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DOES CLINICAL TRIAL SUBJECT SELECTION RESTRICT THE ABILITY TO GENERALIZE USE AND COST OF HEALTH SERVICES TO "REAL LIFE" SUBJECTS?

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Abstract

Objectives: To explore one aspect of the external validity of the randomized controlled trial (RCT), specifically how being selected for inclusion in a trial and having participated has influenced the use and cost of asthma-related health services.
Methods: Services used by asthmatic users of inhaled corticosteroids (iCSTs) having previously participated in an RCT (TS, n = 46) were compared with individuals who had never participated (NS, n = 51).
Results: TS were more likely to use higher ($\geq$400 μg) daily doses of iCSTs than NS (OR, 3.3; 95% CI, 1.1–8.3) but less likely to visit emergency departments (OR, 0.3; 95% CI, 0.1–0.7). Total asthma-related costs did not differ significantly.
Conclusions: Subject differences may impede generalizing from RCTs to real life.

Keywords: Clinical trial, Economic evaluation, Asthma, Cost-effectiveness

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The randomized controlled trial (RCT) is the source of much of the data for the effect and the cost of specific treatments in health care. The RCT classically uses a carefully screened group of subjects with homogeneous characteristics under relatively artificial and controlled conditions and for a short time period. However, decision makers using effect and cost data for planning and budgeting are interested in long-term data in heterogeneous populations under real-life conditions. The strength of the RCT is its internal validity, but the external validity is less laudable (8;10;23). The problem of how to generalize the results of the RCT to other situations is particularly difficult when the economic impact of the intervention is under scrutiny (9;16).

This paper explores the external validity issues of the RCT, specifically pertaining to the selection of subjects. The problems associated with demographic differences (age, gender, comorbidities, and the like) have been discussed elsewhere (8;9;10;16;23), but there has been little examination of the impact of having been selected to participate in a trial for individuals of comparative demographic characteristics. It is this factor on which we focus, and how that may reflect in an inherent difference in patterns of resource consumption. The example of the treatment of asthma by inhaled corticosteroids (iCSTs) was chosen to explore this question. Inhaled corticosteroid therapy is an important part of the treatment of asthma (4).

In theory, only the marginal differences between treatments in RCTs are of interest, but in reality average effect and cost so estimated are often used for the purposes of modeling the economic impact of various treatments. Therefore, we explored the use of asthma-related health services as the main variable of difference between RCT and non-RCT patients. Furthermore, because optimal use of iCSTs should result in the minimum utilization of alternative treatments for the disease, including short-term beta-2 agonists (6) and visits to physicians, emergency departments, and hospitals, health services such as these have been included as study end points in economic evaluations of asthma medications (2;3;5;7;12;13;14;17;18;19;21;22;24). Therefore health service use is a relevant end point from both a clinical and economic standpoint.

We compared two groups of subjects with asthma: those who had been enrolled in clinical trials (examining the efficacy of various bronchodilators or inhaled steroid regimens) (the TS group), and those who had never participated in a drug trial (the NS group). Both the selection bias (individuals chosen for their lack of comorbidity and ability to adhere to medication use protocols) and participation in an RCT (increased learning, interest in pleasing the investigator) influence the use and cost of health services. Specifically, our hypothesis was that asthma would be better controlled in the TS subject than the NS subject. This better control would be reflected in use of asthma-related services, in that the TS subjects would use more iCSTs, but the NS group would use more "rescue" type services, such as physician visits, emergency department visits, and short-acting bronchodilators.

METHODS

Sample Selection

For the trial sample (TS), companies marketing iCSTs and three research groups identified clinical trial studies (of various inhaled bronchodilators or inhaled corticosteroid regimens). Studies had to last at least 8 weeks, involve adult patients with asthma taking iCSTs, and had to be carried out in Quebec between January 1, 1990 and March 1997. The subjects who had taken an iCST during these trials were identified, and their consent was sought.

For the normal setting sample (NS), six pharmacies in the city of Montreal and seven in Quebec City were asked to recruit subjects with asthma, selecting for period of medication

use and characteristics (asthma severity, use of iCSTs, smoking history) comparable to the TS. No physician diagnosis was available. Inclusion criteria were: a) subject-reported physician diagnosis of asthma; b) pharmacy-recorded use of iCST; c) subject-reported history of relatively stable asthma for the preceding 4 years; and d) consent to allow access to health use records. Exclusion criteria were participation in any drug-related clinical trial and characteristics corresponding to major clinical trial exclusions, including physician diagnosis of emphysema, use of four or more short-term courses of oral steroid treatment in a 12-month period, and, if over 45 years of age, a smoking history exceeding 20 pack-years (average number of packs per day times number of years smoking).

Data Collection

TS subjects' use of health services was collected for a maximum period of 6 months immediately following the clinical trial, which qualified them as candidate subjects for this study. The NS subjects' use of health services was collected, and a window not exceeding 6 months was created in the same time frame as the TS subjects' period of health services use. For most subjects, the collection period was 6 months.

All defined health services were collected, consisting of: a) the anti-asthma prescription medications dispensed to the subjects by their community pharmacies (iCSTs, bronchodilators, theophyllines, oral corticosteroids, and antibiotics); b) consultations with family practitioners, respirologists, or internal medicine specialists; c) emergency department visits; and d) hospitalizations with a main diagnosis of asthma. Use or non-use of other major classes of medications during the study period was noted to estimate major comorbidities (antineoplasics, antiparkinsonians, cardiovascular medications, antihypertensives, anticonvulsants, antidepressants, antidiabetics or insulin, cyclosporin). Asthma severity was estimated on the basis of the prescribed dose of anti-asthma medications as contained in the pharmacy records. The dose of iCST required to control the patient's asthma forms part of the tri-part score recommended for determining the degree of disability of the disease (1), and is the only element available for the subjects recruited. If more than one prescribed dosage was in the file, the most recently listed during the data collection period was used. Subjects with severe asthma were defined as subjects prescribed 1000 μg or more per day of iCST equivalent to beclomethasone.

Physician consultation information was obtained from the data banks of the government-funded provincial health insurance (RAMQ), and hospitalization information from the provincial ministry of health. Physician visits were not restricted to any particular diagnosis, because although specificity of the diagnosis in this database is high, sensitivity is low.

Costs for drug use were calculated by multiplying the prescription medications dispensed as recorded in the pharmacy files by prices based on the 1996 list of medications covered by the public plan, together with 6.5% wholesale upcharge and a pharmacy service fee of $7.77 per prescription dispensed (the average 1996 fee per the pharmacy owners' association, AQPP). Hospitalization costs were based on the 1996 cost per diem for a hospital stay (517 Canadian dollars [Can $]) for Sacré-Cœur Hospital, which was one of the three sites recruiting subjects for the study. The cost of physician visits was based on provincial reimbursement levels for 1996. The cost of emergency services included emergency department physician visits and the 1995 per-episode cost of Can $128 for Sacré-Cœur Hospital. Total asthma-related costs were the sum of the above.

Data Analyses

Quantities dispensed of iCSTs and short-term bronchodilators were calculated on a daily basis by dividing the total quantity dispensed during the measured period by the number of

days in that period. All other quantities and cost of services were estimated on an annual basis. Continuous variables were tested for normal distribution. Non-normally distributed variables were either transformed into base 10 log or category variables. The influence of the independent variables of age group, gender, city, comorbidity, and year of data (1995 or 1996; 1990–94) was tested by simple linear or logistic regression analysis. Those found to be significant ($p < .05$) were then entered with the group variable (TS vs NS) in multiple regression analyses to estimate the adjusted results. The analysis of the data was done with SPSS for Windows version 7.5.1. The threshold for significance was an α of 0.05.

RESULTS

Samples

For the TS group, 157 subjects of an identified 245 candidates were recruited (64%). Only nine subjects actively refused to participate in the study; the others were lost to follow-up or failed to return the consent form. For the NS group, a total of 52 subjects were recruited.

Data

Complete health services use information was available for all but one NS subject, but for only 75 of the TS subjects. The main reason for lack of complete data is that many pharmacies periodically purge their electronic patient records of prescriptions inactive for 2 years or more. Table 1 contains the description of the subjects for which all health services information was available.

The actual data collection period for drug use varied, but the average was 176 days. There were demographic differences between the two groups. Subjects in the NS group were more likely to be female ($p < .01$, Pearson chi-square), older ($p = .04$), and have one or more severe comorbidities ($p = .04$). Although not significant, a higher proportion of the TS group was found to have more severe asthma ($p = .31$). The exclusion for smoking appears to account for the gender difference in the NS group. The difference in comorbidity is likely to be the result of the selection process for clinical trials.

Medications: Proportion of Users, Quantity, and Cost

There was no significant difference between the proportion of users of one or more prescriptions of short-term bronchodilators, iCSTs, oral corticosteroids, theophyllines, antibiotics, or long-acting bronchodilators (data not shown), either uncontrolled or after adjusting for differences in statistically significant control variables. The average annual cost of iCSTs was higher in TS subjects (Can $291, SD = 324) than in NS subjects ($182, SD = 301) ($p = .04$, Mann-Whitney). The average annual cost of all anti-asthmatic medications was also higher, but the difference was not statistically significant ($468, SD = 454 vs $350, SD = 449; $p = .07$, Mann-Whitney).

Because the data were non-normally distributed, the average daily quantity of iCSTs was divided into two categories (based on a figure close to the mean): low or none (less than 400 mcg per day), or moderate to high (400 mcg per day or more). Annualized costs of iCSTs were divided into two categories, low or none (less than Can $150), or high ($150 or more). Costs for anti-asthma medications other than iCSTs were divided into low or none (less than $100), or high ($100 or more), and costs of all anti-asthma medications, low or none (less than $250), or high ($250 or more). These divisions were based roughly on their respective median values and resulted in a fairly even distribution of the cases. The results of the comparisons between the two groups by logistic regression are found in Table 2. TS subjects were more likely than NS subjects to use 400 mg or more of iCST daily and to have a cost of $150 or more of iCST per year,

Table 1. Description of Subjects

	Former trial sample n = 46		Normal setting sample n = 51	
	n	%	n	%
Gender				
Male	18	39.1	8	15.7
Female	28	60.9	43	84.3
Age group				
20 to 44	17	37.0	22	43.1
45 to 59	16	34.8	7	13.7
60 to 79	13	28.3	22	43.1
Asthma severity[a]				
Mild/moderate	12	26.1	19	37.3
Severe	28	60.9	28	54.9
Unknown	6	13.0	4	7.8
Comorbidities (major)[b]				
None	37	80.4	31	60.8
One or more	9	19.6	20	39.2
Location				
Montreal	28	60.9	30	58.8
Quebec City	18	39.1	21	41.2
Overall	46	100	51	100

[a]Calculated from prescribed dosage of anti-asthma medications. Those with 1,000 μg per day or more were assumed to be severe; the others were assumed to be mild to moderate.
[b]Major comorbidity was coded for use of medication according to the pharmacy records in one or more of the following categories: antineoplasics, antiparkinsonians, cardiotropes, antihypertensives, anticonvulsants, antidepressants, antidiabetics or insulin, and cyclosporin.

but no statistically significant difference was shown in the costs of other anti-asthma medication.

Physician Services: Proportion of Users, Quantity, and Cost

Individuals in the TS group tended less ($p = .05$) to visit a general practitioner (69.6%) than NS group (86.3%) (OR, 0.4; 95% CI, 0.2 to 1.0), and were less likely to have an emergency department visit (OR = 0.2; 95% CI, 0.1 to 0.7), but were more likely to see a specialist (OR = 11.8; 95% CI, 4.3 to 32.1). These results remained significant when adjusted for significant control variables.

Again using the median of the variable, the number and cost of physician visits were regrouped into two categories. Results of the regression analyses comparing the two groups are found in Table 2.

Hospitalizations

There were no hospitalizations in the NS group and only one in the TS group.

Overall Costs

Estimated total annual asthma-related health services costs were Can $696 (SD = 583) for the TS group and $688 (SD=629) for the NS group. Overall costs were non-normally distributed (skewness = 1.3). To normalize the data, a sum of $100 was added to total annual costs, and then the sum was transformed to base 10 log. The simple linear regression comparing the groups (TS vs. NS) was nonsignificant ($p = .63$). In a multiple regression of group

Table 2. Anti-asthma Medication and Physician Services Use, Trial Sample, and Normal Setting Sample: Log Linear Regressions on Average Quantities and Costs

Log linear regression	Crude regression of group[a] (n= 97)	Adjusted regression of group[b] (n= 87)
Average daily quantity (μg) of:	*(OR, 95% CI)*	*(OR, 95% CI)*
iCSTs (<400 vs. ≥400)	3.3 (1.4–8.1)	3.0 (1.1–8.3)[c]
Average annual cost ($ Can) of:		
ICSTs (<150 vs. ≥150)	3.1 (1.3–7.2)	3.3 (1.1–9.7)[c]
Other anti-asthma med (<100 vs. ≥100)	0.7 (0.3–1.7)	—
Any anti-asthma med (<250 vs. ≥250)	2.0 (0.9–4.6)	—
Average annual number of:	*(OR, 95% CI)*	*(OR, 95% CI)*
General practitioner (<4 vs. ≥4)	0.2 (0.1–0.6)	0.3 (0.2–0.5)[d]
Specialist (0 vs. ≥1)	11.8 (4.3–32.1)	12.0 (3.5–40.4)[e]
Total ambulatory (<4 vs. ≥4)	0.6 (0.3–1.3)	—
Average annual cost ($ Can) of:		
General practitioner (<85 vs. ≥85)	0.2 (0.1–0.5)	0.3 (0.1–0.6)[d]
Specialist (0 vs. ≥1)	11.8 (4.3–32.1)	12.0 (3.5–40.4)[e]
Total ambulatory (<120 vs. ≥120)	0.9 (0.4–1.9)	—

[a]Group (trial = 1, normal setting = 0).
[b]Ten subjects were excluded because of missing asthma severity data.
[c]Adjusted for severity of asthma.
[d]Adjusted for age group.
[e]Adjusted for age group and severity of asthma.

together with those variables significant by simple regression, group stayed nonsignificant ($p = .72$; adjusted R-squared, 0.22).

DISCUSSION

When comparing the cost of total asthma-related health services in real life (nontrial) conditions, we found no difference between individuals who had never been the subject of a clinical trial and those who had participated. Higher total anti-asthma costs were associated with increased age, more severe disease, and more recent treatment period. There were, however, some interesting differences between the two groups seen in certain categories of health services use and cost: former trial participants were likely to use higher doses of inhaled steroids and at a higher annual cost, were more likely to see a specialist, and had fewer visits to general practitioners at a lower annual cost than individuals who had never so participated. These findings are in line with our original hypotheses.

The information on the use of health services was gathered in the same way for both groups and under the same conditions. We did not attempt to examine all health-related costs. Some costs related to the disease have been missed, and some costs attributable to comorbidities have been included. However, the criteria for inclusion of services were the same for both groups, and there is no reason to believe that there will be a systematic difference between the two groups. A systematic difference in drug use would have to be reflected in the self-reporting of the names of pharmacies, because information on drug use came directly from the pharmacy and not the patient.

Because the data collection period for the former trial participants followed immediately after their participation in a clinical trial, some of their behaviors may still be modified by that participation. It would therefore be expected that the modifications would diminish over time, and the results we have attributed to subject selection are partially due to temporary improvements in compliance to medications, for example.

We could not have applied an RCT design using physician recruiting because the study objective was to recruit NS individuals who had not been chosen nor necessarily

had even been candidates for clinical drug trials. For this reason, we attempted to control for various factors in the analyses, but also at the outset to create comparable groups using inclusion and exclusion criteria for the NS group comparable to trial criteria. The difficulty we had in finding eligible subjects is indicative of the stringency of these requirements. Individuals excluded due to previous participation in a clinical trial are particularly revealing—the "creaming" of the healthier segment for the trial population is not a fantasy in this disease group. The experience of two recruiting pharmacies provides an example: of 37 individuals asked to participate, seven (19%) had participated in a trial. Smoking history was also a particular problem. However, we did not expect that the population of asthmatics in the community would be identical to that of those recruited for clinical trials; the hypothesis was that a selection bias exists. We believe that our data have confirmed this bias.

The sample size is too small to demonstrate moderate differences in the total cost of health services. Costs in health care tend to be highly variable, particularly hospital and emergency visits with a relatively low population occurrence and a high unit value. If real differences do exist between the two populations, it may not have been seen because of this limitation. Even with a p value of .15 and using a β of 0.3, the difference seen between the two groups would only have been significant if the overall standard deviation was Can $275 or less; however, the observed SD was over $600.

Severity of disease has been measured by a proxy: the prescribed dose of anti-asthma medications. This leads to a possible confounding by different compliance patterns in the two groups. A treating physician may tend to increase the dose of his patient's medications thinking the asthma is uncontrolled at a lower dose, when in reality the lack of control is due to nonoptimal compliance with the therapy. There is substantial evidence that even clinical trial subjects have poor compliance with their medication regimens (11;15;20), and subjects in the normal setting are likely to be even less adherent. The severity proxy index may be insufficient to account for the differences. A study has shown that specialists' patients had more severe asthma than the patients of general practitioners (25). In the community, a large proportion of subjects with asthma demonstrating difficulties with their disease would have already been referred by their family practitioners to a specialist, thus possibly recruited into an RCT; therefore, the population from which the NS subjects can be recruited would have relatively less severe disease.

Additionally, there could be other hidden differences that would not be normally controlled for in epidemiologic studies. We could postulate that patients are more likely to be referred to specialists if they are better able to express themselves and describe their symptoms and their difficulties. Certainly the specialists are likely to select their patients for trials who are more likely to be able to meet the run-in period requirements, and these individuals are likely to be more compliant.

CONCLUSION

Even when controlling for measured differences in demographics, the use and cost of certain types of asthma-related health services (iCSTs, general practitioner and specialist physician visits) differed between an individual who had been the subject of a clinical trial and a subject who had never participated in a trial.

Our study could detect no difference in overall cost of asthma-related health services; between these two groups, however, problems of external validity attributable to the selection/nonselection of individuals for trials may account for an underestimation of the use in real life of the services of general practitioners, an overestimation of the use of specialists, and overestimation of the use of inhaled corticosteroids.

POLICY IMPLICATIONS

The external validity of clinical trials may be particularly weak when used for health resource utilization information. The characteristics of patients who are the subjects of clinical trials involving iCSTs for asthma may differ considerably from the characteristics of asthma patients in real life; consequently the control of the disease and thus the effect of the treatment and the utilization of health services and costs associated could also differ. The age, gender, and asthma severity of the average trial subject may not be the same as the average member of the general population, which will be treated by the anti-asthma medication. Trial subjects are usually selected for certain characteristics, including a lack of comorbidities, a history of stable disease, and their proven compliance to treatment. The demographic and disease characteristics of subjects can be investigated in epidemiology studies, but the other characteristics influencing compliance may be much more difficult to examine. Relaxing inclusion criteria, simulating real-life treatment patterns, and using general practitioners as investigators may all help to increase the external validity of the clinical trial.

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