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Acknowledgements—Our thanks to the Cancer Research Campaign and the Royal Marsden Hospital for support, and to Lisa Wickens and Sarah Milan for assistance with data management.

Pergamon

European Journal of Cancer Vol. 30A, No. 7, pp. 907–910, 1994
Elsevier Science Ltd
Printed in Great Britain
0959–8049/94 $7.00+0.00

0959-8049(94)E0132-N

Informed Consent in European Multicentre Randomised Clinical Trials — Are Patients Really Informed?

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This study was designed to examine the standard of consent used by investigators in European randomised clinical trials (RCT). The participants of 12 multicentre RCTs published in the *European Journal of Cancer* in the years 1990–1992 were asked to complete a short questionnaire regarding their practice of obtaining consent in the trial reported. Anonymity was assured. Replies were received from 60 of 88 clinicians contacted. Data showed that 12% of clinicians did not inform their patients about the trial prior to randomisation. Thirty-eight per cent of clinicians did not always tell patients that they had been assigned to their treatment randomly. Only 32% of clinicians used written consent, 21% used written information without obligatory signing, 42% used verbal consent, and in 5% no consent was sought. Even when information was given, only 58% of clinicians gave full information on all aspects of the trial and 42% gave information on the proposed treatment arm only (27% revealing inclusion in an RCT). When examined by geographical origin, clinicians in northern Europe were more likely to obtain full consent than those from southern Europe. Similarly, the level of consent was higher in trials of supportive care than in trials testing curative or palliative antitumour therapies.

Key words: clinical trials, informed consent
Eur J Cancer, Vol. 30A, No. 7, pp. 907–910, 1994

INTRODUCTION

RANDOMISED CLINICAL trials (RCTs) have become the accepted method of assessing the usefulness of therapies, both new and old. As RCTs have developed, it has become customary, in most developed countries, that patients are asked to participate in the process of deciding whether they should be included in the trial—knowing that they will be allocated to one or two or more treatment options by chance [1]. The standard of such consent usually demanded is one of so-called "informed consent" [2]. Thus, in addition to knowing about the potential randomisation,

Table 1. *Multicentre randomised clinical trials published in the* European Journal of Cancer, 1990–1992 *and subject to survey**

Year of Publication	Volume	First page	No. of clinical collaborators† C	M	R	Participating countries	Tumour type	Type of therapy
1990	26	779	10	8	7	F,I,B,PL	Oropharynx	Radiotherapy
1991	27	750	14	6	4	I	Leukaemia	Chemotherapy
1991	27	821	7	6	5	F,I,B	Head and neck	Chemotherapy
1991	27	954	6	5	4	GB,CND	Prostate	Palliative
1991	27	1137	4	4	3	D	Breast	Palliative
1991	27	1383	8	4	3	NL	Urothelial	Chemotherapy
1992	28A	96	17	12	9	NL,IRL,F,I	Lung	Chemotherapy
1992	28A	801	9	7	4	NL,GB,B	Breast	Surgery
1992	28A	890	6	6	5	S,DK	Breast	Palliative
1992	28A	1018	23	12	8	B,F,D,A	All	Palliative
1992	28A	1392	10	9	3	GB	Myeloma	Interferon
1992	28A	1823	14	8	5	I	Colorectal	Chemotherapy

*All addresses were not available. †The figures indicate the number of all clinical collaborators (C) (excluding statisticians and commercial employees), the number of doctors to whom the questionnaires were mailed (M) and the number of replies (R). Participating countries: F, France; I, Italy; B, Belgium; PL, Poland (no replies); GB, Great Britain; CND, Canada+; D, Germany; NL, Holland; DK, Denmark; A, Austria+; IRL, Ireland; S, Sweden.

the patient should know about all the treatment options, their likely efficacies and side-effects. Where studies have been carried out, it seems unlikely that this "gold-standard" of true informed consent can be easily achieved [3].

This short paper, rather than looking at the patients perception, simply aims at trying to determine whether the goal of informed consent was attempted by clinicians or if it was bypassed in some way. If a significant proportion of clinicians feel unable to ask for informed consent, the role and the way this process is carried out needs to be re-examined.

PATIENTS AND METHODS

The participants (where addresses were available) of 12 multicentre RCTs published in the years 1990–1992 in the *European Journal of Cancer* were circulated a simple one-page questionnaire asking about their usual practice of obtaining consent in the trial reported. Table 1 lists the trials included in the study and details of responders. None of the trial reports mentioned postrandomisation consent, suggesting that the protocols called for prerandomisation consent. Participants were assured anonymity, and were asked to fully reveal how they applied the informed consent demanded in the trial protocol.

RESULTS

Questionnaires (see Table 2 for questions) were sent to 87 clinicians identified in the 12 trials. The physicians represented nine countries and a variety of trials testing questions in chemotherapy, immunotherapy, radiotherapy, surgery and supportive care. Sixty clinicians (69%), 40 in therapy studies and 20 in supportive care studies, replied.

The data for all clinicians together shows that 53 (88%) informed the patient about the study before randomisation. Seven (12%), however, did not inform the patients prior to randomisation even though it was likely that the protocol demanded this. Clinicians were asked whether they clearly told patients that they would be, or had been, assigned to their treatment randomly. Thirty-seven (62%) stated that they always did this, 17 (28%) said sometimes and 6 (10%) said that they did not do this. Consent may be sought by various means and clinicians were asked how this was done. Nineteen (32%) used a written consent form signed by the patient, 21% used written information without obligatory signing, 42% verbal consent and in 5% no consent was sought.

Informed consent also relies on the quality and quantity of information given to patients. When asked about the extent of information provided, 35 (58%) said they gave full information about all the treatment options and on the randomisation procedure. Sixteen (27%) gave information on the proposed treatment arm only, but indicated inclusion in an RCT. Nine (15%) clinicians only gave information on the proposed treatment arm. When asked for their preferences in future trials, 42 (70%) favoured prerandomisation consent with total disclosure about both arms of the trial, seven (12%) wanted postrandomisation consent with total disclosure about both arms of the trial after randomisation. Eleven (18%) clinicians wished for postrandomisation consent with partial disclosure about the randomised arm only. These data have been analysed according to geographical area (Mediterranean versus non-Mediterranean) and by whether the therapy being tested was used with the intent of disease control/eradication or was simply supportive in nature. These groups were selected since there were sufficient clinicians in each group for analysis and because there were *a priori*, suggestions that attitudes may be different in these groups. Data for these groups are shown in Tables 2 and 3. Clinicians in the different geographical areas were equally represented in the therapy and supportive care trials.

DISCUSSION

The data presented clearly show that a proportion of clinicians feel unable to ask patients to participate fully in the process of consent to inclusion in a RCT. Although 88% of clinicians did

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Received 7 Feb. 1994; accepted 18 Feb. 1994.

Table 2. Mediterranean clinicians (France/Italy) compared with non-Mediterranean clinicians (U.K./Ireland/Sweden/Denmark/Germany/Belgium/Netherlands)

Question		Number (%) replying: Mediterranean (27 clinicians)	Non-Mediterranean (33 clinicians)	Statistical value
(1)	When did you inform the patient about the study?			
	(a) Before randomisation	21 (78)	32 (97)	$P = 0.56$ Fisher's exact test
	(b) After randomisation	6 (22)	1 (3)	
(2)	Did you clearly tell the patient that the treatment would be/had been randomly assigned?			
	(a) Yes, always	9 (33)	28 (85)	$\chi^2 = 16.8$
	(b) Sometimes	13 (48)	4 (12)	df = 2
	(c) No	5 (19)	1 (3)	$P = 0.0002$
(3)	The consent was*:			
	(a) Written and signed by the patient	10.5 (39)	8.5 (26)	$\chi^2 = 11.1$
	(b) Written information without obligatory signing	1 (4)	11.5 (35)	df = 2 $P = 0.011$
	(c) Verbal	12.5 (46)	13 (39)	
	(d) No consent sought	3 (11)	—	
(4)	What was the actual extent of information during the consent procedure?*			
	(a) Full information about all the treatment options and on the randomisation procedure	9 (33)	26 (79)	$\chi^2 = 14.2$ df = 2
	(b) Information on the proposed treatment arm only, but indicating inclusion in a prospective RCT	10 (37)	6 (18)	$P = 0.0008$
	(c) Information on the proposed treatment arm only	8 (30)	1 (3)	
(5)	Your preference regarding the consent procedure in future trials?*			
	(a) Prerandomisation consent with total disclosure about both arms of the trial	15 (56)	27 (82)	$\chi^2 = 4.98$
	(b) Postrandomisation consent with total disclosure about both arms of the trial after randomisation	5 (18)	2 (6)	df = 2 $P = 0.0828$
	(c) Postrandomisation consent with patient disclosure about the randomisation arm only	7 (26)	4 (12)	

*If more than one answer applies, indicate approximate % of patients in each category. RCT, randomised clinical trial.

Table 3. Supportive care trials versus those aimed at tumour control or eradication (therapy)

Question*		Supportive (20 clinicians)	Therapy (40 clinicians)	Statistical values
1.	(a)	20 (100)	33 (83)	$P = 0.096$ Fisher's exact test
	(b)	—	7 (18)	
2.	(a)	19 (95)	18 (45)	$\chi^2 = 14.2$
	(b)	1 (5)	16 (40)	df = 2
	(c)	—	6 (15)	$P = 0.0008$
3.	(a)	10.5 (53)	8.5 (21)	$\chi^2 = 4$
	(b)	4.5 (23)	8 (20)	df = 3
	(c)	5 (25)	20.5 (51)	$P = 0.26$
	(d)	—	3 (8)	
4.	(a)	17 (85)	18 (45)	$\chi^2 = 9.7$
	(b)	3 (15)	13 (33)	df = 2
	(c)	—	9 (23)	$P = 0079$
5.	(a)	17 (85)	25 (63)	$\chi^2 = 4.7$
	(b)	—	7 (18)	df = 2
	(c)	3 (15)	8 (20)	$P = 0.098$

*See Table 2 for details.

inform their patients of the RCT before randomisation, this left seven (12%) who did not comply with prerandomisation consent. Six of these came from Mediterranean countries and one was of northern European origin. All clinicials taking part in supportive therapy trials informed the patient prior to randomisation, whilst seven of 33 (17.5%) undertaking "therapy" trials failed to do so.

On the difficult point of fully disclosing randomisation, only 62% of all clinicians said that they always did this. Once again, there were significant differences between the geographical areas the clinician came from and between the different therapeutic intents of the trial. Only 33% of Mediterranean clinicians always gave information on randomisation compared with 85% of their colleagues from northern European countries ($P = 0.0002$). Where clinicians were carrying out supportive care trials, 95% always informed patients about randomisation, whilst only 45% of clinicians carrying out studies of palliative or curative therapy always did so ($P = 0.0008$).

The method of obtaining consent was also very variable ranging from written signed consent to verbal to no consent. The differences between clinicians in different geographical regions was less marked, though there was still a trend for northern European clinicians and clinicians in supportive care studies to give a higher standard of consent.

The amount of information given was also very variable with especially large differences between Mediterranean and non-

Mediterranean clinicians (full disclosure 33 versus 79%; $P = 0.0008$). Supportive care studies showed a similar picture compared with 'treatment' studies (85 versus 45%, $P = 0.0079$).

When asked what they wished to see in the future there was continued variability. Overall, 70% wished to see full disclosure and informed consent prior to randomisation, 12% wished for postrandomisation full informed consent and 18% wished for only partial disclosure (of the treatment arm) following randomisation. Differences between Mediterranean and northern European colleagues were once again evident (Table 2).

These results are disturbing since they show that the level of informed consent often falls short of that demanded in a trial protocol. Not all clinicians replied to the questionnaire (60/87), but even if all the clinicians choosing not to take part had given fully informed consent this would still have left a fairly high proportion failing to comply with informed consent. However, this scenario seems intrinsically unlikely—it could be argued that clinicians not taking part in the study may have been less likely to have given informed consent. In addition, the data suggest that the awareness of the need for consent may have led clinicians to underestimate the proportion in which they did not obtain informed consent. For example, in Table 2, only 11% said they did not seek consent from patients (question 3), but in question 4, 30% said they only provided information on the treatment arm, which is hardly informed consent.

Cultural attitudes to frank disclosure of information about disease and RCTs are known anecdotally to vary within Europe, and this survey clearly shows that clinicians in Mediterranean countries (France and Italy in this case) felt less able to give full information than their counterparts in northern European countries. Similarly, where questions concentrate on comparing two or more palliative or curative therapies there may be greater potential for distress, than when the trial compares supportive care therapies. Full disclosure about the treatments may in the case of palliative/curative therapies require discussion of treatment efficacy and survival which may dissuade some clinicians from frank disclosure and informed consent.

Whilst clinicians questioned seemed to want to move further towards full prerandomisation informed consent, 30% still preferred a postrandomisation consent procedure. This technique, proposed originally by Zelen [4] has clear advantages in that the patient may find the reduced uncertainty beneficial. However, ethical problems may ensue if following randomisation there is only partial disclosure which is solely about the treatment arm. When full disclosure about both arms is given after randomisation, this is regarded as ethical but it increases the proportion of patients refusing the assigned treatment. This in turn means more patients need to be recruited since patients refusing the assigned treatment must still remain in the trial regardless of their subsequent treatment—thus potentially diluting the result [5].

At present, there is insufficient experience with this technique to know if it is beneficial. It may, in certain circumstances, make randomisation very much easier, and despite the trial requiring larger numbers, may result in a more successful study. When it fails to greatly increase accrual, its use may be counterproductive since the increased accrual fails to match or exceed the requirement for more patients consequent upon the number of patients refusing the allocated treatment [5]. It has been suggested that postrandomisation consent is most likely to be beneficial when there are major differences between the two treatments being compared [5].

This paper underlines the fact that prerandomisation informed consent remains a problem for the doctor and, in the case of previous reports, the patient [3, 6]. There is a need for continued debate on the best ways of obtaining consent for incusion in RCTs. This paper shows that the dialogue will need to take into account regional variations in attitudes to disclosure of information to the patient and the therapeutic intent of the trial. More research on the best ways of informing patients, teaching doctors how to do this and helping them deal with the emotional burden of such an approach is required.

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