Opt-e-scrip

Opt-e-scrip, Inc.
101 Timberbrooke Drive
Bedminster, NJ 07921

June 28, 2004

Department of Health and Human Services (HHS)

Re: Docket No. 2004S-0170--Medicare Prescription Drug, Improvement, and Modernization Act of 2003, Section 1013: Suggested Priority Topics for Research.

Dear Sir or Madam:

Opt-e-scrip, Inc. is pleased to submit this recommendation for research priorities to the Agency for Healthcare Research and Quality (AHRQ) under Section 1013 of the Medicare Prescription Drug Improvement and Modernization Act of 2003.

Background

Opt-e-scrip, Inc. ("OES") develops and markets personalized medicine tests ("PMTs") that optimize a patient's clinical outcomes by statistically comparing the relative effectiveness and side effects of two chronic care drugs or dose regimens in a single prescription. A second, collateral benefit is high double-digit therapeutic substitution rates in favor of generics, which dramatically reduces pharmaceutical expenses. The product is combined with a collaborative care, pharmacy intervention service to encourage patient compliance with the PMT initially, and to enhance subsequent long-term adherence to the better course of therapy.

The Company's PMTs improve clinical outcomes by statistically identifying the best drug or dose regimen for a specific patient by using their own response and side effect data. PMTs are randomized, controlled, blinded, multi-crossover investigations for one patient (referred to as "N-of-1" studies in the literature), which can be configured to compare two chronic care drugs, one drug versus placebo, a high and low dose of the same drug, or mono-therapy versus add-on therapy. OES dispenses only FDA approved drugs, for approved uses, at approved doses.

OES is a privately held disease management company and has a strategic partnership with a national mail-order pharmacy, which allows PMTs to be dispensed in all 50 states pursuant to a valid prescription. OES' methods have been validated, peer-reviewed, and published in the *Annals of Pharmacotherapy* and the *Journal of Managed Care*

2004S-0170 C5

Pharmacy. OES' methods have also been presented to the FDA at an Advanced Scientific Seminar in November of 2002. Independence Blue Cross of Philadelphia with all 4 million members is our first large private customer that has agreed to reimburse for our tests.

Additional Background and Market Need

As additional background, drugs are approved by the Food and Drug Administration (FDA) based on response rates from homogeneous patient groups in clinical studies where one group of patients receives drug while the other group usually receives a placebo. To gain approval the response rate in the group receiving the drug must be statistically higher than the placebo's effect in the other group. Approved drugs commonly demonstrate a response in only about 50% of patients, while the placebo shows a response in about 25% of patients. Therefore, since most drugs, once approved, do not have high efficacy rates even with the placebo effect included, physicians have difficulty predicting whether a drug will be effective in the individual patient.

Furthermore, each patient responds differently to a drug in terms of side effects. In the absence of ways to understand if the drug, the aging process, or environmental factors such as stress are causing side effects, physicians rely on inaccurate means such as gross clinical observation and patient recollection to determine if the side effects are drug related and if they outweigh the drug's benefits. Without a precise way to assess a drug's impact on an individual, physicians often prescribe heavily marketed, name brand drugs rather than less expensive therapeutic substitutes, even though the generic substitutes will often provide comparable or better outcomes.

Physicians treating chronic conditions, therefore, face two issues: 1) whether the patient responds to treatment or gets only a placebo response, either of which often leads to sub-optimal relief for the patient, and 2) whether a responding patient experiences side effects that can be tolerated. True drug response and tolerability are difficult to detect and resolve by community physicians and often result in low patient compliance and adherence with their treatment regimens. For those physicians who take the time to optimize drug therapy it often takes months of repeated patient interactions using trial-and-error prescribing. Even then, the physician does not know with certainty if the therapy has been optimized.

All end-payers, whether Federal, State, or corporate, have a strong need to reimburse for only those premium-priced therapies which actually provide superior outcomes for the patient. However, these payers, along with the pharmacy benefit managers they hire, have no means to predict whether an individual patient will respond better, if at all, to an expensive or inexpensive drug and whether the side effects are tolerable. As a result, given physicians' tendencies to prescribe the latest available medicines because of intensive marketing pressure from the manufacturers, pharmaceutical costs continue to spiral upward despite restrictive access to new drugs and higher and higher patient co-pays.

Recommendations

1. The new type of disease management product and service offered by Opt-e-scrip, Inc. should be tested immediately among Medicare/Medicaid patients suffering from osteoarthritis, gastroesophageal reflux disease, and allergic rhinitis, in three separate demonstration projects in a single market. The purpose of the demonstration projects will be to confirm the results from the validation studies that are included in the table on page 4 and that showed: a) patients' outcomes can be optimized; b) high rates of therapeutic substitution in favor of generics will result as a collateral benefit from PMT usage; and c) adverse events at the individual patient level will occur at much higher rates than drug labeling would suggest.

   Additionally, the purpose of the demonstration projects would be to show that compliance and adherence would improve among patients using PMTs versus patients not using the PMTs, since having patients themselves help determine the right drug with the fewest side effects would encourage adherence. The project would also suggest that the high costs associated with hospital admissions due to non-adherence could be avoided with broad PMT usage.

   Finally, and perhaps most importantly, the results for each patient would be anonymously aggregated into a large database and stratified by drug in order to create an optimal drug formulary for administering the new Medicare Prescription Drug Benefit. Ideally, all name brand drugs and all generic drugs for each therapeutic area would be included initially in the formulary. However, once the database becomes sufficiently large, those drugs generating severe adverse events in a material percentage of various target populations could be excluded from the formulary.

   It must be noted that PMTs should be made available on an ongoing basis if positive results are confirmed in the demonstration projects. This is necessary to account for the introduction of new drugs into the market place, both in the targeted therapeutic categories of interest, as well as for other new drugs in other categories which could have unintended consequences from a drug-drug interaction standpoint for patients with co-morbidities.

   Attached please find a photograph of a currently commercialized PMT as well as an actual patient report.

2. Once the initial demonstration project has been successfully concluded, we recommend conducting additional demonstration projects for AD/HD, depression, diabetes, and hypertension. These PMTs have already been developed but not yet commercialized. If these additional tests were to be included as a way to manage the Medicare Drug Benefit, we estimate that over 50% of total pharmacy expense could be managed in a more rational manner, i.e., based on evidence from individual patients.

compliance is well recognized among manufacturers and providers. In fact, one recent study conducted in Britain among first time users of chronic care drugs found that fully 25% of them ceased taking their medications within the first 30 days of starting therapy. In our validation studies, OES has found that we can achieve nearly 90% compliance with the PMT with minimal intervention. Our hypothesis is that, once the patient identifies the preferred therapy, adherence rates will improve dramatically since relief will be maximized and side effects minimized.

3. The American Medical Association believes this type of test (the "N-of-1" drug test) is superior for making clinical treatment decisions. In a September 13, 2000 JAMA article (Vol. 284, No. 10) the Evidenced Based Working Group of the AMA ranked all types of clinical data that can be used for making a treatment decision. The "N-of-1" test, represented by OES' PMT, was the highest form of evidence a physician can use. Large, randomized, controlled trials, which are efficacy studies among homogeneous patient groups conducted by manufacturers, are the second strongest form of evidence. Gross clinical observation, which is the current standard of medical practice, was considered to be the weakest basis for making a treatment decision. Please see the attached JAMA article.

4. PMTs would be cost effective for Medicare/Medicaid if they were configured to compare a name brand drug to an inexpensive therapeutic substitute. OES prices PMTs so that payers are price-indifferent between a PMT and a routine branded drug prescription. Payers, therefore, pay no more for the PMT than they would for the branded drug over the same period. However, by reimbursing for a PMT the payer can expect significant savings going forward as a predictable percentage of patients are switched to the less expensive therapy, all in the context of improved or parity outcomes.

Discussion

This recommendation and the underlying technology is consistent with the Congressional mandate and, although not discussed or exposed to other stakeholders, is also consistent with their already submitted comments. Specifically:

1. Personalized Medicine Tests are a practical, already commercialized technology that will help achieve all the longer-term goals articulated in the mandate from Congress. Section 1013 directs HHS to develop, in collaboration with public and private entities, options for the "provision of more timely information . . . regarding the outcomes and quality of patient care, including clinical and patient reported outcomes . . ." "acceleration of the adoption of innovation and quality improvement . . ." and development of management tools for the Medicare, Medicaid, and SCHIP programs to improve oversight by State officials and support Federal and State initiatives to improve the quality, safety, and efficiency of services provided under these programs.

2. This recommendation and OES' disease management technology/service is a pragmatic way to help resolve the key issues articulated in PhRMA's comment dated May 7, 2004, which recommends that research under Section 101 include:

    a) "Analysis of the extent to which the health care system is making optimal use of interventions known to work. Identify areas where interventions are being overused, underused, or misused, and the clinical impact of these sub-optimal uses, and identify potential strategies for making better use of interventions known to be effective and avoiding uses of interventions known to be ineffective or unsafe;"

    b) "Examination of issues related to patient therapy adherence and persistence behavior. Most medicines provide therapy for a given period of time that is dependent upon the patient for effective, continuous delivery. When patients do not comply with prescribed therapy, it can create as significant a barrier to quality as the failure to prescribe it in the first place. When examining effectiveness of medicines in treating priority diseases, it is important to consider the extent and cause of, and potential solution to, problems related to therapy compliance;" and

    c) [The study of] " . . . Effective communication to Medicare and Medicaid beneficiaries to support physician-patient decision-making. Decisions about whether to initiate a treatment, and which therapies to choose, are complex, multi-factorial choices that must be made between a patient and his or her physician. Making these decisions requires the patient and caregiver to consider issues such as concomitant therapies, co-morbidities, drug safety profiles, and other issues related to the individual's medical needs and preferences. It is critical to provide information about treatment choices in ways that recognize these issues and communicate them in ways that the patient can understand."

3. The BlueCross BlueShield Association also submitted a comment on May 7, 2004, which stated "there is a lack of published clinical studies that directly compare the effectiveness and outcomes of available drug treatments for various medical conditions. BCBSA recommends that studies be undertaken for currently used FDA-approved medications in drug therapeutic categories that contain high cost drugs and high utilization. Data from selected Blue Cross and Blue Shield Plans demonstrate that for our senior membership, the following drug therapeutic classes comprise the highest cost and utilization: 1) Cardiovascular, 2) Behavioral health/CNS, 3) Metabolic/hormonal, 4) Gastrointestinal, and 5) Diabetes."

    With the possible exception of metabolic disorders, PMTs are suitable for use in all these disease states. Osteoarthritis was also mentioned by the BCBSA as an area for investigation and, along with gastroesophageal reflux disease, has already been subjected to initial commercial investigation using PMTs, which are being

reimbursed by Independence Blue Cross of Philadelphia for patients from over 200 employer groups.

4. The Academy of Managed Care Pharmacy submitted a comment on May 5, 2004. This comment indicated comparative clinical and cost effectiveness studies are a "fundamentally necessary component of any rational approach to determining the value and usefulness of prescription drugs. Currently, only limited authoritative research exists that distinguishes the effectiveness and safety profile offered by any particular drug as compared to other drugs in the same or a similar treatment class. Physicians, pharmacists, other health professionals, patients and purchasers of health care need objective, easily-accessible evidence-based information regarding the comparative clinical and cost effectiveness of prescription drugs in order to make knowledgeable and informed decisions."

   Importantly, the AMCP made a distinction between efficacy studies and effectiveness studies. Efficacy studies are " . . . the type of clinical trials performed as a part of manufacturer-funded research to obtain data for the Food and Drug Administration's review of products seeking market status. Clinical trials routinely have guidelines that attempt to control variables so that the effect of the drug being tested can easily be evaluated."

   On the other hand, the AMCP points out correctly that effectiveness studies are different since "effectiveness can only be evaluated once a drug is being used in a broad-based population. Effectiveness studies will show practitioners what effects a drug can have when it is prescribed for patients with a variety of characteristics, e.g., patients being treated for more than one disease, patients with differing physiologies, and/or patients with differing physical capabilities and demands."

   The AMCP concluded by saying "although randomized controlled trials that provide direct comparison between medications would be the ideal types of studies for comparative effectiveness research, AMCP realizes that these studies are expensive and not always feasible." However, AMCP is unaware that the PMTs available from OES for all current (and future) therapeutic areas are, in fact, comparative clinical and cost effectiveness studies, provide real-time information to physicians, are designed to result in optimal outcomes for all types of individual patients, and are cost-effective for payers.

Conclusion

Perhaps most importantly, PMTs could be used on an ongoing basis to provide a continuously updated, prospective, clinical database on comparative effectiveness and safety for all chronic care drugs included in a Medicare Formulary. These databases would quickly become larger than the databases submitted to the FDA for drug approval by the manufacturers and could ultimately be stratified by age, sex, and other demographic factors important to Medicare. They also could lead

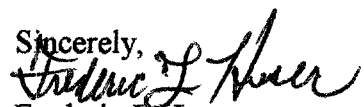
to a more consistent standard of care in making chronic care drug treatment decisions by augmenting the physician's judgment of drug performance with statistically reliable effectiveness and safety data one patient at a time.

Opt-e-scrip, Inc. would also like to make the following closing comment on today's pharmaceutical market place:

> We now have a health care system for delivering pharmaceuticals that is driven by providers' preferences and patients' demands, both of which are largely fueled by manufacturers. In this context, it is important to understand that the manufacturers use efficacy data from homogeneous, group clinical studies and then extrapolate those positive results to heterogeneous populations and individuals.
>
> Unfortunately, drug effectiveness and tolerance is patient specific. Unless the individual patient is the primary source of information on the effectiveness and side effects of a drug, expensive drugs will continue to be prescribed when less expensive therapeutic substitutes can provide parity or superior performance, and *vice versa*. When the patient becomes the primary source of reliable, valid information about the extent to which a benefit has been delivered, then and only then will appropriate choices be made among treatment options. Given this, one way to create a rational Medicare Prescription Drug Benefit, is to research and enable technologies for delivering chronic care medicines that recognize the uniqueness and the importance of each individual patient.

Opt-e-scrip, Inc. would like to thank HHS for the opportunity to submit this comment regarding priorities for research, demonstration, and evaluation. You should note that we are capable of executing against this proposed research and demonstration project immediately upon your agreement to proceed. If you have any questions, please contact me at 973-699-3843 or at fredhuser@opt-e-scrip.com.

Sincerely,



Frederic J. Huser
Chairman & CEO
Opt-e-scrip, Inc.