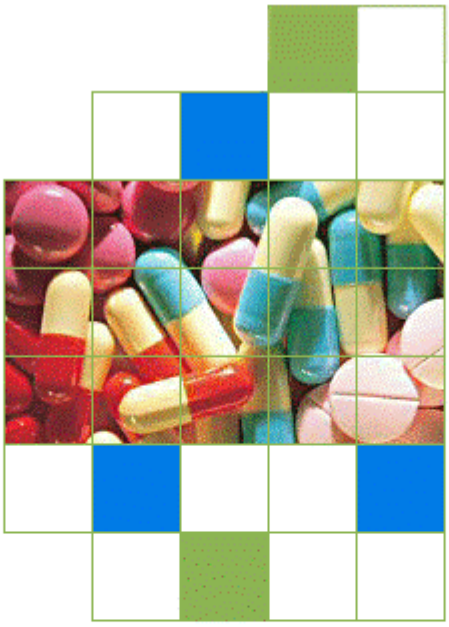
Puget Sound Health Alliance

Rx Clinical Improvement Team Phase 2 Report



Puget Sound Health Alliance
www.pugetsoundhealthalliance.org
2003 Western Avenue, Suite 600 ~ Seattle, WA 98121 ~ (206) 448-2570

Puget Sound Health Alliance

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RX CIT Phase II Final Report
Executive Summary

The Rx CIT was convened in 2006 with the aim of improving the cost-effectiveness, consistency and value in prescribing practices across the Puget Sound Region. The Rx CIT completed Phase I of its work in June 2006 with the recommendations to promote the use of cost-effective generic medications when appropriate, and to eliminate pharmaceutical drug detailing and sampling in physician offices[1].

As Phase I was completed, the members of the Rx CIT suggested that further information be gathered on high-value medications in four classes of drugs selected for their widespread use and the high degree of variation in prescribing patterns seen across these classes. The four classes selected were statins, proton pump inhibitors, non-steroidal anti-inflammatory drugs, and selective serotonin reuptake inhibitors. The CIT further recommended that the Alliance staff gather data from selected plans on generic fill rates within each of these target classes in the Puget Sound Region. In addition, it was recommended that increasing patient adherence to medications for chronic disease be a focus of further work, as an important component of any quality improvement effort. Phase II of the Rx CIT was convened in February 2007 to address these issues.

The Rx CIT evaluated the evidence for efficacy, side effects and cost of medications within the four classes of drugs selected for review, and made the following recommendations for high value prescribing in these classes:

Statins:

1. Use the National Cholesterol Education Program (NCEP) Adult Treatment Panel (ATP) III and American Heart Association (AHA)/American College of Cardiology (ACC) guidelines for target LDL levels when prescribing statins.
2. The generic statins- lovastatin, pravastatin and simvastatin- are recommended as drugs of first choice for the majority of patients.
3. Highest potency brand name statins should be reserved for those few patients who require more than 45-50% reduction in their LDL levels.

[1] Rx CIT Phase I Report:
http://www.pugetsoundhealthalliance.org/members/documents/RxClinicalImprovementTeam.pdf

Proton Pump Inhibitors (PPIs):

1. Generic omeprazole is recommended as the drug of first choice when a PPI is indicated.
2. It is recommended that evidence-based clinical guidelines (such as the Dyspepsia and GERD guidelines issued by the American College of Gastroenterology) be used to guide provider-directed treatment with PPIs.
3. Patient self-directed treatment of dyspepsia or heartburn symptoms with OTC antacids, H2-blockers or the PPI omeprazole is appropriate if symptoms are mild, intermittent or transient. Symptoms that are severe or persistent should be evaluated by a healthcare provider.

Selective Serotonin Reuptake Inhibitors (SSRIs):

1. When prescribing SSRIs for first line therapy, providers should preferentially select a medication for which there is a generic equivalent, such as fluoxetine, paroxetine, sertraline, fluvoxamine or citalopram.

Non-Steroidal Anti-Inflammatory Drugs (NSAIDs):

1. When prescribing NSAIDs, providers should preferentially select low cost generic drugs and avoid COX-2 inhibitors in most patients.
2. In patients with coronary heart disease (CHD) or at high risk for the disease, providers should consider naproxen as a drug of first choice, since it is the only NSAID so far shown to not increase the risk of myocardial infarction.
3. In patients at low risk for heart disease, ibuprofen and other low cost generic and OTC NSAIDs are reasonable cost-effective alternatives.
4. In elderly patients and others at risk for GI bleeding, acetaminophen, tramadol, or short-term use of narcotic agents should be considered first-line analgesic options. The COX-2 inhibitors such as celecoxib (Celebrex) may be used cautiously in patients at risk for GI bleeding, but the GI benefit should be carefully weighed against the increased cardiovascular risk. The combination of naproxen and an H2-blocker or PPI may be a safer alternative, although direct comparisons to COX-2 inhibitors are lacking.
5. Patient-directed therapy with OTC NSAIDs is appropriate for temporary relief of pain in selected patients. Providers should caution patients at risk for heart disease, GI bleeding and those with renal or hepatic insufficiency against the use of NSAIDs. Long-term use of NSAIDs in any patient should be directed by a healthcare provider.

Evidence to support these recommendations is cited in the report. In addition to making recommendations for patients and providers at the point of care, the Rx CIT also formulated recommendations for other stakeholders, including plans, purchasers, pharmacies and Pharmacy Benefit Managers (PBMs) to create a community environment that is supportive of the desired changes in prescribing practices. The Rx CIT set target generic fill rates for each class based on the characteristics of the drugs available in the class.

In response to the request for data on current generic fill rates in the Puget Sound Region, Alliance staff collected data from six regional health plans on the four selected classes of drugs. The Rx CIT set target generic fill rates for each class based on estimated current fill rates as well as the characteristics of the drugs available in the class. Analysis of the data revealed that the estimated potential savings if recommended target generic fill rates for these four classes are reached is over $73million annually in the five-county Puget Sound region. The data is discussed in detail in the report, and a full summary of the analyses is found in Appendix 3.

The greatest opportunity for cost savings is within the statin and PPI classes and particular efforts should be made to educate providers and patients on the advantages of generic options for these drugs. The generic fill rate of NSAIDs is currently high in the Puget Sound region, but that could change if new agents come on the market. It is important to continue to emphasize that COX-2 inhibitors should be the drugs of first choice in only a minority of patients, if any, and that their risk-benefit profile is not favorable for the vast majority of patients requiring an NSAID. Likewise, the generic fill rate of SSRIs is high in this region, but an examination of the broader category of second-generation antidepressants would likely demonstrate a greater opportunity for improvement.

The final challenge identified in Phase I of the Rx CIT was examining patient adherence to medication treatment recommendations, particularly for those with chronic diseases. According to the National Quality Forum, "[p]rescription medication non-adherence is a major barrier to patients fully realizing the benefits of modern medical research."[2] Improving patient adherence to medications is an important component of quality improvement in healthcare.

Reasons for non-adherence vary from one patient to the next, and many patients demonstrate a combination of factors that impede their ability to adhere to medications as prescribed. Such barriers to adherence may include:

[2] National Quality Forum: Improving Use of Prescription Medications: A National Action Plan http://www.qualityforum.org/projects/completed/medications.asp

1. Patient factors

   E.g. Cognitive or language difficulties, physical barriers, forgetfulness or disorganization, lack of motivation, cultural issues, adverse effects of medication

2. Doctor-patient relationship factors

   E.g. Poor communication, discordant models of disease between patient and provider, lack of trust in the relationship, lack of appropriate follow-up

3. Extraneous factors

   E.g. Financial barriers, pharmacy benefit design, poor information flow

It was beyond the scope of the Rx CIT to develop strategies to tackle all causes of poor medication adherence. The discussion and recommendations put forth by the Rx CIT focused on practical suggestions for improving medication adherence by identifying tools, incentives and resources for patients and providers that utilized the strengths of the Alliance and its member stakeholders. Discussion did not address barriers such as language, cognitive difficulties, or culturally diverse models of disease, although the importance of these factors is well recognized.

Health plans, PBMs, pharmacies and purchasers can support efforts by patients and providers to improve adherence to chronic disease medications by addressing some of the barriers to adherence such as financial barriers, pharmacy benefit design and lack of shared information. The Rx CIT selected cost, information exchange, and medication therapy management as areas in which the various stakeholder groups could most efficiently use their resources to effect change. Specific recommendations were made for each of the stakeholder groups in these areas of focus.

Puget Sound Health Alliance

Rx CIT Phase II Final Report

I. Background

In December 2003, King County Executive Ron Sims convened a broad-based leadership group, *The King County Health Advisory Task Force*[3], to develop an integrated strategy to address the systemic problems facing the health care system in the Puget Sound region. In particular, Executive Sims requested that the Task Force focus on three inter-related issues: the increase in health care costs for employees and employer purchasers, quality of care, and the importance of improving the health of the community.

The Task Force described the current system of health care as a "series of disconnected strategies all working concurrently but without a system steward, or neutral leader, to coordinate them and ensure that they are achieving the optimal mix of cost, quality, and health outcomes."[1] As part of their recommendation to develop an integrated strategy, the Task Force advised creating a regional partnership to provide the necessary leadership to forge changes in the existing system.

The Puget Sound Health Alliance (the Alliance) was created to fill this role, with the bold vision to develop a state-of-the-art health care system that provides better care at a more affordable cost, resulting in healthier people in the Puget Sound Region. Its mission is to build a strong alliance among patients, doctors and other health care providers, hospitals, employers and health plans to promote health and improve quality and affordability by reducing overuse, under-use and misuse of health services.

The Alliance has developed an extensive membership of providers, employer/purchasers, hospitals, health care associations, health plans and individual consumers in a five county region composed of King, Snohomish, Pierce, Thurston and Kitsap Counties.

The strategic approach of the Alliance addresses several key elements to improve health, quality, and cost outcomes, including: chronic disease management, scientific evidence to guide providers and patients in value-based medical decision-making, decreased practice variation, and quality measurement and reporting to support practice improvement and allow patients to seek appropriate care.

[3] King County Health Advisory Task Force Final Report, June 2004 [Accessed online 3_06_06 at: ftp://extranet.metrokc.gov/exec/hatf/063004report.doc]

At the June 2005 Alliance Board meeting there was consensus among Board members that the Alliance would initially focus on four conditions: heart disease, diabetes, back pain and depression. There was a strong consensus in the Quality Improvement Committee (QIC), echoed by the Board, that pharmaceutical management should be an area of priority for the Alliance, and therefore pharmacy was added as a fifth area of focus. Clinical Improvement Teams (CITs) made up of local experts representing various stakeholder groups were convened to discuss and make recommendations in each of these areas. The CITs report to the Quality Improvement Committee (QIC) and develop recommendations to the Board on standard guidelines, performance metrics and measurement approaches, and implementation and monitoring strategies for quality improvement in each area.

In the pharmacy CIT, named the Rx CIT, emphasis was on promoting medications of proven high value based on quality evidence, on increasing the use of lower cost generic medications when appropriate, and reducing the variation in prescribing practices. The Rx CIT was convened in 2006 and completed work on Phase I in June, 2006 (see Phase I Final Report on Alliance web site[4]). The team was reconvened in February, 2007 to discuss topics selected for Phase II.

II. Summary of the Rx CIT Phase I

Based upon the recommendations of the Alliance's Quality Improvement Committee (QIC), with approval from the Board of Directors, the Rx CIT was created in November 2005 and met from January 2006 through April 2006 to conduct its Phase I work. Over the course of three initial meetings, the team focused on high impact strategies aimed at improving the affordability and quality of pharmaceutical drugs. Increasing the generic fill rate and focusing on consumer education about generic drugs were quickly identified as the high impact strategies. The group chose to focus their efforts on four therapeutic classes of medications: Statins, Proton Pump Inhibitors (PPIs), Nonsteroidal Anti-Inflammatory Drugs (NSAIDs), and Selective Serotonin Reuptake Inhibitors (SSRIs). Antibiotics were identified as a fifth class of drugs with a need for patient and provider education on appropriate usage.

In its Phase I work the Rx CIT also focused on eliminating drug detailing and free samples in practice locations due to quality and cost concerns. The CIT members emphasized that pharmaceutical and sales representatives do not necessarily provide unbiased information to providers on the efficacy and availability of the range of drugs available in the market, including lower cost generic equivalents. The use of samples can result in patients receiving medication that are more expensive (than generic equivalents) and/or less efficacious. Furthermore, many practices do not adequately track which samples are given to whom, complicating medication management and degrading the overall quality of care.

[4] Rx CIT Phase I Final Report. Puget Sound Health Alliance. Available at: http://www.pugetsoundhealthalliance.org/members/documents/RxClinicalImprovementTeam.pdf

Table 1: Summary of Rx Phase I Recommendations

Recommendation 1: Increase the generic fill rate of medications where appropriate.
1. The Puget Sound Health Alliance will promote the use of generic drugs in the region
2. The Alliance will develop educational campaigns with the aim of reducing brand name drug use, and increasing generic use, by 3% over the next 2 years
3. The educational campaigns will focus on generics in general, as well as 4 classes of drugs: o Statins o Proton Pump Inhibitors (PPIs) o Nonsteroidal Anti-Inflammatory Drugs (NSAIDs) o Serotonin re-uptake inhibitors (SSRIs)
4. The Alliance should develop recommendations for patient incentives to use generics
5. The Alliance should develop a list of "drugs of first choice" to aid providers in their prescribing choices and to reduce variation in prescribing practices across the region.
Progress and Accomplishments:
1. The Alliance Communication Committee has drafted patient education materials on the value and safety of generic medications in general. These materials have been reviewed by the Rx CIT and will be distributed to Alliance members. 2. The Alliance plans to collect data on generic fill rates in the Puget Sound Region as part of its strategy on public reporting of quality indicators. The data will be supplied by plans and collected and collated through the Alliance data vendor Milliman MedInsight. This data will be published on a per country basis rather than by individual providers. The language of the proposed measures on generic fill rates is outlined in Appendix 1. 3. An Op-Ed outlining the Alliance's position on the value of generic medications, authored by the Alliance Executive Director, Margaret Stanley, and a member of the Rx CIT, Dr. John Verrilli, appeared in the Everett Herald[5] (see Appendix 2)
Recommendation 2: Eliminate drug detailing and free samples in provider offices
Progress and Accomplishments:
1. The Alliance issued two public statements which recommended against (1) the distribution of drug samples in physician offices and (2) on-site drug detailing by pharmaceutical representatives in physician offices.[6] These statements have received considerable attention. Anecdotal reports suggest that many more practices in the region are eliminating drug detailing on site since the statement was released (Jennifer Wilson-Norton, personal communication).

[5] Hugh Straley and John Verrilli, Puget Sound Health Alliance. Everett Herald, April 1, 2007. Opinion: With Prescription Drugs, Costliest Isn't Always Best.
Available at: http://www.heraldnet.com/stories/07/04/01/100opi_docs001.cfm [accessed 5-22-07].

[6] Puget Sound Heath Alliance Position Statement on Drug Sampling, Available at: http://www.pugetsoundhealthalliance.org/members/documents/HealthAlliancePosition_RxSamples_053006.pdf, and Puget Sound Heath Alliance Position Statement on Sales Representatives, Available at: http://www.pugetsoundhealthalliance.org/members/documents/HealthAlliancePosition_RxSalesReps_053006.pdf

III. Rx CIT Phase II - Overview

A. Structure of the Rx CIT

The Rx CIT consisted of fifteen local experts representing provider groups, pharmacies, health plans, pharmacy benefit managers (PBMs) and purchasers. The list of members can be found in Appendix 4. Phase II of the Rx CIT was conducted over four meetings, from February through May of 2007.

Oversight: Based on recommendations finalized by the Board in late 2006, the oversight structure of the CITs was revised. Henceforth, the Quality Improvement Committee (QIC) now provides specific recommendations to the Alliance Board of Directors based upon the final report and recommendations of each CIT. The QIC may choose to modify or amend the final report and recommendations via the following process, as approved by the Executive Committee of the Alliance:

- The Rx CIT forwards their report with detailed recommendations (guidelines, measures, and strategies) to the QIC
- The QIC reviews in detail and forwards a recommendation to the Board to either (1) approve the CIT recommendations as is, or (2) make alternative recommendations which are captured in an addendum to the CIT report
- The Board sees both the CIT report and the QIC recommendations and has final decision-making.

B. Scope of Work in Phase II

The work of the Rx CIT Phase II evolved out of the recommendations made in Phase I.

1. While Phase I focused on the value of generic medications in general, the task of Phase II was to make specific recommendations for each of four classes of medications: statins, proton pump inhibitors (PPIs), selective serotonin reuptake inhibitors (SSRIs) and nonsteroidal anti-inflammatory drugs (NSAIDs). The goal was to promote drugs with proven value-based on quality evidence and to reduce unnecessary variation across provider prescribing patterns through such methods as:

a. Recommending a “drug of first choice” approach in the four selected drug classes
b. Recommending a uniform or standardized core formulary or set of standards on formulary design

c. Suggesting benefit design and cost sharing incentives for patients to purchase drugs that have proven value and disincentives (such as increased out-of-pocket costs) to patients to purchase drugs of higher cost but less or uncertain value

d. Developing strategies for engaging each of the four key stakeholder groups that make up the Alliance membership in discussions on increasing the use of cost-effective, high value medications and reducing prescribing variability in the Puget Sound region.

2. The second topic assigned to the Phase II Rx CIT was to make recommendations to increase patient adherence to medications for chronic conditions, and to recommend changes in incentives to encourage increased patient compliance and persistence in taking medications as prescribed.

Recommendations in both topics were structured around two areas of interest:

(1) Point-of-Care Decision-making

(2) Creating a Supportive Community Environment for Change

Recommendations are targeted to each of the five stakeholder groups, in addition to the Alliance, designated at the "5 Ps":

- Patients
- Providers
- Plans (health plans, insurance groups)
- Pharmacy Benefit Managers (PBMs)
- Purchasers (employers, state purchasing agents, union trusts)

Table 2: Summary of Scope and Workplan for Rx CIT

Topics	Site	Stakeholders
Encourage the prescribing of medications of high value in four drug classes ▪ Statins ▪ PPIs ▪ SSRIs ▪ NSAIDs	Point-of-Care Decision-Making	▪ Patients ▪ Providers
	Creating a Supportive Community Environment for Change	▪ The Alliance ▪ Plans ▪ PBMs ▪ Purchasers

Topics	Site	Stakeholders
Increasing patient adherence to medications for chronic disease	Point-of-Care Decision-making	▪ Patients ▪ Providers
	Creating a Supportive Community Environment for Change	▪ The Alliance ▪ Plans ▪ PBMs ▪ Purchasers

C. Evidence Sources

The Alliance is committed to using quality evidence to guide and support its recommendations on quality improvement. In formulating recommendations on high value medications for each of the four selected drug classes, the Rx CIT chose to use the evidence reviewed and summarized in the Oregon Health Sciences University **Drug Effectiveness Review Project** (DERP).[7] Reports as the primary source of evidence on within-class drug comparisons. "The Drug Effectiveness Review Project is a collaboration of public and private organizations—including fifteen states—that have joined together to provide systematic evidence-based reviews of the comparative effectiveness and safety of drugs in many widely used drug classes and to apply the findings to inform public policy and related activities."[8] Washington State is a DERP participating organization. Other sources of guidelines and evidence are cited where appropriate. In addition, the Consumer Reports Best Buy Drug web site[9] provides recommendations that are based on DERP data, and is targeted to the consumer.

IV. Recommendations for Quality Improvement in the Prescribing Patterns of Each of Four Therapeutic Classes of Drugs

A. Recommendations at the Point of Care

Goals for Providers:

- Be aware of cost-effective options when prescribing medications
- Stay up to date on generic options in major classes of drugs
- Prescribe high-value medications, including cost-effective generic drugs, whenever appropriate

[7] Drug Effectiveness Review Project. Web site available at: http://www.ohsu.edu/drugeffectiveness/ [accessed 3-8-07]
[8] Ibid
[9] Consumer Reports Best Buy Drugs. Available at: http://www.crbestbuydrugs.org/ [accessed 4/3/07]

General Tools and Resources for Providers:

Evidence-Based Data on Prescription Drugs
Oregon Health Sciences University Drug Effectiveness Review Project http://www.ohsu.edu/drugeffectiveness/ Independent Drug Information Service (Harvard University and Pennsylvania Dept. of Aging www.rxfacts.org
Formulary Information
Epocrates Online (PDA version also available) www.epocrates.com
CME Opportunities
PowerRx-CE and Mylan Institute of Pharmacy: The Growing Influence of Generic Drugs: What it Means to Pharmacists and Physicians (1.5 hrs AMA Category 1 credit) http://www.powerpak.com/index.asp?page=courses/105412/disclaimer.htm&lsn_id=105412

Goals for Patients:

- Learn about your prescription drug benefit options
- Be an informed consumer of prescription drugs
- Be inquisitive- ask your doctor or pharmacist if a cost-effective generic medication is an appropriate choice for your condition

General Tools and Resources for Patients:

Educational materials
Consumer Reports Best Buy Drugs http://www.crbestbuydrugs.org/
Puget Sound Health Alliance Web Site www.pugetsoundhealthalliance.org http://www.pugetsoundhealthalliance.org/members/resources.cfm#SampleTools

The Rx CIT makes the following specific recommendations for decision-making at the point of care for each of the four classes of drugs selected by the Rx CIT.

1. Statins

Recommendations for Providers and Patients:

1. **Use the National Cholesterol Education Program (NCEP) Adult Treatment Panel (ATP) III and American Heart Association (AHA)/American College of Cardiology (ACC) guidelines for target LDL levels when prescribing statins.**

2. **Generic statins- lovastatin, pravastatin and simvastatin- are recommended as drugs of first choice for the majority of patients.**
3. **Highest potency brand name statins should be reserved for those few patients who require more than 45-50% reduction in their LDL levels.**

Table 3 outlines recommendations for the choice of statins based on the percent LDL lowering required to meet recommended targets.

Table 3: Choice of Statins Based on Percent LDL Reduction

% Reduction in LDL level desired*	Preferred statins
<30%	Lovastatin, pravastatin**, simvastatin
30-45%	Simvastatin
>45%	Consider highest potency branded products. Prescribers should refer to health plan formularies for the most cost-effective options for their patients.

* Percent reduction required to achieve the primary and secondary prevention LDL targets as outlined in the AHA/ACC and NCEP guidelines

** Pravastatin is the least likely of the statins to interfere with the CYP system and for this reason may be the preferred choice in patients on competing medications or on multiple medications for whom drug interactions are a concern.

The Rx CIT chose not to specify which of the highest potency statins [eg. atorvastatin (Lipitor), rosuvastatin (Crestor) or statin combination medications (e.g. simvastatin/ezetimibe (Vytorin)] was most appropriate for those few patients who require a >45-50% reduction in their LDL cholesterol.

Background and Evidence

Definition of statins: The class of cholesterol-lowering drugs referred to as statins are inhibitors of the enzyme HMG-CoA reductase (3-hydroxy-3-methylglutaryl-coenzyme A reductase). They act in the liver to inhibit cholesterol synthesis, thereby lowering blood cholesterol levels. Statins are especially effective in reducing Low Density Lipoprotein (LDL) levels, but may also lower triglyceride levels and raise High Density Lipoprotein (HDL) levels. High LDL and triglyceride levels, and low HDL levels have all been correlated with an increased risk for coronary artery disease, stroke, and other forms of atherosclerotic artery disease[10]

The first statin to appear on the market was lovastatin (brand name Mevacor) in 1989. Since then, six additional statins have entered the market: pravastatin (Pravachol), fluvastatin (Lescol), atorvastatin (Lipitor), simvastatin

[10] Castelli, WP. Lipids, risk factors and ischemic heart disease. Atherosclerosis 124 Supp S1-9, 1996. Available at: http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=8831910&dopt=Citation [accessed 2/7/07]

(Zocor) and rosuvastatin (Crestor). Lovastatin and fluvastatin are also available in extended release formulations (Altoprev and Lescol-XR, respectively).

Primary and secondary prevention studies have confirmed that at least four of the statins (lovastatin, pravastatin, simvastatin and atorvastatin) reduce the risk for coronary heart disease (CHD) and stroke, and reduce mortality in patients with documented CHD.[11] It is considered likely that all the statins have similar effects on CHD and mortality, based on their lipid-lowering properties.[12] Statins may also have anti-inflammatory activity and endothelial protective functions that could contribute to their ability to reduce the risk CHD.[13] Statins are considered the first-line therapy for LDL reduction in patients who can tolerate them.

Guidelines for the management of hyperlipidemia and the role of statins: The Alliance's Heart Disease CIT (convened in 2005-06) recommended the adoption of the evidence-based NCEP ATP III and AHA/ACC guidelines as the basis for clinical decision-making in the management of cholesterol. The members of the Rx CIT likewise recommend the use of these guidelines to guide clinical decisions regarding cholesterol reduction and the use of statins. A summary of the current guidelines is found in Appendix 5.

Selection of statins: When choosing a statin, clinicians and their patients must consider a variety of factors. These include the target LDL cholesterol level based on risk according to accepted guidelines, the percent reduction in LDL cholesterol level required to achieve that target, the efficacy of a given statin in reducing LDL levels, the tolerability and side effects of the drug, and its cost.

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[11] Including:
Shepherd et al. PROSPER study group. Pravastatin in elderly individuals at risk of vascular disease (PROSPER): a randomised controlled trial. PROspective Study of Pravastatin in the Elderly at Risk. *Lancet*. 2002;360:1623–1630; ALLHAT Officers and Coordinators for the ALLHAT Collaborative Research Group. The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial. Major outcomes in moderately hypercholesterolemic, hypertensive patients randomized to pravastatin vs usual care: the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT-LLT). *JAMA*. 2002;288:2998 –3007; Sever PS et al; ASCOT investigators. Prevention of coronary and stroke events with atorvastatin in hypertensive patients who have average or lower-than-average cholesterol concentrations, in the Anglo-Scandinavian Cardiac Outcomes Trial–Lipid Lowering Arm (ASCOT-LLA): a multicentre randomized controlled trial. *Lancet*. 2003;361:1149 –1158; Cannon CP et al, Pravastatin or Atorvastatin Evaluation and Infection Therapy-Thrombolysis in Myocardial Infarction 22 Investigators. Intensive versus moderate lipid lowering with statins after acute coronary syndromes. *N Engl J Med*. 2004;350:1495–1504. Collins R, et al, Heart Protection Study Collaborative Group. MRC/BHF Heart Protection Study of cholesterol- lowering with simvastatin in 5963 people with diabetes: a randomized placebo-controlled trial. *Lancet*. 2003;361:2005–2016; Colhoun HM, et al. CARDS investigators. Primary Prevention of cardioviovascular disease with atorvastatin in Type II diabetes in the Collaborative Atorvastatin Diabetes Study (CARDS): multicenter randomized placebo-controlled trial. Lancet 2004, 364:685-696.

[12] Oregon Health Sciences University Drug Effectiveness Review Project. Drug Class Review on HMG Co-A Reductase Inhibitors (Statins). August 2006. Available at: http://www.ohsu.edu/drugeffectiveness/reports/documents/Statins%20Final%20Report%20Update%204%20Unshaded.pdf [accessed 2/7/07].

[13] Ibid

Efficacy: Not all statins are equal in their ability to lower LDL cholesterol levels. Lovastatin, pravastatin and fluvastatin are considered relative low-potency drugs, and simvastatin, atorvastatin (Lipitor) and rosuvastatin (Crestor) are higher potency agents. Table 4 illustrates the relative efficacy of the various statins in lowering serum LDL levels.

Table 4: Lipid-lowering ability of statins

Statin Dose Per Day	Range of Percent LDL Lowering from Comparative Clinical Trials	Mean Percent LDL Lowering from Manufacturer's Information (and from ATP III if available)
Atorvastatin		
10 mg	28.9-40.2 %	39 %(37%)
20 mg	48.4-46.1%	43%
40 mg	45.1-51.3%	50%
80 mg	48.3-54%	60%(57%)
Fluvastatin		
20 mg	17.0-21.0%	22% (18%)
40 mg	22-26%	25%
80 mg	29.6%-30.6%	36% (31%)
Lovastatin		
10 mg	21.6-24%	21%
20 mg	21-29%	27%(24%)
40 mg	27.9%-33%	31%
80 mg	39%-48%	42%(40%)
Pravastatin		
10 mg	18-24.5%	22%
20 mg	23-29%	32% (24%)
40 mg	25.2-34%	34%
80 mg	-	37%(34%)
Rosuvastatin		
5mg	39.1-46%	45%
10mg	37.1-50.6%	52%
20mg	45.7-52.4%	55%
40mg	53.6-58.8%	63%
Simvastatin		
10 mg	26-33.1%	30%
20 mg	18.5-40%	38% (35%)
40 mg	34.3-43%	41%
80 mg	43-48.8%	47% (46%)

Adapted from: Oregon Health Sciences University Drug Effectiveness Review Project. Drug Class Review on HMG Co-A Reductase Inhibitors (Statins). August 2006. Available at: http://www.ohsu.edu/drugeffectiveness/reports/documents/Statins%20Final%20Report%20Update%204%20Unshaded.pdf [accessed 2/7/07].

As illustrated in the above table, when patients require < 40% reduction in their LDL levels, any of the available statins would be likely to achieve that goal. However, in patients who require > 40% reduction in LDL levels, the high potency statins (simvastatin, atorvastatin and rosuvastatin) would be preferable choices.

Cost: Until recently, only lovastatin was available in generic form. While a good choice for patients requiring <30-40% reduction in their cholesterol levels, lovastatin alone is unlikely to achieve target levels of LDL in patients requiring a greater percentage LDL reduction. Despite the fact that most patients do not require >40% LDL reduction, many clinicians chose a low dose of the higher potency brand name statins, such as atorvastatin (Lipitor) and rosuvastatin (Crestor) or the combination simvastatin/ezetimibe (Vytorin) as first line agents. In fact, Lipitor was one of the top selling drugs in the world in recent years, with worldwide sales estimated at $12 billion in 2005.[14]

In 2006, patents for pravastatin and simvastatin expired and generic alternatives were released into the market. The addition of simvastatin, a high-potency statin, to the list of generics has expanded the therapeutic options and makes a generic medication a good first-line choice for most patients. Table 2 indicates that the highest recommended dose of simvastatin (80 mg) can achieve up to a 48% reduction in LDL, which will bring the majority of patients to their target levels.

Tolerability and side effects: While statins are commonly prescribed, they are not without side effects and the potential for adverse reactions. The most concerning of these are elevations in liver enzymes with the potential for severe hepatotoxicity in rare cases. Although severe hepatotoxicity occurs in < 1% of statin users, routine monitoring of liver function is recommended for all patients taking statins. An even rarer side effect, occurring in < 0.1% of statin users, is rhabdomyolysis, a form of muscle breakdown. Both hepatotoxicity and rhabdomyolysis can be life-threatening. These adverse effects appear to be dose-related, in that they occur with greater frequency at higher doses. It is for these reasons that the NCEP and the AHA/ACC guidelines recommend careful titration of dose when attempting to achieve very low target LDL levels (i.e. < 70 mg/dl) in very high-risk patients.[15]

When determining which agents have the highest value, it is important to consider their safety profiles. Some clinicians have expressed concern that titrating the dose of a statin such as simvastatin to its highest recommended level to achieve a desired LDL target will result in a higher likelihood of side effects than a lower dose of one of the highest potency brand name statins for the same level of LDL reduction.[16] While head-to-head comparisons of all

[14] Berenson A. Lipitor or Generic? Billion-Dollar Battle Looms. New York Times, October 15, 2005. Available at: http://www.nytimes.com/2005/10/15/business/15statin.html?ei=5088&en=1712888c7ecc93fa&ex=1287028800&partner=rssnyt&emc=rss&pagewanted=print [accessed 2/7/07]

[15] AHA/ACC Guidelines for Secondary Prevention for Patients With Coronary and Other Atherosclerotic Vascular Disease: 2006 Update. Available at: http://circ.ahajournals.org/cgi/content/full/113/19/2363 (accessed 2/7/07); AHA/ACC/NHLBI Clinical Advisory on the use and safety of statins. 2002. Available at: http://www.nhlbi.nih.gov/guidelines/cholesterol/statins.pdf [accessed 2/7/07]; Rodney A. Narrative Review: Lack of Evidence for Recommended Low-Density Lipoprotein Treatment Targets: A Solvable Problem Annals of Internal Medicine 2006, 145:521-530 Available at: http://www.annals.org/cgi/reprint/145/7/520.pdf [accessed 2/1/07]

[16] Berenson A. Lipitor or Generic? Billion-Dollar Battle Looms. New York Times, October 15, 2005. Available at: http://www.nytimes.com/2005/10/15/business/15statin.html?ei=5088&en=1712888c7ecc93fa&ex=1287028800&pa

dosing combinations have not been done, several studies, summarized in the Drug Effectiveness Review Project report on Statins,[17] have compared simvastatin to both atorvastatin (Lipitor) and rosuvastatin (Crestor). Only atorvastatin (80 mg daily) and rosuvastatin (20 mg or more) reduced LDL by 50% or greater. However, simvastatin (80 mg daily) achieved reductions of up to 48%. Atorvastatin 80mg had a higher rate of some adverse effects (transaminase elevation) than did simvastatin 80mg daily (although in the trial the LDL-lowering effect of atorvastatin was greater than that of simvastatin). Adverse event rates in patients using rosuvastatin 40mg (maximum recommended dose) were similar to rates in patients using atorvastatin 80mg in short-term trials.[18] Given these results and others summarized in the DERP report, the best available evidence suggests that equipotent doses of statins have similar rates of adverse reactions.

When discussing tolerability, it should also be noted that the statins interact with the liver enzyme CYP system, with the potential for adverse drug interactions. Of the statins, pravastatin has the lowest potential for CYP interaction, and may offer the safest choice in patients on competing medications, or who are on multiple medications.[19]

Tools and Resources for Point of Care Decision-Making for Statins

For providers:

Drug Effectiveness Review Project Report
• Drug Class Review on HMG CoA Reductase Inhibitors (Statins). August 2006 http://www.ohsu.edu/drugeffectiveness/reports/documents/Statins%20Final%20Report%20Update%204%20Unshaded.pdf
Epocrates Drug and Formulary Information
• Epocrates Online (for information on drug choices and formulary selections) www.epocrates.com

For patients:

Consumer Report Best Buy Drugs
• Treating Elevated Cholesterol and Heart Disease – The Statins http://www.crbestbuydrugs.org/drugreport_DR_Statins.shtml

rtner=rssnyt&emc=rss&pagewanted=print [accessed 2/7/07]

[17] Oregon Health Sciences University Drug Effectiveness Review Project. Drug Class Review on HMG Co-A Reductase Inhibitors (Statins). August 2006. Available at: http://www.ohsu.edu/drugeffectiveness/reports/documents/Statins%20Final%20Report%20Update%204%20Unshaded.pdf [accessed 2/7/07].

[18] Ibid

[19] Ibid

2. Proton Pump Inhibitors (PPI's)

Recommendations for Patients and Providers:

1. **Generic omeprazole is recommended as the drug of first choice when a PPI is indicated.**
2. **It is recommended that evidence-based clinical guidelines (such as Dyspepsia and GERD guidelines issued by the American College of Gastroenterology) be used to guide provider-directed treatment with PPIs.**
3. **Patient self-directed treatment of dyspepsia or heartburn symptoms with OTC antacids, H2-blockers or the PPI omeprazole is appropriate if symptoms are mild, intermittent or transient. Symptoms that are severe or persistent should be evaluated by a healthcare provider.**

Background and Evidence:

Definition of PPIs: Proton pump inhibitors (PPIs) are a class of drugs that inhibit stomach acid secretion by blocking the enzyme H^+K^+ ATPase, or "proton pump," in gastric parietal cells that transport hydrogen ions (acid) into the lumen of the stomach. PPIs are more effective stomach acid inhibitors than the older Histamine H-2 blockers (which block only one of several mechanisms of acid stimulation) because PPIs inhibit the final step of acid production.

The first drug in the PPI class was omeprazole (brand name, Prilosec), introduced to the U.S. market in 1989. Since then, four more PPIs have been licensed: lansoprazole (Prevacid, 1995), rabeprazole (Aciphex, 1999), pantoprazole (Protonix, 2000) and esomeprazole (Nexium, 2001). Omeprazole became available over-the-counter (OTC) in the United States in 2003. Omeprazole is also available in combination with sodium bicarbonate (Zegerid).

Appropriate use of PPIs: PPIs are prescribed empirically for symptom relief in common gastrointestinal complaints such as dyspepsia or heartburn, and for the treatment of documented disorders such as gastroesophageal reflux disease (GERD), erosive esophagitis, peptic ulcer disease, nonsteroidal anti-inflammatory (NSAID)-induced ulcer disease, and treatment of *Helicobacter pylori* infection. With the release of OTC omeprazole, patient self-directed treatment of symptoms is also possible. Due to their tolerability and efficacy, PPIs are a popular first line treatment, and concern has been raised that their use may be inappropriate in some cases.

Although it is beyond the scope of the Rx CIT to outline recommended treatment strategies for various gastrointestinal disorders, summaries of the

American College of Gastroenterologists (ACG) guidelines[20, 21] for the treatment of dyspepsia and GERD are outlined in Appendix 6. Providers and interested parties are encouraged to refer to the full set guidelines referenced in the footnotes for further information.

Duration of treatment with PPIs: There is no single recommendation for appropriate length of treatment with PPIs, but rather treatment duration depends on the condition being treated. When used for empiric treatment in dyspepsia, it is recommended that PPIs be discontinued after four to eight weeks. If symptoms recur once the PPI is discontinued, then a further course of treatment is appropriate.[22] However, in patients who experience repeated recurrences, further evaluation by endoscopy or other means is recommended. In contrast, GERD is considered a chronic condition, and the American College of Gastroenterology recommends that patients with GERD continue treatment with PPIs long term if needed to control symptoms.[23]

Effectiveness of PPIs versus antacids and H-2 receptor blockers: A Cochrane review of 18 studies suggests that PPIs are more effective for relieving symptoms of functional dyspepsia than antacids or H2-blockers.[24] PPIs are also generally more effective than H2-blockers or antacids in the control of heartburn symptoms.[25]

Comparison of PPIs: Omeprazole is the only PPI available OTC and as a low-cost generic. It is of interest to examine the efficacy and safety of omeprazole compared to the more expensive alternatives in its class.

The Drug Effectiveness Review Project (DERP) Drug Class Review on Proton Pump Inhibitors[26] compares the efficacy and safety of the five PPIs licensed in the U.S. The report examines and grades the evidence from head-to-head comparison trials looking at a variety of endpoints (including symptom relief

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[20] Talley NJ et al. Practice Guidelines: Guidelines for the Management of Dyspepsia. Am J. Gastroenterology, 2005, 100:2324-2337.

[21] DeVault KR et al. Practice Guidelines: Updated guidelines for he diagnosis and treatment of Gastroesophageal reflux disease. Am J. of Gastroenterology, 2005, 100:190-200

[22] Talley NJ et al. Practice Guidelines: Guidelines for the Management of Dyspepsia. Am J. Gastroenterology, 2005, 100:2324-2337.

[23] DeVault KR et al. Practice Guidelines: Updated guidelines for he diagnosis and treatment of Gastroesophageal reflux disease. Am J. of Gastroenterology, 2005, 100:190-200

[24] Delaney B et al. Initial management strategies for dyspepsia. Cochrane Database of Systemic Reviews, 2007 Issue 1. Available at: http://www.mrw.interscience.wiley.com/cochrane/clsysrev/articles/CD001961/frame.html [accessed 2/14/07].

[25] DeVault KR et al. Practice Guidelines: Updated guidelines for he diagnosis and treatment of Gastroesophageal reflux disease. Am J. of Gastroenterology, 2005, 100:190-200

[26] Oregon Health Sciences University The Drug Effectiveness Review Project Drug Class Review on Proton Pump Inhibitors Final Report, 2006. Available at: http://www.ohsu.edu/drugeffectiveness/reports/documents/PPIs%20Final%20Report%20u4%20Unshaded.pdf [accessed 2/13/07]

and esophagitis healing in GERD, and symptom relief, endoscopic healing, and recurrence rates in peptic ulcer, duodenal ulcer and NSAID-induced ulcer disease). The reports summarizes that "in general, there is very little evidence that there are any important differences in the effectiveness or safety of the five PPIs in the general population, or in relevant subgroups."

Several trials looking at symptom relief and endoscopic healing in erosive GERD showed a somewhat greater efficacy for esomeprazole (Nexium) 40 mg daily compared to omeprazole 20 mg daily, but the DERP points out that because of differences in pharmacokinetics, there is no clear dose equivalent of omeprazole and esomeprazole. Thus, dose comparisons between these two drugs are difficult to make. The ACG does not recommend one PPI over another for the treatment of erosive esophagitis, and in fact points out that long-term treatment with PPIs is made cost-effective by the availability of a generic alternative.[27]

Tools and Resources for Point-of-Care Decision-Making for PPIs

For providers:

Drug Effectiveness Review Project Report
• Drug Class Review on Proton Pump Inhibitors Final Report, 2006. http://www.ohsu.edu/drugeffectiveness/reports/documents/PPIs%20Final%20Report%20u4%20Unshaded.pdf
Epocrates Drug and Formulary Information
• Epocrates Online (for information on drug choices and formulary selections) www.epocrates.com

For patients:

Consumer Report Best Buy Drugs
• Treating Heartburn, Acid Reflux, and Ulcers – The PPIs http://www.crbestbuydrugs.org/drugreport_DR_Prop.shtml

3. Selective Serotonin Reuptake Inhibitors (SSRIs):

The Depression CIT was convened by the Alliance in 2006. As part of its task, it examined the value of generic versus brand name-only SSRIs and other second-generation antidepressants (see Depression CIT Final Report[28]). The Rx CIT has reviewed the recommendations made by the Depression CIT on SSRIs and endorses those recommendations, which are repeated here.

[27] DeVault KR et al. Practice Guidelines: Updated guidelines for he diagnosis and treatment of Gastroesophageal reflux disease. Am J. of Gastroenterology, 2005, 100:190-200

[28] The Puget Sound Health Alliance Depression CIT Final Report, November, 2006. Available at: http://www.pugetsoundhealthalliance.org/members/documents/FINAL_DepressionCITReport_Jan_07.pdf Note: Access requires member log-in. Alliance members may contact the Alliance at 206-448-2570 for log-in information.

Recommendations for Patients and Providers:

1. **When prescribing SSRIs for first line therapy, providers should preferentially select a medication for which there is a generic equivalent, such as fluoxetine, paroxetine, sertraline, fluvoxamine or citalopram.**

Background and Evidence:

Definition of SSRIs: Selective Serotonin Reuptake Inhibitors (SSRIs) are a class of drugs used in the treatment of various psychiatric disorders, including major depressive disorder (MDD), generalized anxiety and panic disorders, obsessive compulsive disorder and others. They act by limiting the reuptake by of the neurotransmitter serotonin by presynaptic neurons in the brain.

Prior to the late 1980's the only options for the treatment of MDD and other mood disorders were the "first generation" antidepressants such as tricyclics and monoamine oxidase inhibitors, both classes of drugs with the potential for significant side effects and drug interactions that limited their tolerability in many patients.

The US Food and Drug Administration (FDA) approved the first SSRI, fluoxetine (brand name Prozac) in 1987. Since then, five other SSRIs have been introduced: sertraline (Zoloft, 1991), paroxetine (Paxil, 1992), citalopram (Celexa, 1999), fluvoxamine (Luvox, 2000), and escitalopram (Lexapro, 2002).

The patent on fluoxetine expired in 2001 and the drug became available in generic form. In recent years other SSRIs have also become available as generics, the most recent being sertraline (Zoloft) in 2006. Currently, the only SSRI that is *not* available in generic form is escitalopram (Lexapro).

Comparison of SSRIs: Second-generation antidepressants, including both the SSRIs and SNRIs (Serotonin-Norepinephrine Reuptake Inhibitors), were the third highest selling drug class in 2003. The SSRIs accounted for almost 60% of this market, or over $6 billion in 2003 U.S. sales.

Review of the literature fails to support the superiority of one SSRI antidepressant over another for first-line treatment of depression in randomized controlled trials. The Drug Effectiveness Review Project Drug Class Review on Second-Generation Antidepressants[29] summarizes an extensive review of the literature by stating, "Fifty-five head to head trials compared the effectiveness and efficacy of one SSRI or other second generation antidepressant to another. All studies addressed the initial use of

[29] Oregon Health and Sciences University Drug Effectiveness Review Project (2006): Drug Class Review on Second Generation Antidepressants Final Report. Available at: http://www.ohsu.edu/drugeffectiveness/reports/documents/Antidepressants%20Final%20Report%20Update%202.pdf [accessed online March 2007]

antidepressants. Overall, effectiveness and efficacy were similar and the majority of trials did not identify substantial differences among drugs."

The report adds the caveat, "the only exception is the comparison of citalopram to escitalopram. Four fair-to-good trials indicate consistently that escitalopram has a greater efficacy for the treatment of MDD than citalopram. However, it may be significant that both citalopram and escitalopram are produced by the same manufacturer who has funded all the trails available. Citalopram is available as a generic whereas escitalopram is still patented." The report also notes the second-generation antidepressants may differ in rate of onset of action or side effect profiles, and that there may be individual variation in response to any given agent.

Despite the above findings, however, many providers continue to prescribe brand name only medications for the treatment of depression. Data from the Washington State Department of Social and Health Services (DSHS)[30] indicate that, despite formulary restrictions, nearly 50% of antidepressant prescriptions filled by DSHS clients are for brand name products. The cost-saving potential is significant, and the Rx CIT recommends that providers be encouraged to preferentially select generic antidepressant medication when possible.

The Depression CIT Report, available on the Alliance web site, offers links to evidence-based clinical guidelines on the management of Major Depressive Disorder, including the use of SSRIs.[31]

Tools and Resources for Point of Care Decision-Making for SSRIs

For providers:

Drug Effectiveness Review Project Report
• Drug Class Review on Second-Generation Antidepressants Final Report. September 2006. http://www.ohsu.edu/drugeffectiveness/reports/documents/Antidepressants%20Final%20Report%20Update%202.pdf
Epocrates Drug and Formulary Information
• Epocrates Online (for information on drug choices and formulary selections) www.epocrates.com

For patients:

Consumer Report Best Buy Drugs
• Drugs to Treat Depression: Antidepressants http://www.crbestbuydrugs.org/drugreport_DR_Antideprs.shtml

[30] Dr. Jeffrey Thompson, Medical Director, Washington State Medical Assistance Administration, personal communication, July 17, 2006.
[31] Depression CIT Final Report. 2006. Puget Sound Health Alliance. http://www.pugetsoundhealthalliance.org/members/documents/FINAL_DepressionCITReport_Jan_07.pdf

4. Nonsteroidal Anti-inflammatory Drugs (NSAIDS)

Recommendations for Patients and Providers:

1. **When prescribing NSAIDs, providers should preferentially select low cost generic drugs and avoid COX-2 inhibitors in most patients.**
2. **In patients with coronary heart disease (CHD), or at high risk for the disease, providers should consider naproxen as a drug of first choice, since it is the only NSAID so far shown to not increase the risk of myocardial infarction.**
3. **In patients at low risk for heart disease ibuprofen and other low cost generic and OTC NSAIDs are reasonable cost-effective alternatives.**
4. **In elderly patients and others at risk for GI bleeding, acetaminophen, tramadol, or short-term use of narcotic agents should be considered first-line analgesic options. The COX-2 inhibitors such as celecoxib (Celebrex) may be used cautiously in patients at risk for GI bleeding, but the GI benefit should be carefully weighed against the increased cardiovascular risk. The combination of naproxen and an H2-blocker or PPI may be a safer alternative, although direct comparisons to COX-2 inhibitors are lacking.**
5. **Patient-directed therapy with OTC NSAIDs is appropriate for temporary relief of pain in selected patients. Providers should caution patients at risk for heart disease, GI bleeding and those with renal or hepatic insufficiency against the use of NSAIDs. Long-term use of NSAIDs in any patient should be directed by a healthcare provider.**

Background and Evidence:

Definition: Nonsteroidal anti-inflammatory drugs (NSAIDs) are analgesic agents used commonly for treating musculoskeletal pain and inflammation, such as in arthritis, sports injuries, low back pain, headaches, menstrual cramps and other conditions. Their pain-relieving activity is due to their ability to block the enzyme cyclooxygenase (COX), thereby reducing the production of prostaglandins, which are mediators of pain and inflammation.

COX-1 and COX-2: There are two forms of the COX enzyme, COX-1 and COX-2. COX-2 is found in joints and skeletal muscle and is a mediator of pain and inflammation in those tissues. COX-1 is found in the stomach lining and helps to protect the stomach from acid. Blocking of COX-1 can lead to gastric bleeding, which is a known side effect of the NSAID class of medications.

Most of the NSAIDs on the market are nonselective COX inhibitors, in that they block both COX-1 and COX-2 enzymes to varying degrees. However, in recent years several COX-2 selective agents have been developed and promoted as

decreasing the incidence of GI bleeding due their reduced effect on COX-1. There is currently only one COX-2 inhibitor, celecoxib (brand name Celebrex), available in the U.S. Two other agents, rofecoxib (Vioxx) and valdecoxib (Bextra) were withdrawn from the U.S. market after concerns were raised about the cardiovascular risk they posed to patients. Another COX-2 inhibitor, etoricoxib, is licensed in Europe. The manufacturer, Merck, recently sought approval from the U.S. Food and Drug Administration (FDA) to market it in this country, but that approval was denied.[32] Novartis has plans to seek FDA approval of its COX-2 inhibitor, lumiracoxib.

Cost: The COX-2 inhibitor celecoxib (Celebrex) is the only NSAID that is currently available as a brand-only medication. All other NSAIDs are available as generics. Several of the NSAIDs—ibuprofen, naproxen, and ketoprofen—are also sold as over-the-counter (OTC) products.

Gastrointestinal (GI) side effects: Because of their effect on COX-1, NSAIDs can cause gastritis, ulcers and GI bleeding. The risk of GI bleeding increases with age. In people taking NSAIDs, the one-year risk of serious GI bleeding ranges from 1 in 2,100 in adults under age 45 to 1 in 110 for adults over age 75, and the risk of death ranges from 1 in 12,353 to 1 in 647.[33] Other risk factors include a prior history of peptic ulcer disease or GI bleeding and current anticoagulant use.

The COX-2 inhibitor celecoxib (Celebrex) is associated with a significantly lower incidence of serious GI complications such as perforation, bleeding and strictures than nonselective NSAIDs in short term trials of less than six months. After 12 months, however, similar rates of GI complications were found with celecoxib (Celebrex) and the nonselective NSAIDs ibuprofen and diclofenac.[34]

Misoprostol is the only agent proven to decrease the risk of serious GI side effects associated with NSAIDs, such as perforation, obstruction or bleeding, but its use is limited by its own GI effects of nausea, diarrhea and abdominal pain. Misoprostol, double-dose H2 blockers and proton pump inhibitors (PPIs) have all been shown to reduce the incidence of endoscopically detected gastric

[32] Recently, the FDA declined approval of etoricoxib for the treatment of osteoarthritis based on the recommendations of its Arthritis Advisory Committee, which voted 20 to 1 to decline approval.. See: http://www.ashp.org/s_ashp/article_news.asp?CID=167&DID=2024&id=20021

[33] Drug Effectiveness Review Project Drug Class Review Report on Cyclo-oxygenase (COX)-2 Inhibitors and Non-steroidal Anti-inflammatory Drugs (NSAIDs) , November 2006 Available at: http://www.ohsu.edu/drugeffectiveness/reports/documents/NSAIDS%20Final%20Report%20Update%203.pdf [accessed 3/7/07]

[34] Ibid

and duodenal ulcers associated with nonselective NSAID use.[35] In patients at risk for GI bleeding, it is not known whether the addition of a PPI or double-dose H2 blocker to a nonselective NSAID is a better strategy than the use of a COX-2 selective agent.[36]

Cardiac Toxicity: After rofecoxib (Vioxx) was released onto the market, it became evident that people taking the medication were at increased risk for cardiovascular events, especially myocardial infarction. Similar evidence was found for valdecoxib (Bextra) and celecoxib (Celebrex). The risk for myocardial infarction in patients taking celecoxib (Celebrex) is almost twice that of people not on the drug.[37]
Data on the nonselective NSAIDs ibuprofen and diclofenac suggest that these agents are associated with a similar risk of myocardial infarction as celecoxib (Celebrex). Naproxen is the only NSAID that has been shown *not* to cause an increased incidence of cardiovascular events over placebo.[38] The American Heart Association (AHA) has issued recent guidelines recommending naproxen as the NSAID of first choice in patients with a history of coronary heart disease (CHD) or at high risk for CHD. According to the AHA, COX-2 inhibitors should be the last line of treatment for such patients.[39]

Other side effects: All NSAIDs are associated with an increased risk of hypertension, edema, congestive heart failure, renal toxicity, and rarely, hepatotoxicity. Except for an increased incidence of elevated liver enzymes (but not severe hepatotoxicity) associated with diclofenac, there is no evidence to suggest a differential risk for these side effects among the NSAIDs.

Partially selective NSAIDs: Some NSAIDs (meloxicam, nabumetone, or etodolac) are partially selective for COX-2, but there is no evidence to suggest that they have any clear safety advantages over nonselective agents.

Effectiveness: There is no conclusive evidence to suggest that any one NSAID is more effective than another in terms of pain relief at recommended doses.

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[35] Ibid
[36] AHRQ Effective Health Care Comparative Effectiveness and Safety of Analgesics for Osteoarthritis-Executive Summary . Available at: http://effectivehealthcare.ahrq.gov/repFiles/AnalgesicsExecSum.pdf [accessed online 3-7-07]
[37] Drug Effectiveness Review Project Drug Class Review Report on Cyclo-oxygenase (COX)-2 Inhibitors and Non-steroidal Anti-inflammatory Drugs (NSAIDs), November 2006, and AHRQ Effective Health Care Comparative Effectiveness and Safety of Analgesics for Osteoarthritis-Executive Summary .
[38] Ibid
[39] American Heart Association NSAID Guideline Update 2007. Available at: http://circ.ahajournals.org/cgi/reprint/CIRCULATIONAHA.106.181424 [accessed online 3-4-07].

Tools and Resources for Point of Care Decision-Making for NSAIDs

For providers:

Drug Effectiveness Review Project Report
• NSAIDS Final Report Update #3,November, 2006 http://www.ohsu.edu/drugeffectiveness/reports/documents/NSAIDS%20Final%20Report%20Update%203.pdf
AHRQ Effective Health Care
• Comparative Effectiveness and Safety of Analgesics for Osteoarthritis-Executive Summary http://effectivehealthcare.ahrq.gov/repFiles/AnalgesicsExecSum.pdf • Choosing a Non-opioid Analgesic for Osteoarthritis- Clinical Guide http://effectivehealthcare.ahrq.gov/dsc/products.cfm?product=4&topic=31
American Heart Association
• AHA NSAID Guideline Update 2007: http://circ.ahajournals.org/cgi/reprint/CIRCULATIONAHA.106.181424

For patients:

Consumer Report Best Buy Drugs
• Treating osteoarthritis and pain- the nonsteroidal anti-inflammatory drugs http://www.crbestbuydrugs.org/drugreport_DR_Nsaids2.shtml
AHRQ Effective Health Care
• Choosing pain medicine for osteoarthritis- Consumer Report http://effectivehealthcare.ahrq.gov/dsc/products.cfm?product=3&topic=31

B. Baseline Data on Generic Fill Rates in the Puget Sound Region

One goal of the Rx CIT and the Puget Sound Health Alliance is to increase the prescription rates of high-value medications in each of four drug classes selected in Phase I of the CIT's work:[40] statins, PPIs, SSRIs, and NSAIDs. The Rx CIT defines high-value medications as those that are effective, safe, and cost-effective. As the above detailed discussion of each of the four classes of drugs indicates, within each class there are safe and effective generic options available that provide cost-effective alternatives to brand-name drugs for the majority of patients. The Rx CIT therefore recommends the preferential prescribing of generic statins, PPIs, NSAIDs, and SSRIs whenever possible.

[40] Rx CIT Phase I Final Report. 2005. Available at: http://www.pugetsoundhealthalliance.org/members/documents/RxClinicalImprovementTeam.pdf Accessed through a site for members only. Members of the Alliance may contact Sean McCliment (sean@putgetsoundhealthalliance.org) for log-in information. [accessed 5-22-07]

In the fall of 2006, the QIC supported a proposal from the Rx CIT that included both a short-term approach and longer-term approach to measuring savings associated with increased use of generic drugs. The longer-term approach, not addressed here, involves using the Milliman MedInsight data warehouse/decision support system to conduct more detailed analyses on the actual paid claims data for prescription drugs from all participating data suppliers. Alliance public reporting of generic fill rates at the county level from the Milliman data analysis is expected by late 2007.

The short-term approach was intended to help the group describe the opportunity around increased generic prescribing. The Alliance staff undertook a data-gathering project to identify the current generic fill rates (GFRs) of these drugs in the five-county area served by the Alliance. Staff requested data from health plans participating in the Alliance – and the larger self-funded employers and union trusts – in the form of summary statistics aggregated by county and by quarter for each therapeutic class, beginning with the first quarter 2004 and continuing through the fourth quarter of 2006. The data collected included:

- Total number of prescription fills (total number of paid claims).
- Total allowed cost (total member paid + total plan paid).
- Number of generic prescription fills (total number of generic paid claims). "Generic" is defined by how the claim was processed.
- Total allowed costs for generic prescriptions.
- Number of brand prescription fills. "Brand" is defined by how the claim was processed.
- Total allowed costs for brand prescriptions.

The following interim analysis was performed by Kerri Petrin, Alliance research analyst, and was presented to the Rx CIT on April 4, 2007. The detailed analysis is found in Appendix 3. Briefly, generic fill rates were calculated by dividing the number of generic scripts by the total number of scripts. Cost savings were estimated using the difference between the average brand name cost and the average generic cost (in the fourth quarter of 2006) multiplied by the number of percentage points required to reach the target generic fill rate. As specified above, it should be noted that the health plans submitted data aggregated by brand status within each of the therapeutic classes. This leaves open the possibility that the drug lists may differ in substantial ways across plans (i.e. whether Vytorin was included in the statins category) and, as discussed below, may partly account for the wide range in GFRs seen across plans. The data and findings presented here were not meant to be a definitive analysis of generic prescribing practices in the Puget Sound Region, but rather an approximation that would allow for a rough estimate of potential cost savings. It should also be noted that the data collection was completed well after the start of Phase II of the Rx CIT, so the CIT's selection of drug classes was not able to be informed by these findings.

The data presented in Appendix 3 indicates that there is greater opportunity for improvement in generic fill rates in some classes of drugs than in others. However, even in those classes in which generic fill rates appear high, such as NSAIDs and SSRIs, there is ongoing opportunity for educating providers and patients on the value of generic drugs. The Rx CIT made specific recommendations and established recommended target GFRs for each class based on its review of the data presented.

1. Statins:

---For all plans/data---	
Q42006 average generic fill rate across plans	44%
Range across plans	24-89%
Change from Q1 2004-Q4 2006	24 → 44%
---For plans that included Vytorin---	
Q42006 average generic fill rate across plans	27%
Range across plans	24-29%
Change from Q1 2004-Q4 2006	7 → 27%
Rx CIT suggested 5 yr target generic fill rate	**75%**
Potential for improvement	48 percentage points
Estimated cost savings per percentage point increase in GFR	$641,062
Estimated annual regional savings if target GFR reached (with Vytorin included) [41]	**$30.8 million**

Discussion:

When looking at the data from all plans, the range of generic fill rates for this class of medications was wide (ranging from a low of 24% to a high of 89%), making meaningful conclusions difficult. The Rx CIT speculated that one reason for this wide range may have been a discrepancy in whether the combination medication Vytorin (simvastatin/ezetimibe) was included as a brand name drug in this class—a potentially significant confounder, as Vytorin has a significant market share among the statins (estimated at 7.5% in 2005 by one source).[42] Further information was obtained from plans as to whether or not they had included Vytorin in the data they supplied.

Briefly, two participating plans included Vytorin as a brand-name statin and four did not. The Rx CIT recommends that Vytorin be included in future analysis in the long-term Alliance project on generic fill rates. The CIT members further recommended using only the data submitted by plans that included Vytorin for the financial calculations presented here. These plans constituted the majority (59%) of prescriptions used in this analysis. The

[41] Vytorin™ (simvastatin/ezetimibe) is a combination medication containing a statin that some plans included in their calculations, while others did not.
[42] Vytorin outsells rival cholesterol drugs; CNNMoney.com, July 26, 2005. Available at: http://money.cnn.com/2005/07/26/news/fortune500/vytorin/index.htm [accessed 4/4/07]

average GFR for plans that included Vytorin was 27% in Q4 2006, compared to 69% for those that did not. This discrepancy emphasizes the significant market share of Vytorin in this class.

It was recognized that not all statins are equivalent in their potency, and that some patients will require a higher potency medication to reach target LDL levels. Therefore the Rx CIT felt that a conservative target generic fill rate of 75% was a reasonable expectation. That goal may be an overly conservative estimate, however, as the patent of the high-potency Lipitor is due to expire in 2010, at which point a generic version of the drug is likely to become available, thus further widening the therapeutic options of generics in this class

The Rx CIT also felt that further research into the percentage of patients who reach target LDL goals, as well as the number of patients on low-dose high-potency brand name statins who could reasonably be switched to a generic medication with equivalent effect, would be useful.

Recommendation:
The Alliance should include Vytorin as a brand name drug in the statin class when gathering data on generic fill rates.

2. Proton Pump Inhibitors (PPIs)

Q42006 average generic fill rate across plans	52%
Range across plans	3-82%
Change from Q1 2004-Q4 2006	20 → 52%
Rx CIT suggested 5 yr target generic fill rate	**95%***
Potential for improvement	43 percentage points
Estimated cost savings per percentage point increase in GFR	$842, 068
Estimated annual regional savings if target GFR reached	**$36.2 million**

*Target estimate assumes that the PPIs lansoprazole (Prevacid) and pantoprazole (Protonix) are available as generics within five years

Discussion:

In the PPI class, the availability of omeprazole as both an over-the-counter (OTC) product and as a generic medication confounds the data, since plans treat the OTC product differently. Some plans cover OTC omeprazole in Tier 1, some plans do not cover OTC products but place generic omeprazole in Tier 1, and some plans require prior authorization for any prescription PPI, including generic omeprazole, to encourage the use of the OTC product. The range for generic fill rates for PPIs across all plans was 3-82%, with the 3% low value coming from a plan corresponding to the latter scenario, with a prior authorization requirement for all prescription PPIs.

The outlying 3% fill rate notwithstanding, the range in generic fill rates for PPIs remained very wide (28-82%), with an average GFR of 52%. The wide range likely reflects the use of OTC products, which may or may not be included in the denominator and numerator depending on a plan's formulary structure, and highlights one of the difficulties in measuring generic fill rates in this class of medications. Because plans with the lowest generic fill rates are also likely to have low numbers of total prescriptions for PPIs (and higher use of OTC products), this issue will be less of a confounder when total data across plans is aggregated by the third-party vendor Milliman. The Rx CIT recommends that the data for PPIs be normalized to help account for the use of OTC products by calculating the number of brand name and generic prescriptions written on a per-member per-month basis. This is based on the assumption that plans whose benefit designs encourage the use of OTC products would have total fewer prescriptions per member per month.

Review of the literature suggests that generic omeprazole is as effective as brand name products in almost all studies. However, it was recognized that differing individual side-effect profiles limit the ability to shift to the generic product for some patients. The aggressive five-year target range of 95% was selected on the basis of there being other generic options available, particularly once lansoprazole (Prevacid) and pantoprazole (Protonix) go off patent in coming years. If only a single generic option remains available, the Rx CIT felt the maximum target generic fill rate would more realistically be in the 85-89%.

Recommendation: As the Alliance develops a metric to measure the generic fill rate of PPIs in the Puget Sound region, attention should be paid to how OTC products are handled by plans and how this might affect the generic fill rate both within and across plans. This might be handled by normalizing the data across plans by dividing the number of prescriptions per member per month.

3. Selective Serotonin Reuptake Inhibitors (SSRIs)

Q42006 average generic fill rate across plans	83%
Range across plans	74-97%
Change from Q1 2004-Q4 2006	43 → 83%
Rx CIT suggested 5 yr target generic fill rate	**90%**
Potential for improvement	7 percentage points
Estimated cost savings per percentage point increase in GFR	$716, 737
Estimated annual regional savings if target GFR reached	**$5.0 million**

Discussion:

In the SSRI class, escitalopram (Lexapro) is the only product currently not available in generic form. However, it is generally accepted that there is more individual variation in tolerability and efficacy with antidepressants than with many other classes of drugs. This means that providers are reluctant to switch a patient from an SSRI that has been found to be effective. Thus, the opportunity for moving to a generic option in this class exists primarily with the treatment of patients who have not taken or not had success with a prior brand name product. Over a five-year time frame, it is hoped that most new prescriptions would be for generics, and that the GFR would trend upward, but at a rate somewhat slower than for other classes of drugs. A more conservative five-year target generic fill rate of 90% (rather than the 95% for PPIs, for example) was selected as a realistic goal in this class, even with only a single brand-name product remaining in the class.

When reviewing the data for SSRIs, the Rx CIT agreed that more useful data on GFRs would be obtained by examining not just SSRIs, but all second-generation antidepressants, such as SNRIs (Serotonin-Norepinephrine Reuptake Inhibitors) and bupropion (Wellbutrin™), since these agents have significant market penetration and compete for market share with SSRIs in the treatment of depression.

Recommendation: The Alliance should include all second-generation antidepressants (SSRIs, SNRIs and others) when calculating generic fill rates.

4. Nonsteroidal Anti-inflammatory Drugs (NSAIDs)

Q42006 average generic fill rate across plans	90%
Range across plans	81-99%
Change from Q1 2004-Q4 2006	78 → 90%
Rx CIT suggested 5 yr target generic fill rate	**94%**
Potential for improvement	4 percentage points
Estimated cost savings per percentage point increase in GFR	$346, 985
Estimated annual regional savings if target GFR reached	**$1.4 million**

Discussion:

The generic fill rate for NSAIDs as a class is already high in the Puget Sound Region. The range of 81%-99% leaves more room for improvement for some plans than others. It should be noted that the existence of various OTC NSAID products may skew the data somewhat, as plans treat the OTC products differently on their formularies.

There is currently only one brand-name only product in the NSAID class, the COX-2 inhibitor celecoxib (Celebrex). The Rx CIT emphasizes that the risk-benefit ratio of COX-2 inhibitors make them poor choices for many patients, especially those at risk for cardiovascular disease, and thus should constitute a minor share of the NSAID market. As there is another COX-2 inhibitor currently going through the FDA-approval process, this message should be reinforced as new agents become available.

Conclusions:

The potential savings if recommended target generic fill rates for these four classes of drugs are reached is over **$73 million** annually in the five-county Puget Sound region.

The greatest opportunity for cost savings is within the statin and PPI classes; particular efforts should be made to educate providers and patients on the availability of generic options for these drugs.

The generic fill rate of NSAIDs is currently very high in the Puget Sound region, but that could change as new agents come on the market. It is important to continue to emphasize that COX-2 inhibitors should be the drugs of first choice in only a minority of patients, if any, and that their risk-benefit profile is not favorable for the vast majority of patients requiring an NSAID.

Likewise, the generic fill rate of SSRIs is high in this region, but an examination of the broader category of second-generation antidepressants would likely demonstrate a greater opportunity for improvement.

Recommendations to improve the overall generic fill rate by using performance measurement and reporting:

- **During year one of performance reporting, publicly report generic fill rates at the county level (in four classes of drugs). Report individual provider results to medical groups to encourage increased generic prescribing.**

  After one year of performance reporting generic fill rates at the county level, re-visit whether it is appropriate to begin publicly reporting medical group level performance.
- **Every one to two years, re-visit the generic fill rate targets and recommendations regarding drugs of first choice to consider revising the recommendations based on current performance and changes in drugs available generically in these four classes of drugs.**

- **Publicly report the total generic fill rate (for all classes of drugs) at the county level. After one year of performance reporting, re-visit whether it is appropriate to begin publicly reporting medical group level performance for the total generic fill rate (for all classes of drugs).**

C. Creating a Supportive Community Environment for Change

The purpose of the Alliance is to not only encourage regional consistency on point-of-care issues, such as clinical performance measures and prescribing practices, but also to act as a catalyst to affect change and improve the quality of healthcare services delivered in the Puget Sound Region. After developing goals and recommendations for stakeholders *at the point of care*, i.e. for patients and providers, the Rx CIT's next challenge was to identify and recommend strategies to change behaviors of the stakeholders in the community represented by the Alliance to support improvements in cost-effective prescribing practices. The key community stakeholders, in addition to the Alliance, were identified as:

- Plans (Health Plans, Insurance Groups)
- Pharmacy Benefit Managers (PBMs)
- Purchasers (Employers, state purchasing agencies, union trusts)

The Alliance is committed to evidence-based decision-making and the recommendations for quality improvement at the point of care are based on the best available evidence. However, there is less research available on supportive practices by community stakeholders. In the discussion to follow, the Rx CIT has cited evidence when it exists, but has also used the opinions and advice of national and local experts in crafting recommendations for community stakeholders.

1. The Alliance

Goals for the Alliance:

- Serve as a catalyst for evidence-based quality improvement efforts in prescribing practices involving all stakeholders
- Publicly report clinical performance data to enhance transparency
- Provide resources to providers, patients, purchasers and plans that support high value prescribing practices and reduce prescribing variation in the Puget Sound region.

Recommendations for the Alliance:

- Initiate public reporting of generic fill rates for statins, PPIs, second-generation antidepressants and NSAIDs at the county level for the five counties served by the Alliance.
- Provide information and educational materials to providers regarding the cost-effectiveness, safety, and appropriateness of generic options when prescribing statins, PPIs, SSRIs, and NSAIDs.
    - Information is provided in this report, which will be available on the Alliance web site
    - The Communication Committee will prepare one-page information sheets on each class of drug discussed in this report for providers
- Provide educational material for patients
    - The Alliance will prepare consumer-friendly educations materials on each class of drug designed for patients
- Provide educational materials for employers
    - The Alliance will provide educational materials and resources for small-, medium- and large-sized employers to aid them in understanding and selecting prescription drug benefits for their employees (see also Purchasers for more detail on resources)
- Convene Pharmacy and Therapeutic Committee leaders from around the region to share best practice strategies, tools, and tips on formulary design in an effort to foster regional collaboration around prescription drug benefits.
- Promote a standardized approach within physician practices to monitor chronic disease medication fill rates. Draw from examples of standard, brief questionnaires that can be used during patient visits to assess adherence.
- Work with plans and employers to evaluate and use mail order refill services for chronic disease medications if the plan design offers lower total co-pays for employees/dependents (e.g., co-pay less for 90-day refill than for three separate 30-day refills).

2. Plans

Goals for Plans:

- Provide incentives to patients to choose the highest value medications
- Provide support and/or incentives to providers to look for high-value, cost-effective and safe alternatives for their patients when prescribing common medications

Recommendations for Plans:

- Plan benefit design (patient incentives)
  - It is recommended that plans develop a tiered co-pay system and/or other system of patient incentives to encourage the preferential use of medications for which there is a generic equivalent in the four classes of drugs discussed.
    - Highest value medications, such as generics, should be placed on Tier 1
    - The differential cost to the patient between brand name and generic medication in a tiered co-pay system must be significant in order for the incentive to be effective. It is suggested that a price differential between brand and generic of $20 per month is a minimum requirement to affect behavior.[43]
  - Plans should consider imposing the requirement that there be a minimum number, such as one or two, trials of a generic medication at adequate dose and duration prior to allowing coverage for a brand name medication, regardless of whether or not a patient has a tiered co-pay drug benefit.
- Retail pharmacy reimbursement for services beyond dispensing
  - Consider reimbursement to retail pharmacies for phone calls or faxes to providers with the specific purpose of pointing out generic alternatives when brand-name-only drugs are prescribed.
- Plan/PBM feedback to providers
  - Plans could provide "counter detailing" educational services to providers on specific classes of drugs, including the value of generic medications in these classes.
  - Pharmacy Benefits Managers (PBMs) could provide timely information to providers when non-generic medication is prescribed, with information on generic alternatives.

Tools and Resources for Plans:

Counter detailing
Independent Drug Information Service: www.rxfacts.org

[43] Dr. SuAnn Stone, Director, Pharmacy Services, Regence BlueShield, personal communication, July 17, 2006

3. Purchasers

Goals for Purchasers:

- Understand prescription drug pricing and make appropriate contracting decisions based on that knowledge
- Develop strategies to encourage high value purchasing of prescription drugs by health plans and PBMs
- Make optimal cost-effective prescription drug coverage available to employees

Recommendations for Purchasers:

- Understand prescription drug benefits and pricing in order to choose the most appropriate and cost-effective plans for employees
    - The National Business Coalition on Health (NBCH) has published a guide on prescription drug benefits for employers entitled, "An Employer's Guide to Pharmaceutical Benefits."[44] The guide presents detailed information on formulary design, engaging employees, choosing and managing a PBM, and other topics. The RX CIT recommends this guide as a resource to employers. The Employers Guide to Pharmaceutical Benefits outlines three key elements of pharmaceutical drug plans:
        1. Design incentives:
            - Cost sharing (e.g. co-payments, other out-of-pocket costs); tiered co-payments; generic substitution; incentives or requirements (e.g. mail-order prescriptions); therapeutic substitution
        2. Formulary-based strategies (see table below):
            - Preferred drug lists; prior authorization requirements; formulary "Must Haves" and "Maybes" (outlined in the table below)
        3. Clinical Interventions
            - Disease management

      Each of these items is an important component of a prescription drug benefit option, but no one package of benefits is ideal for all employers. It is important for employers to understand these components so that they can tailor their prescription drug plans to the specific needs of their employees. However, the Rx CIT members point out that multiple custom benefit designs are expensive, and encourages employers to adhere to certain standard plans when selecting prescription drug benefit contracts.

[44] National Business Coalition on Health (NBCH) Employer's Guide to Pharmaceutical Benefits. Available at: http://www.nbch.org/documents/guide_pharm_benefits.pdf [Accessed 3/25/07].

FORMULARY "MUST HAVES" AND MAYBES

Although companies do not determine what drugs are placed on the formulary, it is important for employers to ensure that plans and PBMs have a solid process in *place to select preferred drugs and to keep members informed about which medications are on the preferred list.*

Must haves:
•Drugs recommended in clinical guidelines issued by government agencies and medical societies for prevention and treatment;
•Evidence-based decisions on drug placement;
•A sufficient selection of drugs in each therapeutic class;
•Productivity concerns considered in decisions on drug placement;
•A process for appeals and patient/clinician notification of denial;
•Clinicians making formulary decisions.

Maybes:
•A policy based on CDC recommendations for the appropriate use of antibiotics;
•Out-of-pocket payments covering the full cost differential for branded drugs with generic equivalents;
•A step therapy approach for products whose main benefit is relief from relatively rare side effects;
•A tiered co-pay or reference pricing system that places new products with minimal differences from older drugs on the top tier.

Adapted from National Business Coalition's "Employer's Guide to Pharmaceutical Benefits"[45]

- Obtain information on working with brokers to purchase employee health plans that most effectively meet the needs and expectations of the company and its employees. This is especially important for small and mid-size companies
  - The Alliance will prepare a list of questions to ask brokers when negotiating prescription drug benefit plans so that the plan meets the need of the individual employer and their employees.
- Understand PBM pricing of pharmaceuticals
  - PBM pricing transparency should be encouraged by purchasers when they are contracting for prescription drug benefits. Purchasers must understand the mechanisms of PBM pricing in order to most effectively negotiate PBM contracts that transfer savings to the purchaser and employees.
  - Health care purchasers and some health plans contract with Pharmacy Benefit Managers (PBMs) to manage their prescription benefits. In order to compare different PBM offerings, purchasers typically send out a request for proposal

[45] National Business Coalition on Health (NBCH) Employer's Guide to Pharmaceutical Benefits. Available at: http://www.nbch.org/documents/guide_pharm_benefits.pdf [Accessed 3/25/07].

(RFP). However, when comparing RFPs, it is important to understand exactly what information is included and how that information relates to a purchaser's goals and objectives, including the actual pricing of prescription medications.

- Requests for proposal (RFP) today typically compare the following:
  - Average Wholesale Price (AWP) discounts
  - Dispensing Fees
  - Rebate guarantees
  - Pricing trends
  - Administration (and other) Fees
  - Performance Guarantees
- It is important for purchasers to understand how each of these items effects prescription drug prices, and how they interact. The Alliance staff is preparing a handout on the subject for employers (pending on website). Further information can also be found in the National Business Coalition on Health Employer's Guide to Pharmaceutical Benefits.

Tools and resources for purchasers:

Educational Resources
National Business Coalition on Health (NBCH) Employer's Guide to Pharmaceutical Benefits. http://www.nbch.org/documents/guide_pharm_benefits.pdf

V. Increasing Patient Adherence to Medications for Chronic Disease

One of the challenges identified in Phase I of the Rx CIT was ensuring that patients follow medication treatment recommendations, especially those for chronic diseases. According to the National Quality Forum, "[p]rescription medication non-adherence is a major barrier to patients fully realizing the benefits of modern medical research."[46] Improving patient adherence to medications is an important component of quality improvement in healthcare.

There is clear and mounting evidence that adherence to treatment improves outcomes for a variety of chronic diseases. In one study with patients who had

[46] National Quality Forum: Improving Use of Prescription Medications: A National Action Plan http://www.qualityforum.org/projects/completed/medications.asp

suffered a myocardial infarction (MI), adherence to statins and beta-blockers was associated with a significant reduction in mortality compared to poor adherence.[47] In another study, the PREMIER trial, at one month post discharge following an MI only 66% of patients were taking aspirin, beta-blockers and statins as prescribed. Twelve percent had discontinued all three medications. This latter group was shown to have 3.8 times all-cause mortality at one year than those using at least one medication at one-month post discharge.[48] In a study of diabetic patients, 21% were deemed to have less than 80% adherence to oral hypoglycemic, antihypertensive and statin medications. Medication non-adherence in this study was associated with an increased risk for all-cause hospitalization and mortality.[49] The Institute of Clinical Systems Improvement cites evidence in their guidelines on depression showing that there was an increased incidence of recurrence of Major Depressive Disorder in patients who did not continue their medications for the prescribed period of time, even if they felt better at the time of discontinuation[50]. Recent NCQA HEDIS data shows that only 60% of patients received and continued antidepressants during the 12-week acute phase of treatment for a new episode of depression, and as few as 44% of patients remained on antidepressants for at least six months following diagnosis.[51] Similarly, in Washington State, the Department of Social and Health Services' pharmacy data indicates that only 45% of clients with depression remained on antidepressant medication longer than 12 weeks and a similar number remained on medication for six months.[52]

These results indicate that medication non-adherence is a common problem that is associated with a significant increase in disease burden and mortality.

Medication non-adherence is a multi-factorial problem. Reasons for non-adherence vary from one patient to the next. Many patients experience a combination of factors that impede their ability to adhere to medications as prescribed. Such barriers to adherence may include:

[47] Rasmussen JN et al. Relationship between adherence to evidence-based pharmacotherapy and long-term mortality after acute myocardial infarction. JAMA 2007; 297(2): 177-185.
[48] Ho PM. Impact of medication therapy discontinuation on mortality after myocardial infarction. Arch Intern Med. 2006. 166:1842-7.
[49] Ho PM. Effect of medication non-adherence on hospitalization and mortality among patients with diabetes mellitus. Arch Intern Med 2006; 166:1836-41.
[50] Institute for Clinical Systems Improvement (Minnesota): Depression Major, Adults in Primary Care 2004 http://www.icsi.org/knowledge/detail.asp?catID=29&itemID=180 [accessed online 5/16/06]
[51] National Committee for Quality Assurance, State of Health Care Quality Report 2005. Available at: http://www.ncqa.org/Docs/SOHCQ_2005.pdf [accessed online June, 2006]
[52] Dr. Jeff Thompson, Medical Director, Washington State Medical Assistance Administration, personal communication, July 17, 2006.

1. Patient factors

   E.g. Cognitive or language difficulties, physical barriers, forgetfulness or disorganization, lack of motivation, cultural issues, adverse effects of medication

2. Doctor-patient relationship factors

   E.g. Poor communication, discordant models of disease between patient and provider, lack of trust in the relationship, lack of appropriate follow-up

3. Extraneous factors

   E.g. Financial barriers, pharmacy benefit design, poor information flow

The above list is not all-inclusive, but highlights some of the more common barriers to medication adherence. It is beyond the scope of the Rx CIT to develop strategies to tackle all causes of poor medication adherence. Specifically, barriers such as language, cognitive difficulties, or culturally diverse models of disease will not be the focus of this discussion, although their importance is well recognized. Rather, the following discussion and recommendations focus on practical suggestions for improving medication adherence by identifying tools, incentives and resources for patients and providers that utilize the strengths of the Alliance and its member stakeholders.

A. Recommendations at the Point of Care

Goals for Providers:

- Communicate medication and follow-up instructions clearly to patients
- Understand and recognize poor adherence patterns in patients
- Partner with patients when prescribing medications to maximize the chance of adherence, taking into account patients' beliefs, preferences, financial constraints and physical and cognitive limitations.

Recommendations for providers:

- Recognize and discuss barriers to medication adherence with patients
  - The National Quality Forum's 2004 report, *Improving Medication Adherence: National Action Plan*[53] makes the recommendation that providers develop a set of practices to increase medication adherence among their patients. These include:

[53] National Quality Forum: Improving Use of Prescription Medications: A National Action Plan http://www.qualityforum.org/projects/completed/medications.asp [accessed online 3/24/07]

  - Facilitating care coordination by improving the exchange of information
  - Improving written and verbal communication
  - Routinely assessing patient adherence at each visit
  - Providing tools that enable patients to take charge of their own care
  - Addressing poor adherence resulting from cost/access issues
- The Rx CIT recommends the NQF's *National Action Plan* as a useful framework for providers when thinking about ways to improve medication adherence in their patients. Some of the items from the report will be discussed in more detail below.

- Reconcile medication lists at each visit
  - Encourage patients to bring up-to-date lists of medications and/or a "brown bag" collection of all their medication bottles to each visit, and reconcile these with the medication list in the patient's chart or electronic health record (EHR).
  - Reconcile medication lists between both providers and patients at points of transfer of care, such as at hospital discharge or transfer to long-term care facility, when confusion over new or discontinued medications can lead to poor adherence to recommended treatment.
- Identify patient adherence patterns through information exchange
  - Information exchange between providers and Pharmacy Benefit Managers (PBMs) or retail pharmacies can help identify problems with patient adherence.
    - Several examples of medication information exchange exist in the Puget Sound Region. For practices that have EHR capability, products such as OneHealthPort Mix[54] provide mechanisms by which clinicians and hospitals can access their patient's medication history and pharmacy benefit information at the point of care through their EHRs by connecting to Rx HUB. The information that can be obtained includes detailed information about the medications a patient has had filled or refilled through their health plan for the past year.
    - For practices contemplating the purchase of an EHR, the Rx CIT recommends that they consider purchasing systems that have the capability to interact with databases such as Rx HUB.

[54] OneHealthPort Medication Information Exchange (MIX) program http://www.onehealthport.com/services/clinical_tools_mix.php [accessed online 3/38/07]

- Institute regular follow-up for patients prescribed chronic medications
    - A recent study of patients in British Columbia, Canada who were prescribed a statin showed that patients tend to have many periods of non-adherence when taking long-term medications. Getting patients back on their medication regimen is an important component of quality of care. In the study, return to adherence with the prescribed course of statin therapy was strongly associated with a follow-up visit by the physician who wrote the original prescription (OR, odds ratio, 6.1). Other strong predictors of return to adherence were a visit with another physician (OR 2.9), having a cholesterol test (OR 1.5), having a heart attack (OR 12.2) or hospitalization for other cardiovascular causes (OR 3.6).[55] These results highlight the importance of both regular physician follow-up and taking advantage of teachable moments in improving long-term adherence to medications.
    - Follow-up can occur in person, by email, or by telephone, depending on the condition being treated and the nature of the follow-up. Sometimes, for example, the follow-up could consist of a reminder to have laboratory tests done, or a brief inquiry into how a patient is tolerating their medication.
        - In order to facilitate follow-up, the Rx CIT encourages health plans to consider reimbursement for email or telephone encounters. Such reimbursement could encourage provider utilization of non-traditional encounters that can be more convenient for patients, in turn driving compliance.
        - An example cited by the Rx CIT in the Puget Sound Region is the collaboration between Microsoft and Premera to reimburse providers for email consultation with patients.
        - Group Health Cooperative has an interactive web site that allows for confidential communication between patients and providers.[56] The capitated staff model HMO system of Group Health means that separate reimbursement for such services is not required.
            - Other examples of online follow-up tools exist across the country, including Relay Health, an online tool for patients, including the option for private online consultation with providers.[57]

[55] Brookhart et al. Physician Follow-up and provider continuity are associated with long-term medication adherence: A Study of the dynamics of statin use. Arch. Int. Med. 2007. 167: 847-852
[56] Group Health Cooperative. My Group Health Demo. http://www.ghc.org/ and Goverman IL. Orienting health care information systems toward quality: How Group Health Cooperative of Puget Sound Did It. Jt Comm J Qual Improv. 1994 Nov;20 (11):595-605. cited in, http://www.azdoqit.com/resources/EHR_Systems_Selection_Resources.pdf
[57] Relay Health: https://www.relayhealth.com/rh/default.aspx .and https://www.relayhealth.com/rh/general/onlineQuickTour/default.aspx

- Address financial barriers by prescribing the most cost-effective treatments that are appropriate to each patient.
    - Studies show that prescribing lower-cost medications such as generics or preferred medications on a patient's health plan formulary will improve adherence to therapy, since the barrier of cost is reduced.[58]
    - Providers should prescribe generic medications whenever appropriate, and be knowledgeable about the costs of medications they prescribe.
    - Information on health plan prescription drug formularies is available on Epocrates Online and is downloadable into PDA format.[59]

Tools and Resources for Providers

National Quality Forum: Improving Use of Prescription Medications: A National Action Plan http://www.qualityforum.org/projects/completed/medications.asp
OneHealthPort: Mix (Medication Information Exchange). http://www.onehealthport.com/pdf/MIX_prescribing_providers.pdf
Epocrates Online www.epocrates.com

Goals for Patients:

- Take prescription medications as prescribed by your healthcare provider
- Be a knowledgeable consumer of prescription medications
- Be an active participant in healthcare decision-making- stay informed, engaged, and interactive
- Inform your healthcare provider when you are having difficulty adhering to an agreed-upon treatment plan

Recommendations for Patients:

- Reconcile medications at each visit with a healthcare provider
    - Bring all medications and/or an updated list of medications to all visits with a healthcare provider, including emergency room visits.
    - Make sure a member of your healthcare team reviews your medications and records them in your chart at each visit.

Patient Site: Personal health website (Beth Israel Deaconess Hospital, Boston). https://www.patientsite.org

[58] Shrenk H et al. The Implications of Choice: Prescribing Generic or Preferred Pharmaceuticals Improves Medication Adherence for Chronic Conditions. Annals of Internal Medicine, 2006. 166(3):332-337. Available at: http://archinte.ama-assn.org/cgi/content/full/166/3/332 [Accessed 3/26/07]

[59] Epocrates Online. www.epocrates.com

- Inform your healthcare provider if you are having trouble taking your medications because of:
    - Cost
    - Side effects
    - Too many pills to keep track of or forgetfulness
    - Unclear instructions
    - Any other problems

  Several tools and resources exist to aid patients in understanding and identifying problems with medication adherence. One example is a program set up by GlaxoSmithKline consisting of an interactive web site and other materials called ASK (Adherence Starts with Knowledge)[60].
- Ask your pharmacist for compliance packaging if you are taking more than a few pills a day.
    - Compliance packaging is an aid to keeping track of scheduled medications. One example is called "bingo cards," or blister packs, in which a large card with clear plastic blisters is prepared for each week. It is divided into dosing times (e.g. am, lunch, dinner, pm) for each day, and allows for easy visualization of which pills have been taken and which are due next.
        - Some pharmacists will also fill Medisets, or pill boxes, that have pills for each day's dosing time in a separate compartment. Medisets are in common use in long-term care and other residential facilities, but their increased use in the ambulatory setting is encouraged by the Rx CIT. In some cases, it is appropriate for a patient or a member of the patient's family to fill weekly Medisets.
        - The Rx CIT recommends that pharmacists be reimbursed by plans for providing compliance packaging.
        - Medisets should be reimbursed for any patient who requires more than four pills per day.
- Sign up for refill reminders from your Pharmacy Benefit Manager (PBM)
    - Many PBMs provide refill reminders upon request. Such reminders are sent to patients prior to their medications running out.
    - Currently, most such reminder programs are optional. The Rx CIT recommends that such reminders be provided to all patients, requiring an "opt out" to withdraw, rather than the current "opt in" system.

[60] Adherence Starts With Knowledge. www.adherencestartswithknowledge.com

Resources for Patients:

ASK: Adherence Starts With Knowledge (GlaxoSmithKline) www.adherencestartswithknowledge.com

B. Strategies to Create a Supportive Community Environment for Change

Plans, PBMs and purchasers can support efforts by patients and providers to improve adherence to medications for chronic disease by addressing some of the extraneous barriers to adherence such as financial barriers, pharmacy benefit design and lack of shared information. The Rx CIT selected cost, information exchange, and medication therapy management as areas of focus. Recommendations will be made for specific stakeholders, including purchasers, plans, PBMs and pharmacies at the end of each discussion.

1. Cost:

The high cost of many prescription medications is often a significant barrier to achieving optimal adherence to medications for chronic disease. However, there is evidence to suggest that lowering medication costs can actually improve disease outcomes. A number of organizations have looked at cost as a barrier to medication adherence.

A recent study by the RAND Corporation found that reducing co-payments for patients on cholesterol-lowering medication lowered the rates of hospitalizations (357 fewer hospitalizations annually per 1,000 high-risk patients) because these patients were more likely to fully comply with their doctors' orders to take their medication.[61]

The employer Pitney-Bowes achieved lower total healthcare costs for employees with chronic diseases such as diabetes, asthma and hypertension, by restructuring their pharmacy benefits. The following is an excerpt from an article that appeared in American Journal of Managed Care in April 2007 on the Pitney Bowes experience:

> "Pitney Bowes commissioned an analysis to identify population-based risk factors associated with high-cost health benefit utilization (>$10,000) per year. A major conclusion of this analysis was that disease burden and costs were associated with a lack of

[61] DP Goldman, GF Joyce, and P Karaca-Mandic, "Varying Pharmacy Benefits with Clinical Status: The Case of Cholesterol-lowering Therapy," *The American Journal of Managed Care*, Vol. 12, No. 1, January 2006, pp. 21–28 Cited in: Cutting Drug Co-Payments for Sicker Patients on Cholesterol-Lowering Drugs Could Save a Billion Dollars Every Year Available at: http://www.rand.org/pubs/research_briefs/2006/RAND_RB9169.pdf [accessed 5-11-07]

adherence to pharmacotherapy. For example, patients with diabetes with 9 or fewer 30-day prescription refills for diabetic medications during the year were more likely to enter the high-cost group. Similar observations were made for other chronic conditions, including asthma and hypertension. Before this analysis, Pitney Bowes utilized a standard 3-tier drug benefit plan, in which generic drugs had a 10% coinsurance payment, preferred drugs had a 30% coinsurance payment, and non-preferred brand name drugs required a 50% coinsurance payment.

On the basis of their findings on the impact of poor medication adherence, Pitney Bowes radically redesigned this tiered structure to remove possible financial impediments to medication availability for people with chronic conditions. In the new system, all medications for asthma, diabetes, and hypertension were moved to tier 1 with 10% coinsurance. Anti-diabetic drugs that were affected by this change included several insulin analogs, glimepiride, pioglitazone, rosiglitazone, and single-pill combination oral therapies. Blood glucose testing supplies were also moved to tier 1.For the typical plan participant with diabetes, the average cost of a 30-day prescription decreased by 50%. For many participants, drug costs were reduced by 80%, reflecting the difference between a 50% coinsurance payment and a 10% payment.

Outcome assessments indicated that rates of adherence to diabetes medications increased significantly in response to the change in pharmacy benefits. Suboptimal adherence to insulin therapy decreased by two thirds, and usage of blood glucose meter test strips increased from 28% to 55%. The percentage of members adhering to single-pill combination oral anti-diabetic agents showed particularly impressive increases, with usage of this group of drugs increasing from 9% to 22%.

In response to this shift, the company's total annual pharmacy costs per person increased slightly, from about $26 per month to $35 per month. However, pharmacy costs for individuals with diabetes actually decreased by 7%. Diabetes-related emergency department visit rates also decreased, as did diabetes-associated disability. Overall, the average annual increase in employee health cost from 2000 to 2003 at Pitney Bowes was 8.1% compared with increases of 12% to 15% at benchmark companies."[62]

[62] Berger J. Economic and Clinical Impact of Innovative Pharmacy Benefit Designs in the Management of Diabetes Pharmacotherapy. American Journal of Managed Care. April,2007. http://www.ajmc.com/files/articlefiles/A169_07april_Berger_S55toS58.pdf [accessed 4-30-07]

Pitney Bowes has recently added anti-seizure medications, prenatal supplements, osteoporosis treatments and statins to their lists of drugs available in Tier 1, and other companies have followed suit. Employers such as Marriott, Procter & Gamble and Eastman Chemical Co. have reduced or eliminated co-payments for drugs for certain chronic conditions, such as heart disease, diabetes, and asthma.[63]

A 2004 Rand Corporation study on healthcare benefit design from more than 30 employers and 52 commercial health plans showed that co-payments can have a large effect on use of prescription drugs. "Doubling patients' co-payments for drugs can reduce their use of the most common classes of medications by 25 to 45 percent. The patients most sensitive to price changes are those who are taking medications but are not receiving regular care for their conditions [emphasizing that regular follow-up improves care]. Even the chronically ill who are receiving routine care cut their drug use between eight percent and 23 percent when their co-payments are doubled".[64] In another study on cholesterol lowering drugs, researchers at Rand Corp. estimated that for each $10 rise in the co-payment, average compliance falls by five percentage points.[65] The same study showed that partial compliance or noncompliance resulted in greater use of expensive medical services, such as hospitalizations and emergency departments. The report further suggested that the greatest cost savings could be had by eliminating co-payments for the highest risk patients, such as those who have had a heart attack, while charging low ($10-20) co-payments for lower-risk patients, such as those with elevated cholesterol but no known cardiovascular disease.

Based on these and other studies it is clear that cost is a barrier to adherence for many patients on chronic medications. The Rx CIT recommended several strategies for purchasers and health plans to address the issue of cost.

Goals for Purchasers and Health Plans:

- Recognize that cost is a barrier to compliance with medications for chronic disease, and that decreased compliance, especially among high-risk patients, leads to greater overall health expenditures.
- Develop mechanisms to limit out-of-pocket costs to patients for medications for chronic disease.

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[63] Vanessa Furhmans. New Tack on Copays: Cutting Them. The Wall Street Journal. May 8, 2007. Available at: http://articles.news.aol.com/business/_a/new-tack-on-copays-cutting-them/20070508112509990016 [accessed 5-11-07]

[64] Goldman DP et al, Pharmacy Benefits and the Use of Drugs by the Chronically Ill, Journal of the American Medical Association, Vol. 291, No. 19, May 18, 2004, pp. 2344–2350. Cited in : Fact Sheet: How Cost-sharing affects use of drugs by the chronically ill. Available at: http://www.rand.org/pubs/research_briefs/RB9109/index1.html [accessed 5-11-07].

[65] DP Goldman, GF Joyce, and P Karaca-Mandic, "Varying Pharmacy Benefits with Clinical Status: The Case of Cholesterol-lowering Therapy," *The American Journal of Managed Care*, Vol. 12, No. 1, January 2006, pp. 21–28 Cited in: Cutting Drug Co-Payments for Sicker Patients on Cholesterol-Lowering Drugs Could Save a Billion Dollars Every Year http://www.rand.org/pubs/research_briefs/RB9169/index1.html [accessed 5-11-07]

Recommendations to Purchasers and Health Plans:

- Reduce or eliminate co-payments for *medically necessary* medications for patients with chronic diseases.
    - The CIT recognizes the success of programs such as that instituted at Pitney Bowes, in which all medications for certain conditions are moved into Tier I, with low or no co-pays. However, this does not take into account evidence for drug effectiveness and value, as discussed in detail in the first section of this report. In general, the Rx CIT recommends the preferential use of high value medications with proven efficacy in quality clinical trials. In the four classes of drugs discussed- statins, PPIs, NSAIDs and SSRIs- generic drugs provided the highest value for the majority of patients.
    - The Rx CIT recommends a step-therapy approach to pharmacy benefit design
        - In order to be eligible for the lowest co-payment on a medication, a patient would be required to start with a proven drug in Tier 1, such as a generic medication. The patient could then be switched to a higher cost drug if the generic options fail or are not tolerated. If a higher cost drug is found to be medically necessary for a given patient, the co-payment for that drug would be equivalent to that for a Tier 1 drug.
        - The step edits in this design could be automated in many cases, easing the burden on providers and patients. For example, if a patient had been on a generic Angiotensin Converting Enzyme Inhibitor (ACE-I) for six months, and then received a prescription for an Angiotensin Receptor Blocker (ARB), presumably indicating the ACEI was not tolerated, the automated system would automatically assign the lower co-payment to the new brand name ARB.

2. Information Exchange: Pharmacy Data

Pharmacy benefit managers (PBMs) collect and process prescription data with a rapid turn-around compared to claims data, and are therefore a potential source of timely feedback to providers on medication adherence patterns of patients.

As an example, The Washington Business Group on Health's (now the National Business Group on Health) Linking Pharmacy and Mental Health Benefits Project (2002)[66] collected data from PBM representatives on prescribing patterns for antidepressants.

[66] Washington Business Group on Health's Linking Pharmacy and Mental Health Benefits Project http://www.businessgrouphealth.org/pdfs/mentalhealthfinal.pdf [accessed online 3/24/07]

> " One PBM's data showed that 50% of antidepressant use was for single prescriptions only, while another's found that only 22% of those being treated by a primary care physician fill more than one prescription." The average number of days of antidepressant use for patients receiving a prescription for an antidepressant from a primary care physician was approximately 45 to 60 days [while guidelines for depression care indicate a minimum treatment duration of 9 to 12 months for a first episode of depression, and longer for subsequent episodes[67]]. Clearly, there is room for improvement in adherence to antidepressant treatment regimens, and the WBGH suggested that PBMs could play a role in improving adherence by providing feedback to providers. "Currently, the PBMs do not collect data on physician follow-up for prescriptions of antidepressants, although they do have the capacity to profile physician-prescribing behavior and to send reminders regarding follow-up or other related treatment matters." [68]

The NQF recommends integrating pharmacy data systems with electronic reminder systems, so that a standard system for reminding patients to refill their medications can be implemented at the PBM level.[69]

Goals for PBMs and Retail Pharmacies:

- Assist providers and patients in improving adherence to medications by providing timely information on patterns of adherence and refill reminders.

Recommendations to PBMs and Retail Pharmacies:

- Implement a refill reminder system to patients and providers.
    - An example of such a program is through the PBM Caremark. Caremark provides monthly reports to both providers and patients when a patient misses a refill.
        - In addition to their standard compliance services, Caremark also offers a comprehensive Adherence to Care program to client health plans and purchasers. This program is based on evidence that multifaceted and targeted interventions are more effective in improving adherence than are nonspecific interventions. It focuses on improving adherence to medications for certain chronic conditions, such as diabetes, asthma, hypertension, elevated cholesterol and heart failure. The program utilizes a targeted and

[67] Institute for Clinical Systems Improvement (Minnesota): Depression Major, Adults in Primary Care 2004 http://www.icsi.org/knowledge/detail.asp?catID=29&itemID=180 [accessed online 5/16/06]
[68] Washington Business Group on Health's Linking Pharmacy and Mental Health Benefits Project http://www.businessgrouphealth.org/pdfs/mentalhealthfinal.pdf
[69] National Quality Forum: Improving Use of Prescription Medications: A National Action Plan http://www.qualityforum.org/projects/completed/medications.asp

personalized approach based on individual member responses to a survey. The survey results, in combination with claims data, prior utilization patterns, prescriber identification, demographic data and U.S. census data, drive specific interventions via systematic triggers. The content of the interventions vary, based upon patient specifics such as health literacy, stage of change, and perceived reasons for non-adherence. The interventions are tailored to patients' individual needs and may include reminder letters, emails, PDA messaging, faxes, web-based materials, telephone calls, or interactive voice response systems. Other activities are provided to patients and providers to enhance adherence, including counseling services, planning and tracking tools, onsite visits, enhanced mailings, and others.

- In addition to such targeted approaches, the Rx CIT also recommends providing medication report cards to all patients and their providers on a monthly or quarterly basis. The patient should be encouraged to bring the report card to any provider visit.
- Retail pharmacists could also play a role in providing information back to providers.
  - For example, when a patient does not pick up a prescription that has been called or faxed by a provider a “reverse claim” is generated. Pharmacists could be encouraged, through a financial incentive, to contact providers when a reverse claim is generated (see also Medication Therapy Management services discussed below).
- Information on patient adherence patterns should be relayed to providers in a clear, concise and useable way.
  - The Rx CIT recognizes that in busy practices, providers require information that is easy to visualize and utilize at the point of care. One mechanism would be to color-code medications in a list provided either electronically or manually as red, yellow or green, for the respective identification of when a patient is fully compliant with their medication instructions, partially compliant, or has not refilled a medication.

Goals for Plans and Purchasers:

- Support information exchange between PBMs or retail pharmacies and providers.

Recommendations to Plans and Purchasers:

- Contract with PBMs to provide programs to increase medication adherence among plan participants with chronic diseases.
- Reimburse retail pharmacies for contacting providers when a patient fails to refill a medication.

3. Medication Therapy Management: Aligning Incentives.

The Medicare Modernization Act of 2003 includes Medication Therapy Management (MTM) services as an important component of the "Part D" prescription drug benefit for Medicare beneficiaries. Pharmacies that offer the Part D benefit are now required to incorporate MTM services into the benefit structure. This requirement has highlighted the role of pharmacists in improving patient understanding of and adherence to their medication regimens.

MTM services, sometimes called a pharmacy care services, have been defined as "a distinct service or group of services [provided by pharmacists] that optimize therapeutic outcomes for individual patients"[70] by the Pharmacist Provider Coalition. The Coalition notes that "neither we, nor many private insurers, have extensive experience requiring or reimbursing [MTM services]."[71] The details of implementing MTM or pharmacy care services in the community remain a challenge.

The Federal Study of Adherence to Medications in the Elderly (FAME) Trial[72] enrolled 200 elderly community-based patients of the Walter Reed Army Medical Center, with active cardiovascular risk factors, in a study of the effects of a comprehensive pharmacy care program. Patients received six months of intervention, which included standardized medication education, regular follow-up with pharmacists, and medications dispensed in compliance packaging (time-specific blister packs). After the six months, patients were then randomized to continue the pharmacy care program, or to standard care. In the first six-month period, medication adherence increased from 61.2% at baseline to 96.9%. In follow-up, compliance decreased to 69.1% in the usual care group, but was sustained at 95.5% in the pharmacy care group. In addition, there were significant sustained reductions in blood pressure in the pharmacy care group compared to the usual care group, although this was not seen with lipid levels.

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[70] Pharmacy Profession Stakeholders Consensus Document, July 7, 2004. Included in: Webb CE. Medication Therapy Management- Ready for Prime Time. American Association of Colleges of Pharmacy. Available at www.accp.com/report.rpt0804/art06.pdf

[71] Ibid.

[72] Lee JK et al. Effect of a pharmacy care program on medication adherence and persistence, blood pressure, and low-density lipoprotein cholesterol. JAMA 20065. 296 (21): 2563-2571.

The Asheville Project. One of the most well known examples of a pharmaceutical care program is the Asheville Project. In 1997, the city of Asheville, NC, concerned with the rising cost of prescription drugs for city employees, collaborated with the North Carolina Center for Pharmaceutical Care (NCCPC) to initiate a demonstration project on a novel approach to medication management for diabetic patients. Other employers joined the demonstration, which formally ended in 2001. However, the principles of the project continue, and the ongoing program has expanded to include asthma, hypertension and hyperlipidemia[73],

The Asheville Project provided prescription drug coverage for diabetic patients in conjunction with MTM services provided by local pharmacists, in collaboration with providers. Patients received free diabetic medications and supplies if they actively participated in the program, involving individual consultations with trained pharmacists. To be eligible to participate in the program, pharmacists were required to undergo 32 hours of training sponsored by the NCCPC. In return, they received fee-for-service reimbursement from participating employers (mean reimbursement for visit $27.40).[74]

The program showed favorable outcomes, with the majority of participating patients showing improved glycosylated hemoglobin and lipid levels over baseline, and at each follow-up visit. Total pharmaceutical costs per patient increased over time, but total direct annual health care costs decreased from $7,250 per employee per year at baseline to $4,679 by year 5.[75] In addition, one employer had an average reduction of 41% in sick days for program participants, and an estimated savings of $18,000 per year for increased productivity of program participants.

Both the FAME Trial and the Asheville project indicate that pharmacists can play an important role in increasing medication adherence among community-based patients. The role of motivated employers or purchasers is essential to the success of such programs. Other notable components of the Asheville Project that contributed to its success were that pharmacists received special training, patient incentives in terms of waived co-payments were aligned with the project's goals, and pharmacists received reimbursement for their services. The Rx CIT emphasized the importance of providing financial incentives to patients or employees for participation in the program.

[73] An Innovative Approach to Employee Diabetes Management: How the Asheville Model adds a valuable link to the diabetes care delivery chain. Sanofi-aventis monograph., provided courtesy David McCaughey, sanofi-aventis. Information available from www.sanofi-aventis.com.
[74] Ibid
[75] Ibid, and Cranor, CW. The Asheville Project: Long-Term Clinical and Economic Outcomes of a Community Pharmacy Diabetes Care Program. J Am Pharm Assoc. 2003;43:173–84. Available at: http://www.ncpharmacists.org/associations/4188/files/NCCPCfour.pdf

Goals for Purchasers and Health Plans:

- Align patient incentives with participation in programs designed to improve medication adherence
- Engage all members of the health care team in improving medication adherence by appropriate reimbursement policies.

Recommendations for Purchasers and Plans:

- Consider instituting and reimbursing Medication Management (MTM) services by pharmacists for employees or members with certain chronic diseases, such as diabetes, heart disease, asthma and hypertension.
    - The Rx CIT recommends that important elements be included in the implementation MTM or pharmacy care programs. These include:
        - Appropriate training and credentialing of participating pharmacists
        - Appropriate reimbursement of pharmacist MTM services
        - Alignment of patient incentives, such as reduced co-payments for medications for their disease, with participation in the program
    - In the Puget Sound region, King County initiated a MTM program for its 25,000 employees and health plan members January 1, 2007, contracting with Iowa-based Outcomes Pharmaceutical Healthcare to provide a full menu of face-to-face MTM services.[76] The covered services include prescriber consultations (i.e. formulary- or drug-related problems), patient compliance consultations, patient education and monitoring, and comprehensive medication reviews. Pharmacist reimbursement for such services ranges from $10 to $50 per encounter, depending on the service. Training is required for pharmacists to participate in the program, and is provided free of charge by the Washington State Pharmacists Association in conjunction with Outcomes Pharmaceutical Healthcare. The program is too young to have outcomes data yet available, but Outcomes guarantees that employers will save the entire cost of the program through avoided expenses for pharmaceuticals, medical and hospital care, or Outcomes will refund the difference at the end of the fiscal year.[77]
    - Washington State pharmacists may also bill for MTM services through Medicare Part D programs such as Community Care Rx, via CommunityMTM and Humana Medicare Part D.

[76] Washington State Pharmacist Association: King County Employees. http://www.wsparx.org/File/ProfessionalDevelopment/MTM/mtmkingcounty.asp

[77] Strategies to Improve Compensation for Pharmaceutical Care Services, from Journal of the American Pharmaceutical Association. Exploring New Markets for Pharmaceutical Care http://www.medscape.com/viewarticle/406704_4

- Provide financial incentives to patients who participate in programs designed to improve adherence.
    - One of the lessons from the Asheville Project was that the financial benefits of waived co-payments for medications and supplies were a powerful motivator of patient participation. This principle can be applied not only to pharmacy care programs, but also to other programs or activities that can improve patient compliance.
        - Examples include paying patients who commit to regular follow-up with their provider, monitor their blood sugar level regularly at home, take home blood pressure readings, complete the requisite number of lab tests, etc.
        - An example of a successful patient incentive program is King County Employee's Healthy Incentives[78], in which employees receive premium reductions for completing a health risk assessment and taking appropriate follow-up steps.

Goals for Retail Pharmacists:

- Become active members of the healthcare team through training and involvement in providing MTM services

Recommendations for Retail Pharmacists:

- Obtain training and credentialing in MTM and other pharmacy care services.

Tools and Resources for Pharmacists

The National Association of Chain Drugstores Foundation: Medication Therapy Management Resources http://www.nacdsfoundation.org/wmspage.cfm?parm1=789
Washington State Pharmacist Association Healthwise Pharmacist Network http://www.wsparx.org/File/ProfessionalDevelopment/pdmtm.asp

[78] King County Healthy Incentives Program. http://www.metrokc.gov/employees/HealthyIncentives/default.aspx

Appendix 1: Original Alliance Proposal for Clinical Performance Measures for Generic Fill Rates [79]

Generic Drugs	
What will be compared?	*Actual Clinical Measure*
Percentage of patients prescribed a generic drug, rather than certain categories of brand-name drugs, to reduce cholesterol.	Percentage of patients who were given a generic when prescribed a statin medication
Percentage of patients prescribed a generic drug, rather than certain categories of brand-name drugs, to treat depression.	Percentage of patients who were given a generic when prescribed SSRIs (selective serotonin reuptake inhibitors).
Percentage of patients prescribed a generic drug, rather than certain categories of brand-name drugs, to treat heartburn or gastric acid reflux.	Percentage of patients who were given a generic when prescribed PPIs (proton pump inhibitors).
Percentage of patients prescribed a generic drug, rather than certain categories of brand-name drugs, for pain relief.	Percentage of patients who were given a generic when prescribed NSAIDs (non-steroidal anti-inflammatory drugs).

[79] Note: These are draft measures, currently undergoing review by the Health Information Team. The measures in generic fill rates will be reported on a county-wide basis. The full set of the Puget Sound Health Alliance's Proposed Clinical Performance Measures Set from 2007 can be found at: http://www.pugetsoundhealthalliance.org/ProposedApproachMeasures.html#Recommended [accessed online 3-26-07]

Appendix 2: Op-Ed from the Alliance on Generic Preference

The Everett Herald, April 1, 2007

THE RIGHT STEP FOR PRESCRIPTION DRUGS

By Margaret Stanley, Puget Sound Health Alliance; Hugh Straley, MD, Group Health; and John Verrilli, MD, Minor & James Medical

Recent news coverage of health plans' requirement that patients try less expensive generic drugs before covering more expensive, brand-name prescription drugs, might leave reasonable people concerned.

Don't be.

A variety of prescription drugs are available to treat many conditions. More generics than ever before are now available, and that number is growing as patents for brand-name drugs expire. Manufacturers are producing a wider choice of generic drugs that doctors can prescribe for their patients. And doctors agree that choosing the right drug isn't a "one size fits all" proposition.

Yet, in the absence of a contraindication for any specific patient, common sense (and volumes of scientific evidence) suggest it's best to start with proven drugs that are effective for the vast majority of people. Beyond that prerequisite, there's no point in stepping up to more expensive brand-name drugs, unless a doctor determines it's in the best interest of the patient.

This step-by-step process is the foundation not only of prescribing drugs, but of all medicine. "When you hear hoof beats," young med students are taught from day one, "don't start by looking for zebras."

Neither should doctors look first to the newest or most heavily advertised drugs to treat things like high cholesterol. With prescription drugs, "new" does not necessarily mean better. Sometimes, it means "worse" (remember Vioxx?). Often, the most heavily advertised drugs are no better for most patients than those with long track records of safety and efficacy.

Generally, the most significant difference between well-known brand-name drugs and their generic counterparts is their price. For the vast majority of patients seeking to lower cholesterol, the relatively small differences in formulations between generic and brand-name statin drugs aren't usually sufficient to warrant paying two, three, or ten times as much for the one whose patents have not yet expired.

Importantly, for those patients for whom a higher-priced, brand-name drug does make medical sense, there are alternatives. Many insurers will allow coverage for this "next step" when a doctor concludes it's medically necessary to serve the patient. And even when coverage isn't available, options are.

Public skepticism—perhaps a throwback to the days when managing cost meant limiting access to drugs, doctors and care—is understandable but unwarranted. Those dark days have given way to more enlightened approaches grounded in scientifically-based medicine, quality improvement and patient engagement.

Old suspicions may die hard, especially amid multi-billion-dollar advertising campaigns by pharmaceutical companies, but before dismissing your doctor's recommendation of a generic drug, consider the following.

The Food and Drug Administration recognizes generics as a safe and smart option. Every single generic drug that reaches the U.S. market passes the same rigorous safety and efficacy review and approval processes as any brand-name drug.

The Puget Sound Health Alliance, comprised of more than 140 physician, consumer, hospital, employer, insurer and other groups, strongly supports the use of generics as drugs of first choice when appropriate for individual patients. Such diverse organizations don't always agree on contentious issues, but on this one, there is strong support.

Most of our region's highly regarded physicians and medical experts concur. Working with the Alliance, they'll be part of a forthcoming effort to help patients see the value in generics as a smart choice for good health and for more affordable care.

Common sense says resist the temptation to believe what you see or hear in advertising or to assume that a brand-name drug means a "better" drug.

In the final analysis, your choice is between scientifically demonstrated results that can also make health care more affordable for you, and the persuasive claims of well-financed drug marketing campaigns.

When you consider whom to trust, remember that education is the strongest medicine, and common sense the best prescription.

Margaret Stanley, is the Executive Director of the Puget Sound Health Alliance

Hugh Straley, MD is Medical Director of Group Health Cooperative and Vice Chair of the Puget Sound Health Alliance Board

John Verrilli, MD, is an Internist at Minor & James Medical and Chief of Medicine at Swedish Medical Center, First Hill and a member of the Alliance's Clinical Improvement Team on Pharmaceuticals

Appendix 3: Generic Fill Rates in the Five-County Puget Sound Region by Quarter 2004-2006

In the fall of 2006, the QIC supported a proposal from the Rx CIT that included both a short term approach and longer term approach to measuring savings associated with increased use of generic drugs. The short term approach included collection and reporting of summary statistics by county from health plans and the larger self-funded employers and union trusts on: (1) total number of prescriptions, (2) total payments, (3) number of generic prescriptions, and (4) total payments for generic prescriptions. (The longer term approach, not addressed here, involves using the Milliman MedInsight database to conduct more detailed analyses on the actual paid claims data for prescription drugs from all participating data suppliers.) See below for further detail on the project's rationale and preliminary conclusions. Also, please refer to the attached spreadsheet for detail on the results of the inquiry.

Overarching goal of the request:

- The members of the Puget Sound Health Alliance collaborate to increase the generic fill rate in certain classes of drugs (statins, SSRIs, PPIs, and NSAIDs) over time to reduce the costs of prescription drugs in the Puget Sound area

Purpose of measuring the generic fill rate:

- Measuring and reporting the generic fill rate at a macro level will show us:
    1. What is our baseline measure of generic fill rate?
    2. What room for improvement do we have for increasing the generic fill rate for certain types of drugs?
    3. What are the potential savings associated with reaching a certain level for generic fill rate?

Activities that support the data request:

- In 2007, the members of the Alliance are ramping up efforts to promote generics -- through a more direct educational campaign aimed at patients, practices, and others.
- The members of the Alliance continue to participate in specific initiatives – both collectively and individually – aimed at increasing the generic fill rate.

Information requested:

The Alliance requested pharmacy data from major health plans in the Puget Sound region. The request was sent with the instructions "The measures should include total book of business, limited to members age 64 and below, excluding Medicare and Medicaid." A spreadsheet (county to zip code cross-walk) accompanied both data requests.

Participating plans:

- Aetna
- Premera
- Regence
- UMP-HCA
- Group Health
- Molina

Together, the plans represent more than 1.9 million covered

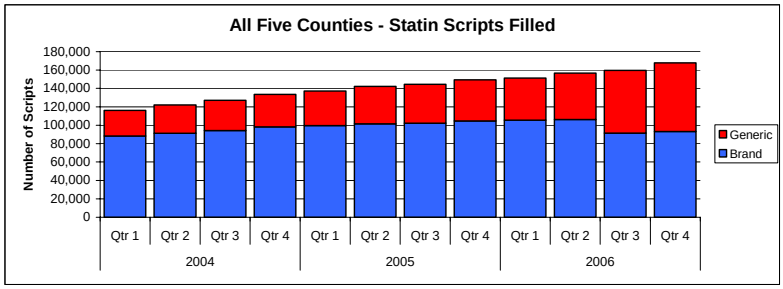
Data Summary:

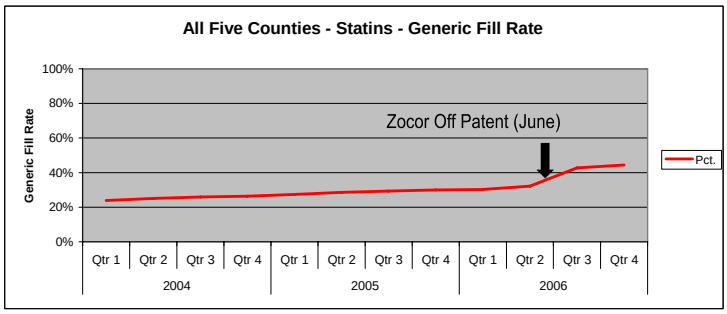
1. Summary: Statins, PPIs, NSAIDs, SSRIs
2. Statins- Vytorin breakout
3. Trends, Range and Opportunity
4. Cost Savings
5. Population Estimates

Statins

Scripts

		Brand	Generic	Total	Pct.
2004	Qtr 1	88,299	27,672	115,971	24%
	Qtr 2	91,341	30,718	122,059	25%
	Qtr 3	94,131	33,028	127,159	26%
	Qtr 4	98,207	35,252	133,459	26%
2005	Qtr 1	99,593	37,583	137,176	27%
	Qtr 2	101,471	40,653	142,124	29%
	Qtr 3	102,212	42,360	144,572	29%
	Qtr 4	104,633	44,737	149,370	30%
2006	Qtr 1	105,537	45,848	151,385	30%
	Qtr 2	106,139	50,575	156,714	32%
	Qtr 3	91,487	68,222	159,709	43%
	Qtr 4	93,289	74,481	167,770	44%





Assumptions:

Overall number of scripts (prescribing rate) will remain at Q4 2006 levels.
Price difference between generic and brand will remain at Q4 2006 levels.

Projections for 2007:

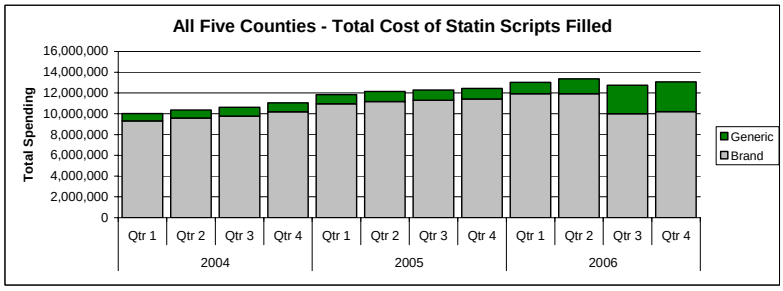
	Total Scripts	Current # Generics	If 1%* Increase	Difference	Cost Savings
Qtr 1	167,770	74,481	76,159	1,678	$119,281
Qtr 2	167,770	74,481	76,159	1,678	$119,281
Qtr 3	167,770	74,481	76,159	1,678	$119,281
Qtr 4	167,770	74,481	76,159	1,678	$119,281

Projected Savings: **$477,124**

* 1% is shorthand for one percentage point

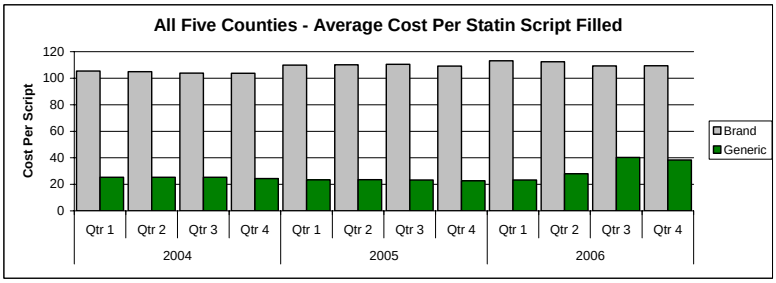
Total Cost

		Brand	Generic	Total	Pct.
2004	Qtr 1	9,318,983	700,809	10,019,792	7%
	Qtr 2	9,580,435	777,560	10,357,995	8%
	Qtr 3	9,781,401	833,400	10,614,801	8%
	Qtr 4	10,191,180	859,344	11,050,524	8%
2005	Qtr 1	10,951,362	880,436	11,831,798	7%
	Qtr 2	11,183,624	956,285	12,139,908	8%
	Qtr 3	11,296,677	986,040	12,282,717	8%
	Qtr 4	11,418,026	1,018,291	12,436,317	8%
2006	Qtr 1	11,939,538	1,068,723	13,008,261	8%
	Qtr 2	11,944,057	1,413,829	13,357,887	11%
	Qtr 3	10,000,953	2,746,216	12,747,169	22%
	Qtr 4	10,208,761	2,855,123	13,063,884	22%



Cost Per Script

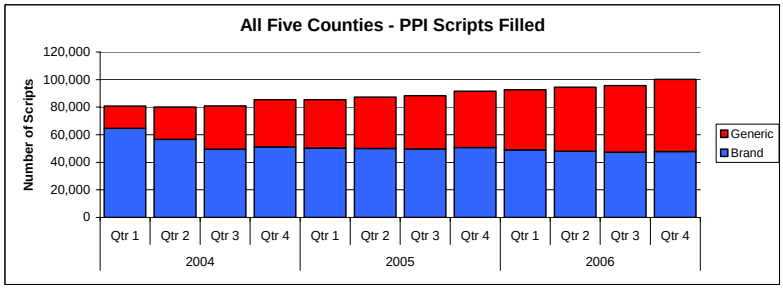
		Brand	Generic	Savings	Gen Pct.
2004	Qtr 1	105.54	25.33	80.21	24%
	Qtr 2	104.89	25.31	79.57	24%
	Qtr 3	103.91	25.23	78.68	24%
	Qtr 4	103.77	24.38	79.40	23%
2005	Qtr 1	109.96	23.43	86.53	21%
	Qtr 2	110.21	23.52	86.69	21%
	Qtr 3	110.52	23.28	87.24	21%
	Qtr 4	109.12	22.76	86.36	21%
2006	Qtr 1	113.13	23.31	89.82	21%
	Qtr 2	112.53	27.96	84.58	25%
	Qtr 3	109.32	40.25	69.06	37%
	Qtr 4	109.43	38.33	71.10	35%

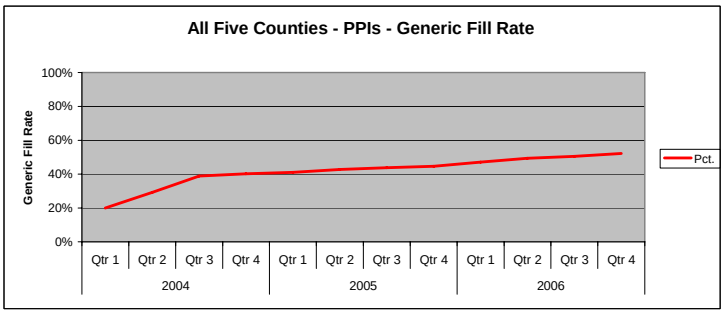


PPIs

Scripts

		Brand	Generic	Total	Pct.
2004	Qtr 1	64,627	16,182	80,809	20%
	Qtr 2	56,604	23,466	80,070	29%
	Qtr 3	49,559	31,423	80,982	39%
	Qtr 4	51,167	34,362	85,529	40%
2005	Qtr 1	50,341	35,072	85,413	41%
	Qtr 2	49,999	37,297	87,296	43%
	Qtr 3	49,603	38,708	88,311	44%
	Qtr 4	50,685	40,869	91,554	45%
2006	Qtr 1	49,053	43,508	92,561	47%
	Qtr 2	47,921	46,665	94,586	49%
	Qtr 3	47,363	48,273	95,636	50%
	Qtr 4	47,894	52,363	100,257	52%





Assumptions:
Overall number of scripts (prescribing rate) will remain at Q4 2006 levels.
Price difference between generic and brand will remain at Q4 2006 levels.

Projections for 2007:

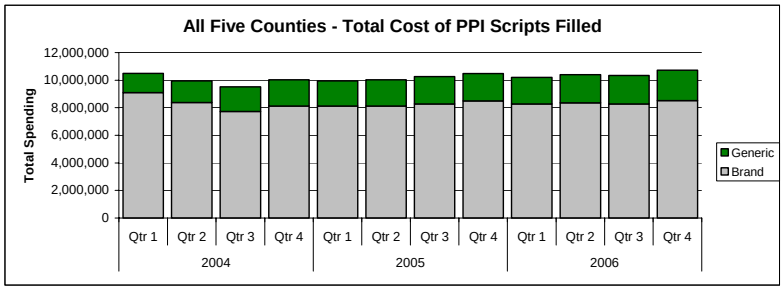
	Total Scripts	Current # Generics	If 1%* Increase	Difference	Cost Savings
Qtr 1	100,257	52,363	53,366	1,003	$135,994
Qtr 2	100,257	52,363	53,366	1,003	$135,994
Qtr 3	100,257	52,363	53,366	1,003	$135,994
Qtr 4	100,257	52,363	53,366	1,003	$135,994

Projected Savings: **$543,976**

* 1% is shorthand for one percentage point

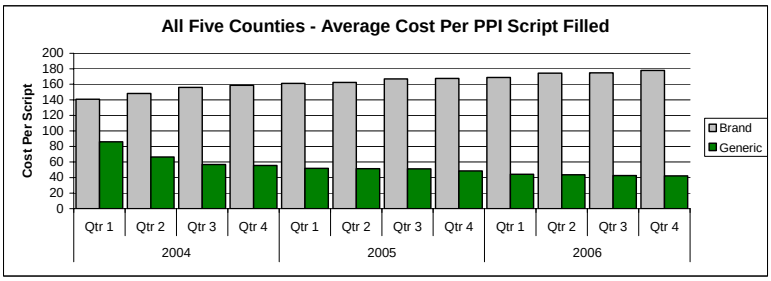
Total Cost

		Brand	Generic	Total	Pct.
2004	Qtr 1	9,107,989	1,390,579	10,498,568	13%
	Qtr 2	8,380,300	1,562,630	9,942,930	16%
	Qtr 3	7,726,658	1,790,378	9,517,036	19%
	Qtr 4	8,125,257	1,909,847	10,035,104	19%
2005	Qtr 1	8,118,030	1,820,270	9,938,299	18%
	Qtr 2	8,121,479	1,916,370	10,037,848	19%
	Qtr 3	8,278,009	1,983,952	10,261,961	19%
	Qtr 4	8,500,379	1,982,586	10,482,965	19%
2006	Qtr 1	8,279,535	1,929,492	10,209,028	19%
	Qtr 2	8,356,874	2,036,925	10,393,799	20%
	Qtr 3	8,274,440	2,064,335	10,338,775	20%
	Qtr 4	8,521,586	2,213,942	10,735,528	21%



Cost Per Script

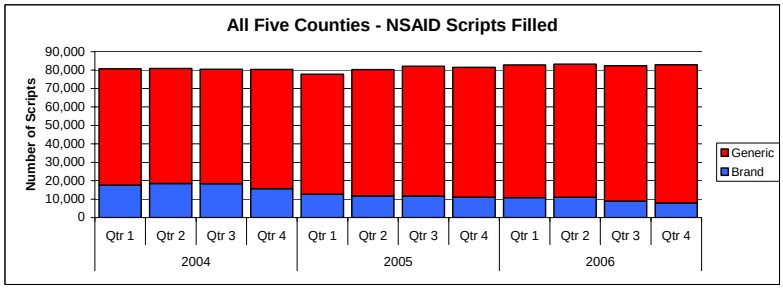
		Brand	Generic	Savings	Pct.
2004	Qtr 1	140.93	85.93	55.00	61%
	Qtr 2	148.05	66.59	81.46	45%
	Qtr 3	155.91	56.98	98.93	37%
	Qtr 4	158.80	55.58	103.22	35%
2005	Qtr 1	161.26	51.90	109.36	32%
	Qtr 2	162.43	51.38	111.05	32%
	Qtr 3	166.89	51.25	115.63	31%
	Qtr 4	167.71	48.51	119.20	29%
2006	Qtr 1	168.79	44.35	124.44	26%
	Qtr 2	174.39	43.65	130.74	25%
	Qtr 3	174.70	42.76	131.94	24%
	Qtr 4	177.93	42.28	135.65	24%

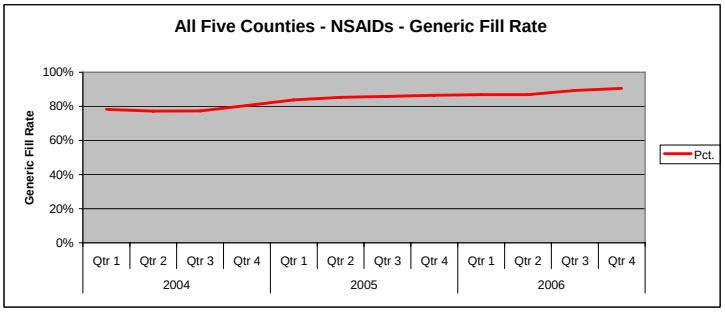


NSAIDs

Scripts

		Brand	Generic	Total	Pct.
2004	Qtr 1	17,631	63,094	80,725	78%
	Qtr 2	18,453	62,446	80,899	77%
	Qtr 3	18,324	62,103	80,427	77%
	Qtr 4	15,661	64,699	80,360	81%
2005	Qtr 1	12,637	65,057	77,694	84%
	Qtr 2	11,841	68,412	80,253	85%
	Qtr 3	11,685	70,353	82,038	86%
	Qtr 4	11,098	70,402	81,500	86%
2006	Qtr 1	10,844	71,858	82,702	87%
	Qtr 2	10,981	72,204	83,185	87%
	Qtr 3	8,857	73,470	82,327	89%
	Qtr 4	7,882	74,990	82,872	90%





Assumptions:
Overall number of scripts (prescribing rate) will remain at Q4 2006 levels.
Price difference between generic and brand will remain at Q4 2006 levels.

Projections for 2007:

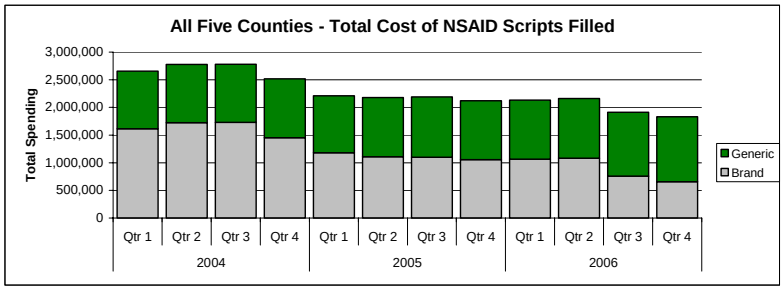
		Total Scripts	Current # Generics	If 1%* Increase	Difference	Cost Savings
2007	Qtr 1	82,872	74,990	75,819	829	$56,038
	Qtr 2	82,872	74,990	75,819	829	$56,038
	Qtr 3	82,872	74,990	75,819	829	$56,038
	Qtr 4	82,872	74,990	75,819	829	$56,038

Projected Savings: **$224,152**

* 1% is shorthand for one percentage point

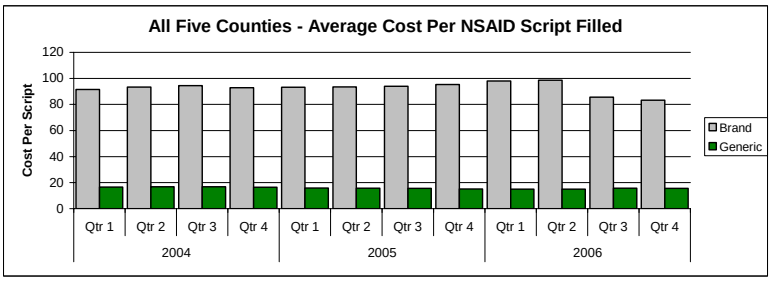
Total Cost

		Brand	Generic	Total	Pct.
2004	Qtr 1	1,614,039	1,041,882	2,655,922	39%
	Qtr 2	1,722,472	1,055,022	2,777,493	38%
	Qtr 3	1,730,610	1,049,328	2,779,937	38%
	Qtr 4	1,454,582	1,063,408	2,517,990	42%
2005	Qtr 1	1,178,229	1,032,830	2,211,059	47%
	Qtr 2	1,107,390	1,072,445	2,179,835	49%
	Qtr 3	1,099,125	1,093,394	2,192,518	50%
	Qtr 4	1,057,691	1,062,415	2,120,106	50%
2006	Qtr 1	1,062,942	1,070,068	2,133,010	50%
	Qtr 2	1,083,260	1,079,609	2,162,869	50%
	Qtr 3	758,311	1,151,302	1,909,613	60%
	Qtr 4	656,396	1,174,185	1,830,581	64%



Cost Per Script

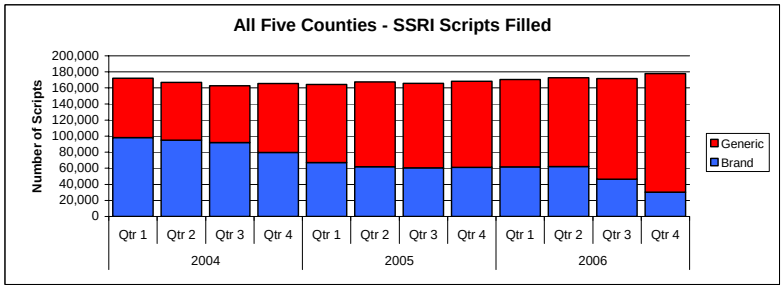
		Brand	Generic	Savings	Gen Pct.
2004	Qtr 1	91.55	16.51	75.03	18%
	Qtr 2	93.34	16.89	76.45	18%
	Qtr 3	94.44	16.90	77.55	18%
	Qtr 4	92.88	16.44	76.44	18%
2005	Qtr 1	93.24	15.88	77.36	17%
	Qtr 2	93.52	15.68	77.85	17%
	Qtr 3	94.06	15.54	78.52	17%
	Qtr 4	95.30	15.09	80.21	16%
2006	Qtr 1	98.02	14.89	83.13	15%
	Qtr 2	98.65	14.95	83.70	15%
	Qtr 3	85.62	15.67	69.95	18%
	Qtr 4	83.28	15.66	67.62	19%

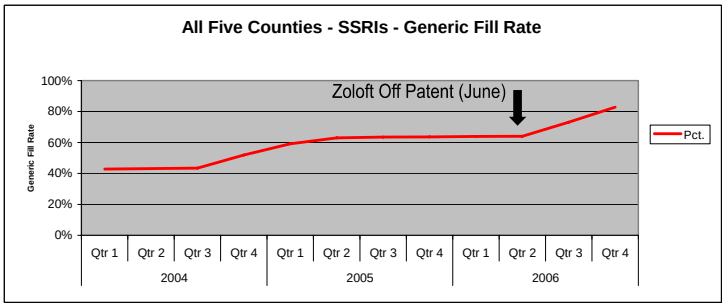


SSRIs

Scripts

		Brand	Generic	Total	Pct.
2004	Qtr 1	98,302	73,650	171,952	43%
	Qtr 2	94,792	72,117	166,909	43%
	Qtr 3	91,932	70,795	162,727	44%
	Qtr 4	79,618	85,719	165,337	52%
2005	Qtr 1	67,090	97,275	164,365	59%
	Qtr 2	61,971	105,369	167,340	63%
	Qtr 3	60,533	105,172	165,705	63%
	Qtr 4	61,303	107,088	168,391	64%
2006	Qtr 1	61,692	108,874	170,566	64%
	Qtr 2	62,154	110,658	172,812	64%
	Qtr 3	46,241	125,279	171,520	73%
	Qtr 4	30,474	147,277	177,751	83%





Assumptions:

Overall number of scripts (prescribing rate) will remain at Q4 2006 levels.
Price difference between generic and brand will remain at Q4 2006 levels.

Projections for 2007:

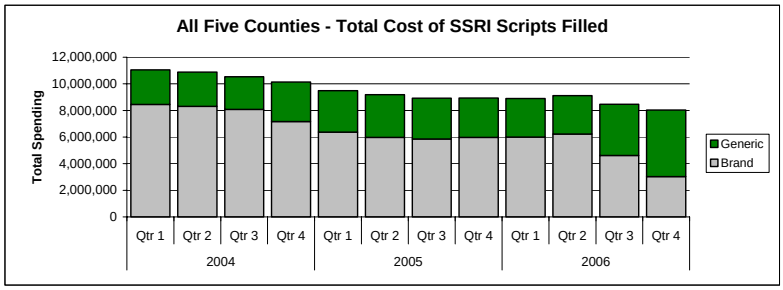
	Total Scripts	Current # Generics	If 1%* Increase	Difference	Cost Savings
Qtr 1	177,751	147,277	149,055	1,778	$115,753
Qtr 2	177,751	147,277	149,055	1,778	$115,753
Qtr 3	177,751	147,277	149,055	1,778	$115,753
Qtr 4	177,751	147,277	149,055	1,778	$115,753

Projected Savings: **$463,012**

* 1% is shorthand for one percentage point

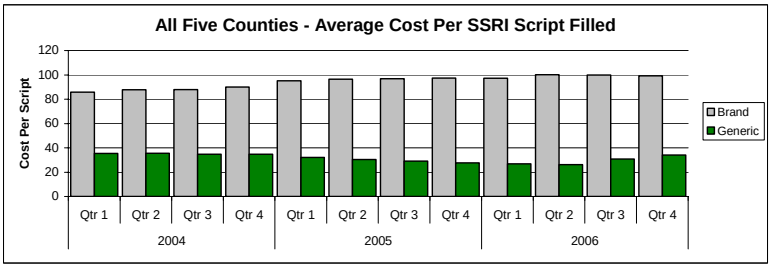
Total Cost

		Brand	Generic	Total	Pct.
2004	Qtr 1	8,446,191	2,607,906	11,054,097	24%
	Qtr 2	8,317,171	2,567,482	10,884,653	24%
	Qtr 3	8,084,354	2,459,608	10,543,962	23%
	Qtr 4	7,162,252	2,980,899	10,143,151	29%
2005	Qtr 1	6,375,656	3,115,802	9,491,458	33%
	Qtr 2	5,974,952	3,214,619	9,189,572	35%
	Qtr 3	5,858,812	3,063,335	8,922,147	34%
	Qtr 4	5,972,140	2,963,773	8,935,913	33%
2006	Qtr 1	5,998,581	2,911,458	8,910,039	33%
	Qtr 2	6,225,448	2,896,880	9,122,328	32%
	Qtr 3	4,617,618	3,852,328	8,469,947	45%
	Qtr 4	3,022,873	5,018,354	8,041,227	62%



Cost Per Script

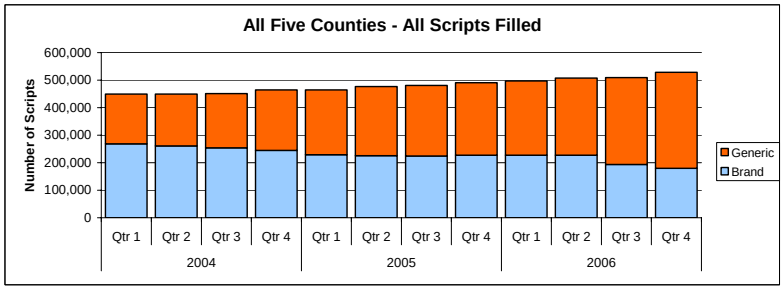
		Brand	Generic	Savings	Gen Pct.
2004	Qtr 1	85.92	35.41	50.51	41%
	Qtr 2	87.74	35.60	52.14	41%
	Qtr 3	87.94	34.74	53.20	40%
	Qtr 4	89.96	34.78	55.18	39%
2005	Qtr 1	95.03	32.03	63.00	34%
	Qtr 2	96.42	30.51	65.91	32%
	Qtr 3	96.79	29.13	67.66	30%
	Qtr 4	97.42	27.68	69.74	28%
2006	Qtr 1	97.23	26.74	70.49	28%
	Qtr 2	100.16	26.18	73.98	26%
	Qtr 3	99.86	30.75	69.11	31%
	Qtr 4	99.20	34.07	65.12	34%

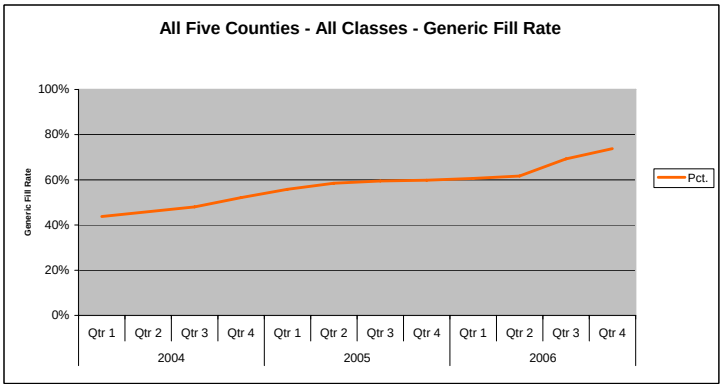


All Scripts

Scripts

		Brand	Generic	Total	Pct.
2004	Qtr 1	268,859	180,598	412,890	44%
	Qtr 2	261,190	188,747	411,647	46%
	Qtr 3	253,946	197,349	411,501	48%
	Qtr 4	244,653	220,032	422,391	52%
2005	Qtr 1	229,661	234,987	421,161	56%
	Qtr 2	225,282	251,731	430,608	58%
	Qtr 3	224,033	256,593	431,917	59%
	Qtr 4	227,719	263,096	439,696	60%
2006	Qtr 1	227,126	270,088	445,753	61%
	Qtr 2	227,195	280,102	454,237	62%
	Qtr 3	193,948	315,244	455,209	69%
	Qtr 4	179,539	349,111	472,853	74%





Generic fill rate (GFR) across the four therapeutic classes reviewed as of Q4 2006: **74%**

Average difference in cost per script between generic and brand name drugs acoss the four therapeutic classes reviewed as of Q4 2006: **$93**

Projected savings* for population included here in 2007 if GFR is increased by 1%: **$1,708,264**

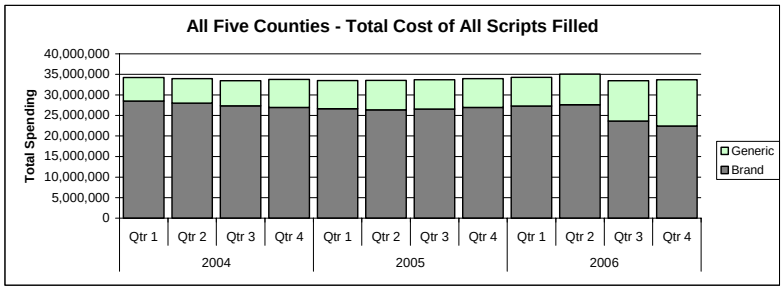
* = Sum total of the savings calculated for each therapeutic class

Projected savings for the insured, non-Medicare population in the Puget Sound region (est. 2,885,112**) in 2007 if GFR is increased by 1%: **$2,644,372**

** = Total 2006 population in the five-county region less those age 65+ and the uninsured (est. by county, approx. 11%)

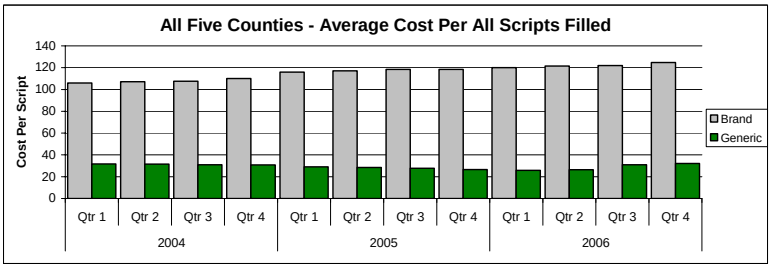
Total Cost

		Brand	Generic	Total	Pct.
2004	Qtr 1	28,487,204	5,741,176	34,228,380	17%
	Qtr 2	28,000,378	5,962,694	33,963,072	18%
	Qtr 3	27,323,022	6,132,714	33,455,736	18%
	Qtr 4	26,933,270	6,813,499	33,746,770	20%
2005	Qtr 1	26,623,277	6,849,338	33,472,615	20%
	Qtr 2	26,387,445	7,159,718	33,547,163	21%
	Qtr 3	26,532,624	7,126,721	33,659,344	21%
	Qtr 4	26,948,236	7,027,065	33,975,301	21%
2006	Qtr 1	27,280,597	6,979,741	34,260,338	20%
	Qtr 2	27,609,639	7,427,244	35,036,883	21%
	Qtr 3	23,651,323	9,814,181	33,465,504	29%
	Qtr 4	22,409,616	11,261,604	33,671,220	33%



Cost Per Script

		Brand	Generic	Savings	Gen Pct.
2004	Qtr 1	105.96	31.79	74.17	30%
	Qtr 2	107.20	31.59	75.61	29%
	Qtr 3	107.59	31.08	76.52	29%
	Qtr 4	110.09	30.97	79.12	28%
2005	Qtr 1	115.92	29.15	86.78	25%
	Qtr 2	117.13	28.44	88.69	24%
	Qtr 3	118.43	27.77	90.66	23%
	Qtr 4	118.34	26.71	91.63	23%
2006	Qtr 1	120.11	25.84	94.27	22%
	Qtr 2	121.52	26.52	95.01	22%
	Qtr 3	121.95	31.13	90.81	26%
	Qtr 4	124.82	32.26	92.56	26%



Statins

Aggregate - Vytorin included

		Brand	Generic	Total	Pct.
2004	Qtr 1	67,331	4,776	72,107	7%
	Qtr 2	68,608	5,448	74,056	7%
	Qtr 3	70,059	5,832	75,891	8%
	Qtr 4	72,678	6,488	79,166	8%
2005	Qtr 1	73,521	7,367	80,888	9%
	Qtr 2	74,059	8,508	82,567	10%
	Qtr 3	74,091	9,415	83,506	11%
	Qtr 4	75,283	10,239	85,522	12%
2006	Qtr 1	75,764	11,080	86,844	13%
	Qtr 2	76,027	14,417	90,444	16%
	Qtr 3	69,717	22,897	92,614	25%
	Qtr 4	72,147	26,560	98,707	27%

Assumptions:

Overall number of scripts (prescribing rate) will remain at Q4 2006 levels.
Price difference between generic and brand will remain at Q4 2006 levels.

Projections for 2007:

	Total Scripts	Current # Generics	If 1%* Increase	Difference	Cost Savings
Qtr 1	98,707	26,560	27,547	987	$52,275
Qtr 2	98,707	26,560	27,547	987	$52,275
Qtr 3	98,707	26,560	27,547	987	$52,275
Qtr 4	98,707	26,560	27,547	987	$52,275
				Projected Savings:	**$209,101**

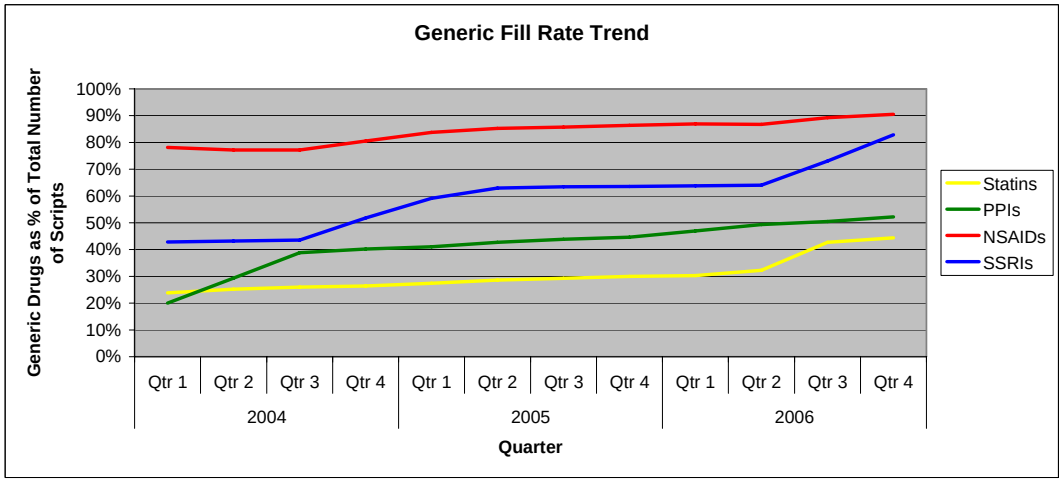
* 1% is shorthand for one percentage point

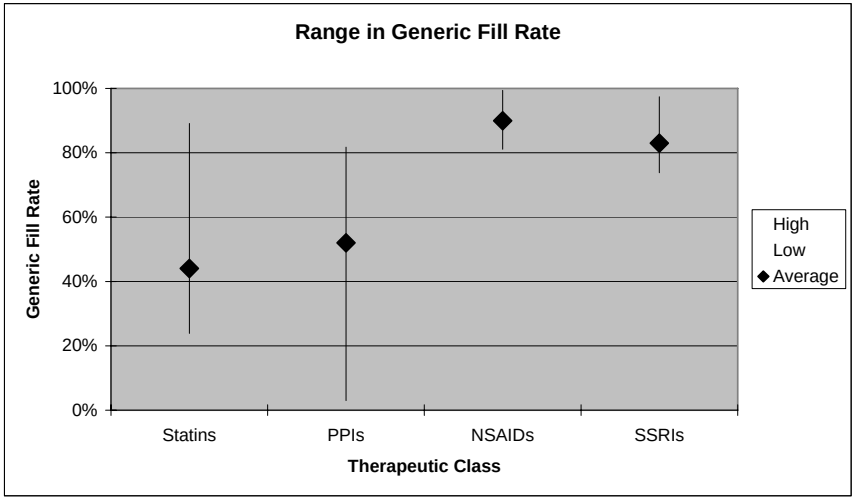
Statins

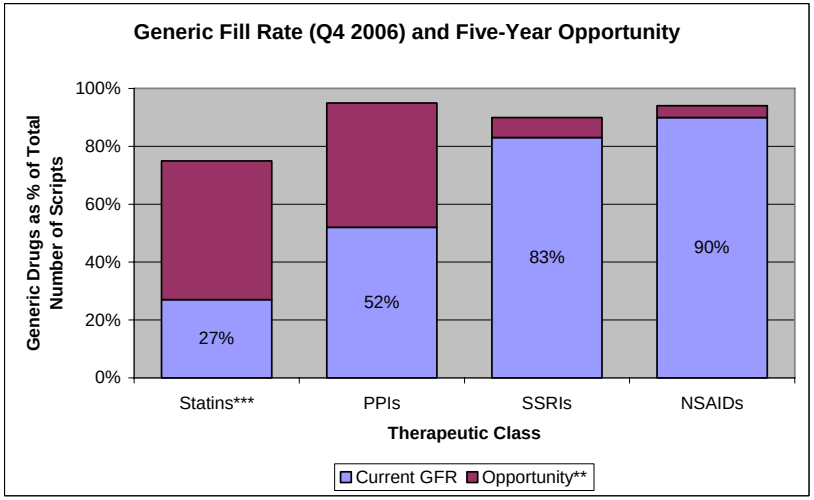
Aggregate - Vytorin NOT included

		Brand	Generic	Total	Pct.
2004	Qtr 1	20,968	22,896	43,864	52%
	Qtr 2	22,733	25,270	48,003	53%
	Qtr 3	24,072	27,196	51,268	53%
	Qtr 4	25,529	28,764	54,293	53%
2005	Qtr 1	26,072	30,216	56,288	54%
	Qtr 2	27,412	32,145	59,557	54%
	Qtr 3	28,121	32,945	61,066	54%
	Qtr 4	29,350	34,498	63,848	54%
2006	Qtr 1	29,773	34,768	64,541	54%
	Qtr 2	30,112	36,158	66,270	55%
	Qtr 3	21,770	45,325	67,095	68%
	Qtr 4	21,142	47,921	69,063	69%

		Statins	PPIs	NSAIDs	SSRIs
2004	Qtr 1	24%	20%	78%	43%
	Qtr 2	25%	29%	77%	43%
	Qtr 3	26%	39%	77%	44%
	Qtr 4	26%	40%	81%	52%
2005	Qtr 1	27%	41%	84%	59%
	Qtr 2	29%	43%	85%	63%
	Qtr 3	29%	44%	86%	63%
	Qtr 4	30%	45%	86%	64%
2006	Qtr 1	30%	47%	87%	64%
	Qtr 2	32%	49%	87%	64%
	Qtr 3	43%	50%	89%	73%
	Qtr 4	44%	52%	90%	83%







Class	High	Low	Average
Statins	89%	24%	44%
PPIs	82%	3%	52%
NSAIDs	99%	81%	90%
SSRIs	97%	74%	83%

	Current GFR	5-yr Target GFR*	Opportunity**
Statins* **	27%	75%	48%
PPIs	52%	95%	43%
SSRIs	83%	90%	7%
NSAIDs	90%	94%	4%

* = recommended by the Rx CIT
** = values given represent percentage points
*** = current GFR for statins represents the average GFR for plans that included Vytorin in their submitted data

Projected Cost Savings

	Per one percentage point increase in GFR…			Estimated savings if generic fill rate reaches…				
	Given Population	All Insured Residents in Region	Current (Q4 2006) GFR	50%	60%	70%	80%	95%
Statins	$477,124	$738,582	44%	$4,431,492	$11,817,313	$19,203,133	$26,588,954	$37,667,684
Statins + Vytorin	$209,101	$641,062	27%	$14,744,426	$21,155,046	$27,565,666	$33,976,286	$43,592,216
PPIs	$543,976	$842,068	52%		$6,736,545	$15,157,226	$23,577,907	$36,208,929
NSAIDs	$224,152	$346,985	90%					$1,734,923
SSRIs	$463,012	$716,737	83%					$8,600,842
Total*	**$1,440,241**	**$2,546,851**		**$14,744,426**	**$27,891,591**	**$42,722,892**	**$57,554,193**	**$90,136,909**

* Total includes sum of values for Statins + Vytorin, PPIs, NSAIDs, and SSRIs

Estimates

	2006 Population*	Percent 65+**	Est. Medicare Population	2006 Pop. Less Medicare	Percent Uninsured***	Est. # of Uninsured	2005 Pop., Less Medicare & Uninsured
King	1,835,300	10.50%	192,707	1,642,594	10.5%	192,707	1,449,887
Snohomish	671,800	10.40%	69,867	601,933	10.7%	71,883	530,050
Pierce	773,500	9.50%	73,483	700,018	11.2%	86,632	613,386
Thurston	228,867	11.80%	27,006	201,861	14.0%	32,041	169,819
Kitsap	231,100	11.50%	26,577	204,524	10.8%	24,959	179,565
	3,740,567	**10.4%**	**389,639**	**3,350,928**	**12.2%**	**408,221**	**2,942,707**

* 2006 population based on the Washington State Office of Financial Management April 1, 2006 population estimates (http://www.ofm.wa.gov/pop/april1/default.asp)

** based on 2000 census

*** Estimated by the Office of Insurance Commissioner in 'The Uninsured and the Cost of Uncompensated Care in Washington State' released from the Office of Insurance Commissioner in August 2006

Appendix 4: Rx CIT Phase II Members

First Name	Last Name	Job Title	Business
Paul	Anderson	Clinical Manager	Swedish Medical Center
Jim	Carlson	Director of Clinical Pharmacy Services	Group Health Cooperative
Steven	Hall	Director, Employer Market, West	Johnson & Johnson
Ray	Hanley	Senior Prescription Program Manager	Health Care Authority
David	Lorber	VP of Clinical Affairs	Caremark
Sepi	Soleimanpour	District Pharmacy Supervisor	Walgreens, Seattle North District
Andy	Stergachis	Professor	University of Washington, Department of Epidemiology
SuAnn	Stone	Director, Pharmacy Services	Regence BlueShield
Sean	Sullivan	Professor of Pharmacy, Director, Pharmaceutical Outcomes Research and Policy Program	Pharmacy & Health Services University of Washington
Yvonne	Tate	Human Resources Director	City of Bellevue
Michael	Tronolone	Medical Director	Polyclinic
John	Verrilli	Internist	Minor & James Clinic
Jennifer	Wilson-Norton	Pharmacy Director	The Everett Clinic
Ed	Wong	Director of Pharmacy	Premera BlueCross
Art	Zoloth	Retired	Formerly of Northwest Pharmacy Services

Chair & Consultant Lead:

Lori Whittaker, MD, MPH

Puget Sound Health Alliance Staff:

Susie Dade, Quality Improvement Director
Kerri Petrin, Research Analyst
Natalie Moe, Committee Coordinator

Appendix 5: Summary of LDL Target Recommendations

The National Cholesterol Education Program (NCEP) Adult Treatment Panel (ATP) III 2001 Guidelines and 2004 update, and the American Heart Association (AHA)/American College of Cardiology (ACC) Guidelines for primary and secondary prevention of CHD[80] recommend specific targets for serum cholesterol and LDL levels based on individual risk for cardiovascular disease.

For primary prevention in the general population, risk factors include gender, age, presence of hypertension or diabetes, and smoking history. A patient's ten-year cardiovascular risk may be calculated using the Framingham Risk Calculator[81], and this calculation is used to determine the target cholesterol levels.

For secondary prevention in patients with known CHD or CHD equivalent, the goal is an LDL level < 100mg/dl. In 2006 the AHA/ACC updated their guidelines to indicate that an LDL target of <70mg/dl is reasonable in very high risk individuals. The updated AHA/ACC recommendations are summarized in Table 2-1.[82]

[80] AHA/ACC Guidelines for Secondary Prevention for Patients with Coronary and Other Atherosclerotic Vascular Disease: 2006 Update. Available at: http://circ.ahajournals.org/cgi/content/full/113/19/2363 (accessed 2/7/07); AHA Guidelines for Primary Prevention of Cardiovascular Disease and Stroke: 2002 Update http://circ.ahajournals.org/cgi/content/full/106/3/388;
AHA/ACC Guidelines for Preventing Heart Attack and Death in Patients with Atherosclerotic Cardiovascular Disease: 2001 Update. Available at:http://circ.ahajournals.org/cgi/content/full/104/13/1577?ijkey=5fdcaa81ee1c3398efe6978cb46eec41854b72c6&keytype2=tf_ipsecsha (accessed 2/7/07); National Cholesterol Education Program Adult Treatment Panel III 2004, available at: http://www.nhlbi.nih.gov/guidelines/cholesterol/ (accessed 2/7/07).

[81] NCEP Framingham Heart Disease Risk Calculator. Available at: http://hp2010.nhlbihin.net/atpiii/riskcalc.htm (accessed 2/7/07).

[82] AHA/ACC Guidelines for Secondary Prevention for Patients with Coronary and Other Atherosclerotic Vascular Disease: 2006 Update. Available at: http://circ.ahajournals.org/cgi/content/full/113/19/2363 (accessed 2/7/07)

Table 2-1: AHA/ACC 2006 Updated LDL Cholesterol Target Recommendations for the Prevention of Coronary Heart Disease[83]

LDL Targets in High Risk Patients
Patients with CHD and other clinical forms of atherosclerotic disease: • Low-density lipoprotein cholesterol (LDL-C) should be <100 mg/dL for all patients • It is also reasonable to treat to LDL-C <70 mg/dL in such patients. • When the <70-mg/dL target is chosen, it may be prudent to increase statin therapy in a graded fashion to determine a patient's response and tolerance • Furthermore, if it is not possible to attain LDL-C <70 mg/dL because of a high baseline LDL-C, it generally is possible to achieve LDL-C reductions of >50% with either statins or LDL-C–lowering drug combinations
Patients without atherosclerotic disease who have diabetes or multiple risk factors and a 10-year risk level for CHD >20%: o The recommended LDL-C goal is <100 mg/dL
Other types of lower-risk individuals who do not have CHD or other forms of atherosclerotic disease: • A reasonable cholesterol level of <70 mg/dL does not apply • In such cases, recommendations contained in the 2004 NCEP ATP III update still pertain.[84]

[83] Ibid

[84] National Cholesterol Education Program Adult Treatment Panel III 2004, available at: http://www.nhlbi.nih.gov/guidelines/cholesterol/ (accessed 2/7/07).

Appendix 6: Guidelines for Treatment of Gastrointestinal Disorders with Proton Pump Inhibitors (PPIs)

The American College of Gastroenterologists (ACG) has developed guidelines for the treatment of common gastrointestinal disorders with PPIs. Summaries of the salient points for the management of dyspepsia and GERD are given below. Individuals are referred to the full set of guidelines for more complete information.

Treatment of dyspepsia [85]

Definition:
Dyspepsia is defined as chronic or intermittent pain in the upper abdomen

Treatment Options:

(1) A "Test and treat" strategy for *Helicobacter pylori* (H. pylori), a bacterium known to induce gastroduodenal ulcers.

- If the test is positive, the patient should be treated with an appropriate regimen of PPIs and antibiotics (duration of currently accepted regimens is 1-14 days).[86]
- If treatment is successful but symptoms do not resolve, an empiric trial of a PPI for 4-8 weeks is suggested.

(2) Empirical treatment with a PPI for 4-8 weeks (an option in areas of low H.pylori prevalence).

- If symptoms do not resolve after 2-4 weeks, then an increase in dose or change to another PPI is reasonable.
- If symptoms persist after the 4-8 week trial, or if they recur after the PPI is stopped, then the test and treat strategy should be followed.
- If symptoms resolve on the PPI, it should be stopped after 4-8 weeks.

If symptoms persist with either of the above regimens, then referral for endoscopy may be considered, although the yield is low in patients below the age of 55 without alarm symptoms or risk factors for significant disease, such as history of smoking or NSAID use.

If patients respond to an initial course of PPI therapy but symptoms recur when it is stopped, then an additional course of the same treatment is warranted.

In patients over 55, empiric therapy is not recommended, and those patients should be referred for early endoscopy.

[85] Talley NJ et al. Practice Guidelines: Guidelines for the Management of Dyspepsia. Am J. Gastroenterology, 2005, 100:2324-2337.
[86] Aibles ZA. Update on Helicobacter pylori treatment Am Fam Physician 2007;75:351-8

Treatment of Gatroesophageal Reflux Disease (GERD) [87]

Definition:
GERD is the abnormal reflux of stomach contents into the esophagus. It can lead to heartburn symptoms, mucosal damage, erosive esophagitis or Barrett's esophagus, a premalignant condition. In patients who present with typical reflux symptoms, 70% will in fact have GERD.[88]

Diagnostic considerations:
(1) If the patient's history is typical for uncomplicated GERD, an initial trial of empirical therapy (including lifestyle modification) is appropriate.
(2) Endoscopy at presentation should be considered in patients who have symptoms suggesting complicated disease, those at risk for Barrett's esophagus by duration of their symptoms, or when the patient or physician feel early endoscopy is appropriate.
(3) It should be noted that a short trial of high dose PPI does not have a high predictive value, beyond typical symptoms, for ruling in or out GERD.[89]

Treatment considerations:
(1) Lifestyle modifications, such as dietary restrictions, timing of meals, smoking cessation, raising the head of the bed, etc., may benefit many patients with GERD, but these changes alone are unlikely to control symptoms in the majority of patients.
(2) Antacids and over-the-counter acid suppressants are options for patient-directed symptom control in GERD. However, when OTC agents fail to control symptoms, or long-term use is required, patients should consult their provider for further diagnosis and treatment.
(3) Acid suppression is the mainstay of therapy for GERD. PPIs provide the most rapid symptom relief and heal esophagitis in the highest percentage of patients. Although less effective that PPIs, H-2 receptor blockers given in divided doses may be effective in some patients with less severe GERD. Efficacy and safety data support continuous PPI therapy as the most effective management for GERD.
(4) Because GERD is a chronic condition, continuous therapy to control symptoms and prevent complications is appropriate. Many patients with GERD require long-term, even lifetime, therapy. Some patients may respond to long-term lifestyle modification and divided dose H2-blocker therapy, but most patients will require long-term use of PPIs to control their symptoms.

[87] DeVault KR et al. Practice Guidelines: Updated guidelines for he diagnosis and treatment of Gastroesophageal reflux disease. Am J. of Gastroenterology, 2005, 100:190-200
[88] Aanen MC et al. Diagnotstic value of the proton pump inhibitor test for gastro-oesophageal reflux disease in primary care. Aliment. Phamacol. Ther 2006, 24:1377-1384.
[89] Ibid; DeVault KR et al. Practice Guidelines: Updated guidelines for he diagnosis and treatment of Gastroesophageal reflux disease. Am J. of Gastroenterology, 2005, 100:190-200