

The Use of Balance Sheets in Developing Clinical Guidelines

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Improving quality while containing costs is arguably the highest priority in health care today. Problems with the quality and cost of care in the United States include wide variations in clinical practice,¹⁻³ medical practices of marginal benefit to patients at increased costs, ineffective practices, and clinical practices initially expected to improve care but that might actually cause harm.⁴⁻⁸ Managed care organizations (MCOs) must provide the best available care to their populations within cost constraints, and clinical guidelines can help achieve this goal. Useful clinical guidelines should contain more than clear recommendations. The evidence and reasoning upon which the recommendations are based need to be explicit, and the expected outcomes of implementing the guideline should be stated.

Group Health Cooperative of Puget Sound is a large MCO in the Pacific Northwest with a current enrollment of approximately 600,000 and more than 900 staff physicians and 2500 nonstaff physicians. Within this MCO teams of providers with administrative and epidemiologic support have developed 30 evidence-based clinical practice guidelines using an explicit approach to analyze evidence systematically and to project the impacts of each guideline on health care outcomes.⁹⁻¹¹ These guidelines are used by providers and patients as an aid to shared decision making, and key outcomes are monitored to check that they have been successfully implemented. Before each guideline reaches its final form, the impacts on all pertinent outcomes (health status, patient satisfaction, provider satisfaction, cost and utilization, and capital needs) are determined by developing a balance sheet.^{10,11}

The balance sheet in clinical guideline develop-

ment work has been described by Eddy¹² as a tool to (1) estimate the health and economic outcomes from clinical research and clinical experience, (2) assist decision makers to develop an accurate understanding of the important consequences of adopting the different options, (3) condense important information into a space that can be grasped visually and mentally at one time, and (4) assist in planning organizational change (eg, organize thinking, structure the analysis of evidence, and focus debates).

A balance sheet is used to ensure that the effects of various clinical practice changes being contemplated by guideline developers have been formally considered before completing and implementing the clinical guideline. Balance sheets have been especially useful in assisting teams developing clinical guidelines at Group Health Cooperative of Puget Sound to consider simultaneously cost, quality, and satisfaction (Table 1). In this paper we provide examples of balance sheets of varying complexity that have helped our health care providers and administrators understand the full range of consequences of adopting different diagnostic or treatment options before guideline implementation. Although patients are not members of our guideline development teams, we try to represent their perspective when developing guidelines.

Clinical Examples of Balance Sheet Use

Eliminating Unnecessary Investigations and Recognizing Barriers to Changing Clinical Practice

A 23-year old man twisted his ankle while playing soccer. Your nurse had arranged for foot and ankle radiographs before his visit with you. The radiograph showed no fracture, and you advised the standard treatment of rest, ice, compression, and elevation.

Wondering how best to determine whether a patient with an ankle injury really needs a radiograph, you search MEDLINE and find a multi-

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Table 1. Functions of the Balance Sheet in Clinical Guideline Development.

Organizes benefits, harms, costs of various clinical practice changes in one chart
1. Benefits can be compared with harms in quantifiable way, eg, number of postoperative pulmonary emboli prevented by subcutaneous heparin and number of major bleeding episodes caused
2. Health outcomes (both benefits and harms) displayed in natural units, eg, deaths avoided
3. Patient and provider satisfaction projected
4. Costs and utilization, including start-up costs, and marginal costs estimated
Can be used to assist decision making regarding individual patients or populations
Shows all the projected impacts of any clinical practice change, eg, guideline implementation
Balance sheet information can be used to create decision support for providers and patients (eg, baseline risk, absolute risk reduction with various treatments, information regarding number of patients needed to treat to benefit 1 patient [NNT])

center study of the Ottawa ankle rules (a set of prospectively validated decision rules).¹³ When introduced to emergency departments at eight hospitals, these rules reduced the use of ankle radiography with no increased rate of missed fractures. Applying this set of rules would save time for the patient and reduce costs. You wonder whether it would be worth encouraging other providers in your MCO to use these decision rules.

You obtain the number of patients who have ankle injuries within your organization and assume that you could achieve a similar change in radiography as experienced in the study (reduction from 83 to 61 percent). After discussing the potential reduction in radiography with a colleague, you decide to broaden your analysis to include other factors, such as patient satisfaction, provider satisfaction, and health outcomes. Although information about waiting times was available in the paper, patient and provider satisfaction was not discussed in detail. In the absence of information on provider satisfaction, you assume that your colleagues and their patients might, at times, find it hard to accept the implications of the decision rules (Table 2).

In view of the substantial savings that the Ottawa ankle rules could generate for your organization, you decide to try to develop an acute ankle injury guideline while recognizing that patient and provider satisfaction issues constitute barriers that need to be addressed.

Table 2. Acute Ankle Injury Radiograph.

Characteristics	Amount
<i>Current</i>	
Number per year	12,450
Unit cost, \$	50
Total annual cost, \$	622,500
<i>Projected</i>	
Change, %	-26
Number per year	9213
Total annual cost, \$	460,650
Annual savings (costs), \$	161,850

Other outcomes of implementing ankle injury guideline: radiation exposure reduced, waiting times reduced 33 min for those not requiring radiograph, satisfaction reduced among patients and providers who disagree with decision rules and expect a radiograph.

Making Uncertainty Explicit

At the end of a busy morning, a pharmaceutical representative visits you to describe the benefits of potassium-sparing diuretics for the treatment of hypertension. He explains that case-control studies of hypertensive patients taking thiazide diuretics show that the rate of sudden death is lowest in those on low doses of thiazide diuretics combined with a potassium-sparing diuretic.¹⁴ You wonder whether you should switch all your patients currently on a thiazide alone to a potassium-sparing diuretic. Recalling your colleague's advice to include all outcomes, you construct a simple balance sheet.

Health outcomes: The only definite improvement in health outcomes is an estimated 50 percent reduction in the number of sudden cardiac deaths. Sudden cardiac death is not the only outcome related to hypertension, however. Low-dose thiazides have been shown to reduce the risk of stroke, heart failure, coronary artery disease, total mortality, and cardiovascular mortality, but the effect of the combination of a thiazide and a potassium-sparing diuretic on these outcomes has not been studied.

Cost: The combination of a thiazide and a potassium-sparing diuretic costs approximately 6 times as much as a thiazide diuretic alone. Although neither drug is expensive, you are aware that little-ticket items, such as these drugs, lead to considerable expense for the organization as a whole. You decide to ignore the cost of testing for hypokalemia because there is uncertainty regarding both the

need to test for hypokalemia in patients on low-dose thiazides alone and the need to test patients on a thiazide and a potassium-sparing diuretic.

Satisfaction: Advertising by the pharmaceutical industry to both providers and patients will stimulate interest in potassium-sparing diuretics. Any attempt to restrict their use might encounter resistance and needs to be addressed sensitively.

In summary, there are known substantial costs, uncertain overall benefits, and forces that are likely to increase the use of potassium-sparing diuretics. You decide against substituting a combination thiazide and potassium-sparing diuretic for a low-dose thiazide diuretic alone as standard treatment of hypertension.

Making Decisions About New, More Effective but More Costly Interventions

While scanning advertisements in a medical journal, you note that alendronate reduces the risk of hip fracture by approximately 50 percent. Knowing that the lifetime risk of hip fracture in women is approximately 15 percent and that hip fracture is frequently followed by a reduction in mobility and a substantial increase in mortality, you wonder whether you should actively encourage older patients to take this drug. You select two randomized controlled trials for critical appraisal.

The first study included women with low bone density, but without a previous symptomatic osteoporotic vertebral fracture. The main outcome in this study was a 48 percent reduction in the relative risk of radiologically detected vertebral fractures.¹⁵ You regard this as an intermediate marker rather than an outcome of clear clinical importance and discard the paper.

The second study was of women with low bone density and a previous osteoporotic vertebral fracture. After 2.9 years of follow-up, the hip fracture rate was 1.1 percent in those randomized to alendronate compared with 2.2 percent in the placebo group. You calculate that the absolute risk reduction is 1.1 percent for 2.9 years, and that you would have to treat 90 patients (100/1.1) for 2.9 years to prevent a single hip fracture (the number needed to treat or NNT). Using the cost of the medication, the NNT, and the duration of treatment, you calculate that the cost to prevent one hip fracture is \$172,000. In addition, there would be 1.7 fewer wrist fractures and 2.5 fewer symptomatic vertebral fractures.¹⁶

The difficulty in establishing how many women within your MCO would be candidates for alendronate therapy precludes the construction of a formal balance sheet, so you briefly document your conclusions. Although this approach does not give a complete picture of the impact of using alendronate at a population level, it is helpful when estimates are considered to be unreliable.

Health outcomes: Alendronate is effective in reducing the risk of osteoporotic fractures. Of some concern are the potential for esophagitis and the absence of long-term safety data on a drug that is permanently fixed to bone. In addition, it is unclear how much advantage alendronate provides to patients taking hormone replacement therapy and higher doses of vitamin D (in this study women received only 250 IU).

Cost: Even if alendronate is restricted to patients with low bone density and a previous osteoporotic vertebral fracture, paying \$172,000 to prevent a hip fracture is not highly cost-effective.

Patient and provider satisfaction: There is likely to be interest among both patients and providers in another therapeutic option for osteoporosis, although this enthusiasm might be reduced upon learning that the patient must take the medication on an empty stomach and remain upright for a half-hour afterward to reduce the risk of esophagitis.

You are reluctant to abandon an effective medication, however, and believe that alendronate would be cost-effective if used in patients at high risk of osteoporotic fracture. Searching MEDLINE, you find a prospective study of more than 8000 community-living women that developed a model for predicting hip fracture risk based on risk factor scoring and bone density.¹⁷ You calculate that if alendronate were offered to women with an annual risk of hip fracture of 3 percent or more, then it would only cost \$44,000 to prevent a hip fracture.

At this point you decide to (1) use the well-established therapies, such as calcium, vitamin D, and hormone replacement therapy, as first-line therapy; (2) stimulate a discussion within your organization as to how much it is willing to pay to prevent a hip fracture, and develop a hip fracture risk-scoring tool that will select those patients in whom alendronate is considered to be cost-effective; and (3) discuss cost and benefit information with patients interested in beginning alendronate therapy who also pay for their own medications.

Table 3. Balance Sheet of Benefits, Harms, and Costs of Strategies for Preventing Deep Vein Thrombosis (DVT) and Pulmonary Embolism (PE) Applied to 1000 Elective Hip Surgery Patients Receiving Prophylaxis for 4 Days.

Intervention Strategies	Intervention Cost per Patient, \$	Relative Risk Reduction	Patients With PE	Patients With Clinical DVT	Major Bleeding Episodes Caused	Total Costs Related to DVTs, Prevention, and Bleeding, \$
No prophylaxis	0	0	40	120	0	380,000
Foot impulse technology (FIT)	97	86	6	17	0	150,000
Intermittent pneumatic compression (IPC) stockings (thigh)	122	38	252	74	0	357,000
Aspirin	4	26	30	89	3	290,000
Warfarin	73	73	11	32	13	199,000
Fixed-dose unfractionated heparin	8	45	22	66	29	269,000
Low molecular weight heparin	128	79	8	25	18	240,000
FIT + aspirin *	101	90	4	12	3	145,000
FIT + warfarin *	170	96	2	5	13	207,000
FIT + fixed-dose unfractionated heparin	170	92	3	9	29	251,000
FIT + low molecular weight heparin *	225	97	1	4	18	268,000
IPC + aspirin *	126	54	18	55	3	305,000
IPC + warfarin *	195	83	7	20	13	282,000
IPC + fixed-dose unfractionated heparin *	130	66	14	41	29	311,000
IPC + low molecular weight heparin*	250	87	5	16	18	331,000

* Unproved benefit of combining these strategies.

Note: Total costs rounded to nearest \$1000. Balance sheet developed as part of deep vein thrombosis prevention guideline at Group Health Cooperative. Although estimates of effectiveness and harms associated with individual preventive strategies are based on literature review, space constraints preclude a detailed description. Costs likely to vary among organizations.

Choosing Between Many Options and Weighing Benefits, Harms, and Costs

So far we have described three examples in which there was a choice between a new approach and an old one. By explicitly setting out costs, harms, and benefits, a balance sheet can be particularly helpful when there are multiple interventions and several outcomes to consider. Prevention of deep vein thrombosis (DVT) and pulmonary embolism after total hip replacement is a good example. There are several possible preventive strategies, including mechanical approaches (foot impulse technology and intermittent pneumatic compression stockings) and medications (aspirin, warfarin, heparin). These interventions vary in their effectiveness, are associated with different rates of bleeding, and have different costs. Keeping all these factors in one's head is difficult. Indeed, some review articles and meta-analyses have concentrated on DVT prevention and paid less attention to the impact of bleeding.^{18,19}

The balance sheet shows that there is no one correct approach (Table 3). If you wanted to mini-

mize costs, you would opt for warfarin alone. For every 1000 patients receiving treatment, an average of 11 would have a pulmonary embolus, 13 would have a major bleeding episode, and 32 would develop clinical DVT. In contrast, if you wanted to minimize the risk of pulmonary embolus, you could combine foot impulse technology with low-molecular-weight heparin, giving a 1 in 1000 risk of pulmonary embolus. This strategy, however, is associated with more major bleeding episodes and higher costs. A pragmatic approach would be to combine foot impulse technology with aspirin, which reduces the risk of pulmonary embolus to 4/1000. This approach would cause only 3 major bleeding episodes per 1000 patients treated and would appear to be the most cost-effective strategy. Given that costs vary from one organization to another, it is possible that two organizations with similar values could adopt different strategies.

Making Explicit All Implications of a Clinical Change

The previous examples illustrate the role of balance sheets in helping providers and planners com-

Table 4. Balance Sheet for Diabetic Glycemic Control Guideline.

Characteristics	Primary Care Visits	Hemoglobin A _{1c} Tests	Diabetic Medication	Total
<i>Current</i>				
Number per year	100,000	40,000	10,000	
Unit costs, \$	100	10	200	
Total annual costs, \$	10,000,000	400,000	20,000,000	30,400,000
<i>Projected</i>				
Change, %	+15	+25	None	
Number per year	115,000	50,000	10,000	
Total annual costs, \$	11,500,000	500,000	20,000,000	32,000,000
Annual savings (costs), \$	(1,500,000)	(100,000)		(1,600,000)

Health outcomes: The mean hemoglobin A_{1c} is expected to fall by 0.5%. During a period of 15-20 years the annual incidence of major complications is expected to fall by approximately 40 (14 fewer diabetics will become blind, 18 fewer patients will develop end-stage renal failure, and 9 fewer lower extremity amputations will be performed). These gains must be balanced against an additional 163 severe hypoglycemic episodes per year. Whereas the reduction in incidence of major complications is expected to occur in both type 1 and type 2 diabetes, the risk of severe hypoglycemia will principally be borne by patients with type 1 diabetes (the absolute annual risk of severe hypoglycemia is expected to increase by 8% in type 1 diabetes).

Provider satisfaction: The concise approach in the guideline to diabetes control should help clarify uncertainties and increase satisfaction. The guideline will increase workload, however, which might create some resistance.

Patient satisfaction: Overall, this guideline should increase patient satisfaction. Patients are likely to have differing views about intensive glycemic control with the associated increase in risk of hypoglycemia, together with heightened awareness that their own behavior will have a direct impact on future risk of complications. Nonetheless, patients are expected to appreciate increased information and a consistent approach applied throughout the MCO even if they change primary care providers.

bine evidence from the literature with local costs and values before choosing between different strategies. Balance sheets are also helpful when considering a new program in its entirety. Consider implementation of a guideline on diabetic glycemic control. Table 4 shows the costs, health

outcomes, and patient and provider satisfaction associated with this guideline. It is important to acknowledge that many figures in this balance sheet are estimates, including an assumption that patients with type 2 diabetes will benefit from glycemic control. Whenever there is uncertainty, we take a conservative approach using high-range cost estimates and low-range estimates of benefit. In the absence of easily available local data regarding rates of major complications of diabetes, we relied on estimates from the medical literature.²⁰ In view of the difficulties of assigning a financial cost to these outcomes and discounting benefits expected many years in the future, we simply state these facts in a footnote.

Discussion

Balance sheets display estimates of benefits, harms, and costs and are best thought of as a type of practical and useful economic analysis. Table 5 summarizes the most common types of economic analysis and their uses in health care.^{12,21,22} Economic analyses can be defined as approaches used to compare alternative strategies in health care using formal, quantitative methods to estimate outcomes and resource utilization.²² Underlying the increasing interest in economic analysis is the

Table 5. Common Types of Economic Analysis.

Type	Description
Cost-effectiveness analysis	Health outcomes reported in natural units, such as deaths avoided, life years gained, cases successfully treated. Cost-effectiveness ratio is measure of amount of benefit provided by an activity for specified amount of cost
Cost-utility analysis	Health outcomes valued or weighted, eg, quality-adjusted life year allows valuing time spent in less than full health. Valuing health outcomes allows comparison of various types of outcomes
Cost-benefit analysis	All outcomes valued in same units (usually dollars). Can determine what consumers will pay for various interventions or services
Balance sheet	Health, satisfaction, cost, and utilization outcomes of current practice and various alternatives listed. Components not combined, and relative importance of outcomes not indicated. Users expected to make judgments based on their values and local conditions

Table 6. Comparison of Efficacy and Effectiveness.

Efficacy	Effectiveness
Best represented by randomized controlled trials in which ideal conditions for interventions can be created because of steps taken to assure full cooperation with medical advice	Reality of practice settings where conditions are usually not ideal – conditions differ from those in randomized controlled trials
Study population might exclude: Complex cases (patients with comorbidities) ²³	Effectiveness is established if more good than harm results from interventions offered ²⁵ to patients:
1. Older patients ²⁴	1. Patients more likely to be older, female, and taking multiple medications or have multiple medical problems
2. Women ²⁴	2. Usually fewer personnel available to deliver care
Frequently optimal support for:	3. Usually less support for encouraging compliance with treatment; follow-up is available
1. Personnel to deliver care	
2. Necessary facilities, equipment	
3. Implementation methods	
4. Attention to patients in form of follow-up, reminders, etc, to prevent dropout	

understanding that there are an astounding and ever-increasing number of health care activities, each associated with different benefits, harms, and costs. A key concept in economic analysis is the notion that interventions can be prioritized beyond benefit to an individual patient or population. Through economic analysis interventions can be ranked by the total benefit they provide to a population for a given cost. Economic analyses have been distinguished from decision analyses and clinical practice guidelines by their explicit measurement and valuation of resource consumption or cost.²²

We believe that balance sheets are a critically important part of an explicit, evidence-based guideline process. They require the collection, interpretation, and integration of valid and clinically important evidence from the medical literature and costs from internally derived organizational data. Frequently information is missing, and estimates are often necessary to complete a balance sheet. For example, how likely is it that the benefits observed in a randomized controlled trial will be achieved in routine clinical practice, ie, the difference between efficacy and effectiveness (Table 6); and realistically what proportion of patients will be treated according to a newly implemented guideline?

Balance sheets display both health outcomes and cost outcomes, but they leave the health outcomes in natural units, such as number of myocardial infarctions prevented or number of hospitalizations avoided. Balance sheets, in contrast to some types of economic analysis, do not place an economic value on health states. Dollar valuing of health states, for example, is the distinguishing

feature of cost-benefit analyses. Because balance sheets leave economic and health outcomes in their natural units, users of balance sheets are required to use their own values and local conditions to guide their recommendations. The balance sheet is thus a tool to assist in the planning of clinical improvement activities. It facilitates decision making by setting out alternatives, and it shows all expected impacts of a guideline or other clinical improvement project. An additional step is required to compare various guidelines. Ranking diagnostic or treatment interventions of different types (eg, a cervical cancer screening program compared with a coronary artery bypass program), requires a cost-utility analysis in which health outcomes are weighted or valued, eg, quality adjusted life years.

Summary

Balance sheets are designed to assist decision-makers regarding outcomes in their practice setting. For this reason, they must include data generated in that practice setting and project the impact of a change in clinical practice on health outcomes, cost, and patient and provider satisfaction. To complete a balance sheet, it is often necessary to make assumptions that should be both conservative and realistic. Balance sheets are particularly useful for presenting all the expected outcomes of implementing a clinical guideline or other change in clinical practice and frequently lead to insights and improvements.

David Eddy's lucid writings have inspired our guideline development work at Group Health Cooperative. We also acknowledge our clinical and administrative colleagues with whom we have discussed and refined these ideas throughout the years.

References

1. Wennberg J, Gittelsohn A. Small area variations in health care delivery. *Science* 1973;182:1102-8.
2. Perrin JM, Homer CJ, Berwick DM, Woolf AD, Freeman JL, Wennberg JE. Variations in rates of hospitalization of children in three urban communities. *N Engl J Med* 1989;320:1183-7.
3. Chassin MR, Brook RH, Park RE, Keesey J, Fink A, Kosecoff J, et al. Variations in the use of medical and surgical services by the Medicare population. *N Engl J Med* 1986;314:285-90.
4. Schroeder SA. Strategies for reducing medical costs by changing physicians' behavior. *Int J Technol Assess Health Care* 1987;3:39-50.
5. Grimes DA. Technology follies. The uncritical acceptance of medical innovation. *JAMA* 1993;269:3030-3.
6. Epstein AE, Hallstrom AP, Rogers WJ, Liebson PR, Seals AA, Anderson JL, et al. Mortality following ventricular arrhythmia suppression by encainide, flecainide, and moricizine after myocardial infarction. The original design concept of the Cardiac Arrhythmia Suppression Trial (CAST). *JAMA* 1993;270:2451-5.
7. Franks P, Clancy CM, Nutting PA. Gate keeping revisited - protecting patients from overtreatment. *N Engl J Med* 1992;327:426-9.
8. Eddy DM. Medicine, money, and mathematics. *Am Coll Surg Bull* 1992;77:36-49.
9. Stuart ME, Macuiba JM, Heidrich F, Farrell RA, Braddick M, Etchison S. Successful implementation of an evidence-based clinical practice guideline: acute dysuria/urgency in adult women. *HMO Pract* 1997;11(4):150-7.
10. Handley MR, Stuart ME. An evidence-based approach to evaluation and improving clinical practice: guideline development. *HMO Pract* 1994;8(1):10-9.
11. Handley MR, Stuart ME. An evidence-based approach to evaluating and improving clinical practice: implementing practice guidelines. *HMO Pract* 1994;8(2):75-83.
12. Eddy DM. Comparing benefits and harms: the balance sheet. *JAMA* 1990;263:2493, 2498, 2501 passim.
13. Stiell I, Wells G, Laupacis A, Brison R, Verbeek R, Vandemheen K, et al. Multicentre trial to introduce the Ottawa ankle rules for use of radiography in acute ankle injuries. Multicentre Ankle Rule Study Group. *BMJ* 1995;311:594-7.
14. Siscovick DS, Raghunathan TE, Psaty BM, Koepsell TD, Wicklund KG, Lin X, et al. Diuretic therapy for hypertension and the risk of primary cardiac arrest. *N Engl J Med* 1994;330:1852-7.
15. Liberman UA, Weiss SR, Broll J, Minne HW, Quan H, Bell NH, et al. Effect of oral alendronate on bone mineral density and the incidence of fractures in postmenopausal osteoporosis. The Alendronate Phase III Osteoporosis Treatment Study Group. *N Engl J Med* 1995;333:1437-43.
16. Black DM, Cummings SR, Karpf DB, Cauley JA, Thompson DE, Nevitt MC, et al. Randomised trial of effect of alendronate on risk of fracture in women with existing vertebral fractures. Fracture Intervention Trial Research Group. *Lancet* 1996;348:1535-41.
17. Cummings SR, Nevitt MC, Browner WS, Stone K, Fox KM, Ensrud KE, et al. Risk factors for hip fracture in white women. Study of Osteoporotic Fractures Research Group. *N Engl J Med* 1995;332:767-73.
18. Clagett GP, Anderson FA Jr, Heit J, Levine MN, Wheeler HB. Prevention of thromboembolism. *Chest* 1995;108(Suppl):312S-34S.
19. Imperiale TF, Speroff T. A meta-analysis of methods to prevent venous thromboembolism following total hip replacement. *JAMA* 1994;271:1780-5.
20. Eastman RC, Javitt JC, Herman WH, Dasbach EJ, Copley-Merriman C, Maier W, et al. Model of complications of NIDDM. II. Analysis of the health benefits and cost-effectiveness of treating NIDDM with the goal of normoglycemia. *Diabetes Care* 1997;20:735-44.
21. Gold MR, Seigal JE, Russell LB, Weinstein MC, editors. Cost-effectiveness in health and medicine. 27-29. New York: Oxford University Press, 1996.
22. Drummond MF, Richardson WS, O'Brien BJ, Levine M, Heyland D. Users' guides to the medical literature, XIII. How to use an article on economic analysis of clinical practice. A. Are the results of the study valid? Evidence-Based Medicine Working Group. *JAMA* 1997;277:1552-7.
23. Greenhalgh T. Is my practice evidence-based? *BMJ* 1996;313:957-8.
24. Gurwitz JH, Col NF, Avorn J. The exclusion of the elderly and women from clinical trials in acute myocardial infarction. *JAMA* 1992;268:1417-22.
25. Fletcher RH, Fletcher SW, Wagner EH. Clinical epidemiology: the essentials, Baltimore:: Williams & Wilkins, 1988.