SPECIAL ARTICLE

QUALITY OF INSTITUTIONAL PARTICIPATION IN MULTICENTER CLINICAL TRIALS

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Abstract We studied the relation between an institution's degree of participation in a multicenter clinical trial and the quality of its participation. The quality of participation was judged on the basis of the percentage of patients entered into the trial who were in fact eligible, who were treated in accordance with the protocol, and for whom the appropriate forms were received. Those who satisfied these criteria were termed "valid" patients. Institutions were divided into two groups, "major participants" and "minor participants," according to the number of patients they en-

tered in the trial. In a detailed analysis of a multicenter trial of chemotherapy for soft-tissue sarcoma, we found that major participants had a significantly higher percentage of valid patients than did minor participants (81 per cent vs. 39 per cent) and that the minor participants were actually detrimental to the study from both scientific and administrative viewpoints. These results suggest that institutions should not participate in multicenter studies unless they can enter some predetermined minimal number of patients per year. (N Engl J Med. 1981; 305:852-5.)

THE advantages and disadvantages of multicenter clinical trials are well known.¹⁻³ Although multicenter trials can generally be completed quickly because of a rapid accrual rate, there may be large differences in the number of patients entered by the different centers, with corresponding differences in the quality of work at each center. Institutional differences in important factors such as patient selection, treatment administration, and evaluation of therapeutic results provide an additional source of variability that must be taken into account when interpreting the results of a study.

Since centers that enter only a few patients in a study will have less experience with the protocol (and perhaps even the disease in question) than other participants, their results may be less reliable. Do these centers make a worthwhile contribution to a multicenter study, or should they be excluded from participation? We have examined this question by developing an evaluation system that may be used to assess the quality of an institution's participation during the course of a multicenter trial. Several examples taken from the field of cancer research are presented.

METHODS

The European Organization for Research on Treatment of Cancer (EORTC), which encourages developments in the treatment of cancer by means of multicenter randomized clinical trials, is international in nature, and membership in an EORTC clinical cooperative group is open to any institution capable of participating in the group's activities. The EORTC offers very limited financial assistance to the cooperative groups, and expenses at the institutional level are usually absorbed by the individual institutions.

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The EORTC Data Center, which receives, processes, and analyzes the data from the clinical trials carried out within the EORTC, has developed criteria for evaluating the quality of participation of an institution in its ongoing trials. During the course of the study all patients are classified into one of two categories: "valid" or "not valid." A patient is considered to be not valid if the on-study form, which gives base-line data for a patient at entry into a trial, has not been received more than six months after the patient is entered into the study, if no information has been received within 18 months for patients still under follow-up, or if a patient is considered to be "not evaluable" by an outside review committee. Although the most common reasons for non-evaluability are ineligibility and protocol violation, such patients are not necessarily excluded from the statistical analysis.⁴ Thus, a valid patient is an eligible, randomized patient who has been treated according to the protocol and for whom the appropriate forms have been received. It should be noted that the EORTC data managers do not visit the individual centers to assist investigators in filling out the required forms. In assessing the quality of an institution's participation in a study, the number and percentage of valid patients that the institution has entered is an important factor. These criteria have been applied to four randomized studies carried out by the EORTC to show the relation between the number of patients entered by an institution and the quality of its work.

RESULTS

Table 1 shows the distribution of valid patients according to the degree of institutional participation during the course of four ongoing Phase III studies. Institutions are classified into one of two categories — "major participants" or "minor participants" — depending on the number of patients they entered in the study. In the three studies of adjuvant therapy for gastrointestinal cancer, major participants were arbitrarily defined as institutions that had entered at least 10 patients in the trial. In the sarcoma study a minimum of 12 patients was required.

In all four studies 50 per cent or fewer of the institutions could be classified as major participants; however, the major participants provided more than 85 per cent of the valid patients in each trial. These data show that the rate of validity is highly correlated with the degree of institutional participation. In each trial the proportion of valid patients is at least 60 per

Table 1. Distribution of Valid Patients According to Degree of Institutional Participation in Four Ongoing Studies.

STUDY	DEGREE OF PARTICIPATION	NUMBER OF INSTITUTIONS	PROPORTION OF VALID PATIENTS TO TOTAL PATIENTS *	PERCENTAGE OF TOTAL VALID PATIENTS
Adjuvant therapy for rectal cancer	Major	8	188/292 (64)	91
	Minor	9	19/47 (40)	9
Adjuvant therapy for gastric cancer	Major	3	79/103 (77)	93
	Minor	6	6/18 (33)	7
Adjuvant therapy for rectal cancer	Major	9	187/312 (60)	92
	Minor	11	16/36 (44)	8
Chemotherapy for soft-tissue sarcoma	Major	9	153/184 (83)	86
	Minor	22	25/58 (43)	14

*Figures in parentheses denote percentages. The figures in this table differ slightly from those in the other tables because Table 1 was written before the final analysis of the soft-tissue-sarcoma study.

cent for the major participants, whereas it is always less than 45 per cent for the minor participants. In order to gain more insight into the differences between major and minor participants with respect to the quality of participation, we examined the final results of the trial carried out by the EORTC Soft Tissue and Bone Sarcoma Group in metastatic soft-tissue sarcoma.⁵

Thirty-one institutions from 11 different countries randomized a total of 246 patients in a period of 33 months from October 1976 to July 1, 1979. Patients were randomized to receive combination chemotherapy — either a slightly modified version of the classic CYVADIC regimen (cyclophosphamide, vincristine, doxorubicin [adriamycin], and dacarbazine [dimethyltriazenoimidazole carboxamide or DTIC]; these patients served as the control group) or a new cyclic schedule of the same drugs. Since advanced soft-tissue sarcoma is relatively rare, major participants were defined as institutions that entered a minimum of 12 patients in the study — a figure that corresponded to an entry rate of approximately five patients per year.

Table 2. Responses to Treatment and Reasons for Non-Evaluability According to Degree of Institutional Participation.*

RESPONSE TO TREATMENT	MAJOR PARTICIPANTS	MINOR PARTICIPANTS	TOTAL
Complete remission	15 (8)	3 (5)	18 (7)
Partial remission	22 (12)	3 (5)	25 (10)
No change	52 (28)	7 (12)	59 (24)
Progression	56 (30)	8 (14)	64 (26)
Early death	7 (4)	2 (3)	9 (4)
Reasons for non-evaluability			
Protocol violation	7 (4)	4 (7)	11 (4)
Incomplete data	2 (1)	13 (22)	15 (6)
Refused treatment	2 (1)	4 (7)	6 (2)
Ineligible	24 (13)	15 (25)	39 (16)
Total	187	59	246

*Figures in parentheses denote percentages.

Of the 31 participating institutions, only nine could be considered major participants. As shown in Table 2, these nine institutions entered 187 patients (76 per cent), whereas the 22 institutions that were minor participants entered only 59 patients (24 per cent). The number of patients entered by each major participant ranged from 12 to 38, and the maximum number of patients from any minor participant was eight, with only one of the minor participants entering more than five patients. The interim assessment given in Table 1, which differs only slightly from the final assessment in Tables 2 and 3, showed that the rate of validity correlated with the degree of participation of the institution ($P < 0.001$ by chi-square test).

Table 2 gives the responses to treatment and reasons for non-evaluability according to degree of institutional participation. Minor participants differed significantly from major participants with respect to the overall percentage of non-evaluable patients (61

Table 3. Distribution of Response Rate and Degree of Evaluability According to Treatment Group.*

INSTITUTION AND TREATMENT	RESPONSE RATE		PROPORTION OF NON-EVALUABLE PATIENTS TO TOTAL PATIENTS
	EVALUABLE PATIENTS	ALL PATIENTS	
Major participants			
Classic schedule	26/75 (35)	26/91 (29)	16/91 (18)
Cyclic schedule	11/77 (14)	11/96 (11)	19/96 (20)
Total	37/152 (24)	37/187 (20)	35/187 (19)
Minor participants			
Classic schedule	6/17 (35)	6/34 (18)	17/34 (50)
Cyclic schedule	0/6 (0)	0/25 (0)	19/25 (76)
Total	6/23 (26)	6/59 (10)	36/59 (61)

*Figures in parentheses denote percentages.

per cent vs. 19 per cent, $P < 0.001$), the percentage of patients who could not be evaluated because of incomplete data (22 per cent vs. 1 per cent, $P < 0.001$), the percentage of patients who refused treatment (7 per cent vs. 1 per cent, $P = 0.05$), and the percentage of ineligible patients (25 per cent vs. 13 per cent, $P = 0.04$).

Table 3 shows the response rate (the percentage of patients with complete or partial remission) according to treatment group for both the major and minor participants. If only the evaluable patients are considered, the response rate does not differ according to the degree of institutional participation (24 per cent vs. 26 per cent). If all patients are included, however, there is a slight (nonsignificant) difference in the response rate according to degree of institutional participation (20 per cent vs. 10 per cent, $P = 0.13$). Among the major participants the difference in response rate by treatment group is significant ($P = 0.006$), regardless of whether all patients or just the evaluable patients are included in the analysis. On the other hand, among the minor participants the difference between treatments is not significant

($P = 0.25$ for evaluable patients and $P = 0.075$ for all patients); however, the small number of patients entered by the minor participants does not permit an adequate comparison. It should be noted, however, that there were no responders on the cyclic schedule among the minor participants and that the degree of the difference depends on whether the non-evaluable patients are included or excluded from the analysis.

There is no difference among the major participants with respect to the percentage of non-evaluable patients in the two treatment groups, but among the minor participants there are more non-evaluable patients on the cyclic schedule than on the classic schedule; again, this difference is not statistically significant ($P = 0.08$).

Originally the critical number of patients, 12, which separates the major participants from the minor ones, was chosen to coincide with an entry rate of approximately five patients per year. Figure 1 shows the distribution of non-evaluable patients according to the number of patients entered in each institution. Except at the institution that entered 14 patients, the percentage of non-evaluable patients entered by the major participants was consistently lower than the percentage entered by the minor participants. These data suggest that an entry rate of five patients per year would be a lower limit for participation in this type of study, and that an even higher rate might help to minimize the number of non-evaluable patients in such a study.

DISCUSSION

These studies cast considerable doubt on the value of including institutions that enter only a very few patients per year in a multicenter clinical trial, and suggest that participation in a multicenter study should be limited to institutions that can enter some predetermined minimal number of patients per year. Two years after the beginning of the soft-tissue sarcoma study, institutions were asked not to participate if they could not enter a minimum of five patients per year. Our findings show that this was a correct policy, since the data from the institutions that entered fewer than five patients per year did not influence the overall results. The same conclusions would have been reached in the same amount of time if the 22 minor participants had not participated in the study. Indeed, the 22 minor participants were detrimental to the sarcoma study for two principal reasons. In the first place, the minor participants contributed to the administrative workload of the data center and the outside review committee. Considerable time and money were spent in writing to these institutions to request missing forms and in processing and reviewing the data that were available for their patients. Although numerous requests for missing information were sent out, 22 per cent of the patients from the minor participants were not evaluable because of incomplete data, as compared with only 1 per cent of the patients from the major participants. Secondly, the minor participants increased the variability of the results and made interpretation of the therapeutic

Figure 1. Distribution of the Percentage of Non-Evaluable Patients According to the Number of Patients Entered by Each Institution.

comparisons more difficult. If an institution enters only a very small number of patients per year, the reason is either that it treats only a few patients with the disease in question each year or that it enters only a small fraction of the eligible patients. In the first case the institution may be relatively unfamiliar with both the disease in question and its treatment; in the second case the patients entered in the trial may not be truly representative of the patient population under study. In both instances a minor participant will be less familiar with the protocol than a major participant — an observation that has been confirmed by the results of this study. Not only did the minor participants have a much higher proportion of patients who were not evaluable (61 per cent vs. 19 per cent), but the proportion of non-evaluable patients was higher among those receiving the cyclic schedule (the new experimental group) than in the control group. Excluding the non-evaluable patients from the treatment comparisons may well bias the results, since the two treatment groups may no longer be comparable in terms of patient characteristics. However, including the non-evaluable patients in the analysis may mean that the cyclic schedule does not receive a fair trial of its efficacy. In either case the reliability of the trial's results will be open to criticism because of the large number of non-evaluable patients entered by the minor participants.

Thus, participants in multicenter trials should be chosen with care. Strict rules concerning an institution's participation in a study are required to reduce the number of non-evaluable patients, an important source of potential bias, to a minimum. Institutions should not participate in a study unless they can enter some minimal number of patients per year. At the time of entry patients should be stratified by institution, so that an entire institution can be dropped from the study if the percentage of non-valid patients from the institution becomes too large or if the entry rate is not high enough. The minimal number of patients to

be entered per year will depend on the rareness of the disease under study and perhaps also on the amount of financial and administrative support available from the Coordinating Center.

Nevertheless, the multicenter trial is still to be considered the method of choice. Indeed, because of the rareness of the type of cancer investigated in the soft-tissue-sarcoma study, it would have been impossible for a single institution to have carried out this trial. However, the results of a multicenter trial still depend on the results from each of the individual participating institutions, and thus strict criteria at the institutional level are necessary to ensure the overall success of the trial. One step in this direction is to require institutions to enter some minimal number of patients per year as a condition for participation.

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MEDICAL PROGRESS

NUCLEAR CARDIOLOGY

(Second of Two Parts)

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CARDIOVASCULAR PERFORMANCE

In 1971, the technique of gated cardiac blood-pool imaging was developed. In this approach, the electrocardiogram is introduced into the imaging process to control the temporal sequence of imaging of the entire equilibrium blood pool.^{97,98} This technique was initially proposed as a means of evaluating both regional wall motion and global left ventricular function. In the following year, first-pass radionuclide angiocardigraphy was described.⁹⁹ In this approach, only the first transit of the radionuclide bolus through the central circulation is analyzed. Since their introduction, these two radionuclide techniques have progressed from the investigational stage to one of widespread clinical application.

Multiple Gated Equilibrium Cardiac Blood-Pool Imaging

This approach provides a means of imaging the entire equilibrium blood pool at various times during cardiac contraction by synchronizing the collection of scintillation data with a physiologic marker suitable for temporally identifying the sequence of the cardiac cycle.¹⁰⁰⁻¹⁰³ Since electrocardiographic events general-

ly have a relatively fixed relation to mechanical activity, repetitive sampling of specific phases of the cardiac cycle from each of many beats can be performed until the cardiac image has an adequate count density. In order to ensure the validity of the multiple gated data, several specific requirements should be met.¹⁰⁰ First of all, cardiac function must be relatively stable during the period of data acquisition. Secondly, the patient's motion relative to the imaging device must be minimized. Thirdly, the radioactive tracer employed must remain at a relatively constant concentration within the intravascular blood pool during the period of data collection. In addition, adequate temporal resolution for a given heart rate must be ensured, and finally, the period of data acquisition must be long enough to provide for adequate count density and consequently appropriate spatial resolution. When all these criteria are fulfilled, gated cardiac blood-pool imaging allows qualitative assessment of the relative size and configuration of individual cardiac structures as well as quantitative evaluation of global and regional biventricular performance.

Technical Considerations

Autologous red cells labeled in vivo with technetium-99m pertechnetate are used almost exclusively. Although the biologic half-life of the labeled red cells is approximately 20 hours, the dominant factor determining blood-pool activity is the physical half-life of the radionuclide (six hours).

Analysis of data from the gated blood-pool study in-

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