

Patient Safety Institute

Economic Value of an Electronic Health Information Exchange (EHIX) Network

Value to the Pharmaceutical Industry

White Paper

**Prepared by
First Consulting Group
Emerging Practices**

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Executive Summary

In the two years since the Patient Safety Institute (PSI) released part one of its analysis on the economic value of health information exchange, entitled *Value to Payers (Private, Medicare, Medicaid, and Self-Insured Employers) and the Uninsured*, significant strides have been made in healthcare information systems. One month after the PSI report, in April 2004, President George W. Bush called for the widespread adoption of interoperable electronic health records for most Americans within 10 years. This created the Office of the National Coordinator for Health Information Technology (ONCHIT), and established health information exchange as a national priority. Other related initiatives have also risen to prominence, such as the Health Information Technology Standards Panel (HITSP), the Certification Commission for Healthcare Information Technology (CCHIT), and the Health IT Policy Council (HITPC). All share the mission of accelerating the adoption of coordinated information technology efforts in healthcare.

Still, progress has been achieved at a slow, measured pace. Many of the issues that were at the forefront of discussions in 2004 remain concerns today. For example:

- Healthcare costs continue to rise,
- Reimbursements are down or flat,
- Safety issues abound in even the best facilities,
- Doctors, nurses, and other clinical resources are decreasing in number,
- Bio-terrorism and the threat of epidemics (e.g. bird flu) remain a concern,
- Health plans and patients are demanding more from providers, and
- Patients are shouldering a greater responsibility for their care and self-management.

These issues and shortcomings of the U.S. healthcare system affect all industry participants in some way, including the pharmaceutical industry. For example, using the telephone as the primary means of communications between providers and patients is an inefficient means to convey important changes in health status such as an adverse reaction to a medication. Without access to all electronic health data, medication adherence monitoring by the provider is extremely difficult and incomplete. This lack of health information also affects subject recruitment for clinical trials, making them longer and more costly to conduct. All of these issues affect patients, providers, and pharmaceutical companies.

In 2004, PSI engaged the Emerging Practices Research Department at First Consulting Group (FCG) to prepare an economic analysis of the value that the PSI Electronic Healthcare Information (EHIX) Network could bring to payers (private insurers, Medicare, Medicaid, Self-Insured Employers, and uninsured individuals). The study analysis

estimated an annual net savings at approximately \$40 billion per year. The benefits of an Electronic Health Information Exchange Network, however, extend further.

To develop a clearer idea of the potential value of a nationwide EHIX Network, the Emerging Practices Research Department at First Consulting Group has constructed a model to estimate the value to the pharmaceutical industry. The value model was based on published research, authoritative statistical resources, interviews with experts in the pharmaceutical industry, and interviews with physicians experienced in conducting clinical trials.

According to this research, the total annual benefit to the pharmaceutical industry of a nationwide electronic health information community is approximately \$31 billion. This figure is based on value estimates that could be delivered across seven key areas, from clinical trials through medication adherence and advertising, and are focused *only* on savings and additional revenue to the pharmaceutical industry, although many of these areas also provide substantial benefits to providers, payers and patients.

Background and Overview

Electronic health information exchange (EHIX Network) enables real-time access to clinical information at the point of care. A nationwide network of EHIX Network-enabled providers would be a voluntary association. The proposed way in which it would operate has been compared to the business model of VISA. Just as VISA collaboratively brings together banks, retailers, and consumers under a distributed network, the EHIX Network brings together healthcare providers, consumers, and data providers. In general, the effect is to facilitate patient safety, improve quality, and lower costs.

Scope and Approach

This report estimates the value that a nationwide EHIX Network could provide to pharmaceutical companies. The model we constructed takes into account the types of benefits that are achievable when a healthcare provider has access to information on a patient's medical history, demographics, medications list, and laboratory results at the point of care. Several value components deal with clinical trials. In these cases, the term healthcare provider includes those acting as principle investigators. An EHIX Network would also open channels of communication with patients' families and caretakers (these stakeholders become involved, for instance, in ensuring patient adherence).

This value model was based on the best available published research and statistical resources. Reviews with pharmaceutical industry experts and physicians with clinical trial experience were conducted as an important check and to provide estimates when no published data were available. In all cases, estimates regarding the impact of the system on processes were conservative in relation to published figures. Finally, the model assumes widespread adoption of the health information infrastructure and supporting end user and industry applications (i.e. 90 percent).

Summary of Findings

The table below lists the seven major value components that were quantified in this study, along with their potential annual value, given full EHIX Network adoption across the US.

Table 1: Potential Benefits of an EHIX Network to the Pharmaceutical Industry

Value Components	Annual Value	
1. Increased speed in conducting clinical trials		\$7.07 Billion
a. Faster recruitment for early and mid-stage trials	\$0.39 Billion	
b. Faster recruitment for late-stage trials	\$2.78 Billion	
c. Additional revenue from being faster to market	\$3.60 Billion	
d. Reduced need for enrollment advertising	\$0.32 Billion	
2. Reducing the costs of data management for clinical trials		\$0.08 Billion
3. Increasing patient adherence during clinical trials		\$0.20 Billion
4. Reducing the cost of post-market surveillance for ADEs		\$0.07 Billion
5. Keeping drugs on the market through conditional prescribing		\$7.32 Billion
a. Fewer drugs pulled from the market	\$1.12 Billion	
b. More drugs passing phase III testing	\$1.54 Billion	
c. More drugs passing phase I and II testing	\$4.63 Billion	
6. Increasing patient adherence and reducing skipped medications		\$15.75 Billion
7. Increasing the efficiency and effectiveness of drug advertising		\$0.48 Billion
a. More efficient TV/print/radio DTC advertising	\$0.19 Billion	
b. More efficient online advertising	\$0.02 Billion	
c. More efficient use of resources in detailing activities	\$0.27 Billion	
A. Improved safety monitoring and ability to conduct registry studies		(Data Not Available)
B. Improved ability to conduct epidemiology studies and track problems		(Data Not Available)
C. Better outcomes research, thus reducing system-wide healthcare costs		(Data Not Available)
Total Potential Benefit – Pharmaceutical Industry		\$31.0 Billion

Discussion of Potential Benefits

The value components listed above take the form of potential savings, additional revenue, or both. While many of these components (e.g. medication adherence and conditional prescribing) provide substantial value to providers, payers and patients, this study focuses on the value to pharmaceutical firms.

In addition, three other sources of value were identified—Registry Studies, Epidemiology, and Outcomes Research—however there was insufficient data available to estimate the potential value of these components. They are listed to indicate that there are other sources that could be added to this model when data becomes available.

The following sections provide a summary of how a nationwide EHIX Network provides quantifiable value to the pharmaceutical industry for each value component. The formulas for the calculations also are included. A one-page view of the complete model

is included in Appendix I which identifies the references for all calculations and data sources.

Subject Recruitment for Clinical Trials

Researchers conducting clinical trials spend enormous time and effort to recruit subjects. In fact, there are entire businesses devoted to assisting with this process. Current recruiting methods include advertising on radio, TV and the newspapers, contacting physicians and hospitals directly, scanning published information, and publishing the trial information on Web sites.

“Over 4,000 enrollees are needed to test a single new drug. ... Companies pay bounties of anywhere from \$500 to \$15,000 per subject to load their trials, plus bonuses for rapid enrollment.”

–Marcia Angell, MD, former editor-in-chief, *New England Journal of Medicine*

Using approved, pre-screened electronic clinical data as would be available in a nationwide EHX Network would allow a rapid assessment of subjects to meet the inclusion criteria. This available electronic information would have sufficient detailed data for recruitment purposes and would be immediately searchable, which allows the rapid identification of subjects interested and eligible for a specific clinical trial. Likely data types available would include current medical, diagnosis and patient demographics.

Using these assumptions for the availability of clinical information we identified four value components for subject recruitment. The first two calculations estimate the savings from completing early/mid phase and late-stage clinical trials more quickly. These calculations assume a reduction in recruitment time from the current average of 180 days to 63 days (a 65 percent decrease). This reduction in time is based on the inline availability of prospective participants, thus cutting out a major part of the recruitment process. The third calculation estimates the additional revenue that pharmaceutical companies will receive as a result of bringing their products to market more quickly and therefore increasing the days the drug is on the market, under patent. It is based on the number of new drugs approved per year, multiplied by the average daily revenue, which is again multiplied by the number of days that are saved in the recruitment process.

The fourth calculation estimates the savings in clinical trial enrollment advertising. Every year, the industry spends over half a billion dollars running advertisements to enroll subjects into clinical trials.¹ Since more participants would be recruited based on the EHX Network available information, the need to advertise can be greatly reduced. We estimated that using the system to identify potential participants could eliminate the need for 60 percent of total enrollment advertising expenditures.

Calculations for Subject Recruitment (Clinical Trials)

1. Decrease in recruiting time/costs for early/mid stage trials: 3,310 early/mid-stage trials per year x \$1,000 saved per day x 180 days x 65% savings in recruitment time
2. Decrease in recruiting time/costs for late stage trials: 640 late-stage trials per year x \$37,000 savings per day x 180 days x 65% savings in recruitment time
3. Additional revenue for earlier introduction of new drugs: 28 new drugs make it to market per year x \$1,100,000 additional revenue per day x 180 days x 65% savings in recruitment time
4. Cost saving for recruiting advertising expense: \$525,000,000 industry-wide advertising spending for clinical trial enrollment x 60% savings in advertising costs

Data Management for Clinical Trials

As a condition of approval, the FDA requires several well-controlled clinical trials studies are performed for every new drug. These trials can take months to set up and years to complete. The multiple phases of clinical testing represent the largest costs of bringing a drug to market.

Pharmaceutical companies spend an average of \$157M per drug on conducting clinical trials. An estimated 17 percent of that amount goes toward managing clinical trial data.

(Source: Drug Information Journal)

Part of the process includes the re-entry of information that is already available in electronic format but not interfaced to the Electronic Data Capture (EDC) application. This data could include lab test results from outside labs, medication data from pharmacies and PBMs, and clinical data from EHRs. With a nationwide EHIX Network, there would no longer be a need to re-enter data, eliminating transcription errors and saving administrative time. Our expert panel estimated that approximately 17 percent of the clinical trial budget for a drug goes toward managing data. Using this figure and estimating that the EHIX Network can reduce the average data management budget for a clinical trial by approximately 10%, the data management saving for late-stage trials would be \$250 million annually, given a three year average trials timeframe.

Calculation for Data Management (Clinical Trials)

1. Cost savings for improved data management: (95 drugs in late-stage trials per year / 3 years per clinical trial) x \$157M per drug spent on clinical trials x 17% of budget spent on data management on average) x 10% savings in data management

Subject Adherence for Clinical Trials

Subject drop-outs due to non-compliance during a clinical trial are another significant cost component. An analysis of published literature and company reports estimated a total non-completion rate of between 22-30 percent, and a weighted average of the per-patient cost of conducting a trial yields an approximate cost of \$6,322 per dropout.^{2,3} Often, subjects require reinforcement and support during a long clinical trial. The ability

to communicate with trial participants outside of the doctor's office would improve the trial compliance. With a nationwide EHX Network, this type of communication would be achievable through a patient portal, designed to provide individualized feedback to participants and their families.

The calculation for the value of improved adherence during trials is based on the average number of non-completions (i.e. participants who drop out of the trial) and the cost of losing and having to replace those participants. There will always be some participants who do not or cannot complete a trial, thus we estimated that better engagement and communication would reduce the non-completion rate by 30 percent.

Calculation for Subject Adherence (Clinical Trials)

1. Cost savings for improved subject adherence: 582 subjects per trial x 27% average non-completion rate x \$6,322 cost per dropout x 640 late-stage trials x 30% fewer dropouts

Adverse Drug Event (ADE) Monitoring

The United States uses a "spontaneous reporting system" for reporting and tracking adverse drug events (ADEs). It is widely recognized that, while the system is relatively unbiased, it suffers from significant under-reporting and is therefore questionable as a reliable early warning system for understanding potential safety issues.

One obstacle to achieving better reporting is the administrative burden placed upon physicians. The EHX Network can help reduce this burden by presenting the physician with a pre-populated form containing pertinent patient data (e.g. demographic information and clinical information where applicable). Adding the rest of the ADE information would be less costly in terms of time and effort.

While it is often physicians who collect these data at the ground level, pharmaceutical companies must compile and analyze them in order to prepare a comprehensive post-market surveillance report. The cost of these monitoring-related activities is estimated to be about \$10 million per drug.⁴ Our panel of pharmaceutical industry experts estimated that new capabilities could reduce the cost of performing data management activities by about 25 percent. From this information we estimate that the online adverse drug event documentation function would save the industry approximately \$70 million annually.

Calculation for Adverse Drug Event Monitoring

1. ADE documentation savings: \$9,700,000 estimated cost of post-market surveillance reporting x 28 new drugs to market per year x 25% savings

Conditional Prescribing

The combination of online availability of clinical data with an open communication channel between patients and their care team can be a valuable tool for prescribing and monitoring a patient's condition for certain medications that are appropriate for a subset of the population, but dangerous or ineffectual for others. For example, the drug Accutane is very effective in treating cystic acne—a very painful and disfiguring type of acne that can occur in teenagers and adults—but is known to cause birth defects when women use the medication while pregnant. The drug was approved in 1982 and later put on a risk management plan by the U.S. Food and Drug Administration to restrict distribution of the drug.⁵ However, as such plans proliferate; they can be too time-consuming and confusing for doctors to keep track of by hand. In the case of Accutane, many dermatologists believe that the current plan inappropriately impedes access to the drug.⁶ The result for Accutane and other drugs in this predicament is that the concern over not being able to properly monitor the dispensing of these prescriptions has prevented patients who would be helped from getting the drug in question and forcing them to seek alternative treatment.

An EHIX Network can provide benefit to the pharmaceutical industry by providing valuable patient clinical information to ensure that certain drugs can be used safely in the market. The network would not specifically alert physicians which drugs to prescribe, but rather it would make it possible for physicians to better monitor a patient's health status (e.g. results from monitoring lab tests) to determine if the drug is effective and safe for this patient.

The first calculation for the conditional prescribing value component estimates the revenue that could be recovered by enabling physicians to prescribe to specific patient populations drugs that otherwise would have been pulled for safety reasons. The average number of drugs approved per year is multiplied by the average percentage of drugs pulled from the market per year. This is multiplied by the average daily revenue to obtain the amount of revenue lost per year due to drugs being pulled for safety reasons. Since there will be additional costs associated with patient condition monitoring we discounted the potential revenue stream by 20 percent. We multiplied this figure by the estimate of the number of remaining commercial life years. Finally, we assumed that conditional prescribing will be possible for 90 percent of drugs that are pulled for safety reasons. This reflects the fact that drugs that make it this far have already been thoroughly tested, and even if they are shown to pose some danger to certain patient populations, they are highly likely to be safe and effective for others. The final calculation indicates that the pharmaceutical industry would receive an additional \$1.12 billion annually.

The second and third calculations for conditional prescribing follow similar logic, except these are drugs that we stopped during clinical trials. In the case of phase III failures, our panel of experts from the pharmaceutical industry estimated that 50 percent of these drugs could go on to be marketed safely to some patient population under conditional prescribing. In the case of phase I and phase II failures, the estimate of the number of drugs that could still be marketed is predictably much lower: approximately 12.5 percent.

Calculations for Conditional Prescribing

1. Additional revenue for drugs not pulled from the market: 28 new drugs approved per year x 2.75% pulled from market per year x \$1.1m daily revenue x 80% revenue x 365 days x (8 years of commercial life - 1.5 years already elapsed) x 90% of failures estimated to be preventable
2. Additional revenue for bringing phase III conditional prescribing drugs to market: 7.5 phase III failures per year x 16% for safety x \$1.1m daily revenue x 80% revenue x 365 days x 8 year average commercial life x 50% of failures estimated to be preventable
3. Additional revenue for bringing phase I and II conditional prescribing drugs to market: 72 phase I and II failures per year x 20% for safety x \$1.1m daily revenue x 80% revenue x 365 days x 8 year average commercial life x 12.5% of failures estimated to be preventable

Patient Adherence

Patient non-adherence to a prescribed medication regimen is a significant healthcare problem. A commonly cited statistic in the industry states that one-third of patients take all of their medications as prescribed, one-third take some of their medications as prescribed, and one-third take none of their medications.⁷ New studies and surveys continue to show figures on non-adherence that fall into these general ranges.⁸ Patient non-adherence is based on many factors. Some medication regimens are highly complex, and are therefore difficult to follow. Other factors are related to patient populations, for instance elderly patients, who have trouble remembering how or when to take their numerous medications.

The EHIX Network can help individuals remain adherent by providing an open channel of communication between patients and their caregivers. Care givers can help explain complex regimens, remind patients to take their medications via emails, text messages, or other modes of communication. With connectivity to Pharmacy Benefit Managers (PBMs) and pharmacies, the system can be used to track patient adherence directly.

Cited estimates of the total lost revenue of non-adherence to pharmaceutical companies go as high as \$40 billion.⁹ Several other studies have published amounts in the tens of billions of dollars, with an average estimate of \$35 billion.¹⁰ Since the published estimates do not have detailed data and formulas supporting the result, we used the most conservative figures available, and then discounted the figure by a percentage based upon how much of the patient non-adherence problem a nationwide EHIX Network could reasonably be expected to address. However we do believe that these are reasonable estimates when one considers the number of prescriptions written in the United States per year (approximately 3.5 billion), the average cost of a prescription (over \$60 per prescription), and the prevalence of non-adherence (which is estimated to be anywhere from 30-45 percent).

Our panel of pharmaceutical industry experts agreed that a nationwide EHIX Network could potentially reduce non-compliance by 45-50 percent. Therefore the annual estimate of additional revenue to the pharmaceutical industry is \$15.75 billion for improved patient adherence.

Calculations for Patient Adherence

1. Additional revenue for improved patient adherence: \$35 billion in revenue lost by the pharmaceutical industry per year due to patient non-adherence x 45% of cost of non-adherence (missed medications) which can be eliminated by an EHIX Network

Advertising

A nationwide EHIX Network is a valuable tool for communication. It can allow pharmaceutical firms to connect with consumers via an online portal. This could lead to finding new ways to increase awareness and education in target patient populations.

Our panel of pharmaceutical experts identified three areas in which the EHIX Network would generate savings for the pharmaceutical industry by making advertising expenditures more efficient and more effective. They are: traditional direct-to-consumer channels (e.g. television, print, and radio), online advertising, and detailing. The first calculation in our model estimates that more targeted advertising could save the pharmaceutical industry 3 percent of the total amount it spends annually on traditional advertising. The second calculation in our model estimates a savings of 10 percent of the total amount the industry spends on online advertising. The last calculation estimates that for the practice of detailing, better information about how their products are used would result in a savings of approximately 5 percent of the annual amount spent in this area.

Calculations for Advertising

1. Savings for major DTC advertising channels: \$6,473,000,000 total spent on TV/print/radio DTC advertising per year x 3% savings from more efficient advertising
2. Savings for online DTC advertising channels: \$170,000,000 total spent on online DTC advertising per year x 10% savings from more efficient advertising
3. Savings for detailing: \$5,300,000,000 total spent on detailing x 5% savings from more efficient advertising

The Bottom Line

A nationwide EHIX Network provides secure and confidential communication, and access to patient information. The value of this IT network has significant and quantifiable benefits to the pharmaceutical industry. Using our model and sources of data, we estimate this value to be approximately \$31 billion annually. As noted, this includes nothing for savings in Outcomes Research, Epidemiology, and Registry Studies. Additionally these figures do not include the additional value the EHIX Network would produce for the bio-technology and medical device firms. The successes of the local and regional initiatives indicate that these benefits under a nationwide information sharing model are reasonable and achievable.

Appendix I

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Bio-Pharmaceutical / Medical Device Value Algorithm

Effects of the electronic health information community appear in bold.

Value Component	Source of Value	Annual Value
1) Patient Recruitment (CT)	Clinical trial recruiting time will be reduced by 65% (from 180 days to 63), and enrollment ad costs will be reduced by 60% .	
	1) 3,310 early/mid-stage trials x \$1,000 saved per day x 180 days x 65% savings in recruitment time	\$387,270,000
	2) 640 late-stage trials x \$37,000 savings per day x 180 days x 65% savings in recruitment time	\$2,770,560,000
	3) 28 new drugs per year making it to market x \$1,100,000 additional revenue per day x 180 days x 65% savings in recruitment time	\$3,603,600,000
	4) \$525,000,000 industry-wide advertising spending for clinical trial enrollment x 60% savings in advertising costs	\$315,000,000
2) Data Management (CT)	Better management of clinical trial data will cut the cost of data management (errors, duplication, etc.) by 10% .	
	1) (95 drugs in late-stage trials per yr / 3 yrs per trial) x (\$157m per drug on trials x 17% spent on data mgmt) x 10% savings	\$84,518,333
3) Patient Adherence (CT)	Better engagement with patients during clinical trial will reduce the average clinical trial non-completion rate by 30% .	
	1) 582 subjects x 27% average non-completion rate x \$6,322 cost per dropout x 640 late-stage trials x 30% fewer dropouts	\$190,740,303
4) ADE Monitoring	Automatic and integrated safety reporting will reduce the cost of post-market surveillance and reporting by 25% .	
	1) \$9,700,000 estimated cost of post-market surveillance reporting x 28 drugs per year x 25% savings	\$67,900,000
5) Conditional Prescribing	Conditional prescribing will allow failed or withdrawn drugs to remain on the market for 90%, 50%, 12.5% .	
	1) 28 approved per yr x 2.75% pulled x \$1.1m daily revenue x 80% revenue x 365 days x (8 - 1.5) commercial yrs left x 90% preventable	\$1,157,476,320
	2) 7.5 phase III failures per yr x 16% for safety x \$1.1m daily revenue x 80% revenue x 365 days x 8 yr commercial life x 50% preventable	\$1,541,760,000
	3) 72 phase I and II failures per yr x 20% for safety x \$1.1m daily revenue x 80% revenue x 365 days x 8 yr commercial life x 12.5% preventable	\$4,625,280,000
6) Patient Adherence	45% of the total cost of patient non-adherence to the pharmaceutical industry can be recaptured through better monitoring.	
	1) \$35 billion in revenue lost by the pharmaceutical industry per year due to patient non-adherence x 45% recaptured by PSI	\$15,750,000,000
7) Advertising	More efficient and effective advertising will save 3% in DTC, 10% online, and 5% in detailing (physician-targeted activities)	
	1) \$6,473,000,000 total spent on TV/print/radio DTC advertising per year x 3% savings from more efficient advertising	\$194,190,000
	2) \$170,000,000 total spent on online DTC advertising per year x 10% savings from more efficient advertising	\$17,000,000
	3) \$5,300,000,000 total spent on detailing x 5% savings from more efficient advertising	\$265,000,000
Total Annual Value		\$30,970,294,957

Additional Significant Sources of Value

Registry Studies	Improved capabilities in safety monitoring and follow-ups will lower the cost of performing registry studies. However, there is not enough data on the cost or commercial use of registry studies to estimate the added value of EHIX. This would likely have a moderate value potential.
Epidemiology	Epidemiological studies will identify issues early and save the healthcare system money. However, this component primarily accrues as a public good to other participants in the healthcare system. Overall, this would provide low-to-moderate amount of value to the system.
Outcomes Research	Better outcomes research as a result of better data will reduce costs to the healthcare system. However, there is not enough data available on commercial use of registry studies to estimate the value of the EHIX Network. This usage could potentially provide a large amount of value.

References

- ¹ Canavan, C. S. Grossman, R. Kush, and J. Walker. "Integrating Recruitment into eHealth Patient Records" *Applied Clinical Trials*, June 2006, 43
- ² CenterWatch analysis of published literature and company reports, documented in the PAREXEL Bio/Pharmaceutical R&D Statistical Sourcebook: 2006-07, p153
- ³ Cutting Edge Information, *Accelerating Clinical Trials: Budgets, Patient recruitment and Productivity*, 2004. Weighted average calculation based on the average per-patient clinical trial cost of trial subjects across phases 1, 2, and 3.
- ⁴ Estimate reflects 25 percent of the original cost of obtaining approval for a new drug. Pharmaceutical industry spending on securing FDA approval was \$3.415 Billion in 2004. This figure, divided by 88 (the average number of New Drug Applications per year from 1993-2005) and multiplied by 25% is \$9.7m.
- ⁵ *Healthfacts*, "Learning from the Accutane Experience," 13:110, July 1988
- ⁶ Pollack, A. "M.S. Drug Can Return, With Limits," *New York Times*, June 6 2006
- ⁷ O'Brien MK, Petrie K, Raeburn J. Adherence to medication regimens: updating a complex medical issue. *Medical Care Review* 1992; 49:435-454.
- ⁸ Osterberg, L. and T. Blaschke. "Adherence to Medication" *New England Journal of Medicine* 2005; 353:487-97
- ⁹ Dendrite Marketing Solutions. "Rx Persistency has dropped to unprecedented lows." http://www.dendrite.com/loyalty/den_prst_insert_final.pdf. (Nov 1, 2006)
- ¹⁰ DataMonitor, "Addressing Patient Compliance," August 2004