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Review

Randomised Consent Designs in Cancer Clinical Trials*

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In 1977, Zelen proposed a new design for clinical trials with the aim of increasing recruitment by avoiding some of the problems associated with obtaining informed consent. These 'randomised consent' designs have proved controversial, and have not often been used. This paper explains the statistical aspects of single and double randomised consent designs and reviews some of the ethical issues. All identified published cancer treatment trials using a randomised consent design are considered in some detail. Reasons for and against the use of these designs are summarised.

Key words: clinical trials, cancer, statistics, ethics, randomised consent design
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INTRODUCTION

ZELEN'S randomised consent designs, proposed in 1977 [1], were motivated by problems associated with persuading physicians to enter patients into clinical trials, in particular because of their difficulties with obtaining informed consent for randomisation. The main element of Zelen's proposal is that patients are asked for their consent to take part after rather than before randomisation. In the single consent form of the design [1, 2] only patients allocated to the experimental treatment(s) are asked to give consent, whereas in the double consent version [3] patients allocated to the standard therapy are also asked. The designs appear to offer clinicians a less intrusive way of attracting sufficient numbers of patients into trials. However, their use has caused controversy regarding ethical issues; the inclusion of patients in a trial without their knowledge has caused particular concern.

There is continuing interest in randomised consent designs as a way around some of the difficulties encountered in running conventional randomised trials [4]. The statistical aspects of randomised consent designs, especially the double consent design, have received limited attention. Some of the issues were considered by Zelen [5], but he did not consider the statistical issues of bias and the effect of loss of blindness, nor the practicalities of explaining the treatment options to patients. The main purpose of this paper is thus to review the statistical aspects of randomised consent designs, particularly for the double consent design, but we also consider the ethical and practical aspects. We focus on clinical trials in cancer but there is almost nothing in the paper that does not apply equally to other medical areas. We concentrate on trials of two treatments, but the arguments extend simply to trials with more than two treatment groups. We have used the common term "randomised consent" for these designs, although "postrandomisation consent" and "preconsent randomisation" are also used and are arguably more explicit.

ALTERNATIVE DESIGNS

In this section, we discuss the conventional design of a randomised controlled trial with two parallel treatment groups, and the corresponding single and double randomised consent designs.

The conventional randomised clinical trial

The conventional randomised clinical trial is illustrated in Figure 1. Once a patient is deemed suitable for the study, informed consent must be sought. It is necessary to explain to the patient the purpose of the study, features of both treatments under study and the essentials of the randomisation procedure, in particular that treatment will be chosen by a chance mechanism. Consenting patients are randomised between the two treatments, which we shall here assume to be a standard therapy (S) and a new treatment (N), although the use of the design is not restricted to such comparisons. For those who do not agree to be randomised (refusals), the choice of treatment is left to the

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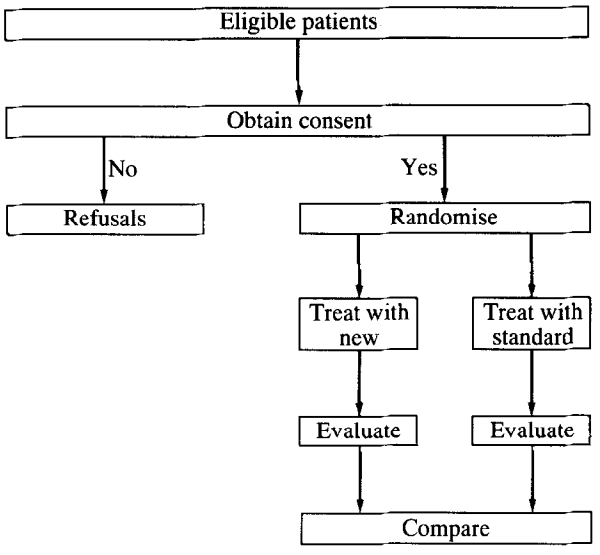

Figure 1. Design and analysis of a conventional randomised clinical trial.

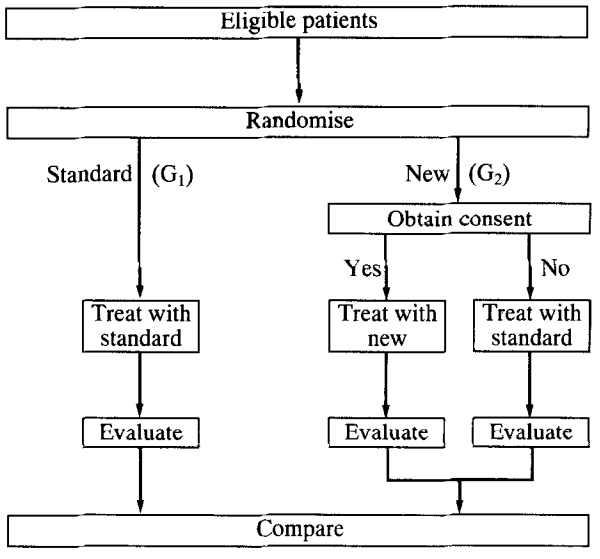

Figure 2. The single randomised consent design.

attending clinician, but they will not subsequently be included in the trial even if they receive one of the treatments under study. If the trial is single- or double-blind, the patient does not know which treatment they received. Although consenting patients may not be fully representative of all eligible patients, the treatment groups are fully comparable, and there is no bias in treatment comparison caused by those who are not willing to be randomised.

At the end of the study, the outcomes of all randomised patients should be reported. Failure to comply fully with the treatment schedule (for whatever reason), or even receiving the wrong treatment, are not grounds for excluding a patient from the statistical analysis. In practice, however, a small proportion of patients is often lost to follow-up. In the analysis of the major endpoints in cancer trials, such as death, local recurrence or appearance of metastatic disease, all patients are counted against the treatment to which they were randomised. Such an "intention to treat analysis" avoids bias due to treatment related withdrawals [6]. The use of an intention to treat analysis is not universally felt to be appropriate, but we will not consider this issue further in this paper.

In most trials, several endpoints will be analysed, and the completeness of the data will vary. Endpoints such as death can usually easily be collected on all trial patients, but a few exclusions may be inevitable. Endpoints collected at follow-up visits will be missing for subjects who withdraw from the study. Incomplete data can lead to biased results.

The single randomised consent design

Zelen [1–3, 7, 8] introduced the alternative design depicted in Figure 2. The important distinction from the conventional design is that randomisation to groups G_1 and G_2 first takes place without the patient's knowledge and hence without his or her consent. Those in G_1 are given the best standard treatment available (S), and nothing is said to them about the existence of the study or their inclusion in it. Patients in G_2 are told that they are in a trial, and their consent to be treated with the new regimen (N) is sought. If they do not wish to have the new treatment they receive the standard treatment. Therefore, half the patients (those in G_2) have some choice of treatment, although they are not given the explicit option not to be in the trial. They know which treatment they will receive whether or not they accept the randomly allocated treatment. By contrast, the other half (those in G_1) are not aware that they are in a trial and have no possibility of obtaining the new treatment.

In the subsequent analysis, when follow-up is complete, groups G_1 and G_2 are compared. Patients in G_1 all received the standard therapy (S), whereas patients in G_2 received a mixture of new and standard therapies (N and S). A statistically significant difference between the groups can properly be attributed to a treatment difference between N and S. However, the magnitude of the treatment effect will be underestimated because of the mixture of treatments in G_2 (see section on Bias). As with the conventional randomised trial, it is the group to which a patient is randomised that should be used in the analysis, rather than the actual regimen followed. The success of the design relies on the tendency of patients to accept the treatment first offered.

There may be problems with evaluation. As patients in G_1 are receiving a standard therapy, only data routinely collected during normal treatment can be obtained and thus used in the analysis. This design is not suitable for a trial which requires more information than is routinely collected. It would be particularly inappropriate to require patients who were not offered the new treatment to attend for investigations that are solely for the purpose of the trial. It is possible that in some trials the completeness of treatment data will differ in the two groups, those in G_2 who are willingly and knowingly on the new treatment (or in some cases the standard treatment) being more conscientious about return visits than those in G_1. One possible consequence may be that relapses would be detected earlier in G_2, leading to bias.

Two further features of the single consent design are that it cannot be single- or double-blind, and it should not be used for placebo-controlled trials, as by definition placebo is not a standard treatment.

Zelen's single consent design is an ingenious attempt to overcome some of the problems inherent in conventional controlled trials, especially those related to obtaining informed consent. However, the design has serious shortcomings. In particular, as patients in G_1 are not informed that they are in a study, this design no longer meets the requirements of many research organisations, including the British Medical Research

Council (MRC) [9]. Ethical aspects are considered further later in this paper.

The double randomised consent design

The double randomised consent design (Figure 3) is similar to the single randomised consent design, except that patients in group G_1 are now also asked for their consent. This option was not mentioned in Zelen's first paper [1], appeared only very briefly in his second and best known paper [2], and is not considered in detail in his later papers in medical journals [3, 7, 8]. However, it seems to have been used as extensively as the single consent design, perhaps because of ethical concerns about the single consent design.

In the double consent design, patients in both groups are asked if they consent to receive the treatment that they were allocated. Patients who decline the (randomised) treatment offered might receive the other trial treatment (or perhaps some other treatment). As with the single consent design, patients are not given the option to refuse to be in the trial. The exact nature of the consent procedure is not clear. Specifically, the amount of information given about the existence and nature of the trial may be reduced, and the other treatment being investigated may not necessarily be explained [5, 10]. These issues are discussed later. As with the single consent design, trials using the double consent design cannot be single- or double-blind and cannot be used when one treatment is a placebo. We note that the term "double consent design" applies also to trials with three or more treatment arms in which consent is sought from all patients.

At the analysis stage, as before, groups G_1 and G_2 are compared on an intention-to-treat basis, i.e. regardless of the treatment actually received. If all patients declining the randomly allocated treatment agree to receive the other trial treatment, the two groups G_1 and G_2 will differ only in the proportions on the two treatments N and S. There will almost certainly be a greater dilution effect than with the single consent design. However, as with the single consent design, any difference beween the groups can properly be attributed to a difference in effectiveness of the two treatments (as long as the average acceptance rate is greater than 50%).

The nature of consent

In a randomised consent design, patient consent differs from that in a conventional trial, because patients are asked to consent to a particular treatment rather than to participate in a trial. As described by Zelen, with both the single and double consent designs, there is no explicit option for patients to refuse to be in the trial, in clear contrast to the conventional design (Figures 1–3). If patients cannot refuse to be in the trial, only evaluations taken from routine treatment can be included, as it is necessary to obtain these regardless of whether patients accept their allocated treatment.

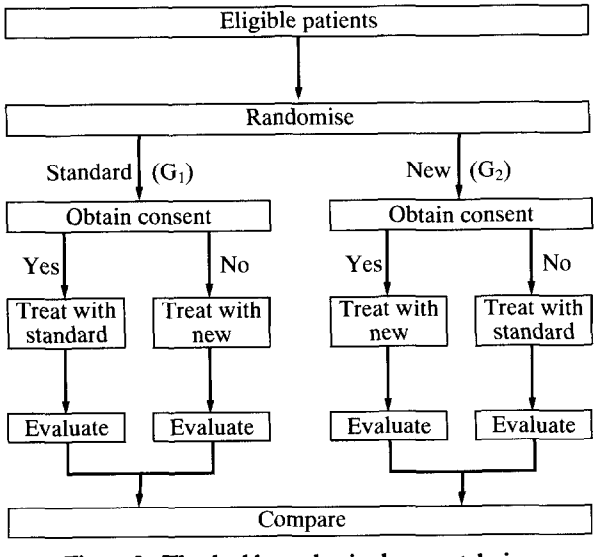

Figure 3. The double randomised consent design.

In practice, however, when they are told that they have already been entered into a trial, some patients may not wish to be in the trial at all. For these patients, there is the practical issue of what treatment they should receive. Although they may receive a treatment that is not one of the trial treatments, as with a conventional trial there is the possibility that they will end up having the same treatment outside the trial that they would have had within the trial. Further, because patients were randomised before consent was sought, the refusers are still within the trial in the sense that they remain in the original randomised groups.

STATISTICAL ASPECTS

Zelen's proposal was aimed at increasing the number of patients entered into randomised trials, by increasing the willingness of clinicians to enter their patients. The statistical rationale behind the designs is that the loss of power arising from some patients not wishing to have their allocated treatment will be more than offset by the increased sample size. In this section, we review this trade-off, and also consider other statistical issues including the underestimation of the treatment difference.

Sample size and power

It was pointed out that the appropriate analysis of data from a randomised consent design is a comparison of the groups G_1 and G_2 formed by randomisation. The inclusion within one or both groups of patients who decline the originally allocated treatment weakens the comparison of treatments by diluting the observed effect, and reduces the power of the trial to detect a real treatment difference [2, 11]. In order to preserve power, the sample size must be increased relative to a conventional design. The magnitude of this increase is considered here.

It is inevitable that some patients will not want the allocated treatment. For simplicity, we assume here that in each group all patients who decline the allocated treatment receive the alternative treatment. We will call the proportion of patients who switch to the other treatment the transfer rate. When comparing the groups as randomised the true treatment effect is "diluted", so that the treatments will appear more similar than they really are. We illustrate this effect with the following example of a double consent design. Suppose that the true 2 year survival rates for treatments A and B are 50% and 70%, respectively. Suppose further that 20% of patients assigned to each treatment decline the allocated treatment and receive the other one. We would expect to observe a survival rate of 54% ($0.8 \times 50\% + 0.2 \times 70\%$) in patients randomised to receive treatment A and 66% ($0.8 \times 70\% + 0.2 \times 50\%$) in patients randomised to receive treatment B. Thus, the expected difference between the treatments is 12% and not 20%, representing an underestimate, or dilution, of 40% in relative terms.

Thus, in this example, if a conventional trial were set up to detect a 20% difference with high probability, a trial using the double consent design would need to be designed to detect a difference of 12% to have the same power. As a consequence, the required sample size would be much larger. Table 1 shows the necessary sample sizes for a two group randomised consent

Table 1. Total number of patients required using a randomised consent design to have the same power as a conventional trial for various rates of transfer from allocated treatment, with increased accrual factor and expected dilution (%) of the estimated treatment difference

	Overall percentage of patients declining treatment allocated (as percentage of total study size)							
	2%	5%	10%	15%	20%	25%	30%	40%
Sample size for conventional design								
250	271	309	391	510	694	1000	1563	6250
500	543	617	781	1020	1389	2000	3125	12 500
1000	1085	1235	1563	2041	2778	4000	6250	25 000
Increased accrual factor	1.09	1.23	1.56	2.04	2.75	4.00	6.25	25
Dilution	4%	10%	20%	30%	40%	50%	60%	80%

See Appendix for calculations.

design having the same power as a conventional trial assuming various overall transfer rates. Similar figures have been presented previously [4, 11–13]. The Appendix explains the calculations. It can be seen from Table 1 that if a trial required 250 patients in a conventional design, then to have the same statistical power the trial would require 694 patients if a double randomised consent design were used and the transfer rate were 20%. Even a 10% transfer rate would mean that 391 patients would be needed.

This surprising result can be explained as follows. Each patient who declines their allocated treatment and transfers to the other treatment effectively removes from the trial a patient in the other group who accepts their treatment. Therefore, the effective sample size is obtained as one minus the sum of the transfer rates in the two groups, i.e. $1 - (0.2 + 0.2) = 0.6$ (or 60%) in the example. The power is a function of the square of the sample size, and thus relates to the square of the effective sample size. In the example, we have $0.6^2 = 0.36$, and the necessary sample size is $250/0.36 = 694$. The increased patient accrual rate required is 694/250 or $1/0.36 = 2.75$. Of course, the transfer rate will not be known in advance, so that the number of patients required can be calculated in advance only by assuming a certain value. In practice, therefore, the sample size needed for the trial to have a given power cannot be known in advance, so that the duration of the study will be related to the transfer rate as well as the accrual rate.

If nearly all patients accept their allocated treatment then clearly there is little practical difference between the power of a conventional design and that of the double randomised consent design of the same size. However, the examples presented later suggest that a transfer rate of 10–25% is common in studies using this design. This level of transfer has a major impact on the patient numbers required to maintain statistical power and produces a final estimate of treatment difference which underestimates the true treatment effect by a substantial amount, as discussed in the next section.

The ability to accrue the necessary number of patients will be related to the proportion of patients who would refuse to be randomised in a conventional trial. By definition, these patients would be included if a randomised consent design was used. The higher the refusal rate, the greater the potential of a randomised consent design to achieve the number of patients required. In the above example, the necessary increased accrual rate to retain statistical power was 2.75. It follows that only if more than 64% (i.e. $100 \times (1-\frac{1}{2.75})$) of patients would refuse to participate in a conventional trial could the extra patients be recruited without involving extra clinicians in the trial. Table 1 shows the increased patient accrual required to retain statistical power for different transfer rates.

We have assumed here that the transfer rate is the same in each group. In practice this is unlikely, but the effect will be similar if the rates are different in the two groups. In the single consent design, group G_1 has a zero transfer rate by definition, so that the overall transfer rate is half the transfer rate in group G_2, and Table 1 still applies.

These calculations also make the implicit assumption that the patients who decline the allocated treatment are no different in their prognosis from those who accept it. In practice, this may well not be the case. Another assumption is that all patients who do not accept their allocated treatment transfer to the other arm of the trial, but this does not always happen. A further implicit assumption is that in a conventional trial all patients agreeing to be randomised receive the allocated treatment. Although this will often not be the case, the proportion of patients not receiving the allocated treatment will usually be very small.

Later in the paper we consider whether cancer trials which changed from a conventional design to a randomised consent design succeeded in increasing accrual adequately to compensate for the loss of power.

Bias

The effect of patient transfer on the observed magnitude of the treatment difference is less often considered. As shown in the above example, the expected dilution of the estimated treatment effect can be considerable.

A serious weakness of the randomised consent design is that it will provide a biased estimate of the true treatment effect. Table 1 also shows the relation between the transfer rate and the dilution effect (bias). As shown in the Appendix, the expected dilution of the treatment effect is the sum of the transfer rates in the two groups. Thus, if the transfer rates were 12% and 20% the observed treatment difference would on average be 68% of the true difference, if we could assume that patients declining their allocated treatment were a random sample of all the patients in each group. In a conventional trial too, some patients do not

receive the intended treatment, so that the intention-to-treat analysis will give an underestimate of the true treatment difference. However, the magnitude of this effect will generally be much lower than that likely in trials using a randomised consent design, judging by the transfer rates in published trials.

It is not safe to reverse the above calculation and multiply the observed effect by 1/0.68 to estimate the true treatment difference, although this has been suggested [14]. Patients who transfer may well have a different risk from those who agree to have the allocated treatment. It might be tempting to use only those patients who accepted the allocated treatment to try to answer this question, but this is not at all advisable. It is a fundamental part of the proposal that in the main analysis the groups are compared as randomised using an intent-to-treat analysis. Comparing only those patients who received the allocated treatments would destroy the random allocation and further weaken, rather than strengthen, the principal inferences that can be drawn from the trial. Analysing only those receiving their allocated treatment might be a useful secondary analysis, however.

The lack of valid estimates of treatment differences is rather unfortunate at a time when there is a welcome trend towards including estimates and confidence intervals as well as *P* values in reporting clinical research [15, 16].

Lack of blindness

One of the cornerstones of the ideal controlled trial is double blindness, whereby neither the doctor nor the patient knows which treatment has been given [17]. Blinding avoids potential biases from knowledge of the treatment received. It is inherent in randomised consent designs that neither patients nor clinicians are blind to the treatment being given. Although most cancer clinical trials cannot be double-blind, there are some which can be. In other fields, and especially with trials using softer endpoints, the inability to use blinding could be a serious deficiency.

Multicentre trials

If, in a multicentre trial, centres are allowed to choose whether they use conventional or preconsent randomisation, and some use each type of procedure, then there will be some confounding between centre and dilution effect. In other words, the larger the transfer rate was in a centre, the smaller would be the expected observed treatment difference.

Zelen [5] suggested that in such trials a weighted analysis could be used, in which the contribution of each centre was related to their transfer rate. In this analysis, a centre with a 25% transfer rate would contribute half as much information to the overall analysis as another centre with the same number of patients using conventional randomisation. As far as we know, this idea has not been taken up. However, Zelen [5] noted that "some studies allowed both randomised consent and conventional randomisation to be used, with the hospitals deciding which method was to be used".

Meta-analysis

The treatment effect is underestimated when a randomised consent design is used, perhaps substantially (Table 1). It may, therefore, be unwise to incorporate trials using randomised consent into a meta-analysis (overview), especially if there is a large transfer rate. The pooled estimate of treatment effect will be reduced, and the test of heterogeneity between studies would not make much sense (although its use is not universally recommended anyway).

IMPLEMENTATION OF THE RANDOMISED CONSENT DESIGN

Although Zelen's proposal [1] was not new, he seems to have been the first to give a detailed consideration of the principles, properties and implications of these designs.

It is impossible to know how often randomised consent designs have actually been used. Zelen [5] was aware of 11 trials using randomised consent designs, including the seven (all cancer trials in the U.S.A.) reported by Ellenberg [11]. In five of these, the design was adopted during the trial in an attempt to increase accrual.

Other published trials have used these designs. A citation search based on Zelen's 1979 paper [2] found fewer than 40 published trials published by 1994 that had used this design and cited the paper, of which eight were in the field of cancer [18–25]. The study by Dundee and associates [25] was a small randomised crossover study of 10 patients. Although the authors say that they used a randomised consent design, it is by no means clear that they did, so we have not considered it further. The most frequent use of the design appears to have been in paediatrics.

We are aware of four other cancer trials that used a randomised consent design but which did not cite Zelen [26–29]. These were all referred to before their completion by Ellenberg [11] and they were also discussed by Zelen [5] but not referenced. It seems certain that the design has been used in other trials but the decription of methods in the published report does not reveal it.

Tables 2 and 3 show some of the main design features of the eleven completed cancer trials. Four trials were of patients with breast cancer, three in cancer of colon or rectum (or both), and one each in cancer of the bladder, lung, stomach and in patients with acute lymphoblastic leukaemia (ALL). The five largest trials, including three of those in breast cancer, were carried out by co-operative groups, three by the National Surgical Adjuvant Breast and Bowel Project (NSABP) [26–28] and one by the Eastern Co-operative Oncology Group (ECOG) [29] in the U.S.A., and one by the Danish Breast Cancer Co-operative Group (DBCG) [21]. None of the trials reported a power calculation, so we cannot tell if they took account of the design, and thus the likely dilution effect, when determining the sample size. However, Moertel and colleagues [18] used unbalanced randomisation in anticipation of patients declining the allocated treatment in one arm of the trial.

Table 4 shows aspects of the analysis and presentation of these trials. The three NSABP trials [26–28] all began using conventional randomisation, but switched to a randomised consent design. In one paper, the reason was given as "patient and physician difficulty with the conventional randomisation process" [26]. No reason for choosing to use a randomised consent design was given in most of the reports.

As far as we can ascertain, no major therapeutic trials using these designs performed in the U.K. have been published. To our knowledge, the designs have not been used by the European Organisation for Research and Treatment of Cancer (EORTC), and we understand that no protocols using the design have been submitted to the U.S. National Cancer Institute for several years (S. Ellenberg, personal communication). (We note that, by contrast, the single consent design is often used in randomised trials of screening or prevention as opposed to therapy, especially where different geographical areas are randomised.)

Table 2. Eleven published cancer trials using randomised consent design

Study/Reference	Site	Year begun	Treatments
Moertel *et al.* [18]	Stomach	1965	Observation 5-FU + radiation
NSABP [26, 30]	Breast	1976	Total mastectomy Segmental mastectomy Segmental mastectomy + radiation
NSABP [27]	Colon	1977	Observation Chemotherapy BCG
NSABP [28]	Rectum	1977	Observation Chemotherapy Radiation
Santen *et al.* [19, 31]	Breast	≤1978	Surgical adrenalectomy Aminoglutethimide + hydrocortisone
Lange *et al.* [20]	ALL	1980	No prophylaxis TMP–SMZ and nystatin
ECOG [29]	Breast	1981	Observation Chemotherapy
DBCG [21, 32]	Breast	1983	Mastectomy Breast conservation
Sell *et al.* [22]	Bladder	1983	Pre-op irradiation + cystectomy Radical irradiation + salvage cystectomy
Ganz *et al.* [23]	Lung (non-small cell)	1984	Supportive care Supportive care + chemotherapy
Riethmüller *et al.* [24]	Colon/Rectum	1985	Observation Monoclonal antibody

5-FU, 5-fluorouracil; BCG, Bacillus Calmette-Guérin; TMP–SMZ, Trimethoprim–Sulphamethoxazole; Pre-op, pre-operative.

Table 3. Design characteristics of 11 cancer trials using a randomised consent design

Study/Reference	Site	No. of patients	Single or double	Comments
Moertel *et al.* [18]	Stomach	62	Single	Study stopped because of concern about prerandomisation
NSABP [26, 30]	Breast	2163	Double	Initially a conventional randomised trial (73% were prerandomised)
NSABP [27]	Colon	1166	Unclear	Initially a conventional randomised trial (64% were prerandomised). No mention of consent procedure used.
NSABP [28]	Rectum	574	Unclear	Initially a conventional randomised trial (55% were prerandomised). No mention of consent procedure used.
Santen *et al.* [19, 31]	Breast	96	Double	
Lange *et al.* [20]	ALL	67	Single	Allocation by odd or even birth date.
ECOG [29]	Breast	536	Unclear	Changed from a conventional design to a randomised consent design to increase the accrual rate, and changed back to a conventional design because a high proportion of patients declined the assigned therapy (32% were prerandomised) (from Zelen [5]). No mention of consent procedure used.
DBCG [21, 32]	Breast	662	Single then double	There was an unclear preconsent procedure before prerandomisation. Changed to double consent design after adverse publicity.
Sell *et al.* [22]	Bladder	183	Single?	Text suggests that this was a single consent design, but no details are given of consent procedure.
Ganz *et al.* [23]	Lung	63	Double	
Riethmüller *et al.* [24]	Colon/Rectum	189	Single	

Table 4. Patients analysed and non-acceptance rates in 11 published cancer trials using randomised consent (RC) design and details of increased accrual in those trials which changed from conventional to RC design*

Study/Reference	How data were analysed	Non-acceptance rates†	Achieved increase in accrual‡	Necessary break-even accrual§
Moertel *et al.* [18]	As randomised	25.6%	–	–
NSABP [26, 30] Breast	As randomised, less 320 exclusions (15%)	10.5%	6×	1.6×
NSABP [27] Colon	As randomised, less 50 exclusions (4%)	11.6%‖	1.25×	1.7×
NSABP [28] Rectum	As randomised, less 19 exclusions (3%)	12.2%‖	2×	1.7×
Santen *et al.* [19, 31]	Only those who received allocated treatment, less 27 exclusions (28%) (of whom 7 declined surgery)	7.3%	–	–
Lange *et al.* [20]	Only those who received allocated treatment (n = 60)	16.7%	–	–
ECOG [29]	As randomised, less 130 exclusions (24%) (85 because of ineligibility)	36.0%¶	2.8×	13.2×
DBCG [21, 32]	As randomised, less 43 exclusions (6%) because of protocol violations	10.7%	–	–
Sell *et al.* [22]	(a) As randomised; (b) only those who received allocated treatment (n = 154)	15.8%	–	–
Ganz *et al.* [23]	All randomised patients were included in the survival analysis, but the two groups were not compared. Quality of life data could not be obtained from 15 patients (24%) who did not wish to participate.	23.8%	–	–
Riethmüller *et al.* [24]	(a) As randomised, less 23 exclusions (12%) (12 because of ineligibility); (b) all randomised patients.	11.1%	–	–

*It is often difficult to work out non-acceptance rates, as most papers give inadequate information about numbers declining the allocated treatment. Also, many trials excluded ineligible patients after randomisation, so that there is also uncertainty regarding the denominator; †Excluding patients entered through conventional randomisation, where relevant. For single consent designs based on one group only; ‡When design changed to RC; from Zelen [5]; §For same power as conventional trial; from Zelen [5]; ‖From Ellenberg [11]; ¶From Zelen [5].

Examples

Lange and associates [20] used the single consent design to evaluate prophylaxis in children with ALL. Indeed, one of their stated aims was "to evaluate the method of randomisation proposed by Zelen". (This trial was not truly randomised, as allocation was based on odd or even birth dates.) The authors largely analysed the data excluding those patients who did not receive the intended treatment, thus excluding 2/37 controls and 5/30 in the prophylaxis group, contrary to Zelen's proposal.

Another trial that used the single consent design was one of breast conservation therapy carried out by the DBCG [21, 32]. Some years into the study, considerable adverse publicity led to conversion to the double randomised consent design. The authors note that the rate of non-acceptance of the allocated treatment rose from 13 to 25% during the course of the trial, presumably corresponding to the change in the design.

The U.K. Cancer Research Campaign Clinical Trials Centre have recently completed a randomised trial evaluating serial carcinoembryonic antigen assay (CEA) as an indicator for second-look surgery in recurrent colorectal cancer. Informed consent is sought from all patients entering the study to allow regular blood sampling for CEA estimation, and at this stage no consent for possible randomisation at a later stage is sought. If, at some point, a significant rise in CEA is observed, then patients are randomised by the Trials Centre to surgery or no immediate treatment (observation alone). The clinician and the patient are both informed only when the allocated treatment is surgery, in which case informed consent is sought from the patient. The trial organisers do not think that it is necessary to inform the patient or the surgeon of the rise in CEA level when the patient is randomised to the observation group, because (a) there is implicit consent to continue with conventional follow-up, which currently in the U.K. does not include CEA monitoring; (b) the study would cease to be blind and there could be possible bias in the clinical follow-up in the observation group; (c) the information could cause unnecessary alarm to patients.

The single consent design was also used in two trials of extracorporeal membrane oxygenation (ECMO) in neonates [33, 34]. These trials were controversial because of their use of adaptive randomisation (the "play the winner rule", see Ware [35]), and were so small as to offer minimal insight into the working of the randomised consent design.

The double randomised consent design has been used in several major trials, although its use remains rare. For example, the design was used in a trial which compared total mastectomy and segmental mastectomy with or without radiation [26, 30]. The ECOG trial [29], comparing chemotherapy with observation after surgery in high risk breast cancer patients, started as a conventional trial, but the design was changed to a randomised consent design because of poor accrual of patients. Subsequently, the design was changed back to conventional randomisation because of the high proportion of patients who did not want the allocated treatment (Table 3) [5].

Participation rate versus dilution rate

The rationale behind Zelen's original proposal was that the increased sample size required would be more than offset by the much higher participation rate—patients cannot refuse to be in

the trial. We consider here the evidence for the success of the design in this respect in those trials that have been published.

In the eleven trials shown in Table 4, the rates of transfer from the allocated treatment averaged 18%, ranging from 10 to 36%. Table 4 also shows, for those trials that changed their design, the increased recruitment obtained with a randomised consent design and the increase necessary to have as much power as a trial with conventional randomisation (figures from Zelen [5]). Only one trial clearly achieved a recruitment advantage from changing the design. In addition to the trials shown in the tables, Ellenberg [11] and Zelen [5] also reported a small (n = 48) Northern California Oncology Group (NCOG) breast cancer trial which achieved a 4-fold increase in recruitment compared to the 3-fold increase needed, and two other very small trials, of melanoma and soft-tissue sarcoma. The melanoma trial is apparently still accruing patients very slowly, while the sarcoma trial was terminated early due to insufficient patient accrual (S. Ellenberg, personal communication).

Aspects of published trials

As noted above, we know of eleven cancer trials using randomised consent designs that have been published (Table 2), mostly in leading journals. None of the reports have discussed the design at length. In four of the trials, it is unclear whether a single or double consent design was used as no information was given about the consent process (Table 3). Some authors analysed the data from only those patients who accepted the offered treatment (Table 4), which is not statistically acceptable and may be clinically misleading, and most excluded some patients.

In trials using a randomised consent design, patients do not in principle have the option not to be in the trial. However, some studies have reported the exclusion of some refusing patients [26, 29]; it is not always clear how refusers were distinguished from those who declined their allocated treatment. Exclusion of refusers makes it impossible to compare the groups as randomised. In several trials, the groups were analysed in relation to treatment received rather than initial treatment allocation, which is counter to the point of the design [2].

It appears from these publications and from informal discussions that editors and referees are not concerned about the use of this design, and are probably unaware of its statistical implications. The need to analyse the groups as randomised is clearly not appreciated by authors, referees or editors.

ETHICAL CONSIDERATIONS

We consider in this section the ethical issues that arise with the use of randomised consent designs. It is not our intention to offer a view, but rather to clarify what the main ethical issues are, and to comment on published views about the ethics of using these designs.

The single consent design

Zelen's first papers concentrated on the single randomised consent design [1, 2]. He proposed that "the physician need only approach the patient to discuss a single therapy" [2]. This approach would indeed reduce the amount of explanation clinicians need to give about the study, but it is not widely accepted as ethical. Indeed, this suggestion seems incompatible with the U.S. federal requirements that Zelen was trying to meet, namely the requirement for "the treating physician to inform the patient about all risks and benefits associated with the trial, the alternative therapies available, and the patient's right to withdraw at any time" [2].

There is widespread use of routine patient data for research purposes, notably in epidemiology and, more relevantly, clinical trials without concurrent controls, and this is widely regarded as acceptable. The control group in the single consent design receive standard treatment, for which no consent would be required if they were not in a trial. Zelen argued [2] that this meant that no consent would be needed for the control group in the single consent design. Further, the experimental treatment can often be considered to be a non-validated intervention, not a proven therapy, so that in not offering it to all patients they are being protected from an unproven and potentially dangerous intervention [36]. It can be argued that the clinician–investigator is morally obligated as a medical practitioner not to provide such non-validated interventions until they have been evaluated and can then be termed treatments [37].

The single consent design is not acceptable to several research funding bodies, including the MRC. Current U.S. federal guidelines also preclude the use of this design [38].

A further issue is whether those patients randomised to the experimental treatment are informed that their treatment was chosen at random. Zelen's main paper [2] is unclear on this, but he seems to imply that patients would not necessarily be told.

In addition to the ethical issues associated with using this design, difficulties can arise from subsequent discovery of the allocation procedure used. Lange and colleagues [20] commented that, "There were instances in our study in which certain parents discovering that other children were receiving prophylactic antibiotics questioned why their child was not receiving antibiotics or why this issue was never discussed".

The double consent design

In the double consent design, consent is sought from both groups. It is not clear in practice whether patients are told that they are in a comparative trial, or whether they are simply asked whether they will accept a specific treatment, with little or no mention of the alternatives. Some guidelines specify that full information should be given to both groups, even when pre-randomisation is used. For example, the MRC's Cancer Therapy Committee guidelines described earlier [9] state that ". . .in certain circumstances it may be preferable to allocate treatment by randomisation before the patient is offered the chance of participating. This may make the explanation of the trial and the proposed treatment easier to give and to comprehend. This procedure is ethically acceptable as long as the patient is told that the proposed treatment has been selected by randomisation, is informed of the other treatment options and is reassured that refusal to participate in the trial will not prejudice his or her treatment".

One of the trials in Table 2 reports a consent procedure that meets the MRC requirements, as follows: "After randomisation, the participating investigators fully explained the purpose of the study, its two treatment arms, and the exact nature of the randomisation process, and obtained written informed consent. The discomforts, risks, side-effects, and potential benefits of the treatment approach to be used and the other therapeutic options available to each patient were outlined" [19]. Others, however, give no information at all about the consent procedure (see Table 2).

The success of the double consent design is dependent upon a high proportion of patients accepting the allocated treatment, and it is likely that the transfer rate will be related to the degree of openness of the clinician. As Fleming has written, "The

design provides a subtle encouragement for the investigator to provide a biased presentation of the relative merits of the treatments" [39], and others have expressed similar concerns [10, 11]. This effect (which may be subconscious) works both to ease the investigator's work in explaining the trial and also to maximise the power of the study by reducing the transfer rate. The statistical success of a trial using randomised consent is directly related, via the dilution rate, to the nature of the information given to patients. A further ethical issue is that, as originally conceived, with this design patients cannot opt out of the trial altogether. However, some trials have excluded some patients who did not wish to be in the trial, but the way in which they were identified is unclear.

To be successful, a trial with a randomised consent design must have a greater accrual of patients than the number that would be randomised in a conventional design. This will occur only if patients are recruited who would not otherwise be in the trial, which will happen if more clinicians are willing to participate or if the same clinicians can persuade more patients to be in the trial, or by a combination of these factors. Unless the refusal rate in a conventional trial is considerable, the increased accrual will require extra clinicians. It has been argued [40] that the accrual of more patients is at the expense of ethics, in that patients refuse to be randomised because they have a preference for one of the treatments. So if patients are more willing to accept a randomised treatment in a trial using a randomised consent design this must be the result of incomplete information. We should note that doubts have been expressed about the completeness of information given to patients in conventional randomised trials. However, here there is not such a strong link between the consent process and the success of the trial.

Need for consent

There is an argument that clinical trials are different from other types of medical research, and that the ethical considerations differ. Given that there is genuine uncertainty about which of two treatments is better, then either can be validly (and ethically) used outside a clinical trial when treating patients without any special consent. However, when a randomised trial is set up to compare the same treatments, elaborate informed consent procedures are required, which may discourage the initiation and hinder the execution of controlled trials. Collins and colleagues [41] have suggested that "in many important respects the ethical considerations for trials comparing different treatments have more in common with routine medical care than with other types of medical research". In other words, such trials are more in line with clinical audit than experimentation, and should be judged as such. This stance should not be taken as an argument in favour of the double consent design, but rather in favour of extending the requirement for informed consent to all patients whether they are in a clinical trial or not. When the clinician is substantially uncertain about which of two (or more) treatments is best, they argue that at present there is a double standard that requires strict informed consent from patients in a clinical trial but is not required for the same treatments outside a trial. The double standard has also been discussed by Chalmers and Silverman, who commented that ". . .a mischievous view has been promoted that the interests of the vast number of patients involved in the poorly controlled experiments of informal medical "tinkering" are less in need of protection than are those of the relatively small number of patients who are involved in planned, properly controlled clinical experiments" [42]. They also observed that other forms of health care are not subject to the same evaluation requirements as drugs.

DISCUSSION

Since Zelen's first proposal [1], very few trials appear to have used his designs. In the field of cancer, we know of just eleven published trials. Half of these were initiated before Zelen published his proposal (Table 2), although at least one [26, 30] was influenced by Zelen's proposed approach before its publication (M. Zelen, personal communication). There are also a few trials that are still in progress. Although these figures will be an underestimate of the use of the design, it is clear that the design has not been as popular as Zelen predicted: "I believe that these designs will dominate the field of randomised controlled clinical trials" [3].

A scientific study that was not bound by any ethical constraints would not seek consent of subjects. It would also enforce compliance with treatment and evaluation regimens. Thus the choice between the various design options above cannot be made solely on scientific grounds. What is ethically acceptable, and the extent to which patients will voluntarily co-operate, clearly has to be taken into account. In this paper, we have tried to concentrate on statistical implications of randomised consent designs, but it is clear that the statistical success of the trial relates directly to the transfer rate which in turn is directly related to the consent procedure.

Zelen's motivation for departing from the conventional design of Figure 1 stemmed from problems associated with persuading physicians to enter patients into clinical trials, in particular the difficulty of obtaining informed consent. When done properly, this can be time consuming, and it is potentially distressing to the patient. Some clinicians do not participate in trials because of this difficulty, and it is likely that others do not give as complete information as some would consider necessary when obtaining consent. There is a need for more research into the different methods of getting patient consent and also ways to persuade more clinicians to participate in clinical trials [10]. As yet it seems that there have been few randomised comparisons of alternative forms of consent [43, 44].

The main attraction of randomised consent designs to doctors may be the apparent simplification of the information given to patients. This can also be seen as their main disadvantage. As the doctor knows their patients' allocated treatment in advance, he or she may reduce the information given about the details of the trial and the alternative treatment(s). Indeed, it is in their interest to do so, not only because it makes the explanation to the patient easier, but also because it will enhance the usefulness of the trial to have as many patients as possible treated according to their random allocation. Zelen [5] mentions one trial which "was able to enlist a large number of physicians who were not comfortable with a conventional randomised trial". This comment implies that with the randomised consent design different, and perhaps reduced, information was given to patients.

Informed consent remains a difficult issue [4, 45]. The assumption that randomised consent designs will lead to more doctors entering patients may not be correct. Taylor and colleagues [46] investigated reasons for slow accrual in one of the trials in our review [26, 30]. The main reason stated for not entering patients was concern about affecting the doctor–patient relationship, with only half as many doctors worried about the difficulty of obtaining informed consent. However, such concern was not related to how likely they were to enter patients into the

trial. A later study of ECOG physicians also found little support for the idea that getting patient consent was a major impediment to recruitment [47].

Zelen's original single consent design [1, 2] clearly makes the difficult informed consent procedure easier for the doctor [48]. Whether one should be recommending the new treatment to patients in group G_2 at the same time as participating in a randomised trial may, however, be questionable. Zelen's single consent design is not allowed in the MRC Cancer Therapy Committee's guidelines, nor by other groups (see, e.g. Zelen [5]), because of the lack of consent for group G_1.

Whether the double consent design reduces the work of the clinician depends upon the type of consent that is sought. If guidelines say that the study must be fully explained to all patients (as is the case at the MRC), there may be little or no saving of the clinician's time. He or she still has to admit not knowing which treatment is better. Further, the sample size must be increased because a proportion of patients will decline to have the allocated treatment. In a conventional trial, clinicians spend time explaining the trial to some patients who subsequently do not agree to be entered into the trial, so it is unclear which design will require more explanation overall. Use of a randomised consent design might decrease the total amount of explanation, but it might well increase it.

If the transfer rate in a trial using randomised consent is not too high, the increased sample size may compensate for the dilution effect, but it is difficult to know in advance whether this will apply. Table 4 suggests that the randomised consent design may well fail in this respect. Further, such compensation applies only to the power of the study, but not to the estimated treatment effect.

It can be argued that the use of a randomised consent design puts doctors in an extremely difficult position. By definition, they should be participating in the trial only if they have a substantial uncertainty about which of the treatments is best, yet they have to give information to patients in the knowledge of the treatment that the patient has already been allocated and also knowing that it is in the interests of the trial for the patient to accept that allocation.

The conventional design of Figure 1 is scientifically valid and ethical and will be appropriate in most circumstances. While we recognise that there can be difficulties associated with the consent procedure in conventional trials, we do not believe that Zelen's double consent design should be used in situations where a conventional design is both possible and practical [49]. There are, however, some treatment comparisons which for scientific reasons should be made, but which will generate high refusal rates when randomisation is offered, such as when the two treatments are dramatically different (e.g. surgery versus radiotherapy). There are also situations where it is felt difficult to get full informed consent to be randomised, such as in some studies of children. The ethical issues associated with the use of randomised consent designs for such trials were outlined earlier.

Conventional randomised trials are not without some problems, but these will affect trials using randomised consent designs too. We have concentrated on those additional issues arising from the use of the randomised consent design. There are several statistical drawbacks with the double consent design, unless the transfer rate is very low. These can be summarised as follows:

(a) More patients need to be randomised to get the same power as a conventional trial. The increased number required may be considerable, so that there is a risk that the use of the design may well reduce the power to detect a real treatment difference.

(b) The treatment difference will be underestimated, perhaps substantially. This is a problem of all intention-to-treat analyses, but the effect is likely to be magnified with the randomised consent design.

(c) The number of patients randomised, and thus also the duration of the trial, will depend on the transfer rate and cannot be determined in advance.

There are, thus, serious statistical arguments against the use of randomised consent designs, which should discourage their use. When it is deemed impossible to carry out a conventional randomised trial, other types of design need to be considered [50–53]. It may be that less scientifically accurate observational studies will have to be recognised as the best that can be conducted. More statistical research is needed into improving the design and analysis of non-randomised clinical trials [38], and hence the reliability of findings from such studies.

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APPENDIX. SAMPLE SIZE NECESSARY FOR A TRIAL WITH A RANDOMIZED CONSENT DESIGN TO GIVE THE SAME POWER AS A CONVENTIONAL TRIAL

Consider a conventional randomised trial with two parallel groups, A and B, with a binary endpoint (such as death). Let N be the total sample size to give the required power to detect a true difference δ between proportions, where $\delta = p_A - p_B$. We assume that there are $N/2$ patients in each group. If the proportions of patients declining their allocated treatments in a double randomised consent design are r_A and r_B, then the expected proportions with the outcome in each group are p^*_A and p^*_B, and the expected treatment difference is

$$\begin{aligned}\delta^* &= p^*_A - p^*_B \\ &= [p_A(1 - r_A) + p_B r_A] - [p_A r_B + p_B(1 - r_B)] \\ &= (p_A - p_B)(1 - r_A - r_B).\end{aligned}$$

As sample size is a function of the square of the difference between treatment groups, the required sample size for a trial using a randomised consent design is approximately

$$N^* = \frac{\delta^2}{\delta^{*2}} N.$$

The necessary increase in sample size is thus given by the accrual factor δ^2/δ^{*2}, given by $(1 - r_A - r_B)^{-2}$ [3, 11]. The expected treatment difference is $\delta^* = \delta(1 - r_A - r_B)$, so that the dilution effect is $\delta - \delta^* = r_A + r_B$.

Table 1 shows the accrual factor and the dilution factor for various transfer rates. These values apply equally to the single consent design, for which $r_A = 0$.

The above calculations assume that the decision of patients to refuse their allocated treatment is independent of their prognosis.