Anesthesiology
1999; 91:969–78

Randomized Trial of Informed Consent and Recruitment for Clinical Trials in the Immediate Preoperative Period

Paul S. Myles, M.B.B.S., M.P.H., M.D., F.F.A.R.C.S.I., F.A.N.Z.C.A., Helen E. Fletcher, R.N.,†*
Sesto Cairo, M.B.B.S.,‡ Hilary Madder, M.B.B.S., F.A.N.Z.C.A.,§
Roderick McRae, M.B.B.S.(Hons), B.Med.Sc.(Hons), F.A.N.Z.C.A., F.F.I.C.A.N.Z.C.A.,†
James Cooper, M.B.B.S.,‡ Debra Devonshire, M.B.B.S.,‡ Jennifer O. Hunt, R.N.,† Jo Richardson, M.B.B.S.,‡
Howard Machlin, M.B.B.S., F.A.N.Z.C.A.,§ E. Brian Morgan, M.B.B.S., F.A.N.Z.C.A.,§
John Moloney, M.B.B.S., F.A.N.Z.C.A.,§ Glen Downey, M.B.B.S., F.A.N.Z.C.A.§

Background: **The standard process of obtaining informed consent sometimes prevents physicians or patients from participating in clinical trials, partly because they are concerned about eventual treatment allocation or the physician is concerned the patient might harbor some uncertainty about the best treatment. Alternative randomization methods have been advocated that may address these and other concerns.**

Methods: **After institutional ethics committee gave its approval, the authors interviewed 770 patients before operation and asked them to consider enrolling in a mock anesthesia trial. Patients were allocated randomly to one of five methods of randomization and consent: one-sided informed consent (the most common approach), prerandomized consent to experimental treatment, prerandomized consent to standard treatment, one-sided physician-modified informed consent, or one-sided patient-modified informed consent. Recruitment rates were compared and sociodemographic and perioperative predictors of recruitment were identified.**

Results: **The randomization method did not result in any significant difference in recruitment rates: one-sided informed consent, 55.6%; prerandomized consent to experimental treatment, 53.3%; prerandomized consent to standard treatment, 53%; one-sided physician-modified informed consent, 60.7%; and one-sided patient-modified informed consent, 56.7% ($P = 0.66$). Multivariate predictors of recruitment were patient age >45 yr (odds ratio, 1.44; 95% confidence interval [CI], 1.08 to 1.93), English-speaking at home (1.49; 1.0 to 2.21), and male researcher–male patient interaction (1.37; 1.20 to 1.57).**

Conclusions: **No evidence emerged that alternative randomization and consent designs resulted in increased recruitment rates compared with simple one-sided informed consent for a sham anesthesia trial in patients awaiting elective surgery. Older, male patients were more likely to provide consent. (Key words: Consumer principle; equipoise; ethics; prerandomization.)**

THE most rigorous clinical study design is a prospective, double-blinded, randomized controlled trial, in which each patient has an equal chance of being allocated to a particular treatment group (which may include one of several active treatments or inactive placebo). The ethical principle underlying this process includes the concept of equipoise, in which the clinician and patient have no particular preference or reason to favor one treatment over another.[1–3] The conflicting roles of researcher and clinician are sometimes difficult to resolve or justify in this situation.[1–7] The patient must also provide informed consent freely, a process that requires adequate disclosure of information, competency and understanding, and self-determination.[1,4,8–10]

Patients approached before elective surgery are often anxious and preoccupied, and they also may be limited by concurrent disease. They may never have been hospitalized, or, if they have, may have negative recollections of their past experiences. It is conceivable that their ability to cope will be challenged further by a request to enroll in a research trial. Feelings of anxiety, vulnerability, confusion, or mistrust may dominate their thought processes. Such feelings restrict their ability to process new information or to freely provide informed

* Senior Lecturer and Head of Research.

† Research Assistant.

‡ Anesthetic Resident.

§ Anesthesiologist.

Received from the Department of Anaesthesia and Pain Management, Alfred Hospital, Melbourne, Australia. Submitted for publication January 11, 1999. Accepted for publication April 28, 1999. No specific project grant was required to support this study. The anesthesia research assistants were funded by the Anaesthesia Research Special Purposes Fund of The Alfred, Melbourne, Australia. Presented in part at the 1999 Annual Scientific Meeting of the Australian and New Zealand College of Anaesthetists, Adelaide, South Australia, May 8–12, 1999.

Address correpondence to Dr. Myles: Department of Anaesthesia and Pain Management, Alfred Hospital, PO Box 315, Prahran, Victoria, 3181 Australia. Address electronic mail to: p.myles@alfred.org.au

Reprints will not be available.

consent.[8,10] These issues have been explored previously,[4,8–15] but there is no information about how or why patients come to a decision in the immediate preoperative period.

Recruitment and consent for randomized controlled trials have been challenged through the years,[16–22] and recently alternative study designs have been suggested that include consideration of patient preferences.[5–7,18,19] Gore[19] coined the term *consumer principle* to describe a valid method of how a patient or clinician can modify the chance that the patient will be allocated to a particular treatment group. This process allows a measure of self-determination when there are varying degrees of uncertainty regarding the best treatment. We could not find examples of this method in the literature. Prerandomization is a process in which the patient is first randomized to a particular treatment group and then approached (with knowledge of their treatment allocation) for informed consent.[20] Zelen[20] originally proposed this method to exclude patient notification and consent if they had been allocated to receive standard treatment. Examples of prerandomization in anesthesia and critical care trials can be found in the literature.[23,24] It has been suggested that variations in the randomization and consent process can improve recruitment rates.[20–22] However, this information is insufficient for our purpose, because results are derived from volunteers and not from those who are about to undergo (sometimes major and life-threatening) surgery.

We evaluated five alternative randomization schedules in patients in the immediate preoperative period to determine which method of randomization and consent provided the best recruitment rate. We also analyzed patient, surgical, and researcher characteristics to determine predictors of successful recruitment.

Materials and Methods

After we received ethics committee approval, we approached adults scheduled for elective surgery and invited them to participate in this trial. We excluded patients with poor English comprehension, known psychiatric disorders, intellectual disability, or those already enrolled in another research trial. Potential participants were approached after they were hospitalized, either the day before or the morning of surgery. Patients were interviewed at the bedside, in one of several surgical wards. In most cases, this was by the anesthesiologist responsible for their care. Alternatively, a research nurse experienced in clinical trial explanation and obtaining informed consent approached the patients. The researchers included 10 consultant anesthesiologists (eight men, two women), five residents (three men, two women), and two research nurses (both women). After an explanation of the purpose of the trial (see Appendix 1, Explanatory Statement 1), patients were asked to provide informed consent to be studied. It was explained to them that participation would have no real effect on them and that the trial medication considered did not exist.

We collected patient demographic information including level of education, employment status, extent of English spoken at home (as a surrogate marker of lesser degrees of English comprehension), and the circumstances at the time of recruitment (timing of interview with respect to surgery and whether a family member or friend was present). We asked the patients to rate their current life expectancy on a five-point scale: 1 = expect to live at least 20 yr, 2 = expect to live at least 10 yr, 3 = expect to live at least 5 yr, 4 = expect to live at least 2 yr, 5 = not expected to live 2 yr. The anesthesiologist also rated the patient's life expectancy at the completion of the interview; this rating was not provided to the patient. Perioperative risk was defined by the American Society of Anesthesiologists physical status score (ASA status).

Preoperative anxiety was graded on a 100-mm visual analog scale, where 0 = "I am completely relaxed about my operation," and 100 mm = "I am extremely nervous about my operation."

The anesthesiologist graded the extent of surgery as minor or major. Because the level of anxiety associated with major surgery (neurologic, thoracic and cardiac, vascular, and colorectal) might have affected recruitment rates, patients were stratified into major or minor surgery groups and then allocated using computer-generated random blocks of six and ten.

Once randomized, each patient was given a description of a sham anesthesia trial investigating an imaginary experimental drug that we called Imaginon, along with a printed explanatory statement (see Appendix 1, Explanatory Statement 2). This process generally required 10–20 min. Then they were asked to give their consent.

Alternative Randomization and Consent Designs

Group 1: One-sided Informed Consent. The current, standard randomized controlled trial design is applied: If the patients consent, they have an equal chance of receiving either the experimental drug or the standard drug; if the patients do not give consent, they will re-

ceive the standard drug. The following paragraph was included at the end of Explanatory Statement 2:

This study will be "double-blinded," in that neither you nor your doctor will know which drug you are to receive until after the study is completed. If you agree to participate in this research study, you will receive either Imaginon or our usual anesthetic drug. This will be decided on a randomized "chance" basis (like tossing a coin). If you do not want to participate in this trial, you will receive the usual anesthetic drug.

Group 2: Prerandomized to Experimental Drug, Consent for Experimental Drug. The patients are informed that they have been randomized to receive the experimental drug and are then asked to provide consent (with this knowledge); if they do not give consent, they receive the standard drug. The following paragraph was included at the end of Explanatory Statement 2:

If you agree to participate in this trial, you will receive the new drug, Imaginon. However, if you do not want to participate, you will receive the usual anesthetic drug.

Group 3: Prerandomized to Standard Drug, Consent for Standard Drug. The patients are informed that they have been randomized to receive the standard drug and are then asked to provide consent (with this knowledge); if they do not give consent, they receive the experimental drug. The following paragraph was included at the end of Explanatory Statement 2:

If you agree to participate in this trial, you will receive the usual anesthetic drug. However, if you do not want to participate, you will receive the new drug, Imaginon.

Group 4: Clinician-determined Consumer Principle (One-sided Physician-modified Informed Consent). There is no clinical equipoise. The patient is told that the physician believes that the experimental drug may be superior to the standard drug, and so the patient is informed that if they give consent, they have a greater chance of receiving the experimental drug. The following paragraph was included at the end of Explanatory Statement 2:

This study will be "double-blinded" in that neither you nor your physician will know which drug you are to receive until after the study is completed. Your doctor has looked at the scientific evidence and believes the new drug, Imaginon, may well be superior. In view of this, if you agree to participation this trial, you will have a 70% chance (*i.e.*, 7 of 10) of receiving this new drug. You also have a 30% chance (*i.e.*, 3 of 10) of receiving the usual anesthetic drug. If you do not want to participate in this trial, you will receive the usual anesthetic drug.

Group 5: Patient-determined Consumer Principle (One-sided Patient-modified Informed Consent). The patients are told that they are allowed to increase, or decrease, their chances of receiving the new experimental drug (compared with the chances of receiving the standard drug) after consenting. The following paragraphs were included at the end of Explanatory Statement 2:

This study will be "double-blinded" in that neither you nor your physician will know which drug you are to receive until after the study is completed. If you agree to participate in this trial, you can choose to decrease, or increase, your chances of receiving the new drug, Imaginon. Without a choice, there is a 50% chance that you will receive the new drug or the usual anesthetic drug. You can chose this option if you have no preference for either drug.

If you have a preference for the new drug, Imaginon, we can actually increase your chance of being given this drug to 60%, 70%, or 80% (as you choose).

If you have a preference not to be given the new drug, we can decrease your chance of being given this drug to 20%, 30%, or 40% (as you choose).

If you do not want to participate in this trial, you will receive the usual anesthetic drug.

Our primary end point was the recruitment rate; secondary end points were selected patient, surgical, and researcher characteristics that were predictors of recruitment.

A preliminary estimate of sample size was based on a difference of 20% in recruitment rates between groups, with a baseline of 75%. Accepting a type 1 error of 0.05 and a type 11 error of 0.20, the required number was calculated at 132 patients per group (Clinical Trials Design Program V1.0; Biosoft, Cambridge, UK). We recruited 770 patients for this trial.

Statistical Analyses

Recruitment rates among the groups were compared using chi-square analysis. Factors associated with patient consent were analyzed using chi-square (or chi-square for trends) and univariate odds ratios. Exploratory stepwise logistic regression analyses were used to identify clinically useful predictors of consent before operation (such as age, gender, ASA status, life expectancy, surgical characteristics [extent and type]), with a P value of 0.05 for entry and rejection of additional variables. A further regression analysis was performed after dichotomizing the identified significant variables (according to clinical application[25]) to calculate the adjusted odds ra-

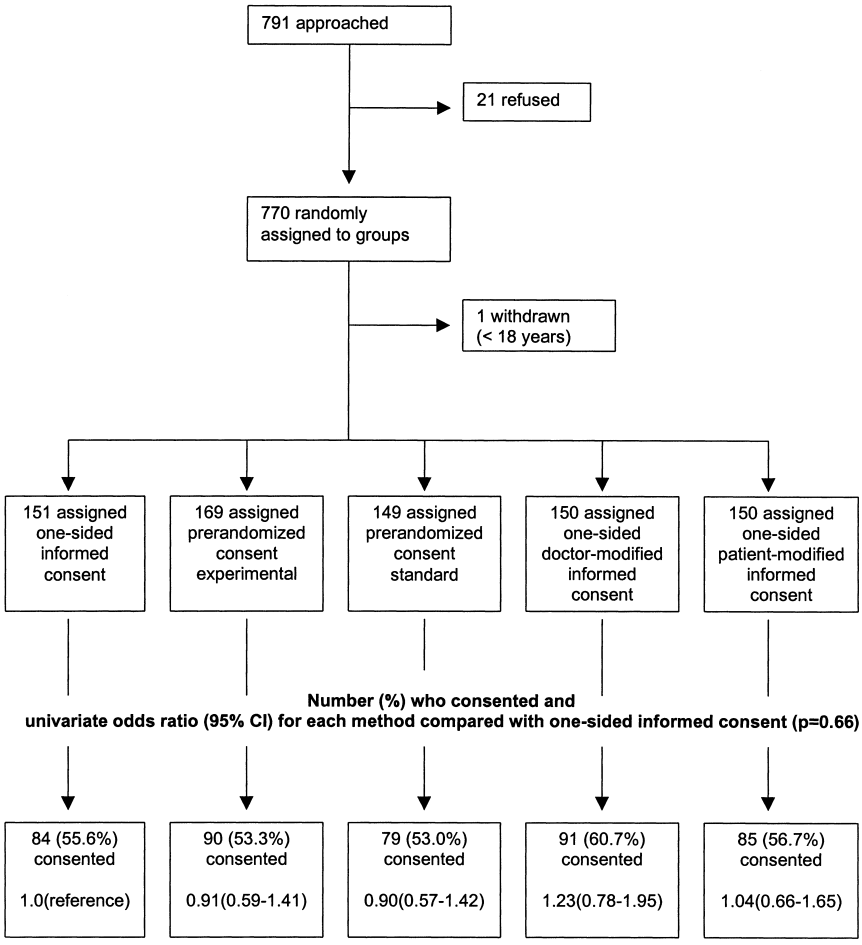

Fig. 1. Trial profile and results.

tios. Recruitment rates and odds ratios are presented with their 95% confidence intervals (95% CIs). A P value < 0.05 was considered significant.

Results

We approached 791 patients, and 770 gave their consent to participate in the study. One patient was withdrawn because he was younger than 18 yr (fig. 1). One patient refused to answer questions regarding his education level and life expectancy. There were no significant differences among the groups in patient demographics, extent of English spoken at home, whether a family member or friend was present at the time of interview, or surgical characteristics (table 1). There were no differences in preoperative anxiety level or patient- or anesthetist-rated life expectancy (table 2).

The method of randomization did not result in any significant difference in recruitment rates (fig. 1). There was no significant difference in the preoperative anxiety level (visual analog scale) between those who consented and those who did not: 35.7 (27) mm *versus* 39.5 (30) mm, $P = 0.21$.

Tables 3 and 4 show the univariate and multivariate predictors of consent. Logistic regression identified the following factors as significantly associated with consent: patient age, English spoken at home, and interaction between patient and researcher gender (male patients were more likely to consent and male researchers were more likely to obtain consent compared with their female counterparts). Specifically, male researchers approaching male patients had a recruitment rate of 70%; female researchers approaching female patients had a recruitment rate of 43%.

Table 5 lists the reasons why patients gave or refused to give consent. Consent rates were higher in those patients who thought the experimental treatment, Imagination, was a better treatment: 57% *versus* 43%, $P < 0.001$.

Table 1. Patient Demographics, Circumstances at the Time of Recruitment, and Surgical Characteristics (%)

Factor	One-sided Informed Consent (n = 151)	Prerandomized Consent Experimental (n = 169)	Prerandomized Consent Standard (n = 149)	One-sided Doctor-modified Informed Consent (n = 150)	One-sided Patient-modified Informed Consent (n = 150)
Age (yr)					
18–30	20	23	15	21	21
31–45	23	22	30	30	29
46–64	31	30	27	26	29
>64	27	26	28	23	21
Male gender	57	57	60	56	49
Occupation					
Professional	28	20	20	29	25
Office worker	19	27	26	23	25
Laborer	38	33	38	25	35
Home duties	9.3	10	10	14	9.3
Unemployed	6.6	10	5.4	8.7	5.3
Education					
<10 yr	23	24	24	21	26
10 yr	36	30	33	27	30
12 yr	13	19	22	23	14
Tertiary	29	27	22	29	30
English spoken at home					
Always	88	77	82	85	88
Mostly	6.6	10	8.1	6.7	5.3
Sometimes	4.6	5.3	8.7	4.7	5.3
Rarely	0.7	7.7	1.3	4.0	1.3
Family member or friend present	22	28	22	29	29
ASA status					
I	33	37	39	39	34
II	42	36	36	40	44
III	21	22	20	19	19
IV	4.0	5.3	5.4	2.0	3.3
Admitted on day of surgery	72	71	69	75	80
Major surgery	28	28	31	23	22
Type of surgery					
General	28	27	24	28	29
Orthopedic	17	18	18	15	15
Urologic	9.9	8.3	6.0	8.0	9.3
Ear, nose, and throat	5.3	7.1	7.4	6.0	10
Cardiac	12	8.3	12	7.3	11
Plastic	5.3	2.4	6.0	7.3	4.7
Vascular	4.0	10	4.7	6.7	4.7
Other	19	19	26	29	17

ASA = American Society of Anesthesiologists physical status score.

Discussion

To our knowledge, this is the first prospective study of several randomization and consent designs in the immediate preoperative period using actual patients. Despite the recognized problems with the conventional randomized controlled trial and the purported advantages of these newer randomization methods, we did not find any significant difference in recruitment rates in our study population. Therefore, we conclude that these alternative designs offer little or no advantage over conventional randomization and one-sided informed consent.

Our overall recruitment rates were 53% to 60%. This is higher than in other reports,[24] possibly because of the sham nature of the proposed trial, which might have favored patient participation. Our experience with previous clinical trials is that 60–80% of eligible patients agree to participate. Gallo *et al.*[22] reported recruitment rates of >80% in their cohort of healthy volunteers, even with conventional randomization. However, their participants were younger, more highly educated, and perhaps more motivated toward clinical research. Overall, 16% of our patients has a preoperative anxiety visual

Table 2. Preoperative Anxiety, Life Expectancy, and Researcher Characteristics

Factor	One-sided Informed Consent (n = 151)	Prerandomized Consent Experimental (n = 169)	Prerandomized Consent Standard (n = 149)	One-sided Doctor-modified Informed Consent (n = 150)	One-sided Patient-modified Informed Consent (n = 150)
Preoperative VAS anxiety level (mm)	35.7 (27)*	39.2 (29)*	39.4 (28)*	37.3 (28)*	35.0 (28)*
No. of patients (%) with anxiety VAS ≥70	21 (14)*	32 (19)*	27 (18)*	25 (17)*	21 (14)*
Patient-rated life expectancy (yr)					
> 20	64	67	64	76	77
10	23	24	27	12	16
> 5	11	7.7	8.1	10	5.4
> 2	2	0.6	0.7	2.0	1.4
≤ 2	0	1.2	0	0	0.7
Anesthesiologist-rated life expectancy (yr)					
> 20	50	53	54	63	63
10	26	18	21	16	15
> 5	16	18	16	14	14
> 2	6.6	8.9	8.1	6.0	4.0
≤ 2	1.3	1.8	0.7	0.7	4.7
Researcher characteristics					
Male gender	40	45	43	43	26
Consultant	29	23	26	25	20
Resident	28	36	33	28	25
Research nurse	43	41	42	46	55

VAS = visual analog scale.

* Mean (SD) or number (%).

analog scale ≥70 mm. Our recruitment rates should be more representative of clinical trials, incorporating actual patients with genuine preoperative concerns and anxieties.

Several factors may have contributed to our inability to find any differences among the study groups. First, the sham trial that patients were asked to contemplate was not directly related to their surgical condition or likely anesthetic outcome and may have had secondary importance to them. Furthermore, our findings may have been affected by patients' recognition that they would not actually receive an experimental drug. We did not consider it ethical to deceive patients about the nature of the trial. The most common reason for refusal was the perceived additional risk associated with Imaginon. Interestingly, patients prerandomized to standard treatment had similar refusal rates, with most (87%) stating that they wanted the alternative treatment (Imaginon).

It has been suggested that prerandomization offers advantages in the setting of an extremely complex design or a risk that is difficult to understand.[20,22] Our trial design as presented in the conventional randomized controlled trial format was relatively easy to understand (*i.e.*, a simple 50:50 chance of receiving the standard or new drug). This may have contributed to the inability of prerandomization to increase recruitment in our case. This is in contrast to the findings of Gallo *et al.*,[22] who showed that the refusal rate was highest with this design. They concluded that if patient preference is stronger (or likely to be) for a new treatment of, for example, cancer with a poor prognosis or the acquired immune deficiency syndrome, and if a patient cannot receive the experimental treatment outside the trial, then a double randomized consent design would be detrimental. Our sham study was different in that the choice of anesthetic drug was probably not perceived to be of primary importance to patient outcome. For this reason, our findings should not be extrapolated to major intervention trials or in patients with life-threatening conditions. Patient preferences are more likely to be important in trials that require specific patient effort or participation.[13,18] This may also explain why we did not find any advantage in the patient-determined consumer principle design.

We found the following characteristics to be unrelated to patient recruitment rates: anxiety level, ASA status, extent and type of surgery, occupation, or the presence

Table 3. Univariate Predictors of Patient Consent

Factor	% Consent	Univariate OR (95% CI)	*P* Value*
Age (yr)			
18–30	47	1.0 (reference)	
31–45	53	1.26 (0.83–1.91)	
46–64	61	1.78 (1.17–2.69)	
> 64	60	1.74 (1.13–2.67)	0.003
Gender			
Male	61	1.0	
Female	49	0.80 (0.70–0.92)	< 0.001
Occupation			
Professional	51	1.0	
Office worker	60	1.45 (0.96–2.19)	
Laborer	61	1.52 (1.04–2.23)	
Home duties	42	0.69 (0.41–1.17)	
Unemployed	50	0.96 (0.53–1.17)	0.009
Education			
< 10 yr	57	1.0	
10 yr	62	1.20 (0.81–1.78)	
12 yr	54	0.89 (0.57–1.39)	
Tertiary	49	0.71 (0.48–1.06)	0.029
English spoken at home			
Always	58	1.0	
Mostly	53	0.82 (0.47–1.40)	
Sometimes	43	0.56 (0.30–1.03)	
Rarely	33	0.37 (0.16–0.87)	0.003
Family member or friend			
Present	50	1.0	
Not present	58	1.19 (1.0–1.14)	0.054
ASA status			
I	53	1.0	
II	57	1.15 (0.83–1.59)	
III	57	1.19 (0.80–1.76)	
IV	61	1.39 (0.65–2.98)	0.26
Admitted time			
Day of surgery	54	1.0	
Day before surgery	62	1.22 (1.0–1.47)	0.043
Extent of surgery			
Major	54	1.0	
Minor	56	1.04 (0.90–1.20)	0.61
Patient-rated life expectancy (yr)			
> 20	53	1.0	
10	62	1.44 (1.0–2.07)	
> 5	61	1.36 (0.81–2.29)	
> 2	80	3.54 (0.74–16.8)	
≤ 2	67	1.77 (0.16–19.6)	0.018
Anesthesiologist-rated life expectancy (yr)			
> 20	53	1.0	
10	54	0.97 (0.67–1.41)	
> 5	61	1.32 (0.87–1.99)	
> 2	58	1.14 (0.64–2.04)	
≤ 2	64	1.50 (0.50–4.56)	0.20
Researcher gender			
Male	66	1.0	
Female	49	0.75 (0.66–0.84)	< 0.001
Consultant	66	1.0	
Resident	60	0.76 (0.51–1.13)	
Research nurse	48	0.47 (0.33–0.68)	< 0.001

* Chi-square or chi-square for trend.

OR = odds ratio; CI = confidence interval; ASA = American Society of Anesthesiologists physical status score.

Table 4. Significant Multivariate Predictors of Patient Consent

Factor	Adjusted OR (95% CI)	*P* Value
Age (yr)		
≤ 45	1.0 (reference)	
> 45	1.44 (1.08–1.93)	0.015
English spoken at home		
Not always	1.0	
Always	1.49 (1.0–2.21)	0.048
Researcher: patient gender interaction		
Female:female	1.0	
Male:male	1.37 (1.20–1.57)	< 0.001

OR = odds ratio; CI = confidence interval.

of a family member or friend when consent was sought. Some of these have previously been suggested as important,[12,15] but our study suggests that their effect is insignificant after adjusting for confounding. Older patients tend to be sicker and have poorer prognoses; it is probable that age is the main determinant of recruitment.

Other factors were identified as having an influence on recruitment. Patient age >45 yr was a significant predictor. This may reflect a difference in age-specific values and attitudes about clinical trials. It is conceivable that an older patient is accustomed to a paternalistic manner in the physician–patient relationship and therefore may be less likely to refuse recruitment. This consideration is particularly relevant for group 4 (clinician-determined consumer principle). Perhaps some elderly patients perceive their existence is due in part to advances in modern medicine and consider this an opportunity to repay society. They may also have fewer concerns about long-term risk, or, conversely, they may perceive they have more to gain. This contention is supported by our finding that patients with poor life expectancy were more likely to participate, as has been observed by others.[22] In addition, the most common reason for consenting appeared to be an altruistic one, with most of those who gave consent believing it would help others.

English spoken at home was another significant predictor of recruitment. We excluded patients with poor English comprehension, so information about such patients has been missed. This supports the importance of trial participants' comprehension when they are considering consent. The balance between altruism and perceived improvement in care, compared with perceived risk and desire for more information (see table 5), appeared to determine the participants' ultimate decisions in most cases. Therefore, a clear understanding of trial procedures and potential benefits and risks remains an essential component of the consent process. Others

Table 5. Reason Patients Consent and Opinions as to Whether the Proposed Treatment ("Imaginon") was Better*

Patient Responses	One-sided Informed Consent (n = 151)	Prerandomized Consent Experimental (n = 169)	Prerandomized Consent Standard (n = 149)	One-sided Doctor-modified Informed Consent (n = 150)	One-sided Patient-modified Informed Consent (n = 150)
Main reason why patient consented	n = 84	n = 90	n = 79	n = 91	n = 85
It may help others	60 (71)	43 (48)	25 (32)	51 (56)	52 (61)
It may help the doctor	5 (7.0)	14 (16)	2 (2.5)	4 (4.4)	4 (4.7)
Their care would be better	13 (16)	21 (23)	9 (11)	27 (30)	22 (26)
They had little choice	0	0	1 (1.3)	0	0
Liked "new" things	2 (2.4)	6 (6.7)	1 (1.3)	4 (4.4)	1 (1.2)
No particular reason	4 (4.8)	6 (6.7)	41 (52)	4 (5.5)	6 (7.1)
Main reason why patient refused	n = 67	n = 79	n = 70	n = 59	n = 65
Too risky	34 (51)	34 (43)	3 (4.2)	32 (53)	36 (55)
Wanted more information	16 (24)	27 (34)	4 (5.6)	11 (18)	18 (28)
Do not like research	5 (7.5)	4 (5.1)	0	9 (15)	1 (1.5)
Wanted new drug	1 (1.5)	1 (1.3)	62 (87)	2 (3.3)	0
No particular reason	11 (16)	13 (17)	2 (2.8)	7 (12)	10 (15)
When compared with the standard drug, the new drug "Imaginon" was					
Better	73 (48)	73 (43)	53 (35)	77 (51)	68 (45)
Worse	6 (4.0)	5 (3.0)	5 (3.4)	2 (1.3)	3 (2.0)
Unsure	72 (48)	91 (54)	91 (62)	71 (47)	79 (53)

* Number (%).

have noted that the way information is presented can affect patient choice.[6,11,19,26,27] We made efforts to avoid deception by explaining that our proposed trial did not include testing an actual anesthetic drug. Nearly one half the patients thought that Imaginon was better than the usual drug, whereas most of the remaining patients were unsure (based on the information provided to them) (see appendix 1). This reflects confusion with the concept of equipoise and has been described by others.[3,5,22] It probably arises from the wording we used in our consent form, which stated ". . . there is some evidence that this new drug, Imaginon, results in less side effects. . . " This was intentional, because it reflected the usual rationale for conducting clinical trials.[22] We found that patients who thought that the experimental treatment, Imaginon, was better than standard treatment were more likely to consent; this has also been observed by others.[4,22]

The interaction of male researcher–male study participant was more likely to result in consent. This may have been confounded by gender differences between the (female) research nurses and (mostly male) consultant interviewers in our study, because female clinicians had similar recruitment rates to their male counterparts. Men may be more accepting of risk-taking behavior and therefore be more likely to participate in a trial even if it involves some risk. Also of interest is that trained, experienced research nurses had the lowest recruitment rates. As alluded to earlier, this may be related to the absence of paternalism, or perhaps patients being interviewed by physicians directly involved in their care believed that they were under some sort of obligation (or pressure) to participate.

Silverman and Altman[13] proposed that ongoing studies will help decipher the complex interaction between physicians and their patients when faced with the need to act under conditions of uncertainty. Full and frank disclosure may cause considerable patient anxiety and uncertainty, not only for the trial itself but, perhaps more importantly for the patient, for their own outcome.[1,3,6,10,12,13] For this reason, many patients prefer to be directed by their physician. Yet this cannot be a major influence, because we did not observe an increased recruitment rate in group 4.

Ellenberg[21] has highlighted ethical difficulties with prerandomization in that the very act of randomization enrolls patients in a study before they have given their consent. Although patients have the option to accept or refuse the assigned treatment, they are not given the

option of withdrawing entirely from the study. Ellenberg[21] also emphasized certain practical problems with data analysis. Truog[28] has discussed some of these issues with reference to a recent trial of extracorporeal membrane oxygenation in neonatal respiratory failure. Because we found no evidence of superior recruitment rates with prerandomization, we would agree with Ellenberg and support abandonment of its use in most circumstances. Gore and others have considered the difficulties of equipoise and patient preference,[3,19,17] with Gore[19] suggesting the method of modified informed consent (groups 4 and 5). Here there are lesser degrees of uncertainty (or individual equipoise[3]). This may reduce the dilemma of physician–patient attitudes to conventional randomization and increase recruitment without greatly reducing statistical power.[2,29] Nevertheless, we found no evidence that this would increase patient acceptance, although it remains possible that clinician cooperation with trial recruitment may be enhanced in other circumstances.

Obtaining informed consent for clinical trials on the day of surgery has been studied previously[14,15,30] and is an important consideration given the increasing trend to day-of-admission surgery. Patients generally prefer to be approached for consent well in advance, but they still accept recruitment on the day of surgery if approached appropriately (*i.e.*, in a private setting, with adequate time to consider trial information).[14,15,30] Fifty-one percent of patients preferred not to know about the trial before admission, because it only increased their level of anxiety.[15] We found on univariate testing that patients were more likely to consent if approached the day before surgery, but this was no longer significant after adjusting for confounding. Tait *et al.*[30] highlighted some of these issues in a survey of parents considering recruitment of their child into clinical trials. Our study may also provide some information for other similar clinical circumstances in which patients may be feeling stress and need to be recruited within a limited time frame, such as in the emergency department, intensive care unit, and with some surgical trials.

The lack of significant differences in recruitment among the randomization methods in our study may reassure those researchers who have supported conventional randomization and informed consent. It remains a suitable method for recruiting patients in the immediate preoperative period.

The authors thank Jenny Hall and Tony Weeks for assisting in data collection and Mark Reeves and Paul Komesaroff for reviewing the manuscript.

References

1. Schafer A: The ethics of the randomised clinical trial. N Engl J Med 1982; 307:719–24

2. Freedman B: Equipoise and the ethics of clinical research. N Engl J Med 1987; 317:141–45

3. Gifford F: Community-equipoise and the ethics of randomised clinical trials. Bioethics 1995; 9:127–48

4. Cassileth BR, Zupkis RV, Sutton-Smith K, March V: Informed consent—Why are its goals imperfectly realized? N Engl J Med 1980; 302:896–900

5. Clayton DG: Ethically optimized designs. Br J Clin Pharmacol 1982; 13:469–80

6. Kadane JB: Progress towards a more ethical method for clinical trials. J Med Philos 1986; 11:385–404

7. Hellman S, Hellman DS: Of mice but not of men. Problems of the randomized clinical trial. N Engl J Med 1991; 324:1585–9

8. Ingelfinger FJ: Informed (but uneducated) consent (Editorial). N Engl J Med 1972; 287:465–6

9. Meisel A, Roth LH: What we do and do not know about informed consent. JAMA 1981; 246:2473–7

10. Tobias JS, Souhami RL: Fully informed consent can be needlessly cruel. BMJ 1993; 307:1199–1201

11. Simel DIL, Feussner JR: A randomised controlled trial comparing quantitative informed consent formats. J Clin Epidemiol 1991; 44: 771–7

12. Wilke HJ, Ellis JE, Sodhi JS, Mingay DJ: Why patients consent to participate in clinical anesthesia research projects (Abstract). Anesth Analg 1996; 82:S491

13. Silverman WA, Altman DG: Patient's preferences and randomised trials. Lancet 1996; 347:171–4

14. Mingus IVIL, Levitan SA, Bradford CN, Eisenkraft JB: Surgical patient's attitudes regarding participation in clinical anesthesia research. Anesth Analg 1996; 82:332–7

15. Montgomery JE, Sneyd JR: Consent to clinical trials in anaesthesia. Anaesthesia 1998; 53:227–30

16. Byar DP, Schoenfeld DA, Green SB, Amato DA, Davis R, De Gruttola V, Finkelstein D, Gatsonis C, Gelber RD, Lagakos S, Lefkopoulou M, Tsiatis AA, Zelen M, Peto J, Freedman LS, Gail M, Simon R, Ellenberg SS, Anderson JR, Collins R, Peto R, Peto T: Design considerations for AIDS trials. N Engl J Med 1990; 323:1343–8

17. Silverman WA: Patients' preferences and randomised trials (Editorial). Lancet 1994; 343:1586

18. Brewin CR, Bradley C: Patient preferences and randomised clinical trials. BMJ 1989; 299:313–15

19. Gore SM: The consumer principle of randomisation (Letter). Lancet 1994; 343:58

20. Zelen M: A new design for randomised clinical trials. N Engl J Med 1979; 300:1242–5

21. Ellenberg SS: Randomisation designs in comparative clinical trials. N Engl J Med 1984; 310:1404–8

22. Gallo C, Perrone F, De Placido S, Giusto C: Informed versus randomised consent to clinical trials. Lancet 1995; 346:1060–4

23. Myles PS, Buckland MR, Cannon GB, Bujor M, Langley M, Breaden A, Salamonsen RF, Davis BB: Comparison of patient-controlled analgesia and conventional analgesia after cardiac surgery. Anaesth Intensive Care 1994; 22:672–8

24. O'Rourke PP, Crone RK, Vacanti JP, Ware JH, Lillehei CW, Parad RB, Epstein M: Extracorporeal membrane oxygenation and conventional medical therapy in neonates with persistent pulmonary hyper-

tension of the newborn: A prospective randomized study. Pediatrics 1989; 84:957–63

25. Harrell FE, Lee KL, Califf RM, Pryor DIB, Rosati RA: Regression modelling strategies for improved prognostic prediction. Stat Med 1984; 3:292–304

26. Dehn TCB: Patients are unwilling to enter randomised trials (Letter). BMJ 1994; 309:126

27. McNeil BJ, Pauker SG, Sox HC, Tversky A: On the elicitation of preferences for alternative therapies. N Engl J Med 1982; 306:1259–62

28. Truog RD: Randomized controlled trials: Lessons from ECMO. Clin Res 1993; 40:519–27

29. Korn EL, Baumrind S: Randomised clinical trials with clinician preferred treatment. Lancet 1991; 337:149–52

30. Tait AR, Voepel-Lewis T, Siewart M, Malviya S: Factors that influence parents' decisions to consent to their child's participation in clinical anesthesia research. Anesth Analg 1998; 86:50–3

Appendix 1. Explanatory Statements.

Explanatory Statement 1 (read before *the patient has been enrolled and allocated to a specific recruitment method)*

This is a research study in which we invite your participation. We are interested in *why* some patients agree to participate in a research study.

This is a pretend (mock) research study, so you will not actually receive any experimental drug or procedure.

We are asking you to imagine that we are investigating a new anesthetic drug called *Imaginon*. If you consent to this study, we will ask you to read the information over the page and make up your own mind. We expect this will take you about 10 minutes.

If you have any questions, feel free to ask them now. Remember that this is only a pretend situation and will in no way influence the anesthetic drugs that you would otherwise receive. All drugs that we give you during your operation are licensed and recommended for anesthesia.

You will receive our usual anesthetic care, with no changes in the way in which your operation is performed. This study does not involve any extra needles or blood tests; no extra drugs will be used. Most patients having surgery at this hospital are being asked to participate in this trial. If you agree to participate in this trial, we will ask you to rate how anxious you feel at the moment.

Results from this study will be published in a medical journal. Details we will record include your age, sex, type of employment (if any) and level of education. No patient names will be used, and your confidentiality will be protected. Only the investigators involved in this study will have access to your details. These details will be stored securely in a locked office for a mandatory 7 years and will then be destroyed. You are able to withdraw from this study at any time without affecting current or future treatment.

If you have any questions, you can contact Dr. Paul Myles through the Alfred Hospital (ph 9 276 2000). If you would like to discuss any aspects of this study with someone not directly associated with it, you can also contact Ms. Rowan Frew, Ethics and Research Administrative Officer (ph 9 276 3848). The Research and Ethics Committee of the Hospital is responsible for approving and monitoring research projects.

Explanatory Statement 2 (read after *initial consent is provided by the patient)*

Imaginon is a new drug in anesthesia used to put you to sleep for your operation. Anesthetic drugs can sometimes result in side effects, such as pain at the injection site (during injection), low blood pressure, prolonged sleepiness or tiredness, nausea and vomiting, and dizziness. There are other serious side effects, but these are very rare. There is some evidence that this new drug, Imaginon, results in fewer side effects, but because it is a new drug, we do not know if there are any rare, serious side effects. It is also more expensive. The only way to decide whether this new drug is better for anesthesia is to perform a research study on people such as you.

Regardless of the drug you are given, you will receive all our usual care, and any decision you make today will not affect your treatment in any way.

We plan to see you after your operation and measure how well you recover, and whether you have any side effects caused by this new drug. There are no painful procedures, or extra blood tests, because of this trial.

[Each patient had *one* of the following methods of randomization and consent randomly selected to be included in this second Explanatory Statement (see Materials and Methods)]

1. This study will be double-blinded, in that neither you nor your doctor will know which drug you are to receive until after the study is completed. If you agree to participate in this research study, you will receive either Imaginon or our usual anesthetic drug. This will be decided on a randomized, chance basis (like tossing a coin). If you do not want to participate in this trial, you will receive the usual anesthetic drug.
2. If you agree to participate in this trial, you will receive the new drug, Imaginon. However, if you do not want to participate, you will receive the usual anesthetic drug.
3. If you agree to participate in this trial, you will receive the usual anesthetic drug. However, if you do not want to participate, you will receive the new drug, Imaginon.
4. This study will be double-blinded, in that neither you nor your doctor will know which drug you are to receive until after the study is completed. Your doctor has looked at the scientific evidence and believes the new drug, Imaginon, may well be superior. In view of this, if you agree to participate in this trial, you will have a 70% chance (*i.e.*, 7 of 10) of receiving this new drug. You also have a 30% chance (*i.e.*, 3 of 10) of receiving the usual anesthetic drug. If you do not want to participate in this trial, you will receive the usual anesthetic drug.

This study will be double-blinded, in that neither you nor your doctor will know which drug you are to receive until after the study is completed. If you agree to participate in this trial, you can choose to decrease, or increase, your chances of receiving the new drug, Imaginon. Without a choice, there is a 50% chance of receiving the new drug or the usual anesthetic drug. You can chose this option if you have no preference for either drug.

If you have a preference for the new drug, Imaginon, we can actually increase your chance of being given this drug to 60%, 70%, or 80% (as you choose).

If you have a preference not to be given the new drug, we can decrease your chance of being given this drug to 20%, 30%, or 40% (as you choose).

If you do not want to participate in this trial, you will receive the usual anesthetic drug.