Glossary

Terms used in therapeutics

Allocation concealed: deemed to have taken adequate measures to conceal allocation to study group assignments from those responsible for assessing patients for entry in the trial (e.g., central randomisation; sequentially numbered, opaque, sealed envelopes; sealed envelopes from a closed bag; numbered or coded bottles or containers; drugs prepared by the pharmacy; or other descriptions that contain elements convincing of concealment.

Allocation not concealed: deemed to have not taken adequate measures to conceal allocation to study group assignments from those responsible for assessing patients for entry in the trial (e.g., no concealment procedure was undertaken, sealed envelopes that were not opaque, or other descriptions that contain elements not convincing of concealment).

Unclear allocation concealment: the authors of the article did not report or provide us with a description of an allocation concealment approach that allowed for classification as concealed or not concealed.

Blinded: any or all of the clinicians, patients, participants, outcome assessors, or statisticians were unaware of who received which study intervention. Those that are blinded are indicated in parentheses. If "initially" is indicated (e.g., blinded [patients and outcome assessor initially]), the code was broken during the trial, for instance, because of adverse effects.

Blinded (unclear): the authors did not report or provide us with an indication of who, if anyone, was unaware of who received which study intervention.

Unblinded: all participants in the trial (clinicians, patients, participants, outcome assessors, and statisticians) were aware of who received which study intervention.

WHEN THE EXPERIMENTAL TREATMENT REDUCES THE RISK FOR A BAD EVENT

RRR (relative risk reduction): the proportional reduction in rates of bad events between experimental (experimental event rate [EER]) and control (control event rate [CER]) patients in a trial, calculated as |EER—CER|/CER and accompanied by a 95% confidence interval (CI).

ARR (absolute risk reduction): the absolute arithmetic difference in event rates, |EER—CER|

NNT (number needed to treat): the number of patients who need to be treated to prevent one additional bad outcome; calculated as 1/ARR, rounded up to the next highest whole number, and accompanied by its 95% CI.

WHEN THE EXPERIMENTAL TREATMENT INCREASES THE PROBABILITY OF A GOOD EVENT

RBI (relative benefit increase): the increase in the rates of good events, comparing experimental and control patients in a trial, also calculated as |EER—CER|/CER.

ABI (absolute benefit increase): the absolute arithmetic difference in event rates, |EER—CER|.

NNT: calculated as 1/ABI; denotes the number of patients who must receive the experimental treatment to create one additional improved outcome in comparison with the control treatment.

WHEN THE EXPERIMENTAL TREATMENT INCREASES THE PROBABILITY OF A BAD EVENT

RRI (relative risk increase): the increase in rates of bad events, comparing experimental patients to control patients in a trial, and calculated as for RBI. RRI is also used in assessing the effect of risk factors for disease.

ARI (absolute risk increase): the absolute difference in rates of bad events, when the experimental treatment harms more patients than the control treatment; calculated as for ABI.

NNH (number needed to harm): the number of patients who, if they received the experimental treatment, would lead to one additional person being harmed compared with patients who receive the control treatment; calculated as 1/ARI.

Confidence interval (CI): the CI quantifies the uncertainty in measurement; usually reported as 95% CI, which is the range of values within which we can be 95% sure that the true value for the whole population lies.

Terms used in diagnosis

Sensitivity: the proportion of patients with the target disorder who have a positive test result (a/[a + c]) (Figure).

Specificity: the proportion of patients without the target disorder who have a negative test result (d/[b + d]) (Figure).

Pretest probability (prevalence): the proportion of patients who have the target disorder, as determined before the test is carried out ([a + c]/[a + b + c + d]) (Figure).

Pretest odds: the odds that the patient has the target disorder before the test is carried out (pretest probability/[1 — pretest probability]).

Likelihood ratio (LR): the ratio of the probability of a test result among patients with the target disorder to the probability of that same test result among patients who are free of the target disorder. The LR for a positive test is calculated as sensitivity/(1 — specificity). The LR for a negative test is calculated as (1 — sensitivity)/specificity.

Post-test odds: the odds that the patient has the target disorder after the test is carried out (pretest odds × LR).

Post-test probability: the proportion of patients with that particular test result who have the target disorder (post-test odds/ [1 + post-test odds]).

		Target disorder	
		Present	Absent
Test result	Positive	a	b
	Negative	c	d

Comparison of test results with a diagnostic standard.

Incorporating economic analysis into clinical practice guidelines: a guide for hopeful users

A large health plan has asked you to help them develop a clinical practice guideline for colon cancer screening. The plan currently covers annual fecal occult blood testing (FOBT) and flexible sigmoidoscopy every 5 years as screening methods. Member rates for both types of screening are very low (hence the impetus for the guideline). At the behest of several local gastroenterologists, the plan is also considering whether to cover colonoscopy every 10 years for average-risk people ≥50 years of age. Part of the process involves reviewing the cost-effectiveness literature, because the chief executive officer of the health plan is skeptical that colonoscopy represents a wise use of their ever-tightening budget. You are familiar with US Preventive Services Task Force Guidelines for colon cancer screening. After reviewing several recent cost-effectiveness studies, however, you find them daunting in terms of methodological complexity, terminology, and representation of outputs (a confusing array of large numerical tables and graphs that strongly resemble something you studied in first-year college economics). Is it possible to translate these studies into something you understand, believe reflects sound clinical practice, and believe would be useful to the health plan for their decision making?

The situation just described, an apparent disconnect between costs and clinical practice guidelines and the confusion it causes for readers, is not unusual. Economic analyses are rarely included in guidelines, mostly because each discipline has different and often conflicting views of what constitutes "best practice".[1,2] This exclusion is unfortunate, because both guidelines and cost-effectiveness studies offer important information to help us practice more effective and efficient health care. Decision makers today have a need to synthesise and interpret these studies rapidly and efficiently. This editorial offers suggestions to help clinicians understand cost-effectiveness studies and to use them in developing guidelines. Its approach is similar to the methods for defining and answering clinical queries used by those who practice evidence-based medicine: defining the clinical question, searching for evidence, and evaluating the quality of evidence.

(1) What is the clinical problem that is the subject of the guideline?

In this case we focus on screening options for adults ≥50 years of age who do not have symptoms of and who are at average risk for colorectal cancer.

(2) What interventions are being considered? What is the default intervention, if any?

Guidelines are designed to reduce variation in care, with the goal of using treatments that have been shown to improve desirable outcomes or minimise undesirable ones. Likewise, cost-effectiveness studies most often focus on comparing new with existing care. In the case of colon cancer screening, the health plan already covers flexible sigmoidoscopy and FOBT, treatments with good evidence of efficacy. It is thus reasonable to consider the cost-effectiveness of colonoscopy compared with the following alternatives: no screening, flexible sigmoidoscopy alone, FOBT alone, and sigmoidoscopy plus FOBT.

(3) Search the literature for cost-effectiveness studies

Searching for high-quality economic articles can be laborious, and the outcomes are not always satisfactory,[3] primarily because of overuse of the term *cost-effectiveness* in the literature. Searching for this term will retrieve many articles, but most are not formal economic analyses. To address this problem, I suggest starting by using the medical subject heading (MeSH) for cost-effectiveness analysis, that is, "cost-benefit analysis" (when searching in Medline) with other terms that are specific to the clinical situation and technologies being compared (as outlined in 1 and 2 above). For colon cancer screening in PubMed (www.ncbi.nlm.nih.gov/entrez/query.fcgi), start with "cost-benefit analysis" as well as the content terms "screening, colonoscopy, sigmoidoscopy, and fecal occult blood." Although this approach is not perfect, it improves the specificity of the search and substantially reduces the volume of articles compared with using the last 4 terms alone. In this case, we retrieve 24 articles. Reviewing the abstracts, it appears that several are formal cost-effectiveness analyses of all 3 screening methods. For this exercise, we select 3 recent analyses.[4–6] These will be a good start for the next phase of the evaluation.

(4) What is the bottom line of each study for the interventions being considered?

The bottom line of most economic analyses is an incremental cost-effectiveness ratio—that is, the ratio of the difference in costs over the difference in outcomes for the interventions being compared. While starting with the conclusion does not help us determine the quality of the methods, it allows us to address the question: "If this were true, could it influence how I practise (or write or implement the guidelines)?" The economic analysis could be influential, for example, if it states that a little-used treatment is highly cost-effective, or conversely, that a widely advocated treatment has poor cost-effectiveness. If your answer to the question is "no," then stop reading. If the answer is "yes," we need to go on and review the methods to answer another question: "Is it likely to be true?"

In this case, the 3 studies consider the relative values of colonoscopy, flexible sigmoidoscopy, and FOBT as screening tools for people ≥50 years of age at average risk for colorectal cancer.[4–6] Comparisons worth considering include the value of each compared with no screening and the incremental value of colonoscopy compared with either flexible sigmoidoscopy or FOBT. Because colonoscopy is more costly than the other approaches (at least initially) it is important to ask what one gets for this additional expenditure. Table 1 gives the results.

These results tells us 2 things. Firstly, all 3 studies conclude that compared with no screening, all strategies are reasonably cost-effective when using a (rather arbitrary, but widely cited) threshold of $50 000/life-year gained. Secondly, the articles

Table 1 *Cost-effectiveness of colorectal cancer screening as reported in selected articles**

Interventions compared	"Bottom Line" (cost per life-year gained, 1998 dollars) (reference)†		
	Sonnenberg (4)	Frazier (5)	Vijan (6)
Annual FOBT *v* no screening	$9705	$12 667	$7756
FS every 5 years *v* no screening	$36 509	$12 571	$14 668
Colonoscopy *v* no screening	$10 983	$20 418	$7019
Colonoscopy *v* annual FOBT	$11 382	$76 552	$6243
Colonoscopy *v* FS every 5 years	Dominates‡	$52 903	Dominates‡
Colonoscopy *v* FS every 5 years plus annual FOBT	Not available	$561§	$332 630§

*FOBT = fecal occult blood test; FS = flexible sigmoidoscopy.

†Baseline compliance: Sonnenberg 100%, Frazier 60%, Vijan 75%.

‡Dominates means that the second procedure listed was more costly and less effective than the first procedure.

§FOBT plus flexible sigmoidoscopy is more expensive and more effective than colonoscopy.

reach very different conclusions regarding the incremental value of colonoscopy compared with FOBT and flexible sigmoidoscopy. Sonnenberg[4] *et al* and Vijan[6] *et al* state that compared with FOBT and flexible sigmoidoscopy alone, colonoscopy provides good value; study 2 finds that colonoscopy is only marginally effective.

(5) What factors "drive" the outcome?

Cost-effectiveness analyses are by nature synthetic, usually integrating data from multiple sources to derive the result. Reviewing each source (there can be dozens) for quality and accuracy is impractical for most decision makers. To help with this issue, ask: "What factors drive the outcome, that is, would have the greatest influence on the bottom line of the study if they were changed from their baseline value?" This issue, formally termed *sensitivity analysis*, is a logical next step for evaluating the quality of a cost-effectiveness study. As a rule of thumb, 2–4 factors usually have the greatest effect on the outcome, especially the cost and efficacy of the intervention. If the cost-effectiveness ratio changes from favourable to unfavourable (or vice versa) at plausible values for influential factors, this reduces confidence in the conclusions.[a]

Most cost-effectiveness studies have a sensitivity analysis section that addresses this issue. Unfortunately, it is difficult to identify the most influential factors for the 3 screening methods in the sensitivity analysis sections of the 3 studies. The 2 mentioned consistently are procedure cost and compliance. These are useful because they are seldom specifically evaluated in clinical trials and are likely to vary from setting to setting. Table 2 summarises the sensitivity analysis for these variables.

It seems that varying procedure cost or compliance across a probable range is unlikely to have an extremely adverse effect on the cost-effectiveness of the 3 strategies.

(6) How valid are the most influential variables at their default values?

If the bottom line of the study is highly dependent on specific factors, then these should be scrutinised closely. It is particularly important that influential data are based on the highest quality trials available, preferably randomised controlled trials (RCTs). Of note, the ability of colonoscopy to prevent colorectal cancer or mortality has not been measured in a randomized screening trial. Two articles base their results on 1 case-control study,[7] suggesting that screening colonoscopy reduces the risk for dying of colon cancer. None of these articles would pass the screening criteria for cost-effectiveness studies used by *Evidence Based Medicine* which requires ≥ 1 of the studies included in the analysis of effectiveness to be an RCT. One could easily justify ignoring these articles at this point if the purpose was simply to keep up to date. However, our purpose is to address a policy problem (about screening), and for this the lack of strong evidence should be considered in reaching a decision about colonoscopy. The effectiveness of FOBT, on the other hand, is supported by 3 large RCTs showing benefit in reducing colorectal cancer-related mortality.[8–10] Flexible sigmoidoscopy is intermediate in effectiveness, with 1 small RCT and 2 case-control studies showing benefit.[11–13]

(7) Interpretation: how should the economic studies influence the guidelines?

If we are reasonably confident that the economic studies are valid and cover the major clinical choices facing the organisation, next we need to consider what part (if any) they should play in shaping the guideline. These include issues that extend beyond the scope of the studies, such as implementation costs and the availability of clinicians trained in colonoscopy. Other issues, such as the first-year budget effect of adopting a particular policy, may or may not be available from the economic studies (in this case they are not). All should be considered (and weighted) in conjunction with the economic and clinical data.

The economic studies suggest that given the assumptions about efficacy, compliance, and cost, all methods—including colonoscopy—are relatively cost-effective for colorectal cancer screening compared with no screening. From an evidence-based medicine perspective, the weak supporting clinical evidence of the efficacy of colonoscopy is problematic. The clinical and economic outcomes of FOBT are more certain because efficacy rates are drawn from RCTs, and sensitivity

Table 2 *Sensitivity analysis of screening v no screening for cost and compliance**

Variable	Cost per life-year gained v no screening (1998 dollars)					
	FOBT		Flexible sigmoidoscopy		Colonoscopy	
	Best	Worst	Best	Worst	Best	Worst
Cost	$9705†	$12 667‡	$14 668§	$36 509†	$7019	$20 418‡
	($4)	($38)	($225)	($401)	($550)	($1012)
Compliance	$5530§	$32 500†	$5800‡	$22 161§	$10 983†	$26 000†
	(100%)	(0%)	(100%)	(25%)	(100%)	(0%)

*Results are the most and least cost-effective outcomes among all 3 studies at the stated factor extremes (in parentheses). Direct comparability is limited because of variations in other factors and modelling techniques. Estimates at factor extremes were not available for all studies.

† = reference 4.

‡ = reference 5.

§ = reference 6.

analyses show that the outcomes are probably maintained across a reasonable range of costs and compliance. The same applies to a lesser extent for flexible sigmoidoscopy.

How much "worse" would colonoscopy be from a cost-effectiveness standpoint if the efficacy was not as assumed? Unfortunately, this is not addressed in the economic studies. The studies together suggest that *incremental* gain of switching from FOBT or flexible sigmoidoscopy to colonoscopy is highly uncertain, ranging from "dominant" to very cost-ineffective. As with clinical studies, such a degree of uncertainty should make one pause before adopting a new standard of care for an organisation. Thus, the review of the cost-effectiveness and clinical evidence do not support adopting colonoscopy as a covered screening procedure at this time. At this point it is reasonable to note that "absence of proof is not proof of absence." It could well be that colonoscopy is more effective than FOBT or flexible sigmoidoscopy, even taking into account increased morbidity. However, the onus of proof rests with those who believe this is the case.

Meanwhile, the evidence and cost-effectiveness analyses support screening with FOBT (or flexible sigmoidoscopy when affordable) and justify efforts to increase utilisation of this programme. As it happens, success with such a programme would also increase the use of colonoscopy to evaluate "positive" findings by FOBT.

Conclusion

Economic analyses have much to offer in the creation of clinical practice guidelines. They often "put the pieces together" between treatment and outcome and give a sense of health value for money, this latter issue being an unavoidable fact of life in today's environment. Economic analyses should not dictate clinical practice guideline policies, but they can inform them by identifying the evidence that is available and helping to identify cost-inefficient strategies and making explicit the tradeoffs between benefit and expenditure for others.

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[a]*One-way sensitivity analyses generally understate the uncertainty in the cost-effectiveness ratio. One should check to see if the article presents confidence intervals around the cost-effectiveness ratio. New tecniques that can estimate confidence intervals are being used more frequently today.*

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How to cite material from Evidence-Based Medicine

Citation of material from the Notebook

Milne R, Hicks N. Evidence-based purchasing [EBM Note]. *Evidence-Based Medicine* 1996 May-Jun;**1**:101–2.

Citation for material taken from a structured abstract, written without attribution by a staff member

Antihypertensive drugs decrease mortality, coronary events, and stroke in elderly persons [abstract]. *Evidence-Based Medicine* 1996 May-Jun;**4**:105. Abstract of: Pearce KA, Furberg CD, Rushing J. Does antihypertensive treatment of the elderly prevent cardiovascular events or prolong life? A meta-analysis of hypertension treatment trials. *Arch Fam Med* 1995;**4**:943–50.

Citation for material taken from a commentary to an article

Olds D. Commentary on "Home visiting programmes reduce childhood injury." *Evidence-Based Medicine* 1996 May-Jun;**4**:112. Comment on: Roberts I, Kramer MS, Suissa S. Does home visiting prevent childhood injury? A systematic review of randomised controlled trials. *BMJ* 1996;**312**:29–33.

Correction

The commentary for the abstract "Increased plasma total homocysteine increased the risk of dementia in the elderly"[1] should have acknowledged Bart Sheehan, MRCPsych (from the University Department of Psychiatry, Warneford Hospital, Oxford, UK) as first author.

1 Increased plasma total homocysteine increased the risk of dementia in the elderly [Abstract]. *Evidence-Based Medicine* 2002 Sep-Oct;**7**:160. Abstract of: Seshadri S, Beiser A, Selhub J, et al. Plasma homocysteine as a risk factor for dementia and Alzheimer's disease. *N Engl J Med* 2002;**346**:476-83.