Measuring Economic Outcomes of Cancer
Dennis G. Fryback, Benjamin M. Craig

Economic outcomes are increasingly important in cancer research. This article provides an introduction to the nature and measurement of economic outcomes in cancer and gives the reader entry points to a considerable literature on measuring economic endpoints in health and medicine. Economic outcomes data are defined here as measures of resources consumed in prevention, detection, and treatment of cancer and its sequellae. Part I of this essay discusses the questions addressed by economic outcomes. Part II presents a typology of and introduction to measurement of economic outcomes. Part III discusses important measurement issues and calls for development and validation of standardized protocols and questionnaires to measure economic outcomes, especially at the patient level. [J Natl Cancer Inst Monogr 2004; 33:134–41]

Investigation of cancer prevention, screening, and treatment has generally centered on outcome measures related to traditionally conceived burden of illness—measures that reflect changes in patient symptoms, functionality, and longevity or mortality. Although the economic outcomes have not regularly been collected as a primary endpoint in cancer research, there appears to be an increasing incidence of trials and observational studies in which such outcomes are collected as secondary endpoints.

In part I of this article we discuss generally the types of questions addressed by economic data. In part II, we present a typology of economic measures from a methodological perspective. In part III we discuss ways to improve the accuracy, interpretability, and comparability of economic measures in cancer outcomes research, with a focus both on randomized clinical trials and observational studies that entail primary data collection of economic endpoints. To this end, our strategy is not to present a comprehensive catalog and review of the cancer economics literature, but rather to cite and discuss exemplary applications that illustrate the key points, while also directing readers to other sources providing an in-depth treatment of costing methodology.

Our main thesis is that cancer research studies, by which we mean clinical studies of prevention, detection, and treatment of cancer in humans, should collect alongside the traditional clinical outcome measures a variety of data for use in later economic analyses that are generally secondary to the main study. We will identify “economic endpoints,” using the term to parallel the common use of “clinical endpoints,” to be counts of resources used. It may be the case that economic endpoint data include counts of resources, such as pills, and not dollars. As we will discuss, the secondary users (termed “analysts”) will translate resources into monetary units based on considerations that often go beyond the particular trial or study. We argue that clinical researchers who wish to have their studies inform economic analyses need to include systematic collection of economic endpoints. We do not describe how economic analysis should be performed outside its role as a motivator for the collection of economic endpoints.

PART I. WHY MEASURE ECONOMIC ENDPOINTS?

Traditionally the burden of illness caused by a particular disease is measured in terms of the health outcomes—mortality and morbidity—of the disease. In addition to health outcomes, there are concomitant economic outcomes of disease, defined as resources consumed as a result of the disease and its treatment, such as the cost of services or lost wages. Economic endpoints in cancer research are measures of these resources. Resources consumed for one use are unavailable for other uses; that is, the opportunity to use these resources differently is lost. We use monetary units to represent the value of these resources, but the true economic cost associated with use of resources is the “opportunity cost”—the health that could have been produced—as represented by the best alternative use of those resources that must be foregone.

The total economic burden of cancer is the total of all resources consumed as a result of cancer and its prevention and care. Although the calculation of the total economic burden of a particular cancer or cancer in general and the representation of this total burden as a large dollar figure may be of use in mobilizing political support for cancer care and research, this number is generally not associated with specific actions (1,2). Measurement of economic endpoints in cancer (or any other disease) has a more focused and perhaps more immediately apparent effect when these endpoints are used in cost-effectiveness analyses to evaluate specific interventions to prevent or treat specific cancers. These analyses let us compare the efficiency of alternative interventions when making choices subject to resource constraints. If resources for health care were unlimited, description would be the extent of our interest in economic endpoints—they would be just one more descriptive fact associated with cancer. However, resources are not unlimited, and costs do matter. Cost-effectiveness analyses, a principal use of economic endpoint data, help to guide effective and efficient cancer care decisions.

For example, Pignone et al. (3) reviewed seven modeling studies of the cost-effectiveness of colorectal cancer screening for use by the U.S. Preventive Services Task Force in developing public guidelines and recommendations for such screening. These secondary modeling studies are often of more relevance to treatment policies than are primary tests of hypotheses about costs, because rarely can all costs be examined in one study; hence, primary tests of hypotheses about costs in any one

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trial or observational study may be of only marginal relevance. This fact about economic outcomes, that secondary studies are often more meaningful than primary tests of hypotheses in any single study, is an unusual *modus operandi* for cancer research, where secondary studies are often thought to be *prima facie* less valuable than direct primary experimental tests of hypotheses.

In general, as cancer care has become more effective, it also has become more expensive. These added costs are not without associated benefits because the expenditure has been made to "buy" improved cancer outcomes. The motivation of cost-identification and data-based estimates of costs—of all types—is to provide the data necessary for economic evaluations of interventions. There are now many alternatives for cancer prevention, screening, and treatment, and the existence of alternatives means we must scrutinize the relative health returns of each in relation to its costs. In a sense, spending resources on a particular prevention or therapeutic intervention can be characterized as a substitution of increased economic burden for a reduced human morbidity and mortality burden. Recognizing this, it is natural to ask whether this substitution is being made efficiently; that is, whether we are getting maximal human return for the resources expended. This is the realm of economic analyses such as cost minimization, cost-effectiveness, cost-utility, and cost-benefit analyses (4,5). A major purpose of economic analyses in cancer is to quantify the magnitude of the improvement in cancer health outcomes relative to the magnitude of resources expended to secure those improvements (6).

Sooner or later a balance must be struck between the cost of interventions and their effectiveness, and our focus will be on economic endpoints for cancer screening and treatment studies as a means of providing data for these calculations. Economic outcomes in cancer are not particularly different from economic outcomes in care of other diseases. However, cancer care becomes increasingly important as successes in care of coronary heart disease and the aging of the population place more and more individuals at risk for cancer. At the same time, cancer care will be competing more and more for resources with other health care interventions. Thus, measurement of economic endpoints will become increasingly important as well.

Finally, there may be yet another reason for measuring economic outcomes that impinge on patients. In many cancer interventions the patient can be considered a provider of care along with the oncologist. Patients must find time and organize family resources to participate in demanding and lengthy protocols. This can be taxing on patient and family resources. Normally we think of patient burden as the effect of side effects of treatments, and we think of high-burden therapies as those with high incidence of particularly onerous side effects or sequellae. However, patient burden also has economic dimensions, and facing high economic burden a patient may choose not to adhere to interventions, thereby reducing the health effect of the treatment. The only way to know the economic burden on patients is to measure it.

Our essay draws on a number of sources in which similar materials have appeared. The most general is the work of the U.S. Panel on Cost-Effectiveness in Health and Medicine (4). However, there are many sources that discuss the basic premises of economic evaluations of medical care. For general discussions about the steps in economic analysis and data collection, the reader is referred to the excellent how-to text by Drummond et al. (7). Advanced discussions of strengths and weaknesses of methodology for cost and cost-effectiveness analyses can be found in Luce et al. (8) and Sloan (5). These principles are discussed by Neymark (9) and by Shulman et al. (10) in the specific context of cancer treatment. Neymark also draws attention to earlier discussions in the cancer-related literature on economic analysis by Goddard and Drummond (11), Levine et al. (12), Markman (13), Rees (14), and Yarbro (15). An in-depth treatment of topics in cancer economics is found in the overview monograph by The National Cancer Institute—American Society for Clinical Oncology Economics Working Group (6).

**PART II. A GENERAL CONCEPTUAL MODEL FOR ECONOMIC OUTCOMES**

There are three parts to a general conceptual model for economic outcomes in health and medicine. The first is the general concept of a cost. Second, costs are incurred by many different parties, so we must understand the notion of cost from varying points of view. Third, global estimates of costs are usually modeled and not directly observed *in toto*. Hence the proximal users of economic outcomes data will usually be researchers who construct cost-effectiveness models and decision analyses.

**The Concept of Cost**

It is tempting to think that the cost of a medical intervention is the price of that intervention. However, as noted in all of the sources cited above, the price charged for specific interventions in health care rarely is the cost. Most easily understood is that price often reflects cost-shifting. A frequent and well-reimbursed service, such as radiologic examination, might be used to cross-subsidize an expensive but low-incidence procedure to keep the price of that procedure reasonable. A popular drug may be priced above its production cost to build revenues for the development of future drugs. From an economic point of view, the cost of an intervention is reflected by the resources it consumes. Luce et al. (8) explain:

Direct costs include the value of the goods, services, and other resources consumed in the provision of an intervention or in dealing with the side effects or other current and future consequences linked to it. ... These costs are often thought of as involving—or potentially involving—a monetary transaction, although it is the use of the resource rather than a monetary exchange that defines the direct cost. Direct costs encompass all types of resource use, including the consumption of professional, family, volunteer, or patient time. Because the intervention (e.g., screening) can affect both current and future resource use and costs, these costs should be considered a stream of resource use that can span time, from a year or less for a simple procedure, to a lifetime for preventive intervention or a chronic disease treatment regimen. [8, p. 179, italics added]

Luce et al. (8) note further that an intervention's costs include entrained resources, resources that must be expended as a downstream consequence of the intervention. For example, the costs of a screening intervention include not only the costs of the screening test itself but also the costs of further tests, follow-up services for both true- and false-positive screening results, and the "downstream" net costs from hospitalization and treatment of the cancer.

Direct costs also include patients' out-of-pocket costs. Patients frequently make co-payments for some services covered
by their insurance and for items not covered by their insurance such as over-the-counter drugs. Direct non-health-care costs accrue as well. Patients pay for treatment-related transportation and child care. Day surgery may well require another adult to accompany the patient so the patient does not need to drive after anesthesia; that accompanying person’s time is a direct cost. Family and friends also provide informal care and assistance to the patient, including child care. If these were purchased services, such as from a home care provider, this time would be apparent as a true cost of care. The fact that these services are provided by “volunteers” does not moot them as true costs.

Overhead costs are also economic costs, despite a history of being called “indirect” costs in biomedical research applications and becoming associated in researchers’ minds with somewhat imaginary costs. These costs all share the property that they are difficult to allocate on a per patient or per treatment basis either because this allocation also depends on volume or because these are costs of resources shared across patients of many types. Whether “indirect” or “direct,” these costs are nonetheless real costs. This component of costs is sometimes handled in an aggregate, ad hoc fashion [e.g., (16)], but also by more systematic accounting methods (7). Overhead costs such as clerical salaries, heat and light, libraries, and so forth, are characterized by fixed budgets in the short run but ultimately are variable (in the long run) in the sense that organizations size themselves to overall average patient through-put (17). Thus, these costs are often apportioned to patient care episodes according to a measure of patient volume, such as the specific episode of care to overall annual patient volume in that care organization.

For example, Helms and Melnikow (18) prorate clinic overhead to cervical cancer screening visits according to the average length of a patient visit for cervical cancer screening as a proportion of time for all clinic visits. Two types of data are required to do this apportioning of overhead costs: “fixed” (or slowly changing) data such as the yearly expenditure for each of the components of overhead, the annual number of patient visits (across all causes), and the average time required per visit; and data specific to the study topic, which in this case means the annual number of cervical cancer screening visits and the average time required per visit. Whereas clinic administrative records not specific to a study of cervical cancer screening will suffice for the first type of data, only a study specifically targeted to measuring times for these screening visits will supply data of the second type.

The costs associated with cancer and its interventions involve more than simply the resources traditionally associated with the health care system. First, the patient’s contribution of own-time to prevention, screening, or therapeutic activities constitutes a genuine direct cost. In a very real sense, the patient participates as a “provider” of his or her own care. Second, and more obviously, paid and unpaid caregivers are also providers of cancer care, and their estimated opportunity costs should be incorporated into direct costs. Third, the premature mortality and morbidity associated with cancer can lead to significant productivity-related costs for the patient, the employer, and society as a whole. From the patient’s perspective, this may involve substantial lost earnings (even after factoring in public and private transfer payments), as well as reductions in length and quality of life.

From the employer’s perspective, productivity costs can be viewed as the “friction costs” associated with the inefficiencies of temporary replacement workers or costs associated with recruiting and training a permanent replacement for a worker lost to illness [(7), p. 105]. In practice, these productivity and friction costs are often modeled in a post hoc fashion based on data concerning patient time lost from usual activities and work time lost, rather than being derived from primary data on employer costs. For cost-effectiveness analysis conducted from a “societal perspective” (more on this point of view below), Luce et al. (8) recommend that productivity costs be treated as follows: employment-related friction costs should be included in the direct cost computations, whereas the associated changes in the patient’s length and quality of life should not be measured in monetary terms but rather incorporated in the effectiveness measure, as the associated change in quality-adjusted life years.

The Importance of Point-of-View

Determination of cost depends on point of view, and for each element of potential resource consumption we have to ask, “To whom is this a cost?” For example, the price of a drug paid out-of-pocket by a patient is the cost to that person, although the price may vary substantially, for example, depending whether the person purchases the drug in the United States, Mexico, or Canada.

Cancer interventions have outcomes that affect several parties: patients and their families who pay out-of-pocket costs associated with the illness and who pay with time devoted to coping with the cancer and its treatment; people without cancer (people who are not yet “patients”) who are falsely screened and thus must devote time and perhaps out-of-pocket expenditures associated with follow-up testing; providers of care; third-party payers who cover direct costs of health care; employers who not only pay the third-party payers but who also suffer productivity losses when their employees are affected; the government, either overall or within a specific partition of the budget such as the Centers for Medicare and Medicaid Services (which administers Medicare), the Social Security Administration (which administers disability payments), the Department of Veterans Affairs (in which is housed the Veterans Administration health system), or the Department of Defense (which has its own health system); and society as a whole: “[The societal perspective is a] view point for conducting a cost-effectiveness analysis that incorporates all costs and all health effects regardless of who incurs the costs and who obtains the effects.” [(4), p. 408]. The cost to society is an accounting of all resources consumed as a direct or indirect result of cancer and its care. “Costs shifted from one party to another are not counted as a societal cost, nor are effects on people other than the patient ignored” [(19), p. 449].

Each of these viewpoints brings its own special definitions of what constitutes a cost and what does not, and which costs are represented by prices and which are not. For example, transfer payments, such as provision of Social Security disability payments, are not generally considered a cost from the societal point of view. These payments transfer money from one group of people (taxpayers) to another (disability payment recipients) but don’t actually consume resources available to society as a whole (apart from administrative costs). From the Social Security Administration’s point of view, however, this is a real depletion to their budget. The aggregate societal viewpoint encompasses all of these in one way or another (19). The Panel on Cost-Effectiveness in Health and Medicine has proposed that economic analyses report measures of cost broadly from the societal point.
of view in the “reference” (or base) case analysis so that users can view costs from one consistent viewpoint, but users can also reconstruct the effect from alternative points of view (4,20).

Counting costs versus modeling costs: What primary data for secondary purposes?

So far, this article has concentrated on economic endpoint measures that may be collected as primary data in cancer research. We differentiate collection of the primary economic endpoint data from an economic modeling study, which we construe as an adjunct or secondary analysis intended to construct comprehensive estimates of costs associated with cancer interventions using some blend of primary data, secondary data from existing published sources, or expert estimates (4,6); for example, see Hillner et al. (21) or Hayman et al. (22).

What should be collected as primary data in cancer studies to be maximally useful to secondary economic modeling? The answer is that, insofar as possible, the primary study should collect and report counts of resources consumed as a direct result or further consequence of a cancer intervention. Moreover, these counts should be collected and reported in as much detail as feasible, given study constraints.

In particular, counts reported for relevant subgroups of patients (e.g., stratified by covariates) and for different time horizons (e.g., reported for initial patient therapy and then separately for follow-up periods) are extremely valuable for later economic analyses. Often a valid economic evaluation must not only take into account resources consumed immediately by the intervention but also must project future lifetime resource consumption entrained by the current intervention. In addition to means and standard deviations for counts, the often highly skewed nature of resource use data make it useful also to report medians and selected percentiles of the empirical distribution of the counts, to allow later approximation of the empirical distributions. Reporting of detailed descriptive characteristics of the distributions allows assessment of uncertainty in model-based cost estimates using synthetic resampling techniques (23,24).

Studies in cancer have counted resources with varying degrees of refinement. Using a “micro-costing” approach, Helms and Melnikow (18) examined the costs of cervical cancer prevention services in three outpatient clinics and treatment of cervical cancer in a staff-model health maintenance organization. Comparing the microcosting estimates to costs found in a systematic review of the literature, the authors found that their estimates were lower for prevention services and higher for treatment costs than was generally reported, with these differences sufficient to alter policy recommendations. This approach to counting resource units, which applies sophisticated time-and-motion study techniques, entails a great deal of effort in chart abstraction and direct observation. Because of the labor intensity of this approach, researchers have sought alternative ways to measure economic endpoints using data from administrative sources such as hospital or clinic billing systems (or administrative use records within staff model health maintenance organizations). However, administrative data are usually in the form of charges and, like prices, may not reflect costs for the reasons discussed earlier. Recognizing this deficiency, some researchers have attempted to adjust charge data to better reflect costs.

Many hospitals have accounting systems that provide cost-to-charge ratios by department or cost centers; hospitals that receive Medicare reimbursement must report cost-to-charge ratios to the Centers for Medicare and Medicaid Services. Cost-to-charge ratios can be applied to charge data to approximate cost estimates produced by the microcosting approach. Bennett et al. (25) adopted this method for economic analysis alongside a randomized controlled trial of colony-stimulating factors used in treatment of acute myelogenous leukemia. As with microcosting, data for cost-to-charge ratios are collected for each component department or cost center, then combined to yield an estimate of total cost.

Less satisfactory is the collection only of aggregate costs for a service, set of services, or episode of care—for instance, recording only the total charges for an inpatient stay. Not only do aggregate charges confuse the issue of price versus costs in a manner difficult to disentangle, but study results expressed as aggregate local charges are less transportable to other settings or time frames. Counts of resources are most transportable, because they may be assigned monetary values to reflect costs at different locales or in different time frames from those in which they were originally collected or reported (8). If the primary study reports counts, then concurrent or later adjunct economic modeling analyses can value resource counts in monetary units at then-prevailing prices, reflecting appropriate levels of cost and appropriate points of view, and then can combine these valuations (as appropriate) with projections of future costs and savings beyond the scope of the single data collection study. This approach to summarizing direct costs for treatment of metastatic breast cancer is exemplified by McLachlan et al. (26), for treatment of pediatric T-cell leukemia by Bennett et al. (27), and for treatment of unresectable colorectal liver metastases by Durand-Zaleski et al. (28).

All that said, a number of cancer cost analyses using the Surveillance, Epidemiology, and End Results–Medicare database have assigned aggregate costs to episodes of hospital care (as well as other resource use components) based on the sum of what the Medicare program and the patient paid; for example, the cost comparison by Burkhardt et al. (29) of radiation therapy and radical prostatectomy for early-stage prostate cancer. The key supporting argument for this approach is that such payments are the relevant measure of cost from the payer’s perspective and may roughly approximate costs from a societal perspective if one assumes government payment rules are significantly shaped by reasonable estimates of economic opportunity cost. In addition, Medicare payments vary by geographic area and over time to reflect (albeit crudely) input price differences. The main reservation with using Medicare prices as the sole cost measure is that they do not reflect resource costs to patients and their families, thus missing one of the components of societal costs.

A hypothetical illustration

What sorts of consumed resources should be counted? For illustrative purposes, let us assume the “carrier” study used to derive economic measures is a two-armed prospective randomized controlled trial (RCT) of a (hypothetical) new adjuvant chemotherapeutic agent for lymph node-positive breast cancer tailored according to elements in the patient’s genetic profile—patients with a specific profile receive the agent, and the remainder do not. This RCT is primarily focused on morbidity and mortality endpoints to gauge the incremental effectiveness of the new agent compared with current neoadjuvant therapy, enrolling patients over an 18-month period and observing patients up to 5 years. To allow later modeling of the incremental costs of the
new therapy compared with current practice, we need to count resources consumed, on average, by patients in each arm of the trial. Because the intervention is a treatment, we can divide the resources into three classes: patient selection and work-up measures, treatment measures, and follow-up measures.

Patient selection and work-up measures include counts of tests and procedures for staging and otherwise targeting the treatment to specific genetic subgroups of patients, both for patients ultimately selected for the intervention and for patients worked up to determine suitability for the intervention but ultimately not selected. Because the latter patients’ work-up costs would not have been incurred had this intervention not been contemplated, they must be considered logical results of the intervention even though these patients ultimately do not undergo the intervention. Note that capturing these costs may be difficult within the trial if the RCT itself only randomizes eligible patients. Also counted for these patients should be days of hospital stay for work-up (if applicable and if different from the experience of “current practice” patients). Work-up of patients undergoing current practice should be counted similarly. Patients’ time and out-of-pocket costs should be counted as well. The number of trips to clinics or hospitals for tests or preliminary procedures and the time away from usual activities should be collected for both patients and accompanying adults. Data about modes of transportation and child care during these times also should be collected.

After initial patient selection and workup costs, we turn to cost data collected during treatment. These include counts of procedures, time spent by professionals, drugs administered and their amounts, and concurrent testing to follow the course of treatment. Often, RCT protocols require testing and observation for the purposes of the trial that would not be a part of regular practice were the new intervention to be disseminated into practice. To the extent possible, the trial should count all testing and procedures used during provision of the intervention but report them differentiated between those required for study purposes as opposed to those considered an essential part of the intervention itself or treatment of its complications [for further discussion, see (6,30)].

Finally, all relevant resources should be captured in the follow-up period (beyond initial treatment). Ideally, we should be able to identify and count all procedures, tests, drugs, professional visits, and so forth that patients undergoing both the new intervention and current treatment are likely to encounter in the weeks, months, and even years beyond the first interventions. Again, this will engender direct costs both occurring at the sites of medical care and incurred by the patient and caregiver or caregivers in the home. In addition, in the follow-up period we must count treatment costs associated with any adverse effects; because attribution of adverse event to the treatment may be problematic, usually all treatment costs for the episode of care are counted in each arm of the study. The economic evaluation of costs for surgical interventions in older women with breast cancer by Given et al. (31) illustrated the need for comprehensive inclusion of all costs in an episode of care to understand the true economic effect of treatments; they concluded that costs of second surgeries among women with breast conserving surgery overcame initial lower costs of breast conserving surgery versus mastectomy.

Finally, the data in our hypothetical trial will be subject to censoring beyond the 5-year follow-up because we will not know future resource consumption by trial patients who survive beyond this point (a point frequently determined by considerations such as funding available for the trial). All resource use data collected in the trial will have to be associated with dates of service to permit unbiased statistical estimates of costs in light of these censoring (32).

In response to the main points above, Table 1 displays measures that constitute primary economic endpoint data for trials or observational studies. The table implies a checklist of resource elements that might be collected in a primary study to facilitate later economic modeling. Data elements in the table are broadly representative and not comprehensive, because the precise set of cost elements to be collected will vary depending on whether the interventions of interest are focused on prevention, screening, treatment, supportive care, or some combination of these. More extensive discussion of potential data items is provided elsewhere (6–8).

### Table 1. Recommended data elements for economic endpoints in a randomized clinical trial or other primary data collection study of cancer interventions

<table>
<thead>
<tr>
<th>Resources expended by:</th>
<th>Type of resource cost by point in the care process</th>
</tr>
</thead>
<tbody>
<tr>
<td>Care providers (oncologists, primary care physicians, other medical specialties, clinics and hospitals, home care and visiting nursing services, nursing homes)</td>
<td><strong>Tests, procedures, office visits</strong></td>
</tr>
<tr>
<td></td>
<td><strong>Other professional time (counted as standard visits, or directly measured)</strong></td>
</tr>
<tr>
<td></td>
<td><strong>Clerical time</strong></td>
</tr>
<tr>
<td></td>
<td><strong>All tests, pharmaceuticals and procedures associated with treatment/intervention</strong></td>
</tr>
<tr>
<td></td>
<td><strong>Tests and treatments of any associated complications</strong></td>
</tr>
<tr>
<td></td>
<td><strong>Clerical time</strong></td>
</tr>
<tr>
<td></td>
<td><strong>Hospital length of stay (by level of care)</strong></td>
</tr>
<tr>
<td></td>
<td><strong>Consumables not identified as a regular part of particular procedures</strong></td>
</tr>
<tr>
<td></td>
<td><strong>Time away from usual activities</strong></td>
</tr>
<tr>
<td></td>
<td><strong>Extraordinary child care</strong></td>
</tr>
<tr>
<td></td>
<td><strong>Co-payments above insurance</strong></td>
</tr>
<tr>
<td></td>
<td><strong>Other out-of-pocket expenses</strong></td>
</tr>
</tbody>
</table>

Finally, all relevant resources should be captured in the follow-up period (beyond initial treatment). Ideally, we should be able to identify and count all procedures, tests, drugs, professional visits, and so forth that patients undergoing both the new intervention and current treatment are likely to encounter in the weeks, months, and even years beyond the first interventions. Again, this will engender direct costs both occurring at the sites of medical care and incurred by the patient and caregiver or caregivers in the home. In addition, in the follow-up period we must count treatment costs associated with any adverse effects; because attribution of adverse event to the treatment may be problematic, usually all treatment costs for the episode of care are counted in each arm of the study. The economic evaluation of costs for surgical interventions in older women with breast cancer by Given et al. (31) illustrated the need for comprehensive inclusion of all costs in an episode of care to understand the true economic effect of treatments; they concluded that costs of second surgeries among women with breast conserving surgery overcame initial lower costs of breast conserving surgery versus mastectomy.

Finally, the data in our hypothetical trial will be subject to censoring beyond the 5-year follow-up because we will not know future resource consumption by trial patients who survive beyond this point (a point frequently determined by considerations such as funding available for the trial). All resource use data collected in the trial will have to be associated with dates of service to permit unbiased statistical estimates of costs in light of these censoring (32).

In response to the main points above, Table 1 displays measures that constitute primary economic endpoint data for trials or observational studies. The table implies a checklist of cost/resource elements that might be collected in a primary study to facilitate later economic modeling. Data elements in the table are broadly representative and not comprehensive, because the precise set of cost elements to be collected will vary depending on whether the interventions of interest are focused on prevention, screening, treatment, supportive care, or some combination of these. More extensive discussion of potential data items is provided elsewhere (6–8).
 Nonetheless, data elements in Table 1 indicate basically what is needed to determine resources consumed per patient and hence the variable costs of interventions in the arms of an RCT or other observational studies. A comprehensive listing of cost elements and potential sources of data for them has been produced by the Canadian Coordinating Office for Health Technology Assessment (33). Use of a comprehensive set of standardized cost elements would greatly increase the comparability of economic analyses. However, beyond listing such data elements, there is need for the development and dissemination to researchers of field methods for actually collecting these data in different settings.

The actual valuation (i.e., pricing for the purposes of cost-effectiveness analysis) of these resources per unit consumed will depend on the purposes and perspective of the cost analysis. For instance, valuation of advanced imaging examinations will depend on assumptions about capacity at the performance site. A specialty center may have a lower per exam production cost as a result of higher utilization than would a community care facility. Patients imaged on-site may have lower travel costs and faster turnaround times than patients referred to an imaging center away from the care site. If resource data such as shown in Table 1 are collected in the trial, then analysts will subsequently be able to employ economic modeling to account for a wide range of issues; for example, to incorporate the effect of capacity restraints and resource use management strategies. Technical issues in assigning monetary costs (usually in the form of input prices) to these resources are beyond the scope of this article but are addressed in the methodological reference works cited earlier [e.g., see Drummond et al. (7)].

Part III. Measurement Needs

Many data elements in the first row of Table 1 can be collected in a relatively standardized way. For example, coding of medical procedures and tests is greatly facilitated by standardized definitions in the American Medical Association’s Current Procedural Terminology (34) and its updates and revisions. This coding system is also the basis of Medicare reimbursement. For new procedures not yet given their own codes (such as recently developed contrast agents or pulse sequences for magnetic resonance imaging examinations), individual studies will have to invent, define, and report their own coding. Newly developed treatments will similarly need special coding attention, but most currently available direct medical care has well-known coding systems in place.

Care provided by nonphysician allied health professionals in home or nursing home settings may be less well codified, and individual studies may need to augment standard billing codes to count resources that are consumed differentially by patients in one arm of a study compared with patients in another arm. Where allied health professionals act as independent contractors or agents of a provider organization, their services may be recorded in patient charts or administrative records in standardized time units (e.g., in quarter-hour increments), or these units may be inferred from billed fees. However, the sine qua non for these data elements would be time observations from a direct time-and-motion study, and this very labor-intensive method may be needed to quantify actual patient contact time. Helms and Melnikow (18) use time and motion data to quantify time allocation by health educators and medical assistants as well as physicians in a clinic setting. They note that patient contact time underestimates the “overhead” time commitment of health care professionals and staff; they also captured “meetings, paperwork, telephone calls, breaks, professional development, vacations, and other ‘downtime’” in their time-and-motion study [(18), p. 654]. They conclude that the ratio of worked hours to patient contact hours for health care professionals was 2.02 hours and that for assistants it was 2.68 hours.

We do not know of standardized coding or collection forms for clerical time associated with actions such as patient scheduling, x-ray retrieval, transcription, and so forth. Typically, costs of these resources are included in allocated overhead already bundled with patient visits or with specific tests and procedures—they may not need to be collected in the specific study. However, if unusual clerical or professional staff time is associated with a new procedure or treatment, it should be collected as a data element (e.g., if the study were of a new program of telephone or computer-based counseling of cancer patients, the time associated with calls or sessions should be collected as a unique data element).

Although coding systems are largely in place for data elements in the “Resources expended by care providers” section of Table 1, the comprehensive collection of data for interventions and follow-up care in outpatient and other decentralized settings may pose particular challenges, as data for any given patient may reside at multiple physical sites or data systems. Two recent studies that have admirably coped with these difficulties to produce direct costs estimates based on comprehensive counts of resources consumed are Ramsey et al. (35) and Leighl et al. (36), both of which examine competing therapies for advanced non-small-cell lung cancer.

These challenges notwithstanding, perhaps the greatest need for better and more standardized measures is found in the “Resources expended by patients and others” section in Table 1: the costs incurred outside the health care system by patients, families, and caregivers. To date, these costs have been collected only sporadically, using methods and questionnaires idiosyncratic to each particular study. There are studies, however, that illustrate how such costs might be satisfactorily gathered and analyzed. Rizzo et al. (37) collected economic data in a nonrandomized prospective cohort study of 132 patients undergoing bone marrow transplantation (BMT) for hematologic malignancies. They were particularly interested in comparing costs of patients undergoing BMT as inpatients versus a small group (n = 17) who had BMT as outpatients. They interviewed survivors at their 1-year BMT anniversary using a self-administered questionnaire. The authors’ description of the questionnaire demonstrates the potentially extensive nature of costs to patients.

The questionnaire assessing out-of-pocket costs was developed for this study with the assistance of physicians, nurses, and social workers who care for transplant recipients. It was piloted on a small group of surviving transplant recipients for face and content validity. Results have been reproducible when compared with a similar instrument given prospectively at 3, 6, and 12 months after transplantation in a small group of patients. Categorical response options were given for each question to facilitate easy completion by the patients. Direct non-medical costs covered by the survey included transportation, lodging and meals, telephone, child care, and household assistance expenses while undergoing BMT. Indirect [sic; used here to mean patient productivity costs] costs assessed in the survey included employment status and occupation changes, changes in productivity.
and length of usual work week, disability history, and lost income. The questionnaire also included questions about unreimbursed direct medical costs and the perceived financial impact of BMT-related care. ([37], p. 2813)

Rizzo et al. (37) observed similar out-of-pocket costs in both the inpatient and outpatient BMT groups and conclude that outpatient BMT does not necessarily shift costs to patients, as had been previously hypothesized.

Shireman et al. (38) report time costs for women being screened for cervical cancer. In each of six clinics, a one-page survey questionnaire was distributed to 25 consecutive women attending the clinic for cervical cancer screening, asking for travel times to the clinic, waiting times, and time spent being screened. Assigning monetary costs using a variety of different wage rates to the average 1.75 hours women spent participating in a single screening exam resulted in a finding that patients’ time costs were up to 25% of cervical cancer screening costs—and the methods used in this study undoubtedly underestimate total costs to the women.

Finally, Sculpher et al. (39) report data on costs to patients undergoing advanced colorectal cancer therapy. The economic data were collected in this study from a subset of patients in a prospective RCT of raltitrexed versus fluorouracil plus folic acid (5FU+FA). Two hundred seventy of the 495 patients in the trial completed a cost questionnaire developed for this trial. Similar to the Shireman et al.’s (38) questionnaire, these researchers asked patients about travel time and mode of travel in a typical visit. Using data from the trial about number of visits, U.K. statistics about costs of different modes of travel and wage rates, and so forth, they computed the implied costs of the time associated with treatment and adverse effects. Over the period of the trial, those randomized to 5FU+FA incurred a median of £136 higher travel plus time costs per patient than did those randomized to raltitrexed.

Little is known about how to elicit valid self-reports of time and out-of-pocket costs from patients. The procedure described above by Rizzo et al. (37) is currently state of the art. Their questionnaire was developed and validated for a particular study, however, and development of valid and reliable questionnaires or procedures that might be used more generally to assess these costs should be a priority methodological research area. Patient costs may be influential as a determinant of compliance and can be a significant portion of overall incremental costs of care (such as in the cervical screening study). If patient costs are significantly different for one treatment versus another, such as in the Sculpher et al. (39) study, they can perhaps affect patient compliance with treatments, and hence the effectiveness of the treatments outside the confines of a trial. Perhaps one day cancer researchers will have available validated and standardized data collection tools and “off-the-shelf” techniques to gather patient cost data in the same way that standardized generic quality-of-life instruments are becoming available now.

**CONCLUSION**

Economic measures are important for cancer outcomes research. Increasingly, the costs of care will need to be balanced against the effectiveness of care and competing needs for health care resources. To do this balancing we need to have accurate models of the cost of cancer interventions.

Other areas of outcomes research have standardized tools. This is not the case for cost analysis, and we need such tools to promote accuracy, comprehensiveness, and comparability in cancer cost calculations. Clinical trials and observational studies of interventions provide crucial data not only for comparing the economic effect of interventions during the study period but also for economic modeling efforts to estimate the cost effect of the interventions outside of and beyond the investigation itself. Economic data from a limited trial, appropriately collected, can not only inform the estimates of relative cost (and cost-effectiveness) for the study period itself but also feed directly into economic models that examine economic questions from a multiperiod (even lifetime) perspective and across different geographic units or population groups [see Gold et al. (4) and Drummond et al. (7)]. We will not fully capitalize on opportunities to better understand and measure the cost and cost-effectiveness of interventions until our resource consumption data are sufficiently comparable (both conceptually and operationally) for the meta-analyses and data linkages required for high-quality modeling to be feasible.

At the conceptual level, there is little disagreement about how to define the concept of economic cost burden or to delineate the types of perspectives from which an analysis can be performed. In practice, however, little consensus exists about the best ways to define and collect such information, and this has led to wide variation in how costs are computed and interpreted across studies. This leads to unnecessary variation among studies in the definition of resource consumption and in different methods of executing the accounting analyses. As a consequence, development of standardized questionnaires and data collection forms should be at the top of the cancer economics research agenda.

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