Rationale and design of the Study Assessing the Effect of Cardiovascular Medications Provided as Low-cost, Evidence-based Generic Samples (SAMPLES) trial

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Background Highly effective generic cardiovascular medications are frequently underused, leading to greater overall drug costs and cost-related nonadherence.

Objective We sought to assess an intervention to stimulate appropriate generic cardiovascular drug use without creating administrative or financial barriers that may impede essential medication use.

Trial design The SAMPLES (Study Assessing the Effect of Cardiovascular Medications Provided as Low-cost, Evidence-based Generic Samples) trial is a clustered, randomized controlled trial of the effect of providing physicians with free generic samples of hydrochlorothiazide for hypertensive patients and simvastatin for patients with hyperlipidemia. We will randomize 660 primary care physicians in Pennsylvania, clustered by physician practice, to receive free samples for both conditions or to receive no samples. We will use data on filled prescriptions obtained from a state-sponsored prescription drug assistance program to perform an intention-to-treat evaluation of the impact of the intervention on physician prescribing behavior (proportion of prescriptions that are generic) and patient adherence. Secondary outcomes will include physician adherence to established guidelines and overall prescription drug costs.

Conclusion This trial will define the potential role of an innovative approach to stimulate clinically appropriate cost-effective prescribing. We will determine whether free generic samples can reduce overall drug costs as well as out-of-pocket costs to the patient without sacrificing efficacy and whether this approach results in improved adherence to essential cardiovascular medications. This intervention may also improve adherence to practice guidelines and improve the quality of care received. If effective, this strategy could be used broadly by private insurers or government payers aiming to stimulate more cost-effective and higher-quality care. (Am Heart J 2009;157:613-9.)

Background

Highly effective, evidence-based cardiovascular medication therapy is often underused.[1] Essential cardiovascular medications frequently are not prescribed when appropriate, and patients frequently do not adhere to their use after initiation.[2] Many therapies used to treat cardiovascular disease are highly cost-effective; some are even cost saving.[3] Efforts are needed to ensure that more patients who need cardiovascular therapy are appropriately treated.

Despite substantial underuse, high drug costs remain an important concern. Treatment of hypertension and hypercholesterolemia alone accounts for >$40 billion in annual expenditures in the United States.[4,5] The federal government's portion of those costs has increased with the implementation of the Medicare Modernization Act,[6] leading to calls to stem the rising costs of prescription drugs.[7]

The tension between underuse of appropriate medications and the rising costs of prescription drugs may be reconciled by ensuring that patients take the least expensive among clinically appropriate medications. Numerous studies have documented the potential cost savings that could be realized by greater use of generic medications. Opportunities to switch prescriptions from branded medications to molecularly identical generics were estimated to lead to an 11%

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reduction in overall US drug costs.[8] Managing hypertension in accordance with the Joint National Commission on High Blood Pressure (JNC-VII) guidelines would lead to greater generic drug use and substantial prescription drug cost savings while providing higher-quality, evidence-based care.[9] Using generic medications can also lead to a reduction in out-of-pocket costs, which has been shown to improve patient adherence to medications.[10]

Despite national guideline recommendations to use generic medications as first-line therapies for most hypertensive and hyperlipidemic patients,[11,12] generics are still often underused.[8] One explanation is that pharmaceutical manufacturers stimulate branded drug use by providing free branded samples to physicians, at an annual cost of >$15 billion nationally, eclipsing the cost of office promotion, direct-to-consumer advertising, and hospital promotion combined.[13]

Payers have implemented numerous strategies to encourage generic medication use. These strategies, in general, have erected barriers to expensive branded medications through either administrative hurdles (ie, prior authorization)[14] or patient cost sharing (ie, tiered pharmacy benefits).[15] However, evidence has emerged that such barriers may adversely affect use of essential medications.[16,17] An intervention to stimulate cost-effective medication use without erecting barriers to essential medications could enhance appropriate use and adherence while reducing health care costs.

Providing free generic samples to physicians

We propose to implement and evaluate an intervention to provide physicians with free samples of highly effective generic medications for the treatment of hypercholesterolemia and hypertension. This approach may positively influence choice at the point of drug initiation and does not rely on barriers to higher-cost medications that can adversely affect utilization. This intervention may reduce total spending on prescription drugs, decrease out-of-pocket medication costs, and encourage improved patient adherence to cardiovascular medications.[10] Providing samples of drugs that are commonly identified as first-line therapy may also lead to higher rates of guideline concordance. Therefore, providing free generic samples has the potential to decrease costs and improve quality in cardiovascular care.

Limitations of the existing data and need for a randomized trial

No randomized trials to date have evaluated the provision of free generic samples to physicians. One observational study evaluated an intervention in which kiosks containing generic samples were placed in physicians' offices. The intervention led to approximately a 1% increase in generic prescribing, with cost savings for the insurer that averaged >$1,300 per physician per year. However, this intervention was not randomly assigned and is not generalizable to typical prescription drug sample delivery.[18]

Few published studies have evaluated the effects of branded drug sampling on prescribing behavior and drug utilization. A single, small randomized controlled trial was conducted in which 29 internal medicine residents were randomized to either use or no use of samples. The samples led to significant increases in prescribing advertised, expensive medications, but evaluated only 390 prescriptions in this population and lacked broad generalizability.[19] Two observational studies explored the effect of sampling on prescribing with similar conclusions.[20,21] The available data are not sufficient to accurately quantify the effect of either branded or generic free medication samples on use.

Objective

The SAMPLES (Study Assessing the Effect of Cardiovascular Medications Provided as Low-cost, Evidence-based Generic Samples) trial is a cluster-randomized controlled trial of the effect of providing physicians with free generic samples for antihypertensive and lipid-lowering medications. The primary outcomes will be physician generic prescribing behavior and patient adherence to chronic therapy. Secondary outcomes will include physician adherence to established guidelines and overall prescription drug costs.

Subjects and setting

Physicians selected for the intervention are currently participating in an academic detailing intervention developed by faculty in the Division of Pharmacoepidemiology and Pharmacoeconomics and funded by the Pennsylvania Department of Aging through the Pharmaceutical Assistance Contract for the Elderly (PACE, Harrisburg, PA) program. Academic detailing is a university-based outreach to providers conducted by specially trained health professionals who use face-to-face interactive education about evidence-based prescribing.[22] The program in Pennsylvania has hired and trained 11 “academic detailers,” either nurses or pharmacists, who visit physicians in their offices with the goal of improving the quality of prescribing. The Division faculty perform systematic reviews of the literature, provide recommendations about evidence-based prescribing, and create educational materials for dissemination to physicians and their patients.

More than 310,000 elderly patients are currently enrolled in the PACE program. In 2008, PACE enrollees were enrolled in 1 of 5 participating Medicare Part D

prescription drug plans; PACE provides secondary coverage that supplements the Part D plans to ensure seamless coverage, including coverage throughout the coverage gap. The PACE program receives all claims from participating Part D plans and provides full patient-level records of prescription drug claims paid by both PACE and the Part D plans, which are provided to the research team.

In 2007, detailers educated Pennsylvania physicians about evidence-based prescribing for both hypertension and hypercholesterolemia. A total of 742 primary care physicians are currently visited by detailers and will be randomized to either the intervention or control arms. According to our sample size calculations (see below), 660 physicians will be identified; and half will be randomly allocated to receive samples. The study physicians manage patients with and without coverage from PACE. We will request that intervention physicians provide the samples exclusively to beneficiaries who are enrolled in coverage from PACE. The effects of the intervention will be measured in PACE patients treated by these physicians.

The physician sample in the academic detailing program targets high-volume PACE prescribers. These physicians were identified by sorting all reimbursed prescriptions by prescriber and aggregating prescriptions for all physicians. We identified top prescribers (in cost) within PACE, as well as physicians with the greatest number of PACE program participants.

Randomization

Physicians will be the target of the intervention. To eliminate contamination within practices, we will randomize at the physician practice level using a clustered design. All physicians in a practice will be randomly assigned to the intervention or control groups as a unit.

The arms of the trial are defined as:

1. Intervention arm (arm A)—will receive free samples of both antihypertensive and lipid-lowering medications
2. Control (arm B)—will not receive samples

Study medications

We will offer samples of 1 generic medication for each condition: hydrochlorothiazide (HCTZ) 12.5 mg for hypertension and simvastatin 20 mg for hypercholesterolemia. Hydrochlorothiazide is recommended by the JNC-VII guidelines as first-line hypertension treatment for a large proportion of patients. The JNC-VII guidelines indicate that there are "compelling" situations when medication other than thiazides may be more appropriate as first-line therapy. Our intervention does not restrict, in any way, prescribing of any medication or dispensing of branded samples and should not limit appropriate medication use.

Simvastatin will be used as the free generic sample for hypercholesterolemia. The Adult Treatment Panel III guidelines for prescribing cholesterol-lowering medication do not offer specific guidance about which statin to select.[23] Although there is greater low-density lipoprotein cholesterol reductions in patients taking high-dose atorvastatin or rosuvastatin as compared with simvastatin,[24] simvastatin is appropriate first-line therapy for most patients initiated on lipid-lowering medications for primary prevention. As with samples for hypertension, physicians will not be prohibited from prescribing or dispensing samples for any other statins, preserving the full range of clinical options.

Intervention physicians will be provided with 50 bottles of HCTZ and 36 bottles of simvastatin, each with a 30-day supply. These sample sizes were determined on the basis of the mean number of new prescriptions for physicians for hypertension and hyperlipidemia annually in PACE and were titrated to the budgetary limitations of the study. In total, we will provide intervention physicians with 16,500 months' supply of HCTZ samples and 11,880 months' supply of simvastatin samples.

Intervention

We will deliver the medication samples to intervention physicians in compliance with the Prescription Drug Marketing Act, which regulates the use of prescription drug samples.[25] Clinicians will be asked by the academic detailers to sign a request form to confirm their interest in receiving samples. Those forms will be faxed to Unyson Logistics (Burnsville, MN), a transportation management company with experience in the delivery of prescription drug samples in compliance with Prescription Drug Marketing Act regulations. Sample medications will be purchased, packaged, and labeled by APACE Co in Fountain Run, Kentucky. Unyson will then pick up the packaged samples and deliver them to requesting physicians in their offices. We anticipate that approximately 5 days will elapse between the detailer visit and signing of the request form and the actual delivery of the medication to the requesting physician. We chose to deliver samples with Unyson and not directly by our detailers because of the administrative challenges associated with detailer registration and licensure to deliver and store samples. Detailers will provide physicians with bins to store samples and will assist with placement in the sample closets.

Outcomes and statistical analysis

Primary analyses will be based on intention-to-treat principles. Our unit of analysis is the physician practice for some outcomes and the patient (with adjustment for clustering within physician practices) for others. The investigators assessing and analyzing primary outcomes

Table I. Outcomes and definitions

Primary outcomes	Level of analysis	Definition
Percentage of prescriptions filled for generic medications	Physician practice	Proportion of prescriptions filled by PACE-covered patients of each study physician for generic antihypertensive or lipid-lowering medications
Patient medication adherence	Patient	Amount of prescriptions filled (PDC) within each class in the first year of use of an antihypertensive or lipid-lowering medication
Secondary outcomes		
Medication costs	Patient	The sum of medication costs for all prescriptions used to treat either hypertension or hypercholesterolemia
Guideline adherence	Patient	Proportion of patients who received first-line antihypertensive medications suggested by JNC-VII when medications are initiated

PDC, Proportion of days covered.

are blinded to the treatment assignment. Patients will be assigned to the intervention or control group on the basis of whether their physicians were assigned to the intervention or control arms, without regard to whether the patient actually received a free sample. Physicians who refuse to meet with the academic detailers and do not accept the free samples will nonetheless be analyzed in the group they were assigned to, providing conservative effect estimates. Our primary outcomes will be generic prescribing rates and patient adherence. Secondary outcomes include guideline adherence and total drug costs. (Table I).

Physician prescribing

We will evaluate the proportion of prescriptions for new users of antihypertensive and lipid-lowering medications that were filled for generic drugs in the intervention and control physicians in the 12 months before and after the intervention. The unit of analysis will be the physician practice. We will identify new users of antihypertensive and lipid-lowering medications as patients who fill a prescription for a medication to treat one of these conditions and who have filled no prescriptions in the same therapeutic drug class (eg, β-blockers for hypertension) in the previous 12 months.

We will aggregate all prescriptions filled for new users by physicians within a practice and calculate the proportion of prescriptions filled that were generic. This will be done separately for antihypertensive and lipid-lowering medications by dividing the number of prescriptions filled for a generic medication within each class (the numerator) by the sum of all prescriptions filled within the class for each disease (the denominator). Multivariate regression modeling will be used to determine the relationship between the intervention (yes or no) and the proportion of prescriptions for hypertension or cholesterol management filled that were generic. We will control for physician characteristics (age and gender) as well as the class of medication initiated. We will test the interaction between the physician group (intervention vs control) and the period (pre- or postintervention) to evaluate whether prescribing behavior changed differentially as a result of the intervention. We will also evaluate the relationship between physician characteristics and the efficacy of the intervention using interaction terms to evaluate if certain physician characteristics are associated with a greater response to the intervention.

Patient medication adherence

We will use records of filled prescriptions to evaluate the effects of the intervention on adherence by patients newly starting drugs in the therapeutic categories studied. We will identify new users of antihypertensive and lipid-lowering medications in the 6 months after the start of the intervention. New users must not have filled any prescriptions in the drug class in the 12 months before the first fill. Refill data from pharmacy claims will be used to calculate the proportion of days covered over the year subsequent to initiation of the medication (number of days supply in the year divided by 365). For patients who switch medications within the same class for the same condition, all fills in both classes will contribute to the numerator. We will perform additional analyses evaluating the proportion of patients with the proportion of days covered >80%[10] as well as persistence, measured as absence of any filled prescriptions in >30 days.

We will use multivariable linear regression controlling for clustering at the physician practice level with generalized estimating equations to evaluate the difference in medication adherence in patients whose physicians were offered the intervention and those whose physicians were controls. We will control for physician characteristics and patient characteristics. (Table II) The PACE claims include age, gender, and zip code; zip code will be linked to US census data to include ethnicity predominance and median income in zip code of residence to adjust for neighborhood characteristics. Patients will be censored because of death, nursing home or hospital admission, or loss of benefits. We will use interaction terms to evaluate whether patient or physician characteristics are associated with intervention effects.

Medication costs

We define *medication costs* as the total costs of prescription drugs: the sum of the out-of-pocket expense and the cost to the insurer.[26] We will calculate the sum of medication costs for each filled prescription by summing acquisition costs and copayment charges from pharmacy claims for all new users of antihypertensive and lipid-

Table II. Comorbid conditions and definitions

Characteristic	Definition
Stroke or CAD risk factors	
Prior ischemic stroke or TIA	ICD-9 codes 433, 434, 435, or 436
CHF	ICD-9 codes 425 or 428
Hypertension	ICD-9 codes 401-405
Diabetes	ICD-9 code 250 or use of insulin or oral hypoglycemic
Coronary artery disease	ICD-9 codes 410-414
Peripheral vascular disease	ICD-9 code 440
Previous MI	ICD-9 codes 410 or 412 or DRGs 121, 122, 123
Angina, acute coronary syndrome	ICD-9 411 or 413 or DRG 124, 125, or 132
Smoking	ICD-9 code V15.82
Factors that might influence adherence	
No. of medications filled	Average no. of claims filled per month
Dementia or cognitive impairment	ICD-9 codes 290.1-290.4, 290.8-9, 294.1, 331.0, 331.0-2 046.1-2
Cancer	ICD-9 codes 230.3, 230.4, 162.x, 231.2, 174.x, 233.0, 185.x, 233.4, 140.x-208.x (except 154.2, 154.3, and 154.4)
Depression	ICD-9 codes 293.83, 296.2x, 296.3x, 296.90, 298.0x, 300.4x, 309.0-1, 309.28, 311
Sociodemographic characteristics:	
Age	A continuous variable
Gender	Male or female
Income	Link zip code to median income in zip code of residence
Ethnicity	Link zip code to ethnic characteristics in neighborhood
Health care utilization characteristics	
No. of physician visits	Count of outpatient physician visits

CAD, Coronary artery disease; *ICD-9*, International Classification of Diseases, Ninth Revision; *TIA*, transient ischemic attack; *CHF*, congestive heart failure; *MI*, myocardial infarction; *DRG*, Diagnosis-Related Group.

lowering medications. Free generic samples will be assigned the cost of the average wholesale price, as defined by First DataBank (San Bruno, CA),[27] for a month's supply of the drug; and the cost of all the samples of HCTZ and simvastatin purchased will be added to the antihypertensive and lipid-lowering intervention groups, respectively. We will disregard the costs of branded samples that are not borne by insurers or patients. We will evaluate the costs of medication for patients initiated on treatment of hypertension and hypercholesterolemia in the year subsequent to the intervention as compared with the year before the intervention, controlling for temporal trends in concurrent controls. If we find improvements in patient adherence in the intervention group, the greater absolute number of prescriptions filled will lead to conservative estimates of cost benefits.

The outcome of interest will be total drug costs in the year subsequent to initiation per patient per disease state. We will perform multivariable linear regression controlling for clustering at the physician practice level with generalized estimating equations to assess the effect of the intervention on costs.

Guideline adherence

We will use previously used methods to measure whether free generic samples affect JNC-VII guideline adherence in physicians who initiate antihypertensive medications.[9] We will identify every patient who filled a new prescription for any antihypertensive medication during the study period within the practices of study physicians. To avoid considering antihypertensive drugs prescribed for other indications, we will evaluate linked Medicare health services claims and require patients to have an *International Classification of Diseases, Ninth Revision* diagnosis of hypertension documented at an inpatient or outpatient visit in the 30 days before the prescription fill. New users must have been continuously enrolled in PACE for the year before antihypertensive initiation and may not have filled a prescription for any antihypertensive during that year. We will record data on all other prescriptions filled by these patients in the year before initiation as well as all diagnoses recorded in all outpatient and inpatient encounters or reflected in medications used (eg, insulin for diabetes) during that period. In this way, we will identify the presence of diagnoses potentially related to medication choice, such as diabetes mellitus, congestive heart failure, history of myocardial infarction, reactive airways disease, angina, nephropathy, or benign prostatic hypertrophy.

In keeping with current guidelines, we will consider thiazides to be appropriate first-line hypertension therapy for patients without specific contraindications or indications for another drug. The JNC-VII guidelines include specific indications for certain classes of antihypertensives,[11] which will be identified. For patients with congestive heart failure or diabetes and nephropathy, we will consider angiotensin-converting enzyme inhibitors or angiotensin-receptor blockers as appropriate first-line therapy.[11] For patients with a history of myocardial infarction, β-blockers will be considered first-line therapy,[11] except in patients with reactive airways disease. α-Blockers are listed by JNC-VII as potentially preferable treatment for hypertensive patients with prostatic disease[11] and will be considered guideline-concordant care. For patients with hypertension and angina, calcium channel blockers will be considered an acceptable therapeutic choice.[11]

We will determine whether each new antihypertensive medication was written in adherence with JNC-VII guidelines for both control and intervention physicians in the year subsequent to the intervention. Each patient will only be included in this analysis once; if a patient initiates >1 class of antihypertensives in the year, this analysis will only

include the first prescription. We will conduct multivariable logistic regression models, adjusting for physician clustering as well as physician and patient population characteristics, to evaluate the effect of providing free generic samples on JNC-VII guideline adherence.

Sample size considerations

Our sample size calculations take into account the clustering of PACE patients within physicians' practices, such that all patients seen by 1 primary prescriber can be considered correlated observations. Thus, the sample size required to detect a significant difference in outcomes of the intervention and control groups can be calculated as follows[28]:

$$m = \frac{\left(Z_{1-\alpha/2} + Z_{1-\beta}\right)^2 (\pi_1 p_0(1-p_0) + \pi_0 p_1(1-p_1))(1+(n-1)\rho)}{\left(Z_{1-\alpha/2} = 1.96, Z_{1-\beta} = 0.84\right)} \times n\pi_0\pi_1(p_1 - p_0)^2$$

where m is the number of physician clusters in both groups (estimated as 280 clusters in each group, a total of 330 physicians), n is the total number of new prescriptions per physician (50 antihypertensives per year, 36 statins per year), p_0 is the outcome (eg, proportion of prescriptions that were generic) in arm B (control group), p_1 is the outcome in arm A, π_0 is the percentage of the population in arm B (50%), π_1 is the percentage of the population in arm A (50%), and ρ is the intracluster (intraphysician) correlation, conservatively assumed to be 20% from previous work by our research group. Conservatively assigning the baseline generic prescribing rate to be 50%, we find that we have >99% power to detect a 5% increase in generic prescribing for both antihypertensive and lipid-lowering medications.

Using a similar calculation evaluating power to detect increase in patient adherence, assuming the same intracluster correlation, and using a crude dichotomous outcome to measure adequate adherence (1 = patient fills the second prescription, 0 = the patient does not fill the second prescription), we find that we have 82% power to detect a 5% increase in refilling prescriptions (from 60% to 65%).

Limitations

There are several important limitations to the proposed randomized controlled trial. First, we are unable to provide free samples of all generic cardiovascular medications. Rather, we will provide medications that have been suggested by JNC-VII to be appropriate first-line medication for hypertension and have chosen a statin that is highly effective in the treatment of hypercholesterolemia for most patients except those requiring the greatest intensity of low-density lipoprotein reduction. In our evaluation of guideline adherence, we will also assess whether any patients are less likely to receive appropriate medications as a result of this intervention.

Second, we may be unable to capture some claims for prescriptions filled for low-cost medications at certain pharmacies. Several pharmacies now offer $4 generic prescriptions, a cost less than the copayments charged by PACE or most Part D plans. Some patients may pay out of pocket for these prescriptions, requiring no payment from PACE or a Part D plan. These pharmacies are expected to file claims with the patients' insurers to maintain complete records, but the extent to which this practice occurs is unclear. As a result, we may have incomplete data for some low-cost generic prescriptions that are purchased, leading to conservative estimates of the effect of the trial on generic prescribing rates and adherence.

Third, because of limitations associated with administrative data, we are unable to assess pre- or posttreatment levels of blood pressure or serum lipids; and we will be limited by diagnostic codes used for patient visits and medications prescribed. As a result, we are unable to assess whether the use of free samples affects these clinical measures.

Independent data monitoring board

An independent Data Safety Monitoring Board will meet twice a year to review unblinded data including the number of patients randomized, diagnostic characteristics, and patterns of medication filling to determine if the intervention is leading to increased rates of inappropriate prescribing. The Data Safety Monitoring Board will be composed of independent members and will include a cardiologist, an internist, and a statistician.

All confidential information from claims data will be transformed to untraceable coded person-specific numbers before analysis to protect confidentiality. Approval from the Brigham and Women's Hospital Committee on the Protection of Human Subjects was obtained.

Funding and responsibilities

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Summary

This trial of providing physicians with free samples of effective generic cardiovascular medications will evaluate an innovative approach to encourage cost-effective prescribing and adherence to cardiovascular medications. This intervention may also improve adherence to accepted guidelines and improve the quality of care received. If effective, this strategy could be used broadly by private insurers or government payers aiming to stimulate more cost-effective care. Measuring the effects of this intervention can help determine whether this approach can reduce costs and simultaneously improve appropriate prescribing and adherence to cardiovascular medications.

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