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Impact of on-site initiation visits on patient recruitment and data quality in a randomized trial of adjuvant chemotherapy for breast cancer

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on behalf of the European Association for Research in Oncology (AERO)

Purpose To provide empirical evidence on the impact of on-site initiation visits on the following outcomes: patient recruitment, quantity and quality of data submitted to the trial coordinating office, and patients' follow-up time.

Patients and methods This methodological study was performed as part of a randomized trial comparing two combination chemotherapies for adjuvant treatment of breast cancer. Centers participating to the trial were randomized to either receive systematic on-site visits (Visited group), or not (Non-visited group).

Results The study was terminated after two years, while the main randomized trial continued. Of the 135 centers that had expressed an interest in the trial, only 69 randomized at least one patient (35/68 in the Visited group, 34/67 in the Non-visited group). Almost two-thirds of the patients were entered by 17 centers (10 in the Visited group, seven in the Non-visited group) that accrued more than 10 patients each. None of the prespecified outcomes favored the group of centers submitted to on-site initiation visits (ie, mean number of queries per patient: 6.1 ± 9.7 versus 5.4 ± 6.4 , respectively for the Visited and Non-visited groups). Spontaneous transmittal of case report forms, although required by protocol, was low in both randomized groups (mean number of pages per patient: 1.5 ± 2.0 versus 2.1 ± 2.3 , respectively), with investigators submitting about one-third of the expected forms on time (29% and 39%, respectively).

Limitations This study could not evaluate the impact of repeated on-site visits on clinical outcomes.

Conclusion Systematic on-site initiation visits did not contribute significantly to this clinical trial.

Introduction

The conduct of clinical trials has drastically changed over the last 10 years, for at least two reasons: first, the number of trials has increased, so that every physician is now potentially a clinical investigator, and second, the introduction of international good clinical practice (GCP) requirements has imposed strict rules on the conduct of trials, which simultaneously increase administrative

responsibilities for sponsors and investigators. On-site monitoring visits have become over the years a full branch of quality control, usually involving initiation, on-going and close-out visits.

On-site monitoring visits have several purposes: 1) to ensure that the rights and well being of patients are protected according to ethical and regulatory requirements, 2) to verify the accuracy of data reported versus source data, and 3) to provide training to the site personnel with respect to

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protocol and trial material, thus ensuring comparable conditions between sites. Although monitoring is required by the GCP Guidelines and Regulations, its frequency and intensity is left to the discretion of the sponsor; it is usually determined according to the phase of drug development and the complexity of the clinical trial design [1]. Implementing monitoring through on-site visits is extremely labor-intensive and expensive [2], while the benefits and cost-effectiveness of these visits on the quality of the data remains to be demonstrated. In particular, systematically imposing initiation visits to all sites regardless of the investigators' experience with the trial drugs and procedures is questionable, especially when those visits are carried on by monitors with less experience than the investigators, as is often the case in practice.

The aim of the present study was to assess the impact of on-site initiation monitoring visits on: 1) patients' recruitment, 2) quantity of data spontaneously reported, 3) quality of data, and 4) patients' follow-up time.

Materials and methods

Study design

The present study was carried out within a randomized clinical trial for patients with node positive breast cancer (AERO-B2000) [3]. The randomized trial compared six courses of FEC 100 (5-fluorouracil, epirubicin and cyclophosphamide) with four courses of FEC 100 followed by four courses of Taxol. It was carried out under the auspices of the European Association for Research in Oncology (Créteil, France). Some centers located outside France were not eligible for this study. French centers that had expressed an interest in the trial were randomly allocated by the coordinating office (IDDI, Brussels, Belgium) to either the Visited or Non-visited group, by a minimization technique to ensure balance between groups with respect to center type (public versus private hospitals) and location (greater Paris area versus French provinces). Centers of the Visited group were to be monitored on-site, while centers of the Non-visited group were not. The number of centers that would take part to the trial was not known in advance, and therefore no power calculation could be performed for differences of interest between the randomized groups. Investigators were not informed that they would be randomized to be visited or not, for such information might have ruined the very purpose of the study. They were merely told that the trial budget would not allow for regular, extensive on-site monitoring visits such as those typically performed in registration

trials of new drugs. Investigators requesting on-site visits were visited regardless of the randomized group their center had been allocated to. The study was sponsored by the European Association for Research in Oncology (AERO). Randomization, monitoring, data management and statistical analysis were handled by the International Drug Development Institute (IDDI). Bristol-Myers Squibb (BMS) and Chugai Laboratories provided financial support but had no involvement in any aspect of this study.

On-site monitoring visits

Before the clinical trial started, all centers had received the trial material by mail, including a detailed explanation on the study initiation procedure, addressed to the hospital administration, the investigator, the nursing staff and the pharmacy personnel.

The present study initially aimed at studying the impact of all monitoring visits, ie, initiation, on-going and closeout visits. During initiation visits, the trial monitors met with the investigator, the pharmacist and the trial personnel to review the protocol, inclusion and exclusion criteria, safety issues, randomization procedure, case report form completion, study planning and drug management. During on-going visits, the trial monitors reviewed the inclusion criteria and protocol compliance of each patient, performed source document verification versus case report forms (CRFs), and reviewed adverse events.

The study started in March 2000 and was terminated in March 2002, when the AERO group decided to redirect on-site monitoring visits to centers in which a problem had been identified, either because they had not sent any data to the coordination center, or because they lacked time and adequate administrative support to complete the case report forms. This shift in monitoring activities implied termination of the present study, with most initiation visits completed as planned but only a few on-site visits and no closeout visits.

Case report forms

According to the trial protocol, investigators had to record all relevant information in CRFs and send them as soon as possible to the coordinating office. Case report forms consisted of nine pages for patients with full follow-up, serious adverse events being reported on separate, additional pages. The information collected on the CRF pages was submitted to data management tests in order to detect missing and erroneous values. Queries generated by this process were used to assess the quality of the

data submitted at each center. The mean number of queries per CRF page was defined as the number of queries divided by the number of pages received. The mean number of queries per patient was defined as the number of queries divided by the number of patients. These two means were calculated for each center.

Statistical analysis

The outcomes of interest to assess the impact of on-site monitoring visits were: the number of randomized patients per center, the length of patient follow-up in each center, the number of CRF pages submitted by each center to the coordinating office, and the quality of data assessed by the number of computer-generated data queries for each center. Results were analyzed by randomized group ('intention-to-visit'), regardless of actual site visits to the centers. To account for the randomization at the center level, all statistical tests comparing data at the patient level were adjusted for the intra-center correlation [4].

Results

Participating centers

A total of 135 centers (eight centers located outside France were not concerned with this methodological study) expressed interest in the study and were randomized between March 2000 and March 2002 (Table 1).

Center types and geographic locations were well balanced both in all randomized centers and in centers that entered patients into the trial. The majority of centers (81%) were located in French provinces (outside the Paris area), and there was about an equal split between public (52%) and private (48%) hospitals.

Table 1 Distribution of centers by type and geographic location

		Visited group	Non-visited group
All randomized centers		<i>n</i> = 68	<i>n</i> = 67
Region	Greater Paris	13	13
	Province	55	54
Center type	Public	33	32
	Private	35	35
Active centers		<i>n</i> = 35	<i>n</i> = 34
Region	Greater Paris	7	7
	Province	28	27
Center type	Public	19	20
	Private	16	14

On-site monitoring visits

As of March 2002, 70 monitoring visits had been performed, 64 in the Visited group, and six in the Non-visited group. Of the centers that entered at least one patient into the trial, 32 of 35 (91%) were visited in the Visited group (instead of 100% as planned), and two of 34 (6%) in the Non-visited group (instead of 0% as planned). Most on-site monitoring visits (53 of 70) were initiation visits, performed before any randomization occurred (except for six centers where it was carried out after the first patient had been included). At the time this study was completed, initiation visits had been carried out in 50 out of the 68 centers in the Visited group (74%).

Patient recruitment

Half of the centers had entered at least one patient at the time of this analysis (35 of 68 in the Visited group, 34 of 67 in the Non-visited group) (Table 1). The recruitment pattern differed only slightly between monitored and non-monitored centers with more 'excellent recruiters' in the Visited group than in the Non-visited group (Table 2). There was no statistical difference in the number of patients between groups (302 in the Visited group versus 271 in the Non-visited group) (Table 2). Patients' recruitment continued after the closure of this methodological study, and the main trial recruited 840 patients [3], 731 of them treated in the centers participating to the methodological study.

Data quantity

In March 2002, no case report page had yet been received for nearly half of the patients (54% in the Visited group versus 42% in the Non-visited group). Moreover, five centers in the Visited group (14% of the centers with at least one patient) and three cen-

Table 2 Recruitment pattern in the study groups

	Visited group	Non-visited group
All randomized centers	<i>n</i> = 68	<i>n</i> = 67
No patient	33 (49%)	33 (49%)
1–2 patients	8 (12%)	7 (10%)
(poor recruiters)	[11 patients]	[11 patients]
3–5 patients	12 (18%)	11 (16%)
(average recruiters)	[48 patients]	[42 patients]
6–10 patients	5 (7%)	9 (13%)
(good recruiters)	[36 patients]	[70 patients]
11+ patients	10 (15%)	7 (10%)
(excellent recruiters)	[207 patients]	[148 patients]
Total number of patients	302	271

ters in the Non-visited group (9% of the centers with at least one patient) had not sent any CRF page for any of their patients (Table 3).

The average number of CRF pages received per patient was low, with a non significant tendency for visited centers to turn in fewer forms per patient than non visited centers (1.5 ± 2.0 versus 2.1 ± 2.3 , respectively). Overall, investigators turned in about one-third of the expected CRF pages, 29% for the Visited group and 39% for the Non-visited group, the recruitment activity of a center having no influence on the number of pages submitted to the data management center (Table 3).

Data quality

The mean number of queries per CRF page was equal to 1.9 in both groups (± 2.4 in the Visited group, ± 2.0 in the Non-visited group). Similarly, the mean number of queries per patient was not different for the two study groups (6.1 in the Visited group, 5.4 in the Non-visited group) (Table 4). No significant effect of recruitment could be detected, although poor recruiters in the Visited group had a strikingly high mean number of queries (11.8 versus 1.0 in the Non-visited group). Most queries concerned missing data.

Patients' follow-up

At the time of this analysis, the duration of follow-up did not differ significantly between the

randomized groups, although the proportion of patients with no follow-up at all was larger in the Visited group (82%) than in the Non-visited group (70%). The mean follow-up time, calculated from the date of randomization to the date of last form received, was $1.8 (\pm 3.2)$ months in the Visited group versus $2.5 (\pm 3.6)$ months in the Non-visited group.

Discussion

The initial objectives of this study could only be met partially due its early termination and the small number of on-going monitoring visits. As far as initiation visits, the study does not provide any evidence that these made a difference to patient recruitment. Among centers with at least one patient, the average number of patients was similar in both groups. Nearly half of the centers (66 of 135) that had expressed an interest in the trial ended up not participating, and on-site visits made no difference to this high level of non-participation (Table 1), with 19 of the 68 initiation visits having taken place in non-recruiting centers. The bulk of the patients (80%) were recruited in only 30 centers, and almost two-thirds (62%) in 17 'excellent recruiters' (10 in the Visited group and seven in the Non-visited group, Table 2). There was no impact of monitoring visits on recruitment categories (poor, average, good and excellent).

In terms of the number of CRF pages submitted, no significant difference could be detected between

Table 3 Quantity of data received by study group (as of March 2002)

	Visited group	Non-visited group
<i>Active centers</i>	<i>n</i> = 35	<i>n</i> = 34
Total number of patients	302	271
Number of CRF pages received by patient		
1-2	51 (17%)	44 (16%)
3-5	77 (25%)	96 (35%)
6+	12 (4%)	17 (6%)
Mean	1.5 ± 2.0	2.1 ± 2.3
<i>Centers with at least one CRF pages received vs. expected</i>	<i>n</i> = 30	<i>n</i> = 31
Mean percent number of CRF pages received vs. expected	29%	39%
• for poor recruiters ^a	31%	39%
• for average recruiters	26%	43%
• for good recruiters	39%	30%
• for excellent recruiters	26%	47%
<i>Centers without CRF</i>	<i>n</i> = 5	<i>n</i> = 3
<i>Centers' distribution according to recruitment categories</i>		
• for poor recruiters	3	1
• for average recruiters	2	0
• for good recruiters	0	2
• for excellent recruiters	0	0

^aSee Table 2 for definition.

Table 4 Data quality

	Visited group	Non-visited group
Centers with at least one form received	<i>n</i> = 30	<i>n</i> = 31
Number of CRF pages received	444	571
Mean number of queries per CRF page	1.9 ± 2.4	1.9 ± 2.0
Number of queries: Per CRF page		
0	23%	16%
1	27%	23%
2	17%	32%
3	13%	6%
4-5	13%	16%
>5	6%	6%
Number of patients with at least one form	140	157
Mean number of queries per patient	6.1 ± 9.7	5.4 ± 6.4
Number of queries: Per patient		
0	23%	16%
>0-≤2	27%	19%
>2-≤4	13%	19%
>4-≤6	0%	10%
>6-≤10	17%	29%
>10	20%	6%

the randomized groups, although 54% of centers in the Visited group did not return any CRF page versus only 42% in the Nonvisited group (Table 3). This observation suggests no return on the investment of initiation visits in terms of data submission, despite claims that the personal commitment of study monitors may be a factor in collecting complete data on time [6]. The problem of poor or slow transmission of data often plagues clinical trials and is usually addressed through mail and telephone reminders to reduce missing or late data [7–10]. In the present trial, after termination of the methodological study, the monitors focused their efforts on centers not submitting data on time. This may constitute a cost-effective approach to data collection, without the need for systematic on-site visits.

The quality of the data submitted to the data managers, assessed by the number of queries issued per CRF page and per patient, was similar with respect to on-site visits and to recruitment performance (Table 4). Thus, initiation visits do not seem to have contributed to the quality of the data any more than to their quantity.

The power of this study to detect differences between the randomized groups was unspecified, as the number of centers that would take part to the trial was not controlled. This fact must be borne in mind when interpreting the lack of significant differences between the randomized groups. In addition, all analyses were based on an ‘intention-to-visit’ approach, and the less than perfect compliance to the randomized assignment may have reduced or concealed a true benefit of on-site visits. However, the differences observed on the outcomes of interest were unimpressive and, if anything, favored the Non-visited group.

Initiation visits are often presented as essential to train the study personnel on site. Although important, this aspect of trial initiation could be handled centrally during investigators’ meetings or via net-meeting at considerably lower cost, with the added benefit of encouraging interaction between the investigators. Such an approach is routinely used by many cooperative groups and is endorsed by the ICH Good Clinical Practice guidelines (Section 5.18.3). For instance, the International Studies of Infarct Survival (ISIS) Group held centralized training sessions and performed initiation visits only for centers that lacked a record of excellent documentation [5]. In the present study, investigators’ motivation to recruit, data quality, and spontaneous CRF transmittal to the data center could not be predicted by the presence or the absence of an initiation visit. All centers received explanations about the conduct of the trial by mail and were offered the possibility of an on-site initiation visit upon request: only three centers (4%) in the Non-visited group used that opportunity.

Typically, sponsors implement systematic, frequent on-site monitoring visits of all sites, regardless of the local situation or the trial complexity. ICH Good Clinical Practice (Section 5.18.3) allows for monitoring to be adapted and initiation visits to be replaced by investigators’ meetings, and for the amount of monitored data to be substantially reduced by a statistical sampling method [1].

The major limitation of the present study is that it was terminated after two years, while patient recruitment was still on-going, with most centers in the Visited group having been visited only once (initiation visit). The decision to focus monitoring activities on delinquent centers is consistent with recommendations derived from two extensive studies conducted by the European Organization for Research and Treatment of Cancer (EORTC) [2,11].

The study could not evaluate the impact of repeated on-site visits on the outcomes of interest, in particular on clinical outcomes. This is unfortunate as it would have been the first study to assess the impact of on-site monitoring in a randomized and quantitative way. Data on the benefits and costs of on-site monitoring are scarce, and consequently it is hard to claim when it should be carried out, and if so at what frequency [12]. For trials aimed at drug approval, the pharmaceutical industry has adopted tight monitoring schedules, with on-site visits usually taking place every three to six weeks. In contrast, many clinical trials conducted by cooperative groups do not have provisions for regular on-site monitoring visits, although they often have mechanisms in place to conduct site audits. In contrast to monitoring visits, on-site audits are not aimed at checking 100% of the data, but typically review a sample of the CRFs, a procedure accepted for long-term studies. The National Cancer Institute, for instance, requires site audits once every three years for the trials they sponsor [13]. On-site audits often reveal deviations from GCP requirements and other data problems [14], and as such they play an important educational and regulatory role, yet the impact of these problems on the trial results remains to be established [15]. Statistical approaches have been suggested as cost-effective alternatives to on-site monitoring visits both to minimize missing data [6] and to detect strange data patterns in multicenter clinical trials [16].

The lack of systematic investigations on the actual returns of on-site monitoring is surprising in view of the high labor intensity, and therefore the high cost of this activity, which usually represents well over half of a trial’s total budget. In 2000, Favalli *et al.* evaluated the average cost per site visit in Europe at 1530 euros [2]. This is in line with the budget estimated for the present study. In terms of time spent, each site visit represented roughly 20 hours of work, including time for preparation,

travel, and reporting. The 68 visits performed in this trial represented 1360 hours of work, or about three-quarters of one full-time person-equivalent for one year at the trial's coordinating office. This estimate does not include the time spent on site visits by the personnel at the visited center (four hours per visit on average), nor does it include the travel and subsistence costs of the monitors doing the site visits. Similar findings were reported by the Duke Clinical Research Institute. Califf *et al.* observed that site visits consume a large portion of the clinical research budget and could be substantially reduced by limiting the visits to one per center per year, with reviews of random samples of only 10–20% of the records [5]. Such a recommendation seems realistic in the setting of trials using well-known drugs carried out by academic groups, and provides a cost-effective allocation of the scarce resources usually available in these trials.

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