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ANALYZING DIFFERENCES IN THE COSTS OF TREATMENT ACROSS CENTERS WITHIN ECONOMIC EVALUATIONS

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Abstract

Objectives: Assessments of health technologies increasingly include economic evaluations conducted alongside clinical trials. One particular concern with economic evaluations conducted alongside clinical trials is the generalizability of results from one setting to another. Much of the focus relating to this topic has been on the generalizability of results between countries. However, the characteristics of clinical trial design require further consideration of the generalizability of cost data between centers within a single country, which could be important in decisions about adoption of the new technology.
Methods: We used data from a multicenter clinical trial conducted in the United Kingdom to assess the degree of variation in costs between patients and between treatment centers and the determinants of the degree of such variation.
Results: The variation between patients was statistically significant for both the experimental and conventional treatments. However, the degree of variation between centers was only statistically significant for the experimental treatment. Such variation appeared to be a result of hospital practice, such as payment mechanisms for staff and provision of hostel accommodation, rather than variations in physical resource use or substantive differences in cost structure.
Conclusions: Multicenter economic evaluations are necessary for determining the variations in hospital practice and characteristics that can in turn determine the generalizability of study results to other settings. Such analyses can identify issues that may be important in adopting a new health technology. Analysis is required of similar large multicenter trials to confirm these conclusions.

Keywords: Cost-effectiveness, External validity, Multicenter clinical trials

Assessments of health technologies usually include an economic evaluation. The number of economic evaluations conducted alongside clinical trials continues to grow (e.g., 5;10;18). In part, this may be linked to the growing interest of governments in economic data, which includes requirements for economic data in support of decisions on drug pricing

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and reimbursement and suggestions that clinical trials of nonpharmaceutical therapies consider economic issues relating to the choice of therapy (3;12). Government guidelines for economic evaluation stress the need for efficacy data obtained from randomized clinical trials, although they do not insist that cost data be gathered concurrently (2).

A number of papers have discussed the methodologic issues of conducting economic analyses alongside clinical trials (1;4;9). With the growing experience of conducting economic evaluations alongside clinical trials, many methodologic issues are becoming clearer. These include the identification and exclusion of protocol-driven costs (6;15) and the need for separate reporting of prices and quantities. However, additional issues are emerging; many specifically relating to the generalizability of results outside the trial setting (7;16). Much of the focus of this concern relates to the generalizability of results from country to country with the predominant view being that economic results may vary due to differences in healthcare systems, leading to further differences in treatment costs and the accessibility and use of resources (8;19).

Of equal importance, although little discussed, is the variability in economic outcomes between treatment centers within countries. Although comparisons of centers within countries are not subject to differences in healthcare systems, there may still be differences in both the costs and accessibility of resources. This may make the generalizing of results based on one treatment center inappropriate. Furthermore, analysis of results from more than one center may allow identification of more efficient ways to provide therapy.

The aim of this paper is to assess the nature and determinants of variation in costs between treatment centers using data from a recently conducted study and to discuss the implications for both the interpretation of published studies and the design of future studies.

METHODS

Clinical Trials

Analysis was conducted on data from two economic evaluations conducted concurrently with multicenter clinical trials (5;17). The trials compared conventional radiotherapy with continuous hyperfractionated accelerated radiotherapy (CHART) for patients with head and neck cancer and with carcinoma of the bronchus. Patients were recruited from 10 participating U.K. centers.

Patients undergoing CHART received three daily treatments over 12 continuous days compared with the conventional schedule of daily treatments (Monday through Friday over a 6- to $6\frac{1}{2}$-week period. Thus, CHART patients require therapy outside of normal radiotherapy hours and are likely to be hospitalized during the period of therapy, although certain centers had lower cost hostel wards available for CHART patients.

Study Patients

Data on resource use up to 3 months from study entry were available for 526 head and neck patients (314 receiving CHART and 212 conventional therapy) and 284 bronchus patients (175 CHART and 109 conventional therapy).

Cost Data

Data were collected on the use of hospital and community service resources and patient travel for treatment. For hospital resources, data were collected on the number of bed-days by ward type, radiotherapy treatments by time of treatment, and outpatient visits. Data were collected on the number of contacts between the patient and his or her general practitioner, district nurse, and other community health and social services. Data were also collected on the number of trips, to and from hospital, the length of the trip, and means of travel.

Unit cost data for all hospital costs were derived for each participating center. Hospital travel costs (i.e., ambulance and hospital care) were also derived for each center. Other costs were derived on a national basis.

Analyses

Analyses were conducted for each of four distinct treatment trial subgroups:

1. Head and neck patients receiving conventional therapy;
2. Head and neck patients receiving CHART;
3. Bronchus patients receiving conventional therapy; and
4. Bronchus patients receiving CHART.

Degree of Variation. First, analysis was conducted to identify the degree of variation in costs between centers within each subgroup. The statistical significance of differences in costs between treatment centers was assessed by one-way analysis of variance. This would allow identification of whether the variation in cost between patients was between or within centers. The former was of interest for this analysis.

For each treatment trial subgroup in which differences in costs between treatment centers were statistically significant, analysis was repeated to identify those components of costs for which there was significant variation between centers. This would allow identification of which cost components had significant variation between rather than within centers. Components of costs considered were radiotherapy resource use, other hospital resource use, community resource use, and travel.

For each analysis, statistical significance was assessed at the 5% level with modified Bonferroni corrections.

Determinants of Variation. For each of the cost components where variation between centers was evident, ordinary least-squares regression analysis was conducted to assess the degree to which variation could be explained by various factors. This would allow identification of the causes of between-center variation, thus assisting in determining the generalizability of results and in identifying more efficient clinical practice patterns.

The model attempts to identify the determinants of variation in the cost variance where the underlying determinants of the costs of an episode of care for the individual patient i was assumed as:

$$C_i = \forall_0 + \forall_1 \mathrm{X}_i,$$

where C_i is the individual patient's cost for care, X_i is a vector of independent variables.

The independent variables within the vector X can be divided into a variable relating to unit costs (P), a vector of patient characteristics (PC), and a vector of center characteristics. Center characteristics can be further divided into a vector of identifiable hospital facilities and services (H) and a vector of treatment center dummy variables (D_j); the coefficient for each dummy represents unexplained variation in costs between centers. This leaves an expanded model of the form:

$$C_i = \exists_0 + \exists_1 P_{i+} \exists_2 \mathrm{PC}_i + \exists_3 \mathrm{H}_i + \exists_4 \mathrm{D}_{ji}.$$

All variables were entered into the model, except the dummy variables for the treatment centers, which were entered in a stepwise fashion. An alternative approach would have been to adopt a multilevel model with a fixed effects specification whereby all dummy variables for treatment centers are entered and the intercept term is suppressed (14). However, a

stepwise approach was necessary; otherwise, the incremental effect of the cost index variable and hospital characteristics would be undetermined.

The regression models were tested for both omitted variables and for general heteroskedasticity. The Ramsey RESET test for heteroskedasticity was employed for each model, whereby the error term of the original model was regressed against both the square and the cube of the model's linear function; the significance of the coefficients of the two regression variables are used as a test for heteroskedasticity (11). Another form of the Ramsey RESET test was employed for each model to test for omitted variables. In this test the square and cube of the linear function are added to the original model, and their level of significance is a test of the functional form of the model (13).

RESULTS

Degree of Variation

Based on the 95% confidence intervals for mean cost, the degree of variation within each treatment trial subgroup appears similar (Figure 1). However, the degree of variation between centers appeared to be greater for the experimental therapy (CHART) than for conventional therapy (Figure 2).

For both the head and neck and bronchus patient trials, there was statistically significant variation in costs between centers for CHART patients ($F = 16.56$, $p < .001$, and $F = 16.97$, $p < .001$, respectively) (Table 1). For conventional therapy, there was greater variation within centers with no statistically significant variation between centers after Bonferonni correction. Thus, variation in costs for conventional therapy is likely to be due to patient-specific rather than center-specific factors.

One-way analysis of variance was subsequently conducted to assess the degree of variation between centers in the four components of costs for the two CHART trial subgroups (Table 2). For both the head and neck and bronchus patient trials, there were statistically significant variations between centers in the costs of radiotherapy ($F = 680.07$, $p < .001$, and $F = 668.74$, $p < .001$, respectively) and other hospital resource use ($F = 9.07$, $p < .001$,

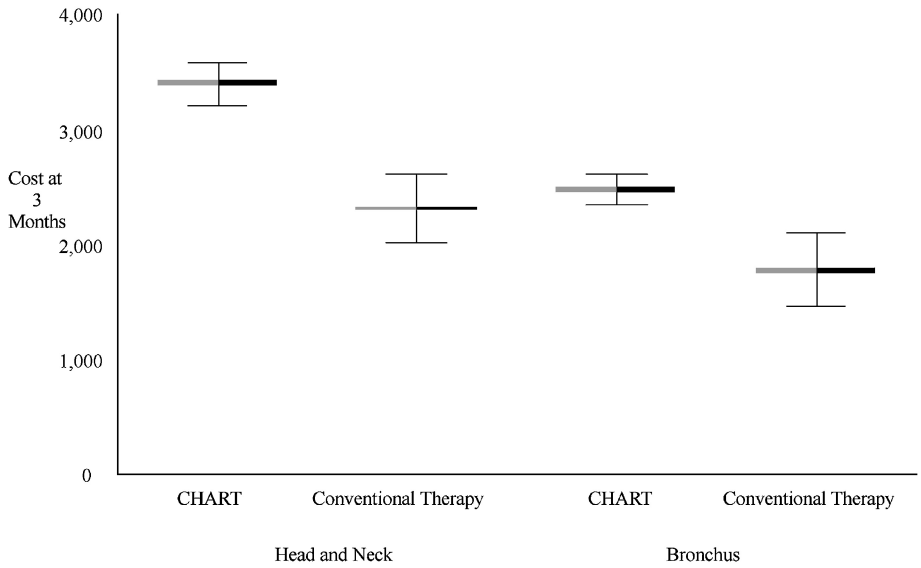

Figure 1. Mean and 95% confidence interval for total cost by treatment trial subgroup.

Table 1. One-way Analysis of Variance: Between Centers in Total Costs by Treatment Trial Subgroups

	Head and neck		Bronchus	
	CHART	Conventional therapy	CHART	Conventional therapy
Mean	3,414.67	2,322.54	2,483.54	1,785.75
(SD)	(1,697.6)	(2,127.8)	(912.08)	(1,696.5)
F ratio	16.56	2.09	16.97	1.29
(p value)	(<.000)[a]	(.032)	(<.000)[a]	(0.251)

[a] Statistical significance of variation between centers assessed at the 5% level with Bonferonni correction.

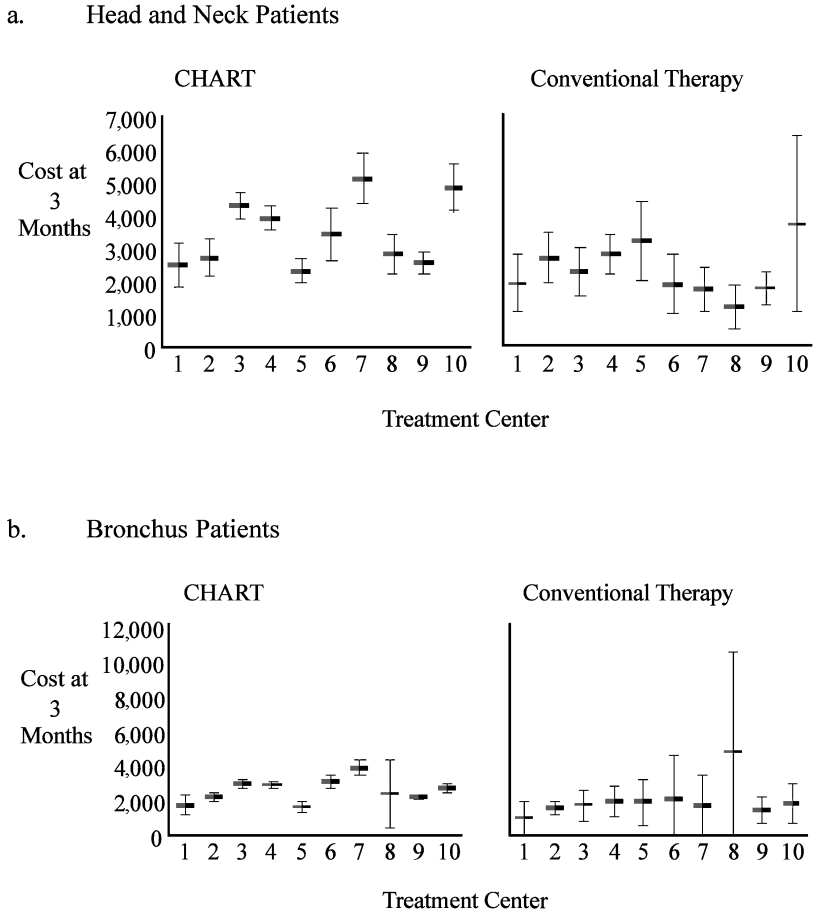

Figure 2. Mean and 95% confidence interval for total cost by treatment center by treatment trial subgroup.

and $F = 8.71$, $p < .001$, respectively). Variations between centers in the costs of travel and community resources were not statistically significant.

Determinants of Variation

Table 3 presents definitions for the variables considered for each model. The list of variables was constrained to the data collected within the clinical trial. Tables 4 and 5 detail the results of the ordinary least-squares regression analysis to identify factors that are determinants of the variation in radiotherapy and other hospital costs.

Table 2. One-way Analysis of Variance: Between Centers in Cost Components for CHART Patients

		Radiotherapy	Other hospital	Travel	Community resources
Head and neck	F ratio	680.07	9.07	2.47	0.86
	(*p* value)	(<.000)[a]	(<.000)[a]	(.010)	(0.558)
Bronchus	F ratio	668.74	8.71	1.21	1.21
	(*p* value)	(<.000)[a]	(<.000)[a]	(.294)	(.286)

[a] Statistical significance of variation between centers assessed at the 5% level with Bonferonni correction.

Table 3. Definitions of Potential Variables for Regression Equations

Variable category	Variable	Definition
Cost data	RIND	Index of the cost of protocol radiotherapy regimen
	WIND	Index of the costs of a hospital ward bed-day
Patient characteristics	AGE	Patient's age
	SEX	Patient's gender: male = 1; female = 0
	ADV	Dummy variable for advanced tumor (T3 or T4)
	WHO	Initial WHO status (no restriction = 0, restricted = 1)
Hospital characteristics	AMTRT	Dummy variable indicating that morning therapy was given typically outside of normal hours
	HOST	Dummy variable indicating that hospital had hostel provision available
Treatment centers	D1,D2 . . . . D10	Dummy variables for each of the treatment centers

Table 4. Ordinary Least Squares Regression Analysis: Radiotherapy Resource Use

	Head and neck		Bronchus	
Variable	Coeff.	(*t* stat)	Coeff.	(*t* stat)
Constant	29.75	(0.76)	−11.27	(0.27)
Cost data				
RINDEX	798.90	(46.50)	97.43	(7.36)
Hospital characteristics				
AMTRT	190.22	(9.88)	878.07	(75.70)
Patient characteristics				
AGE	−0.74	(1.44)	−1.08	(1.85)
WHO	−2.44	(0.21)	10.60	(1.05)
SEX	−18.74	(1.55)	7.39	(0.62)
ADVANCE	−16.98	(1.63)	−11.36	(1.10)
Centers				
C3	−169.56	(9.39)	−105.35	(6.95)
C4			100.31	(5.72)
C5	−110.14	(4.83)	−150.90	(7.35)
C6	−170.83	(6.71)		
C10	−57.50	(2.23)		
R^2	0.974		0.953	

See Table 3 for variable definitions.

Table 5. Ordinary Least Squares Regression Analysis: Other Hospital Resource Use

	Head and neck		Bronchus	
Variable	Coeff.	(*t* stat)	Coeff.	(*t* stat)
Constant	1,611.57	(2.30)	877.40	(1.82)
Cost data				
WINDEX	19.50	(0.05)	735.60	(3.09)
Hospital characteristics				
HOSTEL	−982.93	(5.42)	−999.37	(7.24)
Patient characteristics				
AGE	7.09	(0.97)	−4.57	(0.85)
WHO	506.17	(3.03)	28.73	(0.30)
SEX	−148.70	(0.86)	−239.94	(2.12)
ADVANCE	465.92	(3.11)	176.00	(1.80)
Centers				
C2			581.98	(2.90)
C3	666.16	(3.13)		
C9	−876.13	(3.20)		
C10	1,181.06	(2.69)		
R^2	0.272		0.332	

See Table 3 for variable definitions.

For radiotherapy costs, independent variables identified as determinants of variation were: (a) an index of the cost of protocol radiotherapy regimen, which is a proxy for overtime payments of staff; and (b) a dummy variable denoting whether the treatment center the patient was treated at typically gave the morning CHART treatment during normal working hours (AMTRT). In addition, the coefficients of four dummy variables for treatment centers were significant for the analysis based on head and neck patients, and three such variables were significant for the analysis based on bronchus patients. The coefficients for all other potential variables were not statistically significant and were excluded from the models.

For other hospital costs, independent variables identified as determinants of variation were dummy variables denoting whether the treatment center used a hostel ward (HOST) and whether the patient had an advanced tumor stage of T3 or T4 (ADV). In addition for bronchus patients, sex was also a significant determinant, as was age for head and neck patients. In addition, the coefficients of three dummy variables for treatment centers were significant for the analysis based on head and neck patients, and one such variable was significant for the analysis based on bronchus patients. The coefficients for all other potential variables, including an index of the cost of a hospital bed-day, were not statistically significant and were excluded from the models.

For all models, the Ramsey RESET test showed no significant evidence of heteroskedasticity but did show evidence of omitted variables.

CONCLUSIONS

We explored the issue of the generalizability of results from multicenter economic evaluations by examining the degree of variation in costs between centers in two multicenter randomized controlled trials. The above results identified that significant variation between centers occurred only in the newer experimental therapy and specifically in relation to radiotherapy and hospital costs. Thus, results based on data from individual centers may not be generalizable.

Almost all the variation in radiotherapy costs was explained by differences in unit costs between centers. This was primarily due to differences in payment mechanisms for after-hours treatments and the annual use of equipment rather than the quantity of physical resources used. Thus, unit costs can be seen as a proxy for differences in practices for providing CHART treatments after hours.

For hospital costs, the provision of hostel accommodation and patient characteristics were important determinants of variation between treatments. An index variable for hospital bed-day costs was not a significant predictor. Thus, variation appeared to be due to differences in the provision of services and differences in case mix.

Economic evaluations based on data from more than one treatment center are important because they can allow for the identification of different hospital practices and differences in the provision of services, which may influence both the absolute and incremental costs of treatment. This can then assist in interpolating the study results to other settings and inform issues surrounding the adoption of the new technology in a given country.

In this analysis, variation in costs by center was greater within the newer experimental therapy. One interpretation is that treatment centers may, through experience, have identified the most efficient method for providing conventional therapy but may not have identified the most efficient method for providing the newer therapy.

A further advantage of studies based on a number of centers is that scenario analysis can be adopted to provide insight into the likely cost-effectiveness of newer technologies should all centers adopt the least costly practices. In the case of the CHART clinical trials, adoption of certain practices within the lower-cost centers would have lessened the incremental cost of CHART, thus making the incremental cost-effectiveness ratio more attractive.

This highlights the potential benefit of multicenter clinical economic trials in providing additional information, which may allow more efficient provision of therapy. Thus, conclusions from studies based on data from only one center may not be generalizable to other treatment settings, especially when treatment centers are still early on a learning curve. Within a multicenter evaluation, it may be important to select centers with varying experience with the experimental therapy to ensure generalizability to as wide a patient population as possible.

In the trial, data were collected on the use of composite healthcare resources such as bed-days, outpatient visits, and radiotherapy treatments. If resource use data had been collected in more minute detail addressing the real variations between centers, such as the mechanisms of paying staff for each radiotherapy treatment and nursing provision for ward and hostel bed-days, then calculation of unit costs for each study center may not have been necessary. Clearly, the costs of such data collection would be excessive and the burden on any trial both financially and to the patients and data collectors is unlikely to be acceptable. However, it may be worthwhile that certain center characteristics are recorded to assist in the interpretation of multicenter data. In addition, given the results of this study, collection of unit cost data from at least a sample of treatment centers is necessary for all studies based on a number of treatment centers.

POLICY IMPLICATIONS

The costs of adopting a new health technology can depend critically on precisely how it is implemented. Where economic evaluations are conducted alongside multicenter clinical trials, the potential exists to explore the variation of costs by treatment center and to identify the main local factors affecting costs. This information can be important in policy decisions about adoption of the new technology, both in assessing the generalizability of study results and in identifying more efficient clinical practices.

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