>Total</i> (N = 497)
Sociodemographics			
% Female	62.7%	62.1%	62.4%
Mean Age	54.2	54.6	54.4
% <50 Years of age	30.5%	25.3%	28.0%
% 50–64	60.2%	64.4%	62.4%
% 65+	09.0%	10.3%	09.7%
% HMO	48.0%	48.6%	50.6%
Index statin			
% Lipitor	55.7%	53.0%	54.3%
% Zocor	16.0%	16.6%	16.3%
% Other statin	28.3%	30.4%	15.7%
			29.4%
Mean \$ co-pay	30.4	32.1	31.2
% ≤\$29	45.1%	46.6%	45.9%
% \$30–\$49	40.2%	34.0%	37.0%
% \$50+	14.8%	19.4%	17.1%
% Lipid-lowering agent dispensed 7–12 months prior to index statin	11.1%	10.7%	10.9%
% Index statin not dispensed	04.5%	04.7%	4.6%
% 90-day supply of statin dispensed during 180-day observation period	04.1%	02.8%	03.4%
Health status			
NCEP Risk Classification			
% High risk	41.0%	41.1%	41.0%
% Moderate risk	20.1%	15.0%	17.5%
% No assigned risk	38.9%	43.9%	41.4%
Mean chronic medication dispensed ≤90 days prior to index statin*	3.7	3.3	3.4
% 3+ Medications	62.3%	53.4%	57.8%
Enrollment in cardiac disease management program			
% Not enrolled	70.9%	71.5%	71.2%
% Enrolled prior to index statin	19.3%	17.8%	18.5%
% Enrolled after index statin:	09.8%	10.7%	10.3%

**P* < 0.05.

HMO, health maintenance organization; NCEP, National Cholesterol Education Program.

with a mean age of 54, half of whom were affiliated with the plan as HMO members. A slight majority of subjects were prescribed Lipitor, with the mean member co-pay of approximately \$30. A tenth of subjects had pharmacy claims evidence of being prescribed a lipid-lowering agent during the 7–12 month period prior to the index statin. Fewer than 5% of subjects were not dispensed their index statin, with only 3.4% dispensed a statin prescription with a 90-day supply during the 180-day follow-up observation period. Two fifths of the subjects were classified as “high” risk based on NCEP criteria, and 30% were enrolled in the cardiac disease management program at some point during the 180-day observation period.

Table 2 contrasts the enhanced care controls and experimental subjects on cholesterol-related health beliefs, attitudes, and behaviors obtained from the baseline IVR call. As noted, the number of valid responses varies from item to

item, as subjects had the option to not respond to any given item. With the exception of the item assessing the expectation to continue taking a statin once the subject’s cholesterol drops to a healthy level (with a higher proportion of experimental subjects endorsing this behavioral intention), no statistically significant group differences were detected.

Slightly less than three fourths (72.9%) of subjects reported that they had started taking their statin and had not yet missed a dose. The small proportion of respondents who reported that they had not yet started taking their statin were asked to answer the subsequent questions as though they had already begun taking their medication. Nearly 60% (57.7%) reported that they were “very concerned” about having high cholesterol, although fewer than half (46.8%) reported that it was “very likely” that taking their cholesterol medication exactly as prescribed would lower their cholesterol. Nearly three fourths of subjects (71.8%) cited that the

TABLE 2. CHOLESTEROL-RELATED ATTITUDES, BELIEFS, AND BEHAVIORS OBTAINED FROM THE BASELINE ASSESSMENT BY EXPERIMENTAL CONDITION

	<i>Enhanced Care Control Group</i>	N	<i>Experimental Group</i>	N	<i>Total</i>	N
Statin adherence		244		253		497
% Started statin, never missed dose	74.1%		71.5%		72.9%	
% Started statin, missed 1+ dose	21.7%		22.1%		21.9%	
% Not yet started statin	04.2%		06.3%		05.2%	
Attitudes, beliefs, expectations, doctor–patient relationship						
Concerned about having high cholesterol		242		250		492
% Very	59.1%		56.4%		57.7%	
% Somewhat	33.9%		37.2%		35.6%	
% Not at all	07.0%		06.4%		06.7%	
Likelihood that statin will lower cholesterol		242		249		491
% Very	44.2%		49.4%		46.8%	
% Somewhat/not at all	15.3%		13.7%		14.5%	
% Not sure	40.5%		36.9%		38.7%	
Most important reason for taking statin		197		203		400
% It may help lower my cholesterol	70.6%		72.9%		71.8%	
% My physician told me so	29.4%		27.1%		28.2%	
Decision maker in managing cholesterol		230		246		476
% We work together	74.3%		79.3%		76.9%	
% I do	12.2%		07.3%		09.7%	
% My doctor does	13.5%		13.4%		13.4%	
Take statin once cholesterol is at healthy level*		241		250		491
% Yes	31.1%		41.2%		36.3%	
% No	32.0%		26.8%		29.3%	
% Uncertain	36.9%		32.0%		34.4%	
Motivation and confidence to take statin						
Motivation to take statin everyday		242		252		494
% Low (Score of 1–3 on 5-point Likert Scale)	17.8%		15.9%		16.8%	
% Medium (Score of 4)	16.1%		19.0%		17.6%	
% Extremely (Score of 5)	66.1%		65.1%		65.6%	
Confidence in ability to take statin everyday		240		251		491
% Low (Score of 1–3 on 5-Point Likert Scale)	13.3%		09.6%		11.4%	
% Medium (Score of 4)	19.6%		26.3%		23.0%	
% Extremely (Score of 5)	67.1%		64.1%		65.6%	
Perceived barriers to taking statin						
% Yes—It costs too much.	33.9%	236	27.2%	249	30.5%	485
% Yes—I am concerned about side effects.	42.1%	242	43.2%	250	42.9%	492
% Yes—I may forget to take it.	36.4%	242	36.4%	253	36.4%	495
% Yes—I don’t think it will help.	08.7%	241	07.7%	247	08.2%	488

* $P < 0.10$.

most important reason for taking their statin was to “help lower their cholesterol,” with 76.9% reporting that they “work together” with their doctor to make decisions regarding the management of their cholesterol. Only slightly more than a third (36.3%) reported that they intend to continue taking their statin once their cholesterol is lowered to a healthy level, suggesting that many subjects viewed taking a statin similar to treatment of a time-limited acute condition.

Subjects reported high levels of motivation and confidence to take their statin every day as prescribed, with approximately two thirds of subjects reporting a score of “5” on Likert scales ranging from a low score of 1 to a high score of 5 (“extremely motivated”/“extremely confident”). Finally, subjects were asked about potential barriers (“things that could get in the way”) to taking their cholesterol-lowering medication every day. The largest percentage of subjects (42.9%) reported concerns about side effects, followed by forgetfulness (36.4%), and cost barriers (30.5%); only 8.2% reported that they did not think the statin would help.

Impact of intervention on primary and secondary outcomes

Table 3 displays the impact of the experimental intervention on the primary and secondary persistence/adherence measures, including unadjusted and adjusted odds ratios and accompanying 90% confidence intervals. The small number of cases with missing data on the self-report covariate was assigned the value of the modal category on the item for the purpose of having identical sample sizes for the unadjusted and adjusted odds ratios. For both the primary and secondary outcome measures, when contrasted with the enhanced care control group, the likelihood of being classified as meeting the criteria of success was found to be statistically significantly higher among experimental subjects. For the primary dependent measure (6-month point prevalence persistency), 70.4% of the experimental subjects were persistent as contrasted with 60.7% of enhanced care controls, with an adjusted odds ratio of 1.64 (90% confidence interval 1.19–2.27). As noted, in all instances the adjusted odds ratios are slightly higher than the unadjusted odds ratios due to the fact that experimental subjects were on fewer chronic medications prior to being prescribed their index statin, and tak-

ing fewer concomitant medications was found to be negatively associated with statin persistence/adherence.

Exposure to the experimental intervention was found to have less of an impact on the various secondary outcome measures (odds ratios ranging from 1.41 to 1.43). However, from a clinical perspective, an examination of the most rigorous outcome measure (continuous persistence coupled with a MPR ≥80%), the intervention was found to increase the proportion of subjects meeting this criteria by an impressive 20.9% (45.1% for the experimental group versus 37.3% for the enhanced care controls) with an adjusted odds ratio of 1.41 (90% confidence interval 1.03–1.92).

In an effort to obtain a potentially more precise estimate of group differences, adjusted odds ratios were calculated on the primary and secondary outcomes by entering into a logistic regression model any covariate (including claims-based measures displayed in Table 1 and the baseline self-report measures reviewed in Table 2) that was associated at the univariate level with both experimental group status and the various dependent measures at a *P* value of ≤0.20 (data not shown). These analyses failed to modify the findings reported in Table 3, with group differences on the primary and secondary outcome measures remaining statistically significant at the *P* ≤ 0.10 level.

Post hoc analyses were conducted to assess whether the statistically significant differences detected on the primary and secondary outcome measures between the experimental and enhanced care controls were moderated as a function of any covariate included in Tables 1 and 2. Although power to detect statistically significant interaction effects was quite low, none of the contrasts were found to be statistically significant at the *P* < 0.05 level, suggesting that the impact of the intervention was fairly robust across the broad spectrum of subjects impaneled in the study. Although the interaction term was not statistically significant, there was a trend across all measures for the intervention to be particularly impactful among the relatively small subset of subjects (*n* = 54) who had been prescribed a lipid-lowering agent in the 7–12 month period prior to the index statin. For 6-month point prevalence persistency, only 37.0% of enhanced care controls were found to be persistent as contrasted with 66.7% of the experimental group (*P* < 0.05). Similarly, for continuous persistence coupled with an MPR ≥80%, only 3.3% of controls

TABLE 3. COMPARISON OF ENHANCED CARE CONTROL AND EXPERIMENTAL GROUP SUBJECTS ON PRIMARY AND SECONDARY STATIN PERSISTENCE/ADHERENCE UTILIZATION MEASURES

<i>Outcome Measure</i>	<i>Enhanced Care Control Group</i> N = 244	<i>Experimental Group</i> N = 253	<i>Unadjusted Odds Ratio and 90% CI</i>	<i>Adjusted Odds Ratio⁺ and 90% CI</i>
Primary outcome				
6-month point prevalence persistency	60.7%	70.4%*	1.54 (1.13–2.10)	1.64 (1.19–2.26)
Secondary outcomes				
Continuous persistence	44.3%	52.2% [^]	1.37 (1.02–1.85)	1.41 (1.05–1.94)
Medication possession ratio ≥ 80%	38.9%	47.0% [^]	1.39 (1.03–1.88)	1.43 (1.05–1.96)
Continuous persistence + medication possession ratio ≥ 80%	37.3%	45.1% [^]	1.38 (1.03–1.86)	1.41 (1.03–1.92)

**P* < 0.05, [^]*P* < 0.10.

⁺(Odds ratio adjusted for number of chronic medications in 3-month period prior to index statin and intention to continue taking statin once cholesterol level drops to a healthy level.)

met the criteria of success as contrasted with 25.9% of the experimental group ($P < 0.05$). It would appear that in the absence of a behavioral support program, "statin recyclers" have a low probability of success if restarted on medication within a relatively short time frame of a recent discontinuation of a lipid-lowering treatment regimen.

Process analysis

Table 4 provides the proportion of experimental group subjects successfully meeting the criteria of success on the primary and secondary outcomes within levels of exposure to the program. Slightly less than a third of subjects, (32.8%, $n = 83$) participated in the initial baseline call only, with a quarter (25.3%, $n = 64$) participating in all 3 calls. The remaining 41.9% of subjects ($n = 106$) participated in 2 of the 3 calls. Examination of the outcome measures by level of exposure to the program reveals that there were no differences between subjects who participated only in the baseline call versus those who participated in the baseline call and second call. As noted, the success rate for the various measures increased slightly among the subset of subjects who participated in the third call, although there appeared to be no additional benefit derived from participating in all 3 calls as contrasted with just the first and third call. Nonetheless, when dichotomized into subjects who did or did not participate in the third call, no statistically significant differences emerged on either the primary or secondary outcome measures ($P > 0.20$ in all instances).

Given that the subjects were not randomly assigned to the number and/or sequence of call participation, a series of multivariate analyses were conducted to assess if a clearer picture would emerge with respect to level of exposure to the intervention and success rate when examined within the context of potentially confounding covariates (ie, perhaps participation in the third call was simply a proxy for subjects who would otherwise have a higher or perhaps a lower likelihood of succeeding on the various outcome measures). Based on all available measures from Tables 1 and 2, a stepwise logistic regression (a P value ≤ 0.10 used as the criteria for an item to enter and remain in the equation) revealed that 4 items were found to discriminate between those who did and did not participate in the third call. Results of these analyses (data not shown) revealed that, upon controlling on these 4 covariates, the main conclusions observed

in Table 4 remained unchanged in that participation in the third call yielded only a small to moderate, but non-significant increased proportion of subjects who met the criteria of success on the primary and secondary outcome measures.

Discussion

Results from this trial provide preliminary supportive evidence that a relatively inexpensive intervention using tailored messages derived using IVR technology coupled with mailed print material can increase statin persistence/adherence among patients initiating a statin medication regimen. Favorable health outcomes of prior studies in a variety of therapeutic areas (eg, diabetes, pain management, hypertension) and health behaviors (smoking cessation, physical activity) utilizing IVR technology have been reported in the literature, although equivalent as well as negative findings have also been reported.⁶⁶⁻⁷² Of direct relevance to the current study, as contrasted to a usual care control group, statin new starts exposed to up to 3 interactive and customized IVR calls were found to have a modest (an absolute improvement in persistence at 6 months of 4.6%; 49.3% versus 44.7%) but nonetheless statistically significant improvement in medication persistence.⁷³

The intervention used in this study represents an amalgam of discrete elements borrowed from various evidence-based adherence-enhancing strategies that were, in turn, based on multiple behavioral theories in an effort to maximize the external validity of the findings. The study was designed as a real-world effectiveness trial that would mimic the way the intervention would actually be implemented in a given managed care organization. As such, with the exception of the brief informed consent statement, potential subjects were offered the intervention much as they would any IVR program in their health plan. Given the emphasis on external validity, this study can best be viewed as a first step in a process of understanding which components or combinations of components comprise the active ingredients in the experimental group.

The effectiveness as opposed to the efficacy approach to our evaluation strategy precluded us from obtaining detailed baseline and follow-up data from the subjects, which could have potentially helped identify mediating factors responsible for the observed group differences. For example, a sep-

TABLE 4. ACHIEVEMENT OF PRIMARY AND SECONDARY OUTCOMES MEASURES BY LEVEL OF EXPOSURE TO EXPERIMENTAL INTERVENTION

Outcome Measure	Baseline Call Only N = 83	Baseline Call and Second Call Only N = 41	Baseline Call and Third Call Only N = 65	Participation in All 3 Calls N = 64
Primary outcome				
6-month point prevalence persistency	68.7%	65.9%	73.8%	71.9%
Secondary outcomes				
Continuous persistence	50.6%	46.3%	56.9%	53.1%
MPR $\geq 80\%$	42.2%	39.0%	47.7%	50.0%
Continuous persistence + MPR $\geq 80\%$	43.4%	43.9%	50.8%	50.0%

MPR, medication possession ratio.

arate, freestanding follow-up interview with experimental and control subjects conducted by a research assistant 3 months after the index statin would compromise the “real-world” nature of the program not only in that the follow-up interview could itself constitute a competing intervention of sorts, but requiring subjects to participate in a follow-up survey would likely further reduce the proportion of subjects willing to participate in the study.

Several contributing factors may have been responsible for the improved outcomes observed in the experimental group. As found in other medication adherence interventions, the simple act of reminding patients to refill their prescription on a timely basis may have been a key element contributing to the program’s success (in this instance through the reminder message in the second and third IVR calls). Encouraging a greater proportion of subjects in the experimental group to follow up with their doctor in a timely fashion may be another important contributing factor. Benner et al found that early and frequent follow-up by physicians, especially follow-up of lipid testing, was associated with improved adherence to lipid-lowering therapy. Providing positive reinforcement that taking their statin had successfully lowered their LDL cholesterol helped overcome the low motivation patients have when attempting to manage an asymptomatic chronic condition.⁷⁴ Unfortunately, in the current study we could not directly test this hypothesis because we did not have access to the physician encounters or lab claims. In addition to obtaining information on progress in achieving their LDL goal that likely had a positive impact on the patient’s self confidence to manage their cholesterol, an early follow-up encounter with a physician may have served 2 purposes that fostered adherence/persistence. First, early follow-up provided the opportunity for patients to receive additional educational information from their physician and/or to follow up on questions that were prompted by what they heard during an IVR call (eg, whether they should continue to take their statin once their cholesterol is at a healthy level). Second, an early follow-up encounter also afforded the physician the opportunity to provide the patient with strategies to overcome barriers to adherence (eg, side effects, forgetfulness, cost). As with most studies examining statin adherence, perceived cost barriers were found to be one of the strongest predictors adversely affecting persistence/adherence. For example, Piette et al found that, among patients with cost concerns, the impact of this barrier on adherence was moderated if the patient viewed their physician as trusting. The extent to which the current intervention helped to foster a more trusting relationship between patients and their providers (patients were encouraged to have an open discussion with their providers about any concerns they might have had about taking their medication on a regular basis) may have contributed to the positive outcomes observed for subjects assigned to the experimental group.⁷⁵

Because of the study design’s emphasis on real-world implementation and application, the study methodology did not allow us to assess the incremental benefit of the various program components. For example, would similar outcomes be obtained without the inclusion of the mailed tailored guide? As suggested by the process evaluation, would there be little loss of effectiveness if the second call was eliminated and only the baseline and third call were included as part of

the intervention? Is the monthly interval between calls optimal or would 4 shorter calls separated by a smaller time interval prove to be more effective? There are sophisticated, innovative study designs that could address these important issues, but they were beyond the scope of the current project.⁷⁶

Of equal importance is whether the impact of the intervention would diminish over time in the absence of booster sessions and/or related programmatic activity. Although evidence from many studies reveals a high drop-off in adherence during the initial 6-month period, there remains a steady and sharp decline up to and beyond 12 months after therapy has begun. Future studies will have to assess the utility of the current intervention when examined in the context of a longer time frame.

A limitation is the use of the claims data. Only claims processed through the adjudication system are reflected in the data. Sample medications dispensed in a physician’s office or medications purchased outside of the claims system are not captured in this data. Adherence measures were calculated based on claims data; the assumption was that prescriptions filled were taken by the patient.

Of some concern in the current study is the relatively low proportion of eligible subjects who were reached and ultimately enrolled in the trial. In large part this was a function of the relatively high proportion of subjects (77%) who were never reached by the IVR system after 6 attempts. This noncontact rate was found to be substantially higher than the 50% contact rate routinely observed by the health plan for other IVR applications. Additionally, approximately half of the potential subjects who were contacted refused to provide verbal consent to participate in the call as part of a research study. Of note, a detailed analysis of nonparticipants revealed that with the exception of age, sex, and participation in the cardiac disease management program (study participants were significantly older [54.4 versus 52.2], more likely to be female [62.2% versus 48.3%], and more likely to be enrolled in the disease management program [28.8% versus 19.5%]), no statistically significant group differences were observed. Thus, there was no evidence that study participants differed from nonparticipants with respect to key health status indicators (eg, similar profile on NCEP risk classification and number of chronic medications) or with regard to the index statin (eg, co-payment level, receipt of a lipid-lowering agent in the prior year, whether the index statin was dispensed).

Of particular importance, no statistically significant differences were detected between the enhanced care controls and study nonparticipants (including those not contacted, and those who were contacted and declined to participate in the study or were judged ineligible) on the primary outcome measure (6-month point prevalence persistency), whereas subjects in the experimental group were found to have a statistically significantly higher prevalence rate than detected in all 3 remaining groups. As stated, 70.4% of the experimental group was classified as meeting the criteria for 6-month point prevalence persistency as contrasted with 60.7% of enhanced care controls. The rate of 60.7% among the enhanced care controls was found to be nearly identical and statistically indistinguishable from the 57.8% rate among nonparticipants who were contacted but refused or were classified as ineligible, and the 56.4% of potential subjects

who were never contacted. These differences remained unchanged when examined within the context of 3 statistically significant covariates of age, sex, and enrollment in the health plan's cardiac disease management program. As such, outcome data from the nonparticipants provides strong confirmatory evidence derived from the randomized clinical trial that the experimental intervention did indeed have a favorable impact on increasing statin persistence/adherence.

Ultimately, further research evaluating results longer than 6 months after their index prescription would be warranted, as well as determining the medical outcomes of interest including decrease of LDL values and avoidance of a cardiovascular event. Additional research may benefit from additional recruitment methods such as including physicians or case managers in the enrollment process. The intervention may be better received when recommended by a health care provider versus receiving a cold call as the initial contact. Study outcomes might also be enhanced by utilizing additional intervention strategies such as text messaging refill reminders or having scheduled times for follow-up calls with participants from the VAT.

Although the randomization procedure coupled with the findings from the nonequivalent control groups helped optimize the internal validity of study outcomes, the extent to which the findings would generalize to other patients and/or settings is unknown. Of particular salience to the issue of external validity is whether a similar intervention would be shown to increase adherence rates among statin users who were not new starts, but had been on their medication for varying lengths of time. Subjects in the current study were drawn from a commercial, predominately employed, working/middle class population. The extent to which the observed impact of the intervention would generalize to disadvantaged populations (eg, Medicaid recipients, patients with no regular source of care) or the elderly (Medicare beneficiaries) is unknown. Additionally, the site of the current study was an independent physician association/group model managed care organization; it is unknown if similar outcomes would be observed among patients enrolled in highly integrated delivery systems (eg, Veterans Administration, staff model HMOs) that have a more robust patient educational/support system as a routine part of the delivery of usual care to medication new starts.

The interactive technology systems approach to wellness described in this article and the phenomenon of tailored patient interactions using technology have the potential to change consumers' relationships with their traditional touch points in health care. Interactive technology has the immediate potential to: reach large populations of health care consumers, be a cost-effective method to improve treatment adherence, be easily implemented in diverse health care settings, and be used to engage and motivate consumers to take an active role in improving their medication-taking behavior.

The findings highlighted in this research demonstrate that patients with high cholesterol levels can benefit from personalized, tailored interactive health messages delivered through interactive technology. In the future, voice-activated systems, integrated with Web-based, mobile, and other innovative technological interfaces, will provide the impetus to accelerate the recognition and acceptance of eHealth as an effective and efficient way to engage patients to take an ac-

tive role in managing their treatment regimen and improving their medication-taking behavior.

Disclosure Statement

Drs. Stacy, Schwartz, Ershoff, and Shreve disclosed no conflicts of interest.

References

- Rosamond W, Fegell K, Furie K, et al. Heart disease and stroke statistics—2008 update: A report from the American Heart Association Statistics Committee and Stroke Statistics Subcommittee. *Circulation*. 2008;117:e24–e146.
- Fedder DO, Koro CE, L'Italien GH. New National Cholesterol Education Program III guidelines for primary prevention lipid-lowering drug therapy: Projected impact on the size, sex, and age distribution of the treatment-eligible population. *Circulation*. 2002;105:152–156.
- Persell SD, Lloyd-Jones DM, Baker DW. Implications of changing national cholesterol education program goals for the treatment and control of hypercholesterolemia. *J Gen Intern Med*. 2006;21:171–176.
- Wilt TJ, Bloomfield HE, MacDonald R, et al. Effectiveness of statin therapy in adults with coronary heart disease. *Arch Intern Med*. 2004;164:1427–1436.
- Ward S, Lloyd-Jones M, Pandor A, et al. A systematic review and economic evaluation of statins for the prevention of coronary event. *Health Technol Assess*. 2007;11:1–160.
- Genser B, März W. Low density lipoprotein cholesterol, statins and cardiovascular events: A meta-analysis. *Clin Res Cardiol*. 2006;95:393–404.
- Baigent C, Keech A, Kearney PM, et al; Cholesterol Treatment Trialists' (CTT) Collaborators. Efficacy and safety of cholesterol-lowering treatment: Prospective meta-analysis of data from 90,056 participants in 14 randomized trials of statins. *Lancet*. 2005;366:1267–1278.
- Straka RJ, Mamdani M, Damen J, et al. Economic impacts attributable to the early clinical benefit of atorvastatin therapy—A US managed care perspective. *Curr Med Res Opin*. 2007;23:1517–1529.
- Fintel D, Joyce Amie, Mackell J, et al. Reduced mortality rates after intensive statin therapy in managed-care patients. *Value in Health*. 2007;10:161–169.
- Saseen JJ, Williams SA, Valuck RJ, et al. The performance gap between clinical trials and patient treatment for dyslipidemia: A comprehensive review. *Dis Manage Health Outcomes*. 2005;13:255–265.
- Ellis JJ, Erickson SR, Stevensohn JG, et al. Suboptimal statin adherence and discontinuation in primary and secondary prevention populations. *J Gen Intern Med*. 2004;19:638–645.
- Benner JS, Tierce JC, Ballantyne CM, et al. Follow-up lipid tests and physician visits are associated with improved adherence to statin therapy. *Pharmacoeconomics*. 2004;22:13–23.
- White TJ, Change E, Leslie S, et al. Patient adherence with HMG reductase inhibitor therapy among users of two types of prescription services. *J Man Care Pharm*. 2002;8:186–191.
- Benner JS, Glynn RJ, Mogun H, et al. Long-term persistence in use of statin therapy in elderly patients. *JAMA*. 2002;288:455–461.
- Fitterman LK, William SA. A descriptive review of statin utilization patterns. Poster presented at 2001 American Heart Association's 3rd Scientific Forum on Quality of Care

- and Outcomes Research in Cardiovascular Disease and Stroke: Washington, DC. *Am Heart J.* 2002;144:905–906.
16. Harley CR, Williams SA, McDonough KL, et al. Cholesterol management in a population of managed care enrollees. *J Clin Outcomes Manag.* 2003;10:147–154.
 17. Caspard H, Chan AK, Walker AM. Compliance with a statin treatment in a usual-care setting: Retrospective database analysis over 3 years after treatment initiation in health maintenance organization enrollees with dyslipidemia. *Clin Ther.* 2005;27:1639–1646.
 18. Abughosh SM, Kogut SJ, Andrade SE, et al. Persistence with lipid-lowering therapy: Influence of the type of lipid-lowering agent and drug benefit plan option in the elderly. *J Manag Care Pharm.* 2004;10:404–411.
 19. Yu AP, Yu YF, Nichol MB, Gwardry–Sridhar F. Delay in filling the initial prescription for a statin: A potential early indicator of medication non-persistence. *Clin Ther.* 2008;30:761–764.
 20. Catalan VS, Lelorie J. Predictors of long-term persistence on statins in a subsidized clinical population. *Value in Health.* 2000;3:417–426.
 21. Muller–Nordhorn J, Willich SN. Effectiveness of interventions to increase adherence to statin therapy. *Dis Manage Health Outcomes.* 2005;13:73–82.
 22. Peterson AM, Taliya L, Fineley R. Meta-analysis of interventions to improve drug adherence in patients with hyperlipidemia. *Pharmacotherapy.* 2003;23:80–87.
 23. Haynes RB, Yao X, Degani A, et al. Intervention for enhancing medication adherence. *The Cochrane Database of Systematic Reviews.* 2005;4: CD000011.
 24. Schedlbauer A, Schroder K, Fahey T. How can adherence to lipid-lowering medication be improved? A systematic review of randomized clinical trials. *Fam Prac.* 2007;24:380–387.
 25. Petrilla AA, Benner JS, Battleman DS, et al. Evidence-based interventions to improve patient compliance with antihypertensive and lipid-lowering medications. *J Clin Pract.* 2005;59:1441–1451.
 26. Rimer BK, Orleans CT. Tailoring smoking cessation for older adults. *Cancer.* 1994;74:2051–2054.
 27. Rimer BK, Orleans CT, Fleisher L, et al. Does tailoring matter? The impact of a tailored guide on ratings and short-term smoking-related outcomes for older smokers. *Health Educ Res.* 1994;9:69–84.
 28. Strecher VJ, Kreuter M, Den Boer DJ, Kobrin S, Hosers HJ, Skinner CS. The effects of computer-tailored smoking cessation messages in family practice settings. *J Fam Pract.* 1994;39:262–270.
 29. Skinner CS, Strecher VJ, Hospers H. Physicians' recommendations for mammography: do tailored messages make a difference? *Am J Public Health.* 1994;84:43–49.
 30. Brug J, Steenhuis I, van Assema P, de Vries H. The impact of computer-tailored nutrition intervention. *Prev Med.* 1996;25:236–242.
 31. Brug J, Campbell M, Van Assema P. The application and impact of computer-generated personalized nutrition education: A review of the literature. *Patient Educ Couns.* 1999;36:145–156.
 32. Kreuter MW, Strecher VJ. Do tailored behavior change messages enhance the effectiveness of health risk appraisal? Results from a randomized trial. *Health Educ Res.* 1996;11:97–105.
 33. Cowdery JE, Suggs LS, Parker S. Application of a web-based tailored health risk assessment in a work-site population. *Health Promot Pract.* 2007;8:88–95.
 34. Cochrane GM, Horne R, Chanez P. Compliance in asthma. *Respir Med.* 1999;93:763–769.
 35. Bull FC, Jamrozik K, Blanksby BA. Tailored advice on exercise—Does it make a difference? *Am J Prev Med.* 1999;16:230–239.
 36. Bull FC, Kreuter M, Scharff DP. Effects of tailored, personalized and general health messages on physical activity. *Patient Educ Couns.* 1999;36:181–192.
 37. Timmerman GM. Using self-care strategies to make lifestyle changes. *J Holist Nurs.* 1999;17:169–183.
 38. Lorig KR, Holman H. Self-management education, history, definition, outcomes and mechanisms. *Ann Behav Med.* 2003;26:1–7.
 39. Diabetes Prevention Program (DPP) Research Group. The Diabetes Prevention Program (DPP): Description of lifestyle intervention. *Diab Care.* 2002;25:2165–2171.
 40. Koenigsberg MR, Bartlett D, Cramer JS. Facilitating treatment adherence with lifestyle changes in diabetes. *Am Fam Physician.* 2004;69:309–316.
 41. Marcus AC, Mason M, Wolfe P, et al. The efficacy of tailored print materials in promoting colorectal cancer screening: Results from a randomized trial involving callers to the National Cancer Institute's cancer information service. *J Health Commun.* 2005;10:83–104.
 42. Feldman R, Bacher M, Campbell N, Drover A, Chockalingam A. Adherence to pharmacologic management of hypertension. *Can J Public Health.* 1998;89:116–118.
 43. Kountz DS. Hypertension in ethnic populations: Tailoring treatments. *Clin Cornerstone.* 2004;6:39–48.
 44. Petrilla AA, Benner JS, Battleman DS, Tierce JC, Hazard EH. Evidence-based interventions to improve patient compliance with antihypertensive and lipid-lowering medications. *Int J Clin Pract.* 2005;59:1441–1451.
 45. DiClemente CC, Prochaska JO. Self-change and therapy change of smoking behavior: A comparison of processes of change in cessation and maintenance. *Addict Behav.* 1982;7:133–142.
 46. Hudmon KS, Berger BA. Pharmacy applications of the transtheoretical model in smoking cessation. *Am J Health Syst Pharm.* 1995;52:282–287.
 47. Becker MH. Theoretical models of adherence and strategies for improving adherence. In: Shumaker SA, Schron EB, Ockene JK, McBee WL, eds. *The Handbook of Health Behavior Change.* New York: Springer Publishing Company; 1998:5–32.
 48. Kasl SV. The health belief model and behavior related to chronic illness. *Health Educ Mono.* 1974;2:106–127.
 49. Rosenstock IM, Strecher VJ, Becker MH. Social learning theory and the health belief model. *Health Educ Q.* 1988;15:175–183.
 50. Lorig K, Laurin J. Some notions about assumptions underlying health education. *Health Educ Q.* 1985;12:231–243.
 51. Possidente CJ, Bucci KK, McClain WJ. Motivational interviewing: A tool to improve medication adherence? *Am J Health Syst Pharm.* 2005;62:1311–1314.
 52. Resnicow K, Jackson A, Blissett D. Results of the healthy body healthy spirit trial. *Health Psychol.* 2005;24:339–348.
 53. Basch CE, Sliepecevic EM, Gold RS, Duncan DF, Kolbe LJ. Avoiding type III errors in health education program evaluations: A case study. *Health Educ Behav.* 1985;12:315–331.
 54. Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults. Executive summary on the third report of the National Cholesterol Education Program (NCEP) expert panel on detection, evaluation, and

- treatment of high blood cholesterol in adults (Adult Treatment Panel III). *JAMA*. 2001;285:2486–2497.
55. Bullano MF, Wertz DA, Yang GW, et al. Effect of rosuvastatin compared with other statins on lipid levels and National Cholesterol Education Program goal attainment for low-density lipoprotein cholesterol in a usual care setting. *Pharmacotherapy*. 2006;26:469–478.
 56. Hudson M, Rahme E, Hugues R, et al. Comparison of measures of medication persistency using a prescription drug database. *Am Heart J*. 2007;153:59–65.
 57. Benner JS, Tierce JC, Ballantyne CM, et al. Follow-up lipid tests and physician visits are associated with improved adherence to statin therapy. *Pharmacoeconomics*. 2004;22:13–23.
 58. Caspard H, Chan AK, Walker AM. Compliance with a statin treatment in a usual-care setting: Retrospective database analysis over 3 years after treatment initiation in health maintenance organization enrollees with dyslipidemia. *Clin Ther*. 2005;27:1639–1646.
 59. Gibson TB, Mark TL, Axelsen K. Impact of statin copayments on adherence and medical care utilization and expenditures. *Am J Manag Care*. 2006;12:SP11–SP19.
 60. Thiebaud P, Patel BV, Nichol MB, Berenbeim DM. The effect of switching on compliance and persistence: The case of statin treatment. *Am J Manag Care*. 2005;11:670–674.
 61. Schultz JS, O'Donnell JC, McDonough KL, et al. Determinants of compliance with statin therapy and low-density lipoprotein cholesterol goal attainment in a managed care population. *Am J Manag Care*. 2005;11:306–312.
 62. Ye X, Gross Cr, Schommer J, et al. Association of co-payment and adherence to statin treatment initiated after coronary heart disease hospitalization: A longitudinal, retrospective, cohort study. *Clin Ther*. 2007;29:2748–2757.
 63. Caetano PA, Lam JM, Morgan SG. Toward a standard definition and measurement of persistence with drug therapy: Examples from research on statin and antihypertensive utilization. *Clin Ther*. 2006;28:1411–1424.
 64. Hussein M, Ershoff D, Whitworth J, Watson-Heidari T. Patterns of non-adherence with HMG-COA reductase inhibitors in a health benefits company. *International Pharmaceutical Abstracts ASHP Summer Meeting*. 2004;61:P–58D.
 65. Borenstien M, Rothstein H, Cohen J. *Power and Precision*. Englewood, NJ: Biostat, Inc.; 2001.
 66. Piette JD, Weinberger M, Kraemer FB, McPHee SJ. The impact of automated calls with nurse follow-up on diabetes treatment outcomes in a Department of Veterans Affairs health care system. *Diabetes Care*. 2001;24:202–208.
 67. Naylor MR, Keefe FJ, Brigidi B, et al. Therapeutic interactive voice response for chronic pain reduction and relapse prevention. *Pain*. 2008;134:335–345.
 68. Friedman RH, Kazis LE, Kette A, et al. A telecommunications system for monitoring and counseling patients with hypertension. Impact on medication adherence and blood pressure control. *Am J Hypertens*. 1996;9:285–292.
 69. Reid RD, Pipe AL, Quinlan B, Oda J. Interactive voice response telephony to promote smoking cessation in patient with heart disease: A pilot study. *Patient Educ Couns*. 2007;66:319–326.
 70. Estabrooks PA, Smith-Ray RL. Piloting a behavioral intervention delivered through interactive voice response telephone messages to promote weight loss in a pre-diabetic population. *Patient Educ Couns*. 2008;34–41.
 71. Helzer JE, Rose GL, Badger GJ, et al. Using interactive voice response to enhance brief alcohol intervention in primary care settings. *J Stud Alcohol Drugs*. 2008;69:251–258.
 72. Volmer WM, Kirshner M, Paters D, et al. Use and impact of an automated telephone outreach system for asthma in a managed care setting. *Am J Manag Care*. 2006;12:725–733.
 73. Patel MH, Schaaf DT, Fleszar GJ. The impact of interactive voice recognition technology on adherence to statin therapy. *Value in Health*. 2007;10:A57.
 74. Benner JS, Tierce JC, Ballantyne CM, et al. Follow-up lipid tests and physician visits are associated with improved adherence to statin therapy. *Pharmacoeconomics*. 2004;22:13–23.
 75. Piette JD, Heisler M, Krein S, Kerr EA. The role of patient-physician trust in moderating medication nonadherence due to cost pressures. *Arch Intern Med*. 2005;165:1749–1755.
 76. Collins LM, Murphy SA, Strecher V. The multiphase optimization strategy (MOST) and the Sequential Multiple Assignment Randomized Trial (SMART): New methods for more potent ehealth interventions. *Am J Prev Med*. 2007;32:S112–S118.

Address correspondence to:
Jane N. Stacy, Pharm.D.
Clinical Research Consultant
Humana Inc.
500 West Main Street
Louisville, KY 40202
E-mail: jstacy1@humana.com