Using Costs in Cost-Effectiveness Models for Chronic Diseases

Lessons From Diabetes

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Background: Cost-effectiveness models for chronic diseases frequently require simulating the development of disease complications over a long period. Model development often focuses on disease progression, with less attention devoted to costs.

Objective: To identify key challenges in incorporating costs in cost-effectiveness models for chronic diseases.

Research Design: We use our experience in developing and applying a diabetes cost-effectiveness model to illustrate the challenges in incorporating costs in cost-effectiveness models for chronic diseases.

Results: Costs used in cost-effectiveness analyses for chronic diseases are sometimes drawn from a variety of published sources with little concern about consistency between sources or the underlying functional form for costs. Identifying costs of complications in chronic disease modeling often receives inadequate attention compared to the time and effort devoted to modeling disease progression. Costs of averted complications typically cannot be estimated during a trial, because these complications begin to accrue years after the intervention. Complication costs may be estimated through gross-costing, using an additive cost function with individual complication costs derived from difference sources, or through cost regressions that apply a multiplicative functional form using a single data source. The choice between additive and multiplicative cost functions may affect the cost-effectiveness ratios generated by the model. Current guidelines do not provide much guidance on choosing between the costing approaches.

Conclusions: Developing a set of standard cost estimates might streamline the modeling process for chronic diseases, but standardization will require careful attention to functional form and the selection of appropriate data sets.

Key Words: cost-effectiveness, chronic disease, economic analysis, diabetes

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This article identifies key challenges in incorporating costs in cost-effectiveness models for chronic diseases. Although the challenges are similar across chronic diseases, we focus on the case of diabetes and a particular diabetes cost-effectiveness model to illustrate these challenges more concretely. Our article lays the groundwork for later articles in the volume that provide methods for overcoming these challenges.

Several interrelated challenges must be overcome to build and analyze cost-effectiveness models of chronic diseases. First, the appropriate time horizon for chronic disease is much longer than for acute conditions, because chronic diseases progress gradually over time and because interventions to slow progression may reduce complications years or even decades after the intervention (and its costs) takes place. This means that the model must carefully account for the timing of costs and benefits, as with most models of prevention. In addition, however, the long-time horizon means that it can be costly and difficult to conduct lengthy clinical trials that directly test whether chronic disease interventions improve major health outcomes, such as mortality, heart attacks, strokes, or other serious complications. When clinical trials are infeasible, simulation models are an attractive alternative for making predictions about the likely cost-effectiveness of interventions for chronic disease.

The need to develop simulation models leads to a second major challenge: chronic diseases are usually complex, with progression depending on multiple risk factors and producing several disease complications. As a result, development of a cost-effectiveness model often focuses intently on disease progression. Typically, great care is taken to identify transition probabilities between disease states and to link changes in intermediate health outcomes, such as blood pressure or cholesterol, to long-term and more serious outcomes, such as heart attacks or deaths. Adding interventions to the model further intensifies the focus on disease progres-

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sion. Clinical trials may provide evidence of the intervention's effects on intermediate outcomes, but it is then up to the disease progression model to simulate long-term outcomes. If the model's underlying assumptions about progression are not convincing, the model's conclusions about cost-effectiveness will not be credible.

The intensive focus on disease progression leads to the third challenge for cost-effectiveness modeling: often, costs are treated almost as an afterthought in the modeling process. By the time disease progression modeling is complete, there may be relatively little time or budget left to devote to cost collection. In other cases, economists may be unavailable or allocated insufficient time to assess options and consequences of assigning resources to disease events or health care events.[1]

METHODS

In this article, we use our experience in developing and applying the CDC-RTI diabetes cost-effectiveness model to illustrate the challenges in incorporating costs in cost-effectiveness models for chronic diseases. The CDC-RTI diabetes cost-effectiveness model is a Markov simulation model of disease progression and cost-effectiveness for type 2 diabetes. Several other cost-effectiveness models exist for diabetes[2–4]; our CDC-RTI model is fairly typical of the models that build on Eastman's original work in the area.[5,6] To reflect the chronic nature of diabetes, our model follows patients from diagnosis to either death or age 95. The model simulates development of diabetes-related complications on 3 microvascular disease paths (nephropathy, which can culminate in end-stage renal disease and death; neuropathy, which can culminate in lower extremity amputation and death; and retinopathy, which can culminate in blindness) and 2 macrovascular disease paths (coronary heart disease [CHD] and stroke). The model also contains modules for diabetes screening and prediabetes. Model outcomes include disease complications, deaths, costs, and quality-adjusted life years (QALYs). The model has been used to: estimate the cost-effectiveness of intensive glycemic control, intensified hypertension control, and cholesterol reduction[7]; evaluate optimal resource allocation across intervention programs[8]; assess whether screening for diabetes is cost-effective[9]; show that lifestyle modification is cost-effective in delaying or preventing diabetes among persons with prediabetes[10]; and estimate the cost-effectiveness of screening for prediabetes.[11] The model focuses primarily on direct medical costs, although direct and indirect nonhealth care costs could be added with relatively little difficulty.

Findings

Basic Challenges

Figure 1 provides a simplified illustration of the 5 disease paths within the model's diagnosed diabetes module. Ovals represent disease states, diamonds represent discrete health events, and the Ps in rectangles represent the transition probabilities that govern movements between states.

The point of showing this figure is not to provide a detailed clinical explanation of diabetes progression. Rather, it is to illustrate a common property of chronic disease cost-effectiveness models: chronic diseases are complicated and it takes great effort to create the disease progression component of a cost-effectiveness model. The first step is to specify the basic structure of disease progression. The next step is to scour the clinical and epidemiological literature to find all of the required transition probabilities for the model. Once the structure has been specified and transition probabilities and other parameters have been gathered, the third step is to compile them in a simulation program, no small feat in itself. After initial programming is complete, the final step is to conduct a series of validation exercises to evaluate whether the model predicts disease progression in a reasonable and valid way. By the time all of these steps are complete, building the disease progression component of a cost-effectiveness model for chronic diseases may account for a large share of the overall modeling effort.

The objective of cost-effectiveness modeling is to estimate the incremental costs and incremental effectiveness of an intervention relative to a baseline treatment (eg, usual care or doing nothing). Estimating the incremental effectiveness of interventions for chronic diseases is especially challenging. Randomized clinical trials are generally regarded as providing the best evidence on the potential effects of an intervention on health outcomes. With chronic diseases, however, an intervention may not have a measurable impact on long-term health outcomes such as heart attacks or death until years or even decades after the intervention begins. Therefore, clinical trials of interventions for chronic disease often focus on the intervention's effects on intermediate outcomes, such as blood pressure, cholesterol, and—in the case of diabetes—blood sugar levels (measured by hemoglobin A1c levels). The intervention's effects on long-term outcomes must then be simulated by the disease progression model.

Figure 2 illustrates one of the diabetes model's key interventions and its links to long-term outcomes. The intensive glycemic control intervention attempts to lower hemoglobin A1c levels. Lower A1c levels are expected to slow the development of early microvascular complications, which in turn slows progression to end-stage complications, thereby preventing death and increasing QALYs. The model's parameters for glycemic control are based on the results of the United Kingdom Prospective Diabetes Study, a landmark clinical trial that followed newly diagnosed diabetes patients for 10 years.[12] The trial showed that the intensive control intervention reduced A1c levels and early microvascular complications relative to a standard control arm but could not show a significant effect on end-stage complications because—despite the trial's length—these were rare in both arms of the trial. Therefore, we use the disease progression model to simulate the long-term health effects. Intensive glycemic control is only 1 of the 9 interventions included in the diabetes model, and we take similar approaches in modeling the other interventions. Because modeling the intervention effects correctly is crucial for establishing the credibility of a cost-effectiveness analysis, intervention modeling may also account for a large share of the overall time spent on building the model.

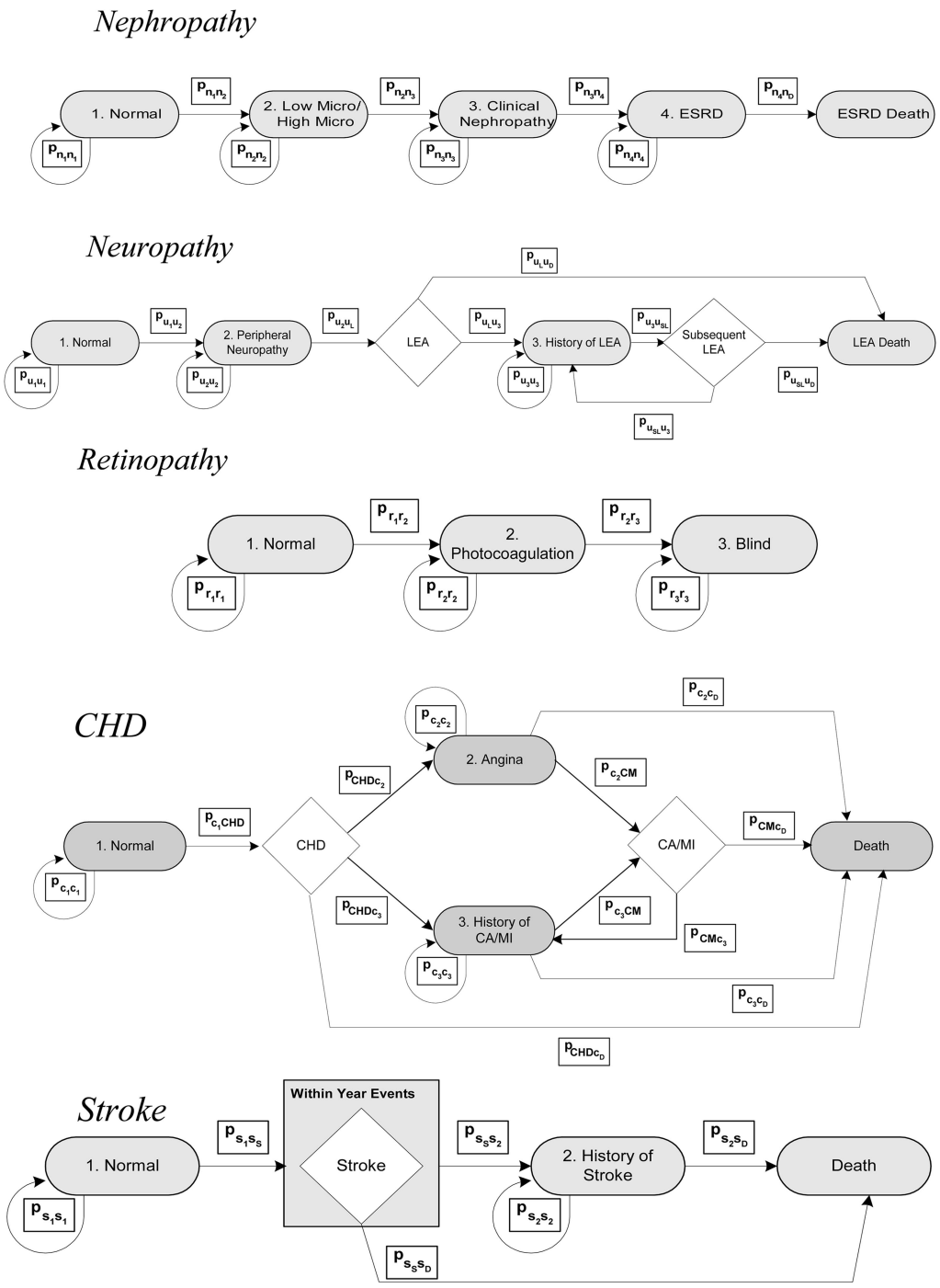

FIGURE 1. Disease Paths. Ovals represent disease states, diamonds represent discrete health events, and p_{ij} represents the transition probability from state i to state j. Note: micro, microalbuminuria; ESRD, end-stage renal disease; LEA, lower extremity amputation; CHD, coronary heart disease; CA/MI, cardiac arrest/myocardial infarction.

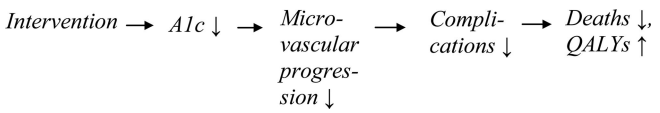

FIGURE 2. Intervention effects in the diabetes model. Note: A1c, hemoglobin A1c.

With so much of the time in cost-effectiveness modeling devoted to disease progression and intervention effects, costs may get relatively little attention. To save time for analyzing the model and reporting results, developers often simply find cost data in the literature from whatever source is convenient and insert the costs in the model without looking at them too carefully. As a result, costs may receive far less

TABLE 1. Alternative Costing Approaches
Costs of Selected Diabetes Complications (Gross-Costing)

Complication	One-Time Costs	Annual Costs
Microalbuminuria	$0	$0
Nephropathy	$1201	$0
End-stage renal disease	$0	$72,488
Peripheral neuropathy	$357	$0
Lower extremity amputation	$33,131	$0
Photocoagulation	$2943	$0
Blindness	$0	$2125
Angina	$2733	$1118
Myocardial infarction	$16,534	$1118
Stroke (age 65–74)	$21,613	$7599

scrutiny and time in the modeling effort than disease progression, intervention effects, or analysis and reporting. The individual costs may be derived from a variety of published sources with little concern about consistency between sources or the effects of the underlying functional form for costs.

In the case of our diabetes model, we used cost estimates from more than a dozen published articles; most, if not all, of these articles used different data sources. Our decision to rely on so many sources was pragmatic: diabetes is associated with a wide range of complications, and to derive new estimates would almost require an original study for each complication.

Measuring Costs

Chronic disease interventions typically have 2 major cost consequences:

- Intervention costs: direct costs of implementing the intervention (eg, tests, intervention materials, extra physician visits, lifestyle counseling).
- Complication costs: if the intervention reduces subsequent disease complications, future health costs may be averted.

The 2 types of costs may require different approaches for cost collection.

Intervention costs can often be measured as a part of the clinical trial that determines whether the intervention improves intermediate health outcomes. The intervention costs can be measured by microcosting (ie, carefully measuring the incremental resources associated with the intervention and multiplying by standard unit costs for each resource).

Clinical trials are too short for measuring the complication costs for many chronic diseases. Because of the long potential delay between an intervention and major complications, the clinical trial period is usually too short to observe statistically different rates of complications between the intervention and control arms of the trial; therefore, statistically significant differences in costs are also unlikely. Even pooling complication costs across arms to determine a single complication cost may be difficult because major complications may be too rare, and costs for individual complications may be too variable. Consequently, complication costs often must be estimated using other data sources and approaches.

One potential approach for estimating complication costs is to cost out individual complications separately for each disease-related complication. This approach, sometimes termed "gross-costing,"[13] usually relies on secondary data or estimates from previously published articles, with costs for different complications often taken from different sources. There may be an initial one-time cost estimate for the year when a complication first occurs and an estimate of annual recurring costs in subsequent years. For example, a stroke may result in high hospitalization costs in the first year and have recurring long-term costs in subsequent years. Our diabetes cost-effectiveness model originally used this approach for complication costs. Table 1 shows the one-time and annual costs for selected costs in the model.

Using multiple sources of data for gross-costing potentially raises a number of issues. The sources may focus on different populations, different health care systems, or different periods, and different estimation techniques may be used to generate each complication cost. This raises questions about how representative the individual estimates are and whether they can be combined meaningfully. Typically, only a single mean value of the cost of a complication is used, suppressing the fact that the cost of a complication can vary widely between individuals. These issues are often ignored in practice. However, most cost-effectiveness studies will at least include 1-way sensitivity analyses to determine whether individual cost parameters affect estimated cost-effectiveness ratios. Probabilistic sensitivity analyses are becoming increasingly common, and these analyses could potentially explore variation in the cost of complications across individuals.

An implicit assumption in gross-costing individual costs separately is that the underlying cost function is additive (so that the cost of having both a history of CHD and a history of stroke equals the cost of having a history of CHD plus the cost of having a history of stroke). This assumption permits the use of separate sources of data for different complications. Costs that are not associated with the disease of interest can also be ignored because they will cancel out in the incremental cost comparison between an intervention and control arm, assuming that the additive functional form is correct and the intervention does not affect life expectancy.

An alternative approach for costing complications is to formally estimate a cost regression that includes cost as the dependent variable and dummy variables for key complications as explanatory variables. The regression approach to costing generally involves more work than the additive costing approach. It requires a large data set, and the proper functional form for the regression must be selected. As Basu and Manning[14] described later in this volume, some of the regression equations are estimated with generalized linear models using a log-link form:

$$E(y \mid y > 0, X) = c \times \exp(X\beta),$$

where y stands for costs or expenditures, c is a scale factor, and X includes dummy variables for complications or conditions. The exponential form is selected to account for the skewed distribution of health care costs. Assuming there are

2 complications, X_1 and X_2, it becomes clear that complications have a multiplicative effect on costs:

$$E(y \mid y > 0, X) = c \times \exp(\alpha + X_1\beta_1 + X_2\beta_2),$$
$$= c \times \exp(\alpha) \times \exp(X_1\beta_1) \times \exp(X_2\beta_2).$$

When complication 1 occurs (ie, $X_1 = 1$), costs are multiplied by $\exp(\beta_1)$. An often overlooked characteristic of this functional form is that the incremental cost of a complication depends on an individual's other complications. Thus, there is no "single" cost of a complication, as in the first, additive approach to costs. In addition, baseline costs in the absence of complications do matter because these costs enter the multiplicative equation. Finally, the multiplicative form complicates efforts to calculate the share of costs attributable to the complication.[15]

In one of the extensions of our diabetes cost-effectiveness models, we used a regression-based cost function to measure complication costs. Table 2 shows the corresponding set of multipliers, which were derived from a study of diabetes costs in a health maintenance organization; in the study, c = 1, and the natural log of costs was regressed on complications and other variables.[16] Using this regression, a female patient with diabetes, microalbuminuria, and hypertension and who used insulin would be estimated to have costs of \$4866 (= \$1684 × 1.25 × 1.17 × 1.24 × 1.59). The incremental cost of hypertension for this patient would be \$950. If the female patient had diabetes and hypertension but did not have microalbuminuria or take insulin, her estimated cost would be \$2088 and the incremental cost of hypertension would be \$404.

The choice between additive and multiplicative models will depend on both practical and theoretical issues. Practically, it may be quicker and cheaper to rely on existing cost estimates from multiple sources, and these costs will usually have to be combined in an additive framework because it would be difficult to combine them multiplicatively. From a theoretical standpoint, additive costing will be most appropriate when detailed data on both costs and diagnoses are available and each cost can clearly be attributed to a single diagnosis. Additive costing becomes more problematic if there are economies of scope in medical care, so that it is cheaper to treat a person's hypertension and high cholesterol in a single visit than in 2 separate visits. Alternatively, the cost of treating a heart attack could be more expensive for a person with both diabetes and hypertension than for a person with only one or neither condition. Applying a multiplicative cost function might be preferred from a theoretical perspective in these cases. It might also be preferred in the case of patients treated by a vertically integrated delivery system, whether the system delivers better economies of scope than less integrated, horizontally organized systems.

TABLE 2. Regression-Based Diabetes Multipliers

Variable	Multiplier
Female	1.25
African-American	0.82
Oral agents	1.10
Insulin	1.59
Microalbuminuria	1.17
Nephropathy	1.30
End-stage renal disease	10.53
History of stroke	1.30
Angina	1.73
History of myocardial infarction	1.90
Peripheral vascular disease	1.31
Hypertension	1.24
Baseline costs	\$1684

An unresolved question is whether using the additive cost approach or using the multiplicative cost function makes a difference in a cost-effectiveness analysis. To investigate this issue, we used our model to estimate the cost-effectiveness of tightly controlling blood sugar levels, alternatively using the additive and multiplicative cost functions (Table 3). In this case, the additive cost function produces lower incremental costs (incremental QALYs are the same in both estimates) and therefore, a lower cost-effectiveness ratio than the multiplicative cost function. Whether the difference between the cost-effectiveness ratios is important lies in the eyes of the beholder. An optimist might note that the difference in incremental costs is relatively small and both cost-effectiveness ratios are lower than the ratios for many health care interventions that have been adopted. A pessimist might focus on the \$12,500/QALY difference between the cost-effectiveness ratios and note that this difference could be enough to affect a policymaker's choice between accepting and not accepting the intervention.

One other important characteristic of chronic disease modeling is illustrated in Table 3. Although the difference in incremental costs between the additive and multiplicative cost functions is relatively small, the difference in cost-effectiveness ratios is relatively large. This outcome occurs because the denominator in the cost-effectiveness ratio, the incremental QALYs produced by the intervention, is small (0.145 QALYs). In cost-effectiveness analyses for primary and secondary prevention of chronic diseases, small QALY differences per patient are generally the rule, rather than the exception, because the interventions are applied to a large number of patients to prevent the development of rare complications over a long period of time.[17] This characteristic underlines the importance of correctly measuring costs because a small change in incremental cost per patient can lead to large changes in the cost-effectiveness ratio when the incremental QALYs per patient are small.

Guidelines for Cost Measurement

Guidelines for cost-effectiveness analyses do not currently provide much guidance on the nuts and bolts of cost measurement. Luce et al[13] provide a comprehensive set of 25 recommendations for cost analysis in Chapter 6 of the treatise on cost-effectiveness in health and medicine by Gold et al, but only one of the recommendations focuses primarily on the cost-measurement issues described in this article (Table 4). Clearly, additional guidance would be useful, and, in fact, the chapter closed by proposing that future research should de-

TABLE 3. Cost-Effectiveness of Tightly Controlling Blood Sugar Levels, Using Alternative Cost Functions

	Additive Costs			Multiplicative Costs		
	Total Cost	**Total QALYs**	**CE Ratio**	**Total Cost**	**Total QALYs**	**CE Ratio**
Baseline	$52,758	12.7547		$55,175	12.7547	
Intervention	$54,185	12.8999		$58,418	12.8999	
Incremental	$1428	0.1452	$9832	$3242	0.1452	$22,300

CE indicates cost-effectiveness.

TABLE 4. Guideline Recommendations for Measuring Costs

Recommendation	Number of Recommendations
Use societal perspective	1
What should be included in numerator	7
What should be excluded in numerator	3
Micro-costing preferred over gross-costing, but choice depends on feasibility, etc.	*1*
Value resources at opportunity costs	2
How to use wages and prices to reflect opportunity costs	10
Use constant $	1
Total	25

Luce et al, 1996[13]; recommendations grouped by author.
Italics added to indicate the recommendation most relevant to this article.

velop a standard set of cost estimates that could be used in cost-effectiveness analyses.

This proposal raises a number of questions. Can we come up with a standardized list of complications or conditions that is useful across a wide range of cost-effectiveness analyses? Would the standard set include both one-time and annual costs? What are the most appropriate data sources for standardized cost estimates? Would the cost list be additive in nature, or would it take the form of a multiplicative cost function based on regressions? Finally, who would develop the standardized costs? Many of these questions are addressed in detail in the articles later in this volume. Our experience suggests that developers of cost-effectiveness models would certainly welcome a standardized list of costs that could be readily incorporated within cost-effectiveness models. Developers would probably prefer a long list of one-time and annual costs that would cover many conditions; although it may be infeasible to generate the full list, costs for common events such as heart attacks, strokes, and cancers will be relevant for many conditions. Some models will incorporate either additive or multiplicative regression-based cost functions; the real question is which type of cost function is appropriate.

CONCLUSIONS

This article illustrates some of the challenges in incorporating costs in cost-effectiveness models for chronic diseases, using a diabetes cost-effectiveness model as a specific example. For practical reasons, relatively little of the effort in building cost-effectiveness models is devoted to cost measurement. However, paying too little attention to costs can threaten model validity and may lead to erroneous conclusions about the cost-effectiveness of interventions. Intervention costs can generally be estimated by microcosting as part of clinical trials. However, measuring complication costs for chronic diseases during a clinical trial is more difficult because complications are relatively rare and the associated costs may be quite variable. Therefore, complication costs will likely need to be estimated using gross-costing for individual events or be derived from cost regressions. Developing a set of standard cost estimates might streamline the modeling process and improve cost-effectiveness analyses, but standardization will require careful attention to functional form and the selection of appropriate data sets.

REFERENCES

1. Fishman PA, Hornbrook MC. Assigning resources to health care use for health services research: options and consequences. *Med Care*. 2009;47(suppl 7):S70–S75.
2. Palmer AJ, Roze S, Valentine WJ, et al. The CORE Diabetes Model: projecting long-term clinical outcomes, costs and cost-effectiveness of interventions in diabetes mellitus (types 1 and 2) to support clinical and reimbursement decision-making. *Curr Med Res Opin*. 2004;20(suppl 1):S5–S26.
3. Brown JB, Russell A, Chan W, et al. The global diabetes model: user friendly version 3.0. *Diabetes Res Clin Pract.* 2000;50(suppl 3): 15–46.
4. Eddy DM, Schlessinger L. Archimedes: a trial-validated model of diabetes. *Diabetes Care*. 2003;26:3093–3101.
5. Eastman RC, Javitt JC, Herman WH, et al. Model of complications of NIDDM. I: model construction and assumptions. *Diabetes Care*. 1997; 20:725–734.
6. Eastman RC, Javitt JC, Herman WH, 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;20:735–744.
7. CDC Diabetes Cost-Effectiveness Group (Corresponding Author: T.J. Hoerger). Cost-effectiveness of intensive glycemic control, intensified hypertension control, and serum cholesterol level reduction for type 2 diabetes. *JAMA*. 2002;287:2542–2551.
8. Earnshaw SR, Richter A, Sorensen SW, et al. Optimal allocation of resources across four interventions for type 2 diabetes. *Med Decis Making*. 2002;22(suppl):S80–S91.
9. Hoerger TJ, Harris R, Hicks KA, et al. Screening for type 2 diabetes mellitus: a cost-effectiveness analysis. *Ann Intern Med*. 2004;140: 689–699.
10. Herman WH, Hoerger TJ, Brandle M, et al. The cost-effectiveness of lifestyle modification or metformin in preventing type 2 diabetes in adults with impaired glucose tolerance. *Ann Intern Med*. 2005;142:323–332.
11. Hoerger TJ, Hicks KA, Sorensen SW, et al. The cost-effectiveness of screening for prediabetes among overweight and obese US adults. *Diabetes Care*. 2007;30:2874–2879.
12. UK Prospective Diabetes Study Group (UKPDS 33). Intensive blood-glucose control with sulphonylureas or insulin compared with conven-

tional treatment and risk of complications in patients with type 2 diabetes. *Lancet*. 1998;352:837–853.
13. Luce BR, Manning WG, Siegel JE, et al. Estimating costs in cost-effectiveness analysis. In: Gold MR, Siegel JE, Russell LB, et al, eds. *Cost-Effectiveness in Health and Medicine*. New York, NY: Oxford University Press; 1996:176–213.
14. Basu A, Manning WG. Issues for the next generation of health care cost analyses. *Med Care*. 2009;47(suppl 7):S109–S114.
15. Trogdon JG, Finkelstein EA, Hoerger TJ. Use of econometric models to estimate disease-specific shares of medical expenditures. *Health Serv Res*. In press.
16. Brandle M, Zhou H, Smith BR, et al. The direct medical cost of type 2 diabetes. *Diabetes Care*. 2003;26:2300–2304.
17. Grosse SD. Assessing cost-effectiveness in healthcare: history of the $50,000 per QALY threshold. *Expert Rev Pharmacoecon Outcomes Res*. 2008;8:165–178.