Practice Analyses and Protocol Analyses of Cost-Effectiveness: An Inconvenient Distinction

Abraham P. Schwab
Assistant Professor
Philosophy Department
Indiana University Purdue University Fort Wayne
2101 E. Coliseum Blvd
Fort Wayne, IN 46805

Funded in part by a grant from The City University of New York PSC-CUNY Research Award Program

Running Head: An Inconvenient Distinction

Word Count: 4680

Keywords: cost-effectiveness, medical research, randomized clinical trials, patient preferences
Practice Analyses and Protocol Analyses of Cost-Effectiveness: An Inconvenient Distinction

Abstract

Using four exemplars of cost-effectiveness analyses, I argue that discussions of and research on cost-effectiveness in medical practice should clearly delineate between protocol and practice cost-effectiveness analyses. Failure to do so risks confusing conclusions that warrant substantial confidence and limited applicability with conclusions with broader applicability but more limited confidence. Further, these different types of analyses incorporate different sets of values into the analysis. In turn I argue that some favor should be shown for those analyses that include a wider array of values.

Keywords: cost-effectiveness, medical research, randomized clinical trials, patient preferences
Given the absolute and relative amounts of money spent on health care in the United States each year, it is no surprise that increasing attention is focused on the effectiveness of the money spent. The sheer number of studies on cost-effectiveness gives some indication of this emphasis—a recent search on Medline (CSA) produced 667 publications with “cost-effectiveness” in the title from 2009 alone (Accessed April 29, 2010). The value of these publications, however, is limited by the diverse methodologies employed when determining “cost effectiveness.” Hence, there are reasons to believe that conclusions reached in such studies will not always, or perhaps even regularly, recommend more cost-effective practice.

The Fundamental Mistake

Put generally, current studies of cost-effectiveness fail to adequately account for the distinctions between medical research and medical practice. In medical practice, the interests of the patient trump the opportunity to improve the knowledge base for medical practice. In medical research, improving the knowledge base of medical practice trumps (with the research subject’s consent) improving the health of the research subjects. These procedural differences significantly affect cost-effectiveness analysis. Specifically, cost effectiveness analyses fall along a spectrum highlighted by two broad categories: protocol analyses and practice analyses. Of these, practice analyses appear to be the most likely to produce policy-guiding conclusions, in part because they draw data from the actual practice of medicine. And yet, too many cost-effectiveness analyses rely heavily on some version of protocol analyses, which draw their data from the rigidly defined protocols of clinical trials, with limited attention to practice. Moreover, none of these analyses make
note of the substantial differences between practice and protocol analyses. This leaves practitioners and policy-makers to determine what value these conclusions have. Given the less than rigorous attention practitioners pay to the voluminous literature for which they are responsible [ref], this is unlikely to be effective.

Throughout the remainder of this essay, cost-effectiveness analyses will be critiqued using the lens of four analyses from the literature. It should be noted that each of these focal studies is a singular goal comparison. Singular goal comparisons analyze the costs of treatments for the same disease or condition. For example, Tran et al. (2007) compare the cost effectiveness of four statins. The analysis is streamlined because all the interventions aim to achieve the same goal. One has only to measure the clinical effectiveness and divide it by the cost. In contrast, multiple goal comparisons compare the cost-effectiveness of treatments for different diseases or conditions. For example, the cost-effectiveness of liver transplants might be compared to the cost-effectiveness of knee replacements. Making such comparisons requires the use of a translational metric—outcomes from apparently incompatible types must be translated into a common metric. As Baron, (2004) as well as others, has shown, Quality Adjusted Life Years (QALYs) can be used as such a metric. The QALY, however, is subject to difficulties in application (e.g., Oregon’s 1988 attempt to determine health care priorities). Willingness-to-pay (WTP) is another translational metric that has its own difficulties in application. (Bleichrodt and Eeckhoudt, 2006; Telser and Zweifel, 2007)

Singular goal comparisons constitute the basis for the analysis in this essay because they are both more numerous and produce tidier conclusions. As noted, the metrics necessary for multiple goal comparisons remain controversial. As such, the use of these
metrics introduces additional noise into conclusions about cost-effectiveness. My goal is to show that even without this additional noise, cost-effectiveness analyses, as they are currently employed, are not adequately organized to provide actionable advice for the practice of medicine.

Value Calibration and the Elasticity of Cost

The studies discussed below presume that determining the most cost effective treatment depends fundamentally on comparing clinically effective treatments. Indeed, these kinds of effectiveness are typically inseparable. Generally, if a known treatment is unaffordable it is as useful as no treatment at all. Also, if the treatment is clinically ineffective, it would usually be more cost effective to do nothing. And yet by some patients, treatment is considered valuable even if there is no demonstrable clinical effect. Think of the common cold--the cold will run its course regardless of any treatments or lack thereof. In such cases, bed rest may be the most clinically and cost effective treatment. Nonetheless, some patients feel much better, and so think it is worth the cost, if they procure antibiotics to treat the cold, even though such treatment has no direct effect on the cold. In other cases, clinically effective treatments are available, but some patients attach no value to them. These patients are not interested in treating their disease or symptoms, and so no treatment is the most cost-effective option.

These exceptional cases highlight the elasticity of the term "cost." Specifically, there are three categories of cost that warrant attention: monetary costs (e.g., how much clinical effect can be purchased by each dollar spent), inter-subjective costs (e.g., how much is it worth to people, in general, to achieve a certain goal), and personal costs (e.g.,
how much is it worth to this individual to achieve this goal). Protocol analyses tend to favor monetary costs to the exclusion of other costs. In these cases the quality of the analysis is likely compromised. For example, because the personal and inter-subjective costs of avoiding edema and/or radiation therapy are not included in Cohn et al.’s analysis (the fourth cost-effectiveness analysis discussed), the validity of their conclusions (drawn solely from monetary assessments) depends on the tenuous hope that the inter-subjective and personal costs associated with these side-effects will correlate with the monetary costs of the treatments.

Striking a balance among monetary, inter-subjective, and personal values requires resolution of the ethical dilemma inherent in current health care systems. On the one hand, there is an ongoing and ever-refined attempt to prioritize patient choice with all its idiosyncrasies, and on the other hand, is the fact that so much funding for health care comes from public coffers. Exclusive attention to the public source of the funds will favor concerns about social justice and likely emphasize monetary and inter-subjective values. Monetary values because they indicate the best improvement in medical condition for each dollar spent. Inter-subjective values because they indicate the means of improving medical conditions favored by a majority of the public. An emphasis on the perspective of the patient, however, will favor concerns about autonomy and personal and inter-subjective values. Personal values because the costs, from the patient’s perspective, include protection of their personal views and plans. Inter-subjective values because these give some indication of the best choice for those cases where personal values are not developed or not relevant. Without resolution of the conflict produced by public funding for personal
choice, attempts to achieve cost-effectiveness will oscillate, likely arbitrarily, between definitions of cost at the individual and social level.

The Indeterminacy of Protocol Analyses: HIV in Resource Limited Settings

Antiretroviral treatments (ARTs) are standard treatments for HIV positive individuals. These treatments have corollary variances in mechanism and cost. Typically, when treating HIV-positive individuals, one ART is used until failure (toxic reaction or failure to limit symptoms). At that point, another ART is tried. Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs) are the least expensive ARTs and so tend to be the most cost-effective initial treatment for an HIV-positive individual. Over time patients become resistant to NNRTIs, making NNRTIs no longer clinically- or cost-effective. Once an individual is NNRTI-resistant, boosted protease inhibitors (PIs) are the ART of choice. For treating a population of HIV positive individuals, the most cost effective treatment strategy might seem to begin by diagnosing every individual’s NNRTI resistance. Using this information, NNRTI-resistant individuals would receive the more expensive, but effective, PI regimen and everyone else would receive the less expensive NNRTI regimen. Both regimens would be used on precisely the right patients.

The expense of diagnosing NNRTI resistance for an entire population, however, negates the cost savings of such personalized care. This problem is particularly poignant in developing countries with increasing HIV positive populations and limited resources for treatments. Instead of diagnosing NNRTI resistance, clinics in these countries are more likely to use NNRTIs as a default treatment. Even though this guarantees some waste
(some patients will be NNRTI resistant), the economic costs of wasted treatments will often be less than the economic cost of diagnosing every patient's NNRTI resistance.

As Walensky et al (2007) note, the strategy of using NNRTI as the default treatment will stop being cost effective once a large enough segment of the patient population has become NNRTI resistant. Estimates of a patient populations’ NNRTI resistance could be gathered from previously treated individuals, which in turn, could identify whether NNRTI or PI is the most cost effective default treatment. The challenge, then, is identifying the tipping point: the moment when it is cost effective to set the default treatment to PI rather than NNRTI.

Using data and analyses from a number of trials, Walensky et al produce a model to identify this tipping point. Theirs is a classic example of a model analysis, a subset of protocol analyses. Model analyses evaluate cost-effectiveness by producing models based on previous research protocols. For reasons of funding, complexity, and perhaps, human subjects protection, these analyses integrate previously gathered data to draw conclusion to guide future practice. As the Walensky et al study illustrates, such studies confront a number of obstacles to providing actionable recommendations.

Walensky et al include data from regionally diverse trials that lack many common features (e.g., one trial measured opportunistic infections, but did not incorporate an ART—be it an NNRTI or PI). Confidence in their conclusions is limited by the increased variability of data included and the inevitable indeterminacy this brings. Undoubtedly, model analyses will produce conclusions that are reliable to some degree, but studies like this one dull the precision of actionable guidance. For example, their model produces results overwhelmingly in favor of NNRTI as default treatment. Only if there is a dramatic
cut in the cost of PI (80%) or a substantial population level NNRTI resistance (39%) would PI be cost-effective as a front line treatment. (Walensky, 978) But, given the inevitable indeterminacy, if the cost for PI drops 60% rather than 80% should a change in the default treatment strategy be considered? What if the NNRTI resistance of a population is 25% rather than 39%?

Model analyses of cost-effectiveness, as one form of protocol analyses, are crippled by the indeterminacy inherent in the incorporation of widely diverse sets of data.

The Artificial Nature of Protocol Analyses: Generic versus Brand-Name Cholesterol Medications

High LDL-C tends to be concentrated in developed world populations. Nonetheless, just as HIV treatments have significant health and longevity effects, so does high LDL-C. Tran et al (2007) analyze the cost-effectiveness of pharmacologic strategies for addressing this problem by executing two evaluations of two brand-name statins and two generic statins. First, they perform a classic cost-effectiveness analysis by dividing the monetary cost of each statin by its clinical effect. Second, they perform a more complicated analysis by incorporating the subjective variable of "willingness-to-pay" (WTP). Typically, WTP analyses attempt to affix a monetary value to some non-monetary good. For example, a WTP analysis could determine how much homeowners are willing to pay to avoid living near an airport (Rahmatian and Cockerill, 2004). Both the classic analysis and the willingness to pay analysis have debilitating difficulties, and they will be taken in order.
While a classic cost-effectiveness analysis could produce tractable and actionable recommendations, Tran et al’s analysis does not. Because their analysis is a typical protocol analysis, it is based entirely on randomized clinical trials. As such, their findings will be limited by difficulties in translation from research to practice settings. They send mixed messages about this difficulty by nothing both that observational studies have indicated Rosuvastatin’s effectiveness in medical practice (e211), and that other studies "have indicated reduced statin effectiveness in the usual care setting outside of clinical trials." (e211) Even on the most generous reading, this is not enough. Noting that there will be a difference between research and practice does not legitimize determinations of cost-effectiveness based entirely on research protocols.

Using data from clinical trials has clear advantages: clean, sometimes more readily available data; conclusions more readily reached and, in most cases, more confidently held. And yet, the very structure that provides confidence in the conclusion also limits confidence about the applicability of this conclusion to practice. Specifically, strictly applied inclusion and exclusion criteria, the rigidity of the protocol, and the additional motivation of the subjects (e.g., monetary and other incentives attached to participation in the clinical trial), all work to confound the application from the clinical trial to clinical practice. Determinations of cost-effectiveness grounded on clinical trials may be misleading because the aforementioned limitations obfuscate the effects of treatment externalities. For example, patient willingness to adhere to certain treatment recommendations may be limited by the lifestyle effects that attach to these treatments. Such effects may range from routine (the frequency with which a drug must be ingested or injected) to the dramatic (bouts of nausea or diarrhea) to the relational (sexual
dysfunction). Additional incentives found in clinical trials (e.g., free care or monetary payment), may also have substantial effects. Inability to account for the effect of these externalities produces two obstacles to translating protocol analysis into actionable advice for clinical practice.

First, the particular weights given to side-effects may be either personal or inter-subjective, both of which create substantial obstacles. On the one hand, the particular value attached to the feeling of nausea will likely be patient-specific: for some patients it will be more important than for others. On the other hand, the long-term costs associated with broad- instead of narrow-spectrum antibiotics are inter-subjective or social. The former is inscrutable during clinical trials and the latter requires a broader population than clinical trials typically allow.

Second, including externalities or indirect costs makes the evaluation of cost significantly more complex. Externalities and indirect costs are difficult to measure because, for example, it is not always easy to tell if eliminating nausea is worth $50 a day or closer to $100 (or perhaps $1000). The best criterion constructed to date appears to be the previously mentioned willingness-to-pay (WTP). As Olsen (2001) suggests, WTP is a comprehensive evaluation of the value of certain health outcomes. As noted above, it is not without its problems.

Because Tran et al.’s analysis builds on conclusions of the protocol analysis, the previously mentioned difficulties will also apply to the WTP analysis. There are, however, additional problems with this WTP analysis. Rather than attempt to determine what individuals are willing to pay to lower their LDL-C, Tran et al. assume complete indeterminacy about the WTP value attached to lowering LDL-C. There is a payoff. It
turns out the generic versions, though less expensive, have a diminished clinical effect. Though Tran et al do not raise the possibility, this could be because of the increased placebo effect that more expensive medications enjoy (Waber et al 2008). Regardless, when placed in the context of WTP, these differences in clinical effect illustrate that as the subjective value of reducing LDL-C approaches zero, a lower-cost but less clinically effective statin is more cost-effective. And yet, the uneven translation of these medications from trial to practice undermines the value of this cost-effectiveness analysis. If Rosuvastatin is 25% less effective in practice and some other statin is only 10% less effective, the included WTP graphs are moot.

Finally, Tran et al's analysis purports to show that Rosuvastatin (one of the brand-name drugs) will be, in the vast majority of instances, the most cost-effective option. Up to this point, their analysis has been taken at face value. There is, however, reason to be suspicious: Tran et al partially disclose a conflict of interest when they acknowledge that AstraZeneca provided the funding for the study. They do not mention that AstraZeneca produces Rosuvastatin, though it is relatively easy to determine (e.g., a simple internet search). At first blush, only partial disclosure would seem to undermine the point of requiring disclosure of conflicts of interest. Unless readers are already aware that AstraZeneca manufactures Rosuvastatin, they are not alerted to the nature of the conflict of interest. This lack, however, will have unclear effect. The conclusions of Cain et al (2004) challenge the value of disclosing conflicts of interest. Their study showed that when advisees (e.g., readers of Tran et al’s article) are alerted to the conflict of interest, they become unsure what to do with the recommendation made by the experts and make more erratic decisions. Hence, in this case, failing to fully disclose may help advisees make more
definitive decisions. At the same time, Cain et al also demonstrated that the act of disclosing the conflict of interest may pervert the advice offered by experts. In their study, advisors who disclosed an existing conflict of interest were much more likely to give advice that was biased by that conflict than advisors who did not disclose an existing conflict. In sum, the partial disclosure by Tran et al may bias their recommendations in favor of AstraZeneca’s Rosuvastatin, even if readers are unaware that the disclosure has occurred.

Other Problems for Protocol Analyses: Timeframes and Outcomes for an Elderly Population

One of the challenges facing medical practice is its ability to match its success in acute care with equally successful chronic care. The elderly are a population of particular concern here: cycles of admission, discharge, and readmission are common, stressful, and costly. Sindaco et al (2007) set out to determine if structured disease management programs (DMPs) are better than usual care at breaking this cycle and improving the health of elderly patients following heart failure.

The particular DMP they evaluated includes "discharge planning, education, therapy optimization, improved communication, early attention to signs and symptoms." (325) Usual care (the control) includes whatever various treatments and services were ordered by the patients’/research subjects’ primary care physician and/or personal cardiologist. The study lasted two years with earlier end points for either death or hospital admission for heart failure. As it turned out, subjects treated with the DMP had a higher
quality of life and functional status than subjects treated with usual care. Further, the DMP also proved to be more cost-effective at a rate of about 1,000 euros per subject.

Despite the substantial clinical and cost improvements, the application of this study has two significant limitations. First and foremost the exclusion criteria of this study, as in all protocol analyses, produce certain obstacles for application. In this case, patients with "coexisting non-cardiac illness likely to reduce life expectancy" were excluded. (325) Because of the specific population in question, it handcuffs the application of the study. As much as this exclusion increases warranted confidence in conclusions about cost (and even clinical) effectiveness, the elderly population is a population more likely than average to have coexisting and complicating conditions. Accordingly, DMPs limited to elderly patients who have suffered a heart attack but have no complicating conditions will have a narrow domain for confident application.

Second, the two-year time frame may obfuscate evaluations of cost-effectiveness. While Sandico et al illustrate a substantial savings per patient, it was likely a corresponding result of the clinical effectiveness of the DMPs. Because the DMP decreased the chance that subjects would be readmitted to the hospital for any reason and maintained higher functional status (327), these subjects were less likely to spend resources during the two years of the study. This does not mean these patients will not return to the hospital at some later time. The money may not actually be saved, but simply deferred to a later time.

The Difficulties of Integrating Protocol and Practice Analyses: Three Treatment Strategies for Endometrial Adenocarcinoma
It is estimated that 10,000 patients are diagnosed with grade 1 endometrial adenocarcinoma each year with treatment costs in the neighborhood of $250 million, which is about $25,000 per patient (Cohn et al 2007 1388). A small savings in relative terms translates into substantial absolute value: a treatment strategy that is 5% less expensive would save about $12.5 million/year. Cohn et al (2007) examine three treatment strategies for grade 1 endometrial adenocarcinoma to determine which one is the most cost-effective. They rely on a number of research studies (including Phase II, Phase III and observational studies) as well as “other sources,” which turns out to be extrapolation from the authors’ clinical experiences. The three strategies that are evaluated: First, Surgical Staging includes total hysterectomy and lymphadenectomy during a single surgery. Second, Frozen Section Analysis requires total hysterectomy followed by analysis to determine the need for lymphadenectomy. If needed, the lymphadenectomy would be performed during a second surgery by a consultant surgeon. Third, No Staging involves total hysterectomy without lymphadenectomy and no analysis of lymph node involvement. With an increased risk of undiagnosed lymph node involvement, No Staging included a greater likelihood of radiation treatment at a later date.

According to Cohn et al’s analysis, Surgical Staging turns out to be the most cost-effective treatment with savings of $1000-2000 per patient, which over ten thousand patients, turns into $10-20 million per year. Compared to Frozen Section Analysis, it does not involve the co-surgeons or additional peri-operative analysis. Compared to No Staging, it carries a much lower likelihood for radiation at some later time.

By including Phase II, Phase III and observational studies supplemented with clinical experience, Cohn et al’s analysis included what Walensky et al's and Tran et al's
analyses did not—data from clinical practice. And yet, Cohn et al's undifferentiated use of these clinical practice inputs undermines these potentially substantial improvements in applicability.

Cohn et al's undifferentiated mixture of observational studies with clinical trials produces noise in the conclusions of such analyses, cultivating the worst of both worlds. First, the confident conclusions of the clinical trials are deflated through mixture with less confident conclusions of observational studies. For example, claiming that radiation is needed after the No Staging strategy in 40% of cases, it would make a difference if the basis is clinical trials, observational studies, or some conglomeration. Second, the value of the wider set of inputs of observational studies is muddled through mixture with the more narrowly constructed clinical trials. If edema is a complication in 10% of surgical staging treatments, again, it makes a difference if this arises from observation or clinical trial.

These problems are further exacerbated by the addition of even less rigidly analyzed clinical experiences used by Cohn et al. They use personal experience as a supplement in those cases when effectiveness and recurrence rates were not available through clinical trials or observational studies. Reliability, however, eludes conclusions drawn from personal clinical experience because of limits on memory and biases in judgment. To an even greater degree than observational studies, the undifferentiated use of personal experience to draw conclusions about cost-effectiveness casts a pall of doubt over any conclusion reached.

Even if these substantial problems are overlooked, the monetary savings Cohn et al identify are simply that: monetary. Even though it is identified the most cost-effective strategy, Surgical Staging automatically includes a lymphadencectomy, which carries an
increased risk of edema (swelling) of the legs. Edema that is caused by surgery involving the lymph nodes can be a particularly frustrating medical condition because treatment is often ineffective. (Ely et al. 2006) Frozen Section Analysis may avoid this complication and its accompanying frustration, and No Staging would certainly avoid it. No Staging, then, may appear to be the most "cost" effective strategy for patients who put a high value on avoiding edema and its complications. No Staging, however, increases the chance patients will need radiation therapy, which can have side effects including digestive complications, irritation of the bladder, and decreased ability and/or desire for sexual intercourse. For these reasons, patients may also put substantial value on avoiding radiation therapy. As these potentially conflicting preferences show, including externalities in cost-effectiveness analyses transforms an analysis of monetary costs and clinical outcomes into the evaluation of an elaborate constellation of trade-offs. Consideration of these trade-offs brings into clear relief (once again) the need for clarity about the role personal preferences and their relative value should play in determinations of cost-effectiveness. It raises the question: "Should patients be allowed to choose a less cost-effective (externalities aside) treatment because of their personal preferences?"

Observational Study or Controlled Trial?

Clinical trials produce high levels of confidence in limited conclusions. Observational studies produce low levels of confidence in widely applicable conclusions. Given these opposing advantages and disadvantages, it may seem that carefully integrating clinical trials and observational studies is ideal. On this view, Cohn et al are on the right track, but need more systematic integration. A relatively recent study by Benson and Hartz
Benson and Hartz (2000) conclude that either observational studies or randomized controlled trials may be enough. They illustrate that observational studies with inclusion criteria similar to randomized, controlled trials produce similar conclusions. That is, this lone study suggests that either observational studies or randomized controlled trials will suffice. Even so, for treatments where side-effects are either dramatic or significant, there may be reason to favor observational studies.

Research Agenda

Additional studies comparing the results of observational studies and randomized clinical trials will be pivotal in the delineation of protocol analyses and practice analyses of cost-effectiveness and their relative usefulness as actionable advice. If the results of the study by Benson and Hartz (2000) can be confirmed regarding cost-effectiveness analyses in general, worries about the differences between protocol and practice analyses may be substantially diminished. Even if that is the case, it seems likely that the differences between these types of analyses will remain uneven—in some cases they will be quite large, in others less so.

Current trends in medical research could also be useful for improving research on cost-effectiveness. Specifically, previously completed registries should be mined for data to base cost-effectiveness analyses and new registries should be pursued either with the sole purpose of cost-effectiveness analyses or with cost-effectiveness analyses being one of multiple purposes.
The Ethics of Effectiveness

Failure to attend to effectiveness at all will fail to fulfill an obligation to patients

Failure to attend to differences in analyses of effectiveness undermines, in a more insidious way, this same obligation.

The Ethics of Effectiveness

The responsibility of the health care system and its practitioners to improve or preserve health in general implies an obligation to pursue the cost-effective delivery of health care. The more cost-effective the means of delivering health care, the more use the system can make of the same amount of resources, the better able the system is to improve or preserve health. What has been shown above is that the pursuit of cost-effective means for delivering health care should include an acknowledgement of the differences between protocol and practice analyses of cost-effectiveness. Only when acknowledging the limits on tractable applications of cost-effectiveness analyses—the limited translation of protocol analyses and the limited confidence of practice analyses—will attempts to achieve cost-effective delivery of health care be ethically sound.

Future analyses of cost effectiveness should clearly articulate the kinds of basis of the analyses as early as the abstract. That is, readers should be immediately aware of the limits attaching to any conclusion drawn in an analysis. This could be accomplished through adoption of the "protocol" and "practice" nomenclature I have used above.

As much as possible, future analyses should avoid protocol analysis when feasible. Until more than a single study has illustrated a confluence of conclusions from randomized clinical trials and observational studies the indeterminacy in translation from clinical trial
to clinical practice lessens the quality of actionable advice regarding cost-effective practice. That said, there are some cases, like perhaps the Walensky study discussed at the beginning of this essay, where some type of protocol analysis is needed for some independent reasons (i.e., protection of subjects).

If protocol analyses are used, any conclusions reached should be confirmed to the degree possible through independent analysis of data from clinical practice. This data should be systematically gathered and analyzed as part of an observational study, registry, or data bank. That is, personal recollections or other unsystematic use of personal experience should be avoided. Confirming the conclusions of protocol analysis with systematically organized and independent practice analyses will have the obvious advantage of providing independent confirmation through the use of a wider array of information.

Finally, all analyses, be they protocol or practice analyses, should explicitly draw attention to the values (monetary, personal, or inter-subjective) to which the analysis attends.

Conclusion

Significant problems dog many cost-effectiveness analyses. In general, the substantive differences between research and practice require more careful attention. Convenient as data gathered from clinical research is, the unfettered translation from research to practice remains unjustified because the role of subjective preferences and other externalities are unaccounted for in these analyses. At the same time, the appropriate weights to attach to externalities and subjective preferences remain unclear. Even though
the inclusion of practice-based information (e.g., observational studies and clinical experience) is desirable, the undifferentiated mixture of this data with data from clinical trials undermines the advantages of both.
Bibliography


