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PRE-RANDOMIZATION IN STUDY DESIGNS

Acceptability and applicability

Ron Schellings

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PRE-RANDOMIZATION IN STUDY DESIGNS

Acceptability and applicability

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ter verkrijging van de graad van doctor
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Introduction

Background of the thesis

The use of pre-randomization in study designs was first described by Marvin Zelen in 1977.¹ The essence of Zelen's original proposal is that potential participants are randomized before informed consent is obtained.^{1, 2} This sequence is contrary to the conventional design in which informed consent is prior to randomization (see Figure 1). The immediate cause for this thesis was a discussion in the mid-Nineties in the Netherlands about the usefulness and ethical acceptability of pre-randomization in medical research. That time, a design using pre-randomization (Zelen design) for a heroin provision trial was proposed.^{3, 4, 5} The use of this design met opposition and disapproval in particular from ethicists and lawyers, but also from physicians and methodologists.⁶⁻¹⁰

Figure 1. The features of the conventional design in comparison with pre-randomization (Zelen's original proposal).

The most important reasons cited in the literature for rejection of pre-randomization are presented in table 1. Finally, the Dutch Parliament agreed upon a medical experiment regarding the effects of heroin provision for long-term heroin addicts conducted according to a conventional study design. Triggered by the conviction that pre-randomization is useful in specific circumstances¹¹⁻¹³ and against the background that it is often rejected on invalid grounds we started a

study into the applicability and acceptability of pre-randomization in study designs. The dissertation approaches the subject of pre-randomization in theory and empirically.

Table 1. Summary of objections in the literature against pre-randomization (in particular the Zelen design).

	Remarks
1	Randomization without informed consent is inadmissible
2	Participants in reference group are unaware of their participation in a trial
3	Participation in the reference group is involuntary
4	Participants in reference group cannot withdraw from the trial
5	Pre-randomization does not meet the requirements of Good Clinical Practice
6	Baseline measurements are always necessary, so informed consent is required in all participants
7	Pre-randomization violates the Declaration of Helsinki paragraphs 20-23
8	Pre-randomization is only applicable if other designs are absolutely unfeasible
9	Pre-randomization has never been used again after Zelen's introduction in 1977 and 1979

Variants of pre-randomization

Marvin Zelen introduced pre-randomization in study designs, that he termed randomized consent designs, to make it easier for physicians to enter patients in randomized clinical trials. Zelen stated that physician reluctance to participate in randomized clinical trials is often a reflection that the physician-patient relationship could be compromised if the physician makes known to the patient his/her inability to select a preferred therapy.^{1, 2, 14} However, this argument has no methodological importance since it only helps investigators to become less frustrated and could undermine the main purpose of a study design, this is the optimal comparability of the study groups. This optimal comparability is achieved only if potential participants, after informed consent, will agree to receive the assigned treatment and the difference in withdrawal of participants between the treatment groups is negligible. If potential participants refuse to contribute to the experimental treatment in Zelen's original proposal there is an apparent loss in statistical efficiency, compared with a conventional design (see appendix).

The interventions in pre-randomization designs can be applied in individuals or on the level of units, or clusters, like for instance primary care practices.¹¹ Besides, after randomization, giving information about the intervention, and obtaining informed consent, can be done 1) only in the experimental group (the so called single-consent design) or 2) in the experimental group and in the reference group (the so called double-consent design).

Cluster randomization is a pre-randomization design in which units other than the individual person are randomized and the intervention is at the level of that

unit or addressed to individuals within that unit. The discussion in the literature surrounding the ethical implications of conducting cluster randomized trials is astonishingly thin on the ground,^{15, 16} especially in contrast to pre-randomization designs in which individuals are randomized.

The informed consent paradigm and absolutism

Conducting scientific research implies a sound informed consent procedure for participants entering a trial. The discussion about the impact of the process of informed consent on patients' autonomy and behavior has been going on.^{15, 17-24} Braunholtz challenges the absolutism of some debaters that informed consent is necessary in all participants independently of the study design by the following example:²⁵ “at this very moment I might be selecting people on the UK voting register (which is publicly available) to be prayed for (by myself). All the participants are to be tagged, so that I am informed if they die. (This is a public service provided by the registrar for birth and deaths, at a cost). This is surely my affair, and not something I need consent for? But I can just as easily randomize people to be prayed for or not; this is now a randomized trial, but still surely my affair? Suppose I now propose to offer the people for whom I am not praying a free health check. The trial might now be regarded as clinical, and as subject to changes required by an ethics committee. But the situation has not changed one iota for those in the 'prayed-for' arm; so why should my proposals for them be subject to the desires of an ethics committee which might, for instance, insist on consent being obtained for all 'participants'.”

This extreme example illustrates the necessity to assess in every study the restriction of the participants' autonomy and the chance of personal harm that could be sustained before and during the trial. Obtaining informed consent is clearly needed in study protocols in which the autonomy of participants is restricted in any way, and/or study maneuvers may cause physical, emotional, and/or social harm.

Legislation and guidelines open to interpretation

The World Medical Association has developed ethical principles written down in the Declaration of Helsinki, to provide guidance to physicians and other contributors to medical research involving human subjects. The Declaration of Helsinki is the most widely accepted ethical code for medical research.²⁶ In addition, in most countries, legislation and/or guidelines are promulgated for the application of informed consent procedures in clinical trials.²⁷⁻²⁹ Many lawyers and ethicists interpret these guidelines as prohibiting research with individuals if informed consent or consent by proxy is not or not fully sought. Others accept not obtaining informed consent as conceivable or at least as not explicitly excluded

by law under very specific conditions. In practice, the decision whether any of these conditions are a valid reason for not (or not fully) obtaining informed consent, has to be made by a research ethics committee for each trial separately.

Research ethics committees protect study participants' rights

Nowadays, (bio)medical research involving human subjects must be reviewed by an independent research ethics committee. The need for such committees is grounded in the Sixties and Seventies.^{30, 31} Although the legislation and guidelines for the composition and method of working of these committees differ substantially between countries,³² they serve the same goal, namely to assess both the scientific and ethical aspects of submitted study protocols.

Outline of the thesis

Chapter 2 is a historical overview of informed consent taking into account that informed consent should be used particularly as a means and not as an end to conduct ethically justifiable research.

Chapter 3 presents a systematic review that describes the use of pre-randomization (randomized consent designs) since the introduction of these designs by Marvin Zelen in 1977.

In chapter 4 we demonstrate the applicability of pre-randomization by means of a fictitious heroin provision experiment.

In chapter 5 we compare the acceptability of a pre-randomization design and a modified form of it by members of medical ethics committees in the United Kingdom and in the Netherlands.

In chapter 6 we describe indications and requirements for the use of pre-randomization and we present guidelines for its optimal application.

Finally, chapter 7 presents a general discussion about the usefulness of pre-randomization in patient-centered and public health research, considering the consequences of inappropriately designed research for health care and public health.

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Appendix

Statistical efficiency (power) pre-randomization design (Zelen's original design) versus the conventional design

Mathematical formulation

Assumptions:

- Let N be the number of eligible participants who are randomly assigned to one of the two treatment groups (both groups have equal size). The reference group (ref) receives standard treatment.
- The proportion of participants that refuse the experimental intervention (exp) is $1-p$ (thus proportion p will participate), they receive standard treatment and will have the same outcome as the reference group.
- All the participants allocated to the reference group will participate in the trial.
- Effect measurements can be obtained for all randomized participants; intention-to-treat analysis is feasible.
- To simplify the formulation it is assumed that the standard deviation of the outcome measure in the experimental group and in the reference group is equal ($\sigma_{\text{exp}} = \sigma_{\text{ref}}$).

	Conventional design	Pre-randomization
Difference in mean effect between experimental and reference group	$E_{exp} - E_{ref}$	$(E_{exp} - E_{ref}) * p$
Standard deviation of this difference	$\sigma \sqrt{2/(p*N)}$	$\sigma \sqrt{2/N}$
Test statistic	$\frac{\sqrt{p}*(E_{exp} - E_{ref})}{\sigma \sqrt{2/N}}$	$\frac{p*(E_{exp} - E_{ref})}{\sigma \sqrt{2/N}}$

Because $p<1$, the test statistic in the pre-randomization design is $\sqrt{p}$ smaller than in the conventional design.

This means that in case of a non-compliance rate of, for instance, 25% in the experimental group in a pre-randomization design, in both study groups 15% (factor $\sqrt{4/3}$) more participants is needed to achieve the same power as in a conventional design.

Informed consent: an end or a means?

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Abstract

Since World War II, a variety of protective measures have been introduced for persons receiving medical care or being involved in scientific research. Increasingly, the concept of informed consent has been accepted as a standard.

In experimental therapeutic research, informed consent still causes controversies; individual benefit being weighed against general benefit. In various types of observational research, informed consent also appears to become such an absolute requirement for many ethicists that observational epidemiological research on the basis of existing data is in danger of becoming impossible.

Both the Declaration of Helsinki and the Personal Registration Act state that, under certain circumstances, it may be possible to deviate from the requirement of obtaining individual informed consent. A supervisory committee or a medical ethics committee could then give permission for such a research project.

Informed consent should not be an end in itself, but a means to protect the individual and to guarantee his/her right to autonomy. Insisting on informed consent in situations where autonomy is respected and no harm or burden is caused, seems to defy the purpose of informed consent.

Problem Definition

In the case of interventions that cannot be blinded, it is difficult to design a valid research design. For an experiment with the controlled provision of heroin the so-called pre-randomization or Zelen design was taken into consideration as an attempt to solve this problem.¹ In this design, the patients are randomized, but only those in the experimental group are asked for their consent; those who refuse their co-operation, receive the regular medical treatment, as do those in the control group. The debate that arose as a result, was almost immediately dominated by earlier statements regarding this research design from both Dutch and foreign literature. The purport of the debate was that this design did not meet the prevailing requirements regarding informed consent.²⁻⁴ At the same time (the second half of the Eighties), there was a discussion in the *British Medical Journal*, which was taken up again in 1998, and which resulted in a positive sound from the editor in chief. The latter returned to a certain extent from a point of view taken earlier and stated that the informed consent procedure should not be an end in itself, and we should find a middle course.^{5, 6}

There is no doubt that informed consent is necessary when study subjects are exposed to (para)medical treatment or when they are prescribed a certain behavior. In the Netherlands, this is regulated by the Medical Research Involving Human Subjects Act (WMO; effective as from mid 1999).⁷ However, if patients in a trial are not approached for, for instance personal measurements, and receive at least the regular care, we believe that informed consent should not be self-evident. In this article, we shall investigate in greater detail the historical arguments concerning informed consent, because we think that in certain situations, the requirement of informed consent defies its purpose.

Right to protection against risks ('primum est non nocere') or the right to autonomy?

'The first obligation is not to cause damage,' is the rule that all physicians consider of paramount importance. It is one of the rules that constitute the basis for medical ethics. Medical intervention is always governed by this principle, both in patient care and later in medical and scientific research. As we will argue later on, this is a rule that - unlike in the past - is increasingly in competition with other medical ethical rules and/or health law, and in particular with the right to autonomy. In the past, medical intervention was hardly the subject of discussion, if at all. The general view was that physicians had the best intentions with their patients. As a result of the great respect that physicians commanded, discussions with patients regarding the preferred treatment were probably rare. In the course of time, however, patients have become more assertive and they no longer accept everything unconditionally. This has introduced in the world of medicine the awareness of the right of self-determination of any human being. Informed

consent was increasingly accepted as the standard for medical intervention, albeit not without any problems. The Medical Treatment Agreement Act (WGBO), which states that patients must be informed in detail and should be asked their explicit agreement for all interventions, dates from 1994, but has been implemented gradually in clinical practice.⁸ As was the case in patient care, both in therapeutic and non-therapeutic research, there was in particular ethical (moral) and legal (judicial) attention for the control of the risks created by the research in question, and not so much on making it possible for the patient to make an autonomous choice. In scientific research, the requirement of informed consent also became more prominent as the basis of the right to autonomy.

The history of informed consent

Current views on informed consent in scientific research have been greatly influenced by the excesses of 'scientific research' under the Nazi regime during World War II. The crimes against humanity committed then, have permanently changed the views on the involvement of human beings in scientific research.⁹ During the Nuremberg Trials against the Nazi leaders in 1948, the court set up guidelines for research, which have become known as the Nuremberg Code.¹⁰ These were the first written guidelines for scientific research. Core elements are voluntary participation in research and informed consent by study subjects. However, this code proved too restricted and was soon felt to be inadequate. The proposals for improvements eventually led to the Declaration of Helsinki, which was drawn up in 1964.^{11, 12} In this declaration, informed consent also plays a key role. The need for informed consent was linked to the nature of the scientific research. For this purpose, an important distinction was introduced: therapeutic research (research combined with patient care) and non-therapeutic research. The Declaration of Helsinki demands informed consent in all cases of non-therapeutic research.

On the other hand, informed consent is apparently not always required in therapeutic research. If physicians deem it of vital importance not to ask for informed consent, then specific reasons for such a proposal must be included in the protocol that is submitted to the research ethics committee. This exception remains in later versions of the Declaration. In spite of its shortcomings, the Declaration of Helsinki is regarded as the core document in the history of research ethics.

The Nuremberg Code was the first code written by any legal system for the field of medicine; the Declaration of Helsinki is a code written by and for professional colleagues. Stimulated by this development, individual scientists started to publish articles. Beecher was one of the first and most prominent ones.¹³⁻¹⁵ Although he emphasized the need for informed consent, he also noted that there are different forms of informing for different types of research. Beecher

was not an advocate of any approach to supervision of experiments that was based on absolute rules. He believed that, however necessary rules and regulations may sometimes be, they generally did more bad than good. Unlike Beecher, the Briton, Papworth, was an avid proponent of principles and rights.¹⁶ It was not clear, however, whether these were regarded as the right to autonomy or the right to protection against risks, or both.

In 1972, an anthology by Katz et al¹⁷ appeared. This publication saw the light on the eve of the disclosure of what may have become the most notorious example of abuse in research in the United States of America: the Tuskegee syphilis experiment. In this experiment, patients - without being told - were involved in a research project in which the natural course of syphilis was 'merely' observed. Even when it had become known that penicillin was effective against syphilis, patients were denied this knowledge and did not receive this medication.¹⁸ This event, in addition to several others that were in violation of the principle of informed consent, led to the discussion on the position of codes in the regulation of biomedical research on humans being brought out into the open.¹⁹⁻²¹ This was the start of a complex interaction between scientific publications, journalism, public indignation and legislation.⁹

Informed consent in behavioral science

The first draft code that discussed ethical standards in behavioral research appeared in 1951.²² It mentioned neither consent, nor informed consent. Under the heading of 'protection of the well-being of study subjects,' the following proposal was made: "Only if the problem to be studied is important and it cannot be studied in any other way, the psychologist may withhold information, or temporarily give misinformation to study subjects, or expose them to emotional stress. If there is any danger of any serious after-effects, the research can only be done after the study subjects have been fully informed with respect to this risk and only then sign up as volunteers." Any attempt to develop principles for research in psychology must therefore be reconciled with the use of 'deception' as a research method.

During the Sixties, 'deception' became the topic of a major moral controversy within the field of psychology. As a result, the interest that had so far only been directed at the ethics of clinical practice was extended in the direction of research ethics. In the Seventies, this led to the creation of a special code, aimed exclusively at research involving human study subjects. In 1966, the 'Wichita Jury Study',²³ in which professors of sociology and law from the University of Chicago studied the deliberations of six different juries without the latter being aware of this, was the first situation in the psychology literature in which the opponents of this type of research in behavioral science emphatically defended the requirement of informed consent on the basis of the autonomy principle. The original researchers, however,

referred to the concept of general welfare and in particular the principle of beneficence: in the interest of general welfare it was intolerable that there were no empirical data and that we were ignorant of what really happened in such a fundamental institution as jury law.

In 1972, the Cook Commission presented a draft behavioral code.²⁴ This also allowed for a deviation from the principle of informed consent and explicitly left room for the possibility of using deception as a research instrument. Although it was considered unethical to involve individuals in research without their knowledge and informed consent, exceptions should remain possible. In particular if (a) it could be shown that the research objectives could not be achieved without using deception; (b) there was sufficient reason for using deception, as shown by the fact that it could be expected that the study subjects would consider this reasonable if they were later informed about the rationale; (c) the researcher would take full responsibility for detecting and eliminating stressful after-effects; and (d) the study subjects would eventually benefit from the research experience. During the period of 1974-1983, two more commissions were created who were to concentrate both on medical and biomedical research, and on behavioral research: these were the National Commission for the Protection of Human Subjects in Biomedical and Behavioral Research and the President's Commission for the Study of Ethical Problems in Medicine and Biomedical and Behavioral Research.²⁵ Both commissions aimed at a uniform code for all types of research, including observational research.

Informed consent in therapeutic research

In therapeutic research, there is the development of using single- and double-blind, randomized experiments for the evaluation of new treatments. The double-blind randomized experiment is increasingly becoming accepted as the gold standard for evaluating new treatments. This has also led to a greater need to protect patients against obtrusive physicians, who may favor the interests of future patients over those of the present ones when they weigh these interests against one another. After all, carrying out a scientific medical experiment implies dropping the current treatment, which may or may not have shown its merit beyond most experts' doubt and to replace it by a new treatment, in order to test the value of that new treatment (the value of which has not been convincingly shown yet). As the researcher affects both the experimental group and the reference group (which may or may not receive a placebo or sham treatment), this requires the informed consent of all participants. The study subjects must be aware of the research conditions, possible side effects et cetera. The basic human rights, and in particular the right to autonomy,^{26, 27} do not allow the interest of the individual to be sacrificed for the interest of society, or the advancement of science, or the scientist.

Baum on the other hand,²⁸ has completely different views. He suggests that patients have a moral obligation to participate in scientific research. He argues in favor of a broadly based support for research, by mobilizing public opinion, informing risk groups, and pointing out the importance of scientific research.

In the Netherlands, protection of the interests of the individual is laid down in the Person Registration Act.²⁹ Prompted by the investigation of failing heart valves, Vandenbroucke and Grobbee published a concerned comment: they fear that the framework of this act will also make informed consent an absolute requirement for observational research, to the extent that in particular epidemiological research on the basis of existing data will become impossible.³⁰ It would no longer be possible to observe and register the behavior of an individual, unless the person involved were first explicitly asked whether observation and registration was allowed. This introduces the so-called Hawthorne effect and carries with it the risk of possible bias.³¹ (This effect consists of the research results being biased because the study subjects know that they are being observed). A possible way out would be offered by stating in the privacy regulations that if scientific research makes use of private data, this requires the permission of a supervisory committee with respect to the registration of individuals. The Medical Research Involving Human Subjects Act (WMO) is aimed at protecting study subjects if such individuals are likely to be burdened by the research.⁷

In most studies, it is necessary to compare the results with data from an 'external' reference group. This involves individuals who have not participated in the experiment, who have no knowledge of the study, who experience no inconvenience or discomfort, and who suffer no damage with regard to their therapy because they receive the same treatment that they would always have had. This is the case, for example, when Zelen's pre-randomization design is used.³² Nevertheless, this type of research is the subject of discussion, because the 'owner' of the data to be analyzed has not given permission for the analysis, and hence it is not allowed.³³

We therefore wonder whether ethicists who specialize in medical therapeutic research should not start a dialogue with their colleagues in the behavioral sciences, in order to prevent that medical therapeutic researchers are forced to apply all kinds of artificial maneuvers.

Conclusion

The principle of not causing damage and the principle of the right of autonomy have, quite rightly, led to a variety of protective measures for the individual: active protection in the form of informed consent, and passive protection in the form of the ban on the use of data without permission. Informed consent is an autonomous authorization by a patient or study subject, with the aim of guaranteeing these rights. The prevailing legislation and regulations in the

Netherlands provide adequate protection of the rights of patients involved in scientific research.

Under certain circumstances, however, we believe that beneficence and justice offer sufficient reason for giving up the right to absolute autonomy. To live in a society where autonomy is the only main goal cannot be the ultimate principle, as Callahan stated.³⁴ Warnock would prefer to change the term 'principle of autonomy' into 'principle of non-exploitation',³⁵ because the key issue is to prevent the possible exploitation of study subjects. Research, including clinical research, is after all not aimed at the welfare of just some individual patients, but at the production of medical knowledge that benefits society as a whole. The individual patient could only benefit by accident. In a research program, study subjects are used as a means; they do not constitute the goal. This is not morally reprehensible if individuals offer their services voluntarily. According to Warnock, there is a great difference between, on the one hand, the situation in which anonymous data, collected in a particular study, are used for a different problem that had not been studied before, and on the other hand, the situation in which drugs for a disease are tested in a randomized trial. In the first case, he argues that there is no damage to the study subjects and the term 'exploitation' would be an exaggeration. It is therefore incorrect to state that not obtaining informed consent in itself causes damage. Sometimes this means exploitation, at other times it does not. Informed consent was never meant as an end in itself, but as a means to obtain protection for the individual and guaranteeing his/her right to autonomy. In those cases in which this right has very little meaning, because there is no possibility of damage or burden, the unconditional requirement of informed consent appears to have missed the mark. That is when informed consent has become an end rather than the means.

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Randomized consent designs in randomized controlled trials: Systematic literature search

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Abstract

Background Three types of randomized consent designs are distinguished, ranked according to the extent to which participants are informed about treatment options: single-consent (those in the experimental group learn about their assigned treatment), incomplete-double-consent (all participants learn about their assigned treatment), and complete-double-consent (all participants learn about all treatments studied). All are methodologically, ethically, and judicially controversial. Even so, their use is justified if blinding is deemed necessary, but impossible to achieve by sham procedures (placebo), and experimental treatment seems attractive to potential participants.

Objective To give a comprehensive overview of the use of randomized consent designs.

Data sources MEDLINE (1/1977-2/2003), EMBASE (1/1984-2/2003), PsycINFO (1/1996-2/2003), the Cochrane Library, and the Science Citation Index database.

Review methods Eligible were studies using a randomized consent design. Cluster randomized trials were excluded. One reviewer selected and data-extracted eligible papers. A second reviewer independently data-extracted 10% of the papers. Data on country of study conduct, year of commencement, area of medicine, type of design, reason(s) for use, details on approval by a research ethics committee, the index and reference intervention, nature of endpoints, and details on collection of data were extracted. Furthermore, for each trial, the rates of non-compliance and loss to follow-up were registered by treatment arm. The three types of randomized consent designs were compared as to differences between the rates of non-compliance and loss to follow-up in the separate trial arms.

Results Randomized consent designs are seldom used ($n=50$). When used, they have often been used in the wrong circumstances (misuse). In 65% of the studies the non-compliance in the index group is larger than in the reference group. Contrary to expectation, trials using the incomplete-double design were associated with significantly higher rates of non-compliance and loss to follow-up in the reference groups than trials employing the other two versions.

Conclusion Trialists and physicians should be aware of the proper indication for the use of randomized consent designs.

Introduction

In 1977, Marvin Zelen proposed the randomized single-consent design, which he elaborated upon in 1979.^{1, 2} The key characteristic of this design is that, *before* informed consent is sought, patients are randomized to an index group or to a reference group. The patients in the index group are approached for informed consent. The patients randomized to the reference group are not approached for informed consent. However, they are given the best standard treatment. Any index patient that declines is also offered best standard treatment. The reason to introduce this design was to avoid problems associated with persuading physicians to enter patients into clinical trials.² In particular, the design was meant to circumvent difficulties with the randomization procedure and obtaining informed consent for participation.³

The randomized single-consent design evoked a wave of criticism from many ethicists and health lawyers, who argued that the participants in the reference group are not even aware of their involvement in a study.⁴⁻⁷ From an ethical point of view, informed consent should be sought from all study participants after an explanation of the purpose of the study, the main features of the assigned and the alternative study arm(s), and effect measurements. The opposition to the randomized single-consent design is reflected in national regulations. For example, since the 1980s, the design is not acceptable to the British Medical Research Council⁸ and to U.S. federal research institutes.⁹ To overcome ethical concerns, the randomized *double*-consent design as a counterpart of Zelen's single-consent design has been introduced.^{3, 10-12} In this design, informed consent is sought in all treatment arms *after* randomization.

A serious methodological drawback of the randomized single-consent design is the large potential for bias due to post-randomization withdrawal from the index group after the informed consent procedure.¹³⁻¹⁴ Since the randomized double-consent design gives randomized patients in all treatment arms an opportunity to refuse their allocated treatment, and opt for alternatives, it is associated with an even greater likelihood of participants' crossing over to other treatment arms. This, in turn, increases the likelihood and the magnitude of bias in the estimate of the true treatment effect as compared to the single-consent design. To minimize the occurrence of this bias, a version of the double-consent design has been used in which participants in the reference group are informed about their own treatment only, but in which information about the alternative treatment is withheld.^{3, 10-12} Further details on why many ethicists think that randomized consent designs are problematic may be found in references 15-18.

In our opinion the use of a randomized consent design should be considered only when blinding with a placebo or sham procedure is impossible, combined with at least one, to some extent, attractive treatment option that participants could easily acquire and implement themselves, such as an over-the-counter drug.^{19, 20}

The main purpose of the present paper is to review systematically all randomized studies using a randomized single or double-consent design and to determine how they were used, the cited reason(s) for their use, and how often reference was made to approval by research ethics committees. To describe the extent to which the use of these designs was differentially successful, we also studied the rates of non-compliance and loss to follow-up, separately for each trial arm. Cluster-randomized trials are also applications of the randomized consent design. However, these are beyond the scope of this review. Also, this is a review of the experience of using randomized consent designs, not a review of the ethical literature on the merits of the design.

Methods

Searches and eligibility

The eligibility criterion was trials in which any type of randomized consent design was used. We searched MEDLINE (Index Medicus 1/1977-2/2003), EMBASE (Excerpta Medica 1/1984-2/2003), PsycINFO (1/1996-2/2003) and the Cochrane Library (2002, issue 2) and the Science Citation Index database (Web of Science by Institute for Scientific Information). The latter was searched using the *cited reference search* option on reference 1, 2 and 12. There were no language restrictions. The search terms used were: Zelen design, pre-randomiz(s)ation, prerandomiz(s)ation, randomiz(s)ed consent design, postrandomiz(s)ation consent, postrandomiz(s)ation design, preconsent randomiz(s)ation, preconsent design, randomiz(s)ed single(-)consent design, randomiz(s)ed double(-)consent design (spelling alternatives are in brackets). We selected studies in which a randomized consent design was used. Any discussion papers and papers focusing on methodological or statistical issues related to a randomized consent design were used as background literature. Titles and abstracts found by the electronic searches were scrutinized by RS. Reference lists of all eligible papers were checked including those of background papers. The selected trials were included in the review if a randomized consent design had been used. Selection and exclusion of full papers was done by RS.

Data extraction

Study characteristics were extracted from the included papers by RS and, as a pilot, a 10% random sample was scrutinized independently by GtR. There were only minor disagreements between the reviewers. Study characteristics were easily resolvable and the level of agreement justified the other 90% of data extraction. Study characteristics that were extracted included country of study conduct, year of commencement, area of medicine, exact type of randomized consent design, cited reason(s) for use of this design, details on approval by a research or medical ethics

committee, the index intervention, reference intervention, nature of endpoints (medical *vs* behavioral), and details on how and when during the trial data were collected. Furthermore, for each trial, the rates of non-compliance and loss to follow-up were registered by treatment arm. We defined *non-compliance* as any violation of the procedures described in the study protocol, for instance the rejection of the allocated treatment (allowing measurement of the outcome, however), the acquisition of additional treatment, or switching from one treatment (arm) to the other (contamination). Non-compliance may reduce the validity of a trial and, in an intention-to-treat analysis, may alter the intended treatment contrast. *Loss to follow-up* was defined as a failure to acquire outcome measurements irrespective of the refusal of treatment allocation. It is indicated by missing data on end points and, as a consequence, these patients cannot be included in the statistical analysis of outcome, unless a ((few) well chosen) value(s) for this measurement is imputed.²¹ A study's internal validity is reduced if the patients who are lost to follow-up are prognostically different from the patients who complete the study *and* the loss to follow-up rates differ between the treatment groups. We analyzed the differences in non-compliance rates and loss to follow-up rates between double-consent designs in which participants received full information on treatment alternatives (the complete-double-consent design), double-consent designs in which information on (the existence of) the alternatives was withheld (the incomplete-double-consent design), and the single-consent design. We expected that the complete-double-consent design, in particular, would be vulnerable to both of these threats to internal validity.

Statistical Analysis

Comparisons of proportions between groups were analyzed with the Kruskal-Wallis test or the Mann-Whitney U test. To test correlation the Spearman rank correlation coefficient was used. To test null hypotheses a significance level of 0.05 (two-sided) was used.

Results

The electronic searches yielded 630 papers and we obtained full papers of 114. Of these, 60 concerned trials in which a randomized consent design appeared to have been used, and 54 papers were discussion papers, and papers focusing on methodological or statistical issues. The reference lists of the latter revealed six additional trials. Thus, initially, 66 papers were included in the review. After a more detailed analysis, it appeared that eight trials had not used a randomized consent design and these were excluded. Thus, 58 papers, representing 50 trials, were formally data-extracted. Six trials were published by more than one paper and data-extraction was done on the most recent paper (Table 1).

Table 1. The results of the systematic search.

Stage	Action	No of citations selected
1	Search	630
2	Duplicates and other topics removed	114
3	Exclusion of non-randomized consent designs	66
4	Exclusion on basis of full text	58
5	Exclusion papers presenting the same study	50

Reasons for use

The *single*-consent design was used in 23 trials. Twenty-seven used the *double*-consent design (Table 2). Of the latter, two began as single-consent studies, but switched to a double-consent design. One trial started using double-consent, but switched to a conventional design in which consent is sought *before* randomization. In four of the 27 double-consent design trials, all participants were fully informed. In 23, information about the alternative treatment was withheld in the reference group.

In 29 of the 50 trials, the reason(s) for using a randomized consent design was/were given. The prevention of contamination as the main reason was cited 8 times in the 23 single-consent, and 8 times in the 27 double-consent designs. Eleven papers cited avoiding problems with randomization as the main reason (seven times in single-consent designs; four times in double-consent designs), including a simpler informed consent procedure, simpler participant recruitment, and avoiding unnecessary confusion and distress for patients, which were thought to be associated with the request for consent. In two of the 17 studies, where baseline data were collected through measurements necessitating personal contact with participants, a single consent design was nevertheless used for reason of avoiding contamination. In one psychiatric study it is unclear whether the participants were able to give consent.⁶³ Of the trials started before 1986, 48 percent mentioned approval by a research ethics committee. This number was 85 percent among trials started in 1986 or after. It is unclear why the other 15% of trials were published without mentioning such approval.

Table 2 see next page

Table 2. Study characteristics of 50 randomized single-consent and double consent

1 st author ^{ref} (country, year)	Year begun	Area of medicine	Disorder	Design	Main reason use design †
Moertel ²² (US, 1984)	1965	Oncology	Gastric carcinoma	Single	Cont
Fisher* ^{23, 24, 25} (US, 2002)	1976	Oncology	Breast cancer	Double	Cont
Fisher * ²⁶ (US, 1988)	1977	Oncology	Rectal cancer	Double	Rand
Wolmark * ²⁷ (US 1988)	1977	Oncology	Colon cancer	Double	-
Santen ,Wells ^{28, 29} (US, 1981, 1982)	< 1978	Oncology	Breast cancer	Double	-
Lange ³⁰ (US 1984)	1980	Oncology	Leukemia	Single	Cont
Andersson ³¹ (Denmark, 1999)	1980	Oncology	Breast cancer	Double	-
Mansour ³² (US 1989)	1981	Oncology	Breast cancer	Double- conventional	-
Hardcastle ³³ (UK, 1996)	1981	Oncology screening	Colorectal cancer	Single	-
Pearl O'Rourke ³⁴ (US, 1989)	1982	Pediatrics	Pulmonary hypertension	Single	Rand
Bartlett ³⁵ (US, 1985)	1982	Pediatrics	Respiratory failure	Single	Rand
Højris ^{36, 37, 38} (Denmark, 1999)	1982	Oncology	Breast cancer	Double	-
Balch ³⁹ (US, 2001)	1983	Oncology	1-4 mm Melanomas	Double	-
Blichert-Toft ^{40, 41} (Denmark, 1992)	1983	Oncology	Breast cancer	Single- double	Other

* studies with two index groups and one reference group.

† Cont: to avoid contamination; Rand: to avoid problems with randomization; Other : other reason.

‡ no information given in the reviewed paper.

§ R: data collected routinely or by means of a register; P: Data (also) collected by personal contact with participants.

designs in different areas of medicine.

Approved by ethics committee	Intervention	Reference	Baseline / effect registration §
- ‡	5-fluorouracil & radiation	Observation	R / R
-	Lumpectomy	Mastectomy	R / P
-	Lumpectomy & irradiation		
-	Chemotherapy	Observation	R / R
-	Radiation therapy		
-	Chemotherapy	Observation	R / R
-	BCG administration		
-	Aminogluthethimide & hydrocortisone	Surgical adrenalectomy	R / R
Yes	Trimethoprim-sulfa- methoxazole & nystatin	No prophylaxis	R / R
-	Chemotherapy (CAF & TAM)	Chemotherapy (CMF & TAM)	R / R
-	Chemotherapy	Observation	R / R
Yes	Faecal-occult-blood test	No intervention	R / R
Yes	Extracorporeal Membrane Oxygenation	Conventional medical therapy	R / R
Yes	Extracorporeal Membrane Oxygenation	Conventional therapy	R / R
Yes	Chemotherapy & radiotherapy	Chemotherapy	R / R
-	4 cm radial excision	2 cm radial excision	R / R
Yes	Breast preserving therapy	Mastectomy	R / R

Table 2. Continued.

1 st author ^{ref} (country, year)	Year begun	Area of medicine	Disorder	Design	Main reason use design †
Sell ⁴² (Denmark, 1991)	1983	Oncology	Bladder cancer	Single	-
Flint ⁴³ (UK, 1989)	1983	Midwifery	Low obstetric risk	Double	-
Ganz ⁴⁴ (US, 1988)	1984	Oncology	Lung cancer	Double	-
Hemminki ⁴⁵ (Finland, 1989)	1985	Public health	None (pregnancy)	Double	Rand
Kronborg ⁴⁶ (Denmark, 1996)	1985	Oncology screening	Colorectal cancer	Single	Cont
Riethmüller ⁴⁷ (Germany, 1994)	1985	Oncology	Colorectal carcinoma	Single	Cont
Korvick ⁴⁸ (UK, 1992)	1985	Internal medicine	Pseudomonas Aeruginosa	Single	Rand
Bryce ⁴⁹ (Australia, 1991)	1985	Obstetrics	Preterm birth	Single	Cont
Lambe ⁵⁰ (US, 1986)	-	Family practice	Smoking	Single	-
Hemminki ⁵¹ (Finland, 1990)	1987	Obstetrics	None (pregnancy)	Double	-
Cogan ⁵² (US, 1988)	-	Obstetrics	Prematurity	Double	-
Labrie ⁵³ (Canada, 1999)	1988	Oncology screening	Prostate cancer	Single	Cont
Gårdlund ⁵⁴ (Sweden, 1996)	1988	Internal medicine	Pulmonary embolism	Single	Rand

* studies with two index groups and one reference group.

† Cont: to avoid contamination; Rand: to avoid problems with randomization; Other : other reason.

‡ no information given in the reviewed paper.

§ R: data collected routinely or by means of a register; P: Data (also) collected by personal contact with participants.

Approved by ethics committee	Intervention	Reference	Baseline / effect registration §
Yes	Radical irradiation & salvage cystectomy	Preoperative irradiation & cystectomy	R / R
-	The 'Know your midwife' scheme	Standard hospital care	P / P
-	Chemotherapy	Supportive care	P / P
Yes	Iron supplementation	Usual care	P / P
Yes	Faecal-occult-blood test	Usual care	R / R
Yes	Monoclonal antibody	Observation	R / R
Yes	Rifampin	Combination antibiotic therapy	R / R
-	Social support	Normal care	R / R
-	Hypnotherapy	Written encouragement to quit smoking	P / P
Yes	Continuous human support	Standard care	R / P
Yes	One-to-one labor support	Standard obstetrical care	R / R
Yes	Prostate cancer screening	Current practice	- / R
Yes	Subcutaneous standard heparin	No prophylactic treatment	R / R

Table 2. Continued

1st author ref (country, year)	Year begun	Area of medicine	Disorder	Design	Main reason use design †
de Lorgeril ^{55, 56} (France, 1999)	1988	Cardiology	Myocardial infarction	Single	Cont
Hölmberg ⁵⁷ (Sweden, 2002)	1989	Oncology	Prostate cancer	Single- double	-
Brus ⁵⁸ (Netherlands, 1998)	-	Rheumatology	Rheumatoid arthritis	Double	Cont
Goy ^{59, 60} (Switzerland, 1999)	1989	Cardiology	Artery stenosis	Single	-
MacVicar ⁶¹ (UK, 1993)	1989	Obstetrics	None (pregnancy)	Single	Cont
Scholes ⁶² (US, 1996)	1990	Primary care, screening	Chlamydial infection	Single	Rand
Collins ⁶³ (UK, 1991)	-	Psychiatry	Chronic schizophrenia	Single	Rand
Cline ⁶⁴ (Sweden, 1998)	1991	Cardiology	Heart failure	Double	Cont
Cherkin ⁶⁵ (US, 1996)	1992	Primary care	Low back pain	Double	Cont
Dennis ⁶⁶ (UK, 1997)	1992	Public health	Stroke	Single	-
Auvinen ⁶⁷ (Finland, 2001)	1993	Urology	Prostate Cancer	Double	-
van der Sande ⁶⁸ (Netherlands, 1997)	1993	Psychiatry	Attempted suicide	Double	Rand
Torgerson ⁶⁹ (UK, 1997)	1993	Internal medi- cine screening	Osteoporosis	Single	Cont

* studies with two index groups and one reference group.

† Cont: to avoid contamination; Rand: to avoid problems with randomization; Other : other reason.

‡ no information given in the reviewed paper.

§ R: data collected routinely or by means of a register; P: Data (also) collected by personal contact with participants.

Approved by ethics committee	Intervention	Reference	Baseline / effect registration §
Yes	Mediterranean diet	Prudent diet	R / R
Yes	Radical prostatectomy	Watchful waiting	R / R
Yes	Education programme	Brochure about rheumatoid arthritis	P / P
Yes	Percutaneous trans-luminal coronary angioplasty	Coronary artery bypass grafting	R / R
Yes	Home from Home	Routine care	R / R
Yes	Chlamydia trachomatis test	Usual care	P / P
Yes	Lithium carbonate	Standard care	P / P
Yes	Education	Routine clinical practice	R / P
Yes	Educational interventions	Usual care	P / P
Yes	Stroke family care worker	Standard care	R / P
Yes	Active role patient in treatment choice	Usual Care	R / P
-	Psychosocial treatment	Care as usual	P / R
-	Osteoporosis screening	No screening	P / P

Table 2. Continued.

1 st author ^{ref} (country, year)	Year begun	Area of medicine	Disorder	Design	Main reason use design †
Lambert ⁷⁰ (UK, 1998)	1994	Rheumatology	Rheumatoid arthritis	Double	-
Vierhout ⁷¹ (Netherlands, 1995)	-	Orthopedics	Locomotor- system disorders	Double	Cont
Dey ⁷² (UK, 2002)	1995	Oncology	Breast lump	Double	Rand
Zhu ⁷³ (US, 2002)	1995	Public health	Smoking	Double	Cont
Hux ⁷⁴ (Canada, 1999)	1995	Primary care	None (prescrip- tion antibiotics)	Double	Cont
Hillsdon * ⁷⁵ (UK, 2002)	1996	Primary care	None	Single	Other
Rodgers ⁷⁶ (UK, 1999)	1997	Public health	Stroke	Double	-
Steiner ⁷⁷ (UK, 2001)	1997	Geriatrics	None (needs elderly people)	Single	Rand
Homer ⁷⁸ (Australia, 2001)	1997	Obstetrics	None (pregnancy)	Double	Cont
Pinto ⁷⁹ (Spain, 2002)	1999	Radiology	Uterine fibroids	Single	-

* studies with two index groups and one reference group.

† Cont: to avoid contamination; Rand: to avoid problems with randomization; Other : other reason.

‡ no information given in the reviewed paper.

§ R: data collected routinely or by means of a register; P: Data (also) collected by personal contact with participants.

Approved by ethics committee	Intervention	Reference	Baseline / effect registration §
Yes	Day care	Inpatient care	P / P
Yes	Joint consultation sessions	Usual care	P / P
Yes	One stop clinic	Dedicated breast clinic	P / P
-	Counseling sessions	Self-help materials	P / P
Yes	Confidentially profiles	No intervention	R / P
Yes	Brief negotiation Direct advice	No intervention	P / P
Yes	Stroke education program	Conventional stroke unit care	P / P
Yes	Nurse-led unit	Conventional care	R / P
Yes	Community-based care	Standard hospital-based care	R / R
Yes	Uterine artery embolization	Abdominal hysterectomy	R / R

Rates of non-compliance and loss to follow-up

Table 3 shows the rates of non-compliance and loss to follow-up for each study design. Table 4 summarizes table 3 by presenting the median rates and interquartile ranges (IQR). For the incomplete-double-consent design, the median rate of non-compliance and loss to follow up is about 15% in both study groups. In the reference groups of the trials using an incomplete-double-consent design, the rates of non-compliance and loss to follow-up were statistically significantly higher than in the trials that used the other two designs. To explore these differences, Figure 1 plots year of study commencement against the field of study (cancer, other diseases and behavior) for the three types of design. All four studies with a complete-double-consent design were cancer trials that were started before 1985. Figure 1 shows that, after 1990 the randomized consent design was no longer used in

cancer trials, whereas the use of the incomplete-double-consent design is restricted to the behavioral field.

As dissatisfaction with the allocated treatment leading to non-compliance and loss to follow-up is an important reason to use a randomized consent design, we plotted the difference of non-compliance and loss to follow-up between the index and reference group against the subject of study for the three types of design (Figures 2a and 2b). In 65% of the studies the non-compliance in the index group is larger than in the reference group. For the loss to follow-up this percentage is 32%. Furthermore there is no correlation between these differences and the year of study ($r=0.01$, and 0.03 , respectively).

Table 3. Rate of non-compliance and loss to follow-up in randomized single-consent and double-consent designs.

1 st author ^{ref} (country, year)	Design / conceal alternative †	Index group / reference group		Non-compliance		Loss to follow-up	
		no. / no.		Index group %	Reference group %	Index group %	Reference group %
Moertel ²² (US, 1984)	Single	39/ 23		23	4	0	0
Fisher* ^{23, 24, 25} (US, 2002)	Double/yes	719/ 731		9	14	12	17
		731/ 731		12	14	14	17
Fisher * ²⁶ (US, 1988)	Double/no	193/ 191		42	3	3	4
		190/ 191		16	3	3	4
Wolmark * ²⁷ (US 1988)	Double/no	379/ 394		5	3	6	3
		393/ 394		4	3	5	3
Santen, Wells ^{28, 29} (US, 1981, 1982)	Double/no	50/ 46		20	46	20	37
Lange ³⁰ (US 1984)	Single	30/ 37		17	3	17	5
Andersson ³¹ (Denmark, 1999)	Double/yes	209/ 206		23	13	23	13
Mansour ³² (US 1989)	Double-con- ventional/yes	273/ 263		19	23	28	20
Hardcastle ³³ (UK, 1996)	Single	76466/76384		41	0	41	2
Pearl O'Rourke ³⁴ (US, 1989)	Single	9/ 10		0	0	0	0

* studies with two experimental groups and one reference group.

† yes: participants are not informed about alternative treatment. no: participants are fully informed about alternative treatment.

‡ data cannot be calculated or traced.

Table 3. Continued.

1 st author ref (country, year)	Design / conceal alternative †	Index group / reference group		Non-compliance		Loss to follow-up	
		no. / no.		Index group %	Reference group %	Index group %	Reference group %
Bartlett ³⁵ (US, 1985)	Single	11/	1	0	0	0	0
Højris ^{36, 37, 38} (Denmark, 1999)	Double/yes	1610/	1639	5	7	4	6
Balch ³⁹ (US, 2001)	Double/yes	238/	230	‡	-	-	-
Blichert-Toft ^{40,41} (Denmark, 1992)	Single- double/yes	450/	455	17	14	4	6
Sell ⁴² (Denmark, 1991)	Single	95/	88	7	13	0	0
Flint ⁴³ (UK, 1989)	Double/yes	503/	498	9	0	3	4
Ganz ⁴⁴ (US, 1988)	Double/no	31/	32	19	19	29	19
Hemminki ⁴⁵ (Finland, 1989)	Double/yes	1358/	1336	6	5	-	14
Kronborg ⁴⁶ (Denmark, 1996)	Single	30967/	30966	33	0	0	0
Riethmüller ⁴⁷ (Germany, 1994)	Single	99/	90	14	0	9	16

* studies with two experimental groups and one reference group.

† yes: participants are not informed about alternative treatment. no: participants are fully informed about alternative treatment.

‡ data cannot be calculated or traced.

Table 3. Continued.

1 st author ^{ref} (country, year)	Design / conceal alternative †	Index group / reference group		Non-compliance		Loss to follow up	
		no. / no.		Index group %	Reference group %	Index group %	Reference group %
Korvick ⁴⁸ (UK, 1992)	Single	58 / 63		10	0	0	0
Bryce ⁴⁹ (Australia, 1991)	Single	983 / 987		9	0	0	0
Lambe ⁵⁰ (US, 1986)	Single	90 / 90		27	0	33	33
Hemminki ⁵¹ (Finland, 1990)	Double/yes	>122 / >118		‡	-	7	18
Cogan ⁵² (US, 1988)	Double/yes	20 / 14		5	0	35	21
Labrie ⁵³ (Canada, 1999)	Single	30956 / 15237		77	6	0	0
Gårdlund ⁵⁴ (Sweden, 1996)	Single	5776 / 5917		12	-	12	0
de Lorgeril ^{55, 56} (France, 1999)	Single	302 / 303		27	0	22	29
Holmberg ⁵⁷ (Sweden, 2002)	Single- double/yes	349 / 349		16	6	0	0
Brus ⁵⁸ (Netherlands, 1998)	Double/yes	32 / 33		9	6	22	9

* studies with two experimental groups and one reference group.

† yes: participants are not informed about alternative treatment. no: participants are fully informed about alternative treatment.

‡ data cannot be calculated or traced.

Table 3. Continued.

1 st author ^{ref} (country, year)	Design / conceal alternative †	Index group / reference group		Non-compliance		Loss to follow up	
		no. / no.	Index group %	Reference group %	Index group %	Reference group %	
Goy ^{59, 60} (Switzerland, 1999)	Single	68 / 66	0	8	0	0	
MacVicar ⁶¹ (UK, 1993)	Single	2304/1206	8	0	8	0	
Scholes ⁶² (US, 1996)	Single	1009/1598	36	0	‡	-	
Collins ⁶³ (UK, 1991)	Single	21/ 23	52	4	52	4	
Cline ⁶⁴ (Sweden, 1998)	Double/yes	96/ 110	17	0	42	28	
Cherkin ⁶⁵ (US, 1996)	Double/yes	262/ 129	26	25	28	28	
Dennis ⁶⁶ (UK, 1997)	Single	210/ 207	0	0	11	11	
Auvenin ⁶⁷ (Finland, 2001)	Double/yes	105/ 105	2	5	2	5	
van der Sande ⁶⁸ (Netherlands,1997)	Double/yes	140/ 134	18	48	0	0	
Torgerson ⁶⁹ (UK, 1997)	Single	799/ 800	29	0	23	24	
Lambert ⁷⁰ (UK, 1998)	Double/yes	59/ 59	19	3	14	14	

* studies with two experimental groups and one reference group.

† yes: participants are not informed about alternative treatment. no: participants are fully informed about alternative treatment.

‡ data cannot be calculated or traced.

Table 3. Continued.

1 st author ^{ref} (country, year)	Design / conceal alternative †	Index group / reference group		Non-compliance		Loss to follow up	
		no. / no.	Index group %	Reference group %	Index group %	Reference group %	
Vierhout ⁷¹ (Netherlands,1995)	Double/yes	169/ 164	15	22	15	22	
Dey ⁷² (UK, 2002)	Double/yes	351/ 344	24	39	41	56	
Zhu ⁷³ (US, 2002)	Double/yes	1973/ 1309	28	32	29	30	
Hux ⁷⁴ (Canada, 1999)	Double/yes	400/ 400	66	71	66	71	
Hillsdon * ⁷⁵ (UK, 2002)	Single	551/ 563 544/ 563	45 48	0 0	68 67	43 43	
Rodgers ⁷⁶ (UK, 1999)	Double/yes	121/ 83	58	0	26	23	
Steiner ⁷⁷ (UK, 2001)	Single	119/ 121	10	0	28	44	
Homer ⁷⁸ (Australia, 2001)	Double/yes	640/ 643	25	21	25	21	
Pinto ⁷⁹ (Spain, 2002)	Single	38/ 19	3	16	0	0	

* studies with two experimental groups and one reference group.

† yes: participants are not informed about alternative treatment. no: participants are fully informed about alternative treatment.

‡ data cannot be calculated or traced.

Table 4. The median rates and Inter Quartile Range (IQR) of non-compliance and loss to follow-up in the index and the reference group in the incomplete-double-consent design, the complete-double-consent design and the single-consent design.

	Median rate (IQR) of non-compliance (%)		Median rate (IQR) of loss to follow-up (%)	
	Index group	Reference group	Index group	Reference group
Incomplete-double-consent design ($n=23$)	17 (9-24)	14 (4-23)	15 (4-28)	17 (5-23)
Complete-double-consent design ($n=4$)*	18 (5-32)	3 (3-25)	5 (3-22)	4 (3-23)
Single-consent design ($n=23$)	15 (7-39)	0 (0- 4)	9 (0-28)	0 (0-24)
Test for difference (p-value)¶	0.99	<0.0001	0.32	0.04

* These four studies represent two studies with one index group and two studies with two index groups. Data analysis is based on six index groups.

¶ Kruskal-Wallis test

Figure 1. Year of study against the subject of study for the complete double-design, the incomplete-double-design, and the single-consent design (N=50).

Figure 2a. Difference in compliance (rate of non-compliance index group minus rate of non-compliance reference group) against the subject of study for the complete-double-design, the incomplete-double-design, and the single-consent design (N=50).

Figure 2b. Difference in loss to follow-up (rate of loss to follow-up index group minus rate of loss to follow-up reference group) against the subject of study for the complete-double-design, the incomplete-double-design, and the single-consent design (N=50).

Discussion

Our search strategy identified 50 studies that used a randomized single-consent or a double-consent design. Although we did our search systematically and painstakingly it cannot be excluded that we missed some trials.

In 1982 Zelen predicted that randomized consent designs would dominate the field of randomized clinical trials.³ However, the absolute number of published trials using these designs appears to be extremely low, which is more in accordance with the expectation of some other authors.^{5, 80, 81} Until the mid-Nineteen-Eighties, the randomized consent design was mainly used in oncology trials in the U.S. and in Scandinavia. Probably due to changing of federal guidelines that restricted the use of the randomized consent design^{8, 9} the double-consent became the choice of

preference. This double-consent approach is still permitted under federal US regulations today.⁵

Both forms of the double-consent design can be disputed. The incomplete informed consent procedure might be considered as unethical.⁸² Our review shows that research ethics committees approved at least 23 trials using a double-consent design. The complete-double-consent design, as used in four US cancer trials in the late-Seventies and early-Eighties, informs the participants in both treatment arms about all the study features. Compared to the traditional trial design, only the timing of information relative to the act of randomization differs. Therefore, one might expect the withdrawal rates to be similar, although possibly unbalanced between the study groups. Therefore, the conventional randomized design is methodologically preferable.

In 11 studies it was indicated that expected problems with the randomization procedure was the main reason for using the randomized consent design. However, the application of the randomized consent design should not have found support from research ethics committees if the main reason is to reduce the work of recruiting patients and decrease the burden for investigators as was reported in references 5, 20, and 82-84.

The differences in non-compliance rates between the complete-double-consent design and the other two designs may be attributed to the fact that the complete-double-consent designs were cancer trials with unattractive and burdening interventions^{26, 27-29, 44} and non-invasive reference interventions.^{26, 27, 44} The low loss to follow up rates in the complete-double-consent designs may be explained by data collection for effect measurements by means of a register, without personal contact with the patients.²⁶⁻²⁹

We have previously argued that if the experimental intervention is attractive and contamination is likely, a randomized consent design would reduce non-compliance and loss to follow-up in the reference group.^{19, 20, 85, 86} However, as Figures 2a and 2b show, in the majority of the studies the rates of non-compliance and loss to follow-up were greater in the index groups than in the reference groups. This might indicate that these studies did not fulfill our attractiveness and contamination requirements.

In his review of cancer trials, Altman et al. concluded that there are serious statistical arguments against the use of randomized consent designs, which should discourage their use.⁸⁰ Reticence about using a randomized consent designs was expressed also by Ellenberg.⁴ Given the experiences in some cancer trials using a randomized consent design, Ellenberg argued that, because of scientific concerns (contamination), and ethical concerns (incomplete information), the application of these designs should be considered a last-resort measure. We agree with Altman et al. and Ellenberg that these designs should not be used without compelling reason. However, situations requiring a randomized consent design do exist, for instance,

in case of a heroin-provision experiment¹⁹. Summing up, the number of trials in which a randomized consent design was used is very small; the complete-double-consent design has not been used since 1985; over years the subject of the studies changed from medical to behavioral interventions; and in 22% of the studies problems expected with the randomization procedure was reported as the main reason for using a randomized consent design. We think that for the majority of the studies reviewed here, the use of a randomized consent design was unjustified.

In our opinion, the use of randomized consent designs should be restricted to studies in which contamination is otherwise unavoidable. More importantly, the significance of the study question should be in balance with the infringement of the participant's rights¹⁵. Therefore, a research ethics committee should decide whether this balance is right in any particular study and the application of the randomized consent design justified.

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The Zelen design may be the best choice for a heroin-provision experiment

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Abstract

Recently, the Dutch Parliament agreed upon the conduct of a randomized clinical trial on the effects of heroin provision on general health, psychosocial and criminal behavior in long-term addicts. Previous studies failed to establish the effects beyond reasonable doubt. The main reasons why previous trials failed are massive dropout or non-compliance in the control group.

Designing a new heroin provision trial, we concluded that the Zelen design provides the best guarantee for obtaining valid study results. Compared with the traditional design, the Zelen design probably reduces non-compliance and dropout considerably, thus increasing validity. Depending on the study population, the Zelen design may reduce study precision. However, in a trial aimed at badly integrated addicts the Zelen design can be conducted without loss of precision because baseline measurements will only weakly correlate with effect measurements.

The arguments favoring the Zelen design may be generalized to trials in which the experimental treatment is highly attractive to the study participants. However, the use of the Zelen design precludes blinding of participants who receive the experimental treatment.

We argue that the conduct of studies that predictably tend to produce invalid results is ethically dubious. The ethical problem of studying participants without their consent can be solved by a slight modification of the Zelen design in which the sampling of a control group is postponed. Both the traditional and the Zelen design can imply ethical problems. Both designs can be ethically justifiable and should not be rejected on a priori grounds.

Introduction

In agreement with the advice of the Health Council, the Dutch Parliament agreed upon a medical experiment regarding the effects of heroin provision for long-term heroin addicts.^{1,2} The main hypothesis is: Provision of heroin, in addition to available standard treatment, decreases the harm caused by drug dependence. The outcome measures, in hierarchical order, will be general health, psychosocial and criminal behavior of long-term heroin addicts. Previous studies suffered particularly from high dropout and non-compliance rates in the control group³⁻⁵ or did not use a control group.⁶ Therefore, these studies have been insufficiently informative with regard to the effectiveness of heroin provision.

We set out to design an alternative study that would address this pragmatic question and would be less susceptible to dropout and non-compliance while retaining the usual experimental rigor. In the Netherlands, standard treatment for long-term drug addicts is delivered by health services and consists of methadone maintenance and social aid.

The traditional design versus the Zelen design

Previous trials³⁻⁵ were conducted as traditional randomized trials in which addicts' consent was obtained before randomization. Addicts who were randomized to a no-heroin provision control group had a clear reason to be disappointed, complied badly, dropped out in large numbers and, in this way, adversely affected the trials' validity. Thus, the challenge is to design a study in which disappointment leading to disruptive behavior is avoided. In a design that is known as the Zelen design, randomized consent design, or pre-randomization,^{7,8} eligible addicts are randomized, but only in the experimental group is informed consent obtained.

Many investigators reject the use of the Zelen design altogether,⁹ claiming that, in general, a number of the randomized participants will refuse the experimental treatment, possibly causing irreparable incomparability of the treatment groups as a result of this potentially selective dropout.^{10,11} Many ethicists reject the Zelen design because control subjects are studied without the latter's consent. We will argue that in a heroin provision experiment, the validity argument may not hold and may even be reversed. The ethical objections may be lessened, and probably reversed, by taking into account the validity argument and by analyzing the meaning of the term study participation in a design that differs from the traditional randomized trial.

Dropout and non-compliance

Potentially, the most serious threat to the comparability of treatment groups is dropout leading to incomplete data collection and missing data on effect

measurements. A study's internal validity is reduced if the addicts who drop out are prognostically different from the addicts who complete the study and the dropout rates differ between the treatment groups.

Non-compliance is another factor that may reduce a trial's validity. Addicts may either reject their allocated treatment or may take additional treatment with an impact on general health, psychosocial or criminal behavior. Both types of non-compliance will alter the treatment contrast in an intention-to-treat analysis.

Figure 1 Dropout in the traditional design and in the Zelen design.
Du = unconditional dropout from the trial;
De = dropout form experimental treatment;
Ds = dropout from standard treatment.

Figure 1 (*left*) shows a flow chart of the traditional design. For ease of notation we denote nonparticipation occurring before randomization as a type of dropout. Three types of dropout can be distinguished. First, there is unconditional dropout (Du): addicts who deny informed consent and refuse to participate altogether. Second, there is dropout under the standard treatment condition (Ds): addicts who, after randomization continue to receive normal care without heroin provision (the standard treatment condition), but refuse to participate in effect measurements and other activities that the study protocol may stipulate. Third, is dropout under the experimental treatment condition (De): addicts who reject the heroin provision. As Figure 1 (*right*) shows, in the Zelen design, dropout occurs in the experimental group only (Du and De), and, as critics correctly noted, only if

this dropout were strictly random would the validity of the trial be preserved. However, in a heroin-provision trial aimed at long-term addicts, the experimental treatment is so attractive that dropout will most likely be negligible and will not seriously affect the validity of the results. By contrast, in a heroin-provision trial using the traditional design, the fractions D_u and D_e will be small, but dropout in the standard treatment group (D_s) will very likely be substantial. After all, in the traditional design, as soon as the addicts allocated to the control group are informed about their allocation, they will be disappointed. The disappointment may lead to the following problems:

1. The addicts may change their behavior on phenomena that may be the focus of effect measurements (for example, psychosocial functioning). In fact, it is the informed consent procedure combined with (unfortunate) randomization that elicits the disappointment and which should be regarded as an intervention in itself.
2. The addicts may not be willing to participate in the effect measurements at all (D_s).
3. The addicts may become recalcitrant and punish the investigator by providing unreliable answers.
4. The addicts may demand heroin provision and a refusal by the investigational team may lead to annoying behavior at the health services or in adjacent neighborhoods.

The probability that these phenomena occur in the traditional design, after an informed-consent procedure, seems much higher than in the Zelen design.

Validity and precision

In the preceding section, we argued that the chances of obtaining valid results in a heroin-provision trial are probably higher with the use of the Zelen design than with the traditional design. However, the use of the Zelen design precludes taking nonstandard measurements in the control group at baseline. In this section, we qualitatively discuss the implications this has for the trial's precision. Note also that the points 1 and 2 in the preceding list are likely to reduce the trial's precision by introducing random error.

The precision depends on the relation between the size of the effect and the corresponding variance. Part of this variance can be eliminated by using the individual before-after differences in the statistical analysis instead of using the last measurement only. A reduction in the variation has the advantage that fewer participants are needed to render a given treatment difference statistically significant; that is, the trial will become more efficient statistically. So, omitting baseline measurements may influence the precision of the trial.

The choice between the traditional design and the Zelen design depends on weighing the loss of precision due to omitting baseline measurements (Zelen) against the loss of validity due to selective dropout and non-compliance in the control group (traditional). The research question confronting the Dutch Parliament concerns a spectrum of heroin users ranging from moderately societally integrated (as measured by, for instance, the Addiction Severity Index ¹²) to very poorly integrated addicts. If the trial focused on moderately integrated heroin users, we expect the effects on health and psychosocial behavior to be small. Furthermore, the correlation between baseline and end measurement may be high because of the addicts' relatively stable way of life. In this case, performing a baseline measurement may decrease the variance of the effect measurement and may be very useful. Furthermore, the likelihood of dropout and non-compliance is limited, resulting in a fair chance of valid results. Both aspects could favor the traditional design.

Figure 2. Study design for a randomized heroin-provision experiment.

By contrast, for badly integrated heroin users, the circumstances are much more unstable. We expect the correlation between baseline and end measurements to be low, whereas the effect on health and psychosocial behavior might be fairly large. Moreover, dropout and non-compliance due to the disappointment of allocation to the standard group will be a greater problem in these addicts compared to the

better integrated ones. Consequently, if the study population consists of the badly integrated heroin users, the Zelen design seems preferable. Until now, the Dutch Parliament has focused on the older addicts, with a long history of heroin abuse, who are in bad health and whose level of psychosocial functioning is low.

A heroin provision experiment in badly integrated addicts

The attractiveness of the intervention implies that many heroin addicts will volunteer for heroin provision. So, in the traditional design, the addicts in the control group will be frustrated after being refused the desired intervention. Theoretically, in the Zelen design there will be no frustration; however, in practice some addicts in the control group, being aware of the experiment, may demand participation in the provision group, which will then be denied. This may cause disappointment and some of the problems already described here. It should be much easier, however, to explain to disappointed addicts that only about 10% of all addicts were selected for the experiment than it will be to pacify the unfortunate control addicts who were confronted with a 50% expectation of heroin-provision as would occur in the informed-consent procedure of any traditional design using a fixed allocation ratio of 50%. Furthermore, if the population from which the experimental group is sampled is large compared with the size of the trial, not every addict in the (future) control group may be aware of the experiment. By contrast, in the traditional design, every addict in the control group is alerted by the informed-consent procedure.

To limit the disruption of the drug scene to a brief time interval, we propose to select potential addicts at one time using data routinely collected for health care evaluation purposes. As far as relevant, these data can also be used as baseline values (age, gender, duration and type of drug use, etc.). For the effect measurements concerning health and psychosocial behavior, a personal appointment with each addict is necessary. A design that minimizes dropout and non-compliance and maximizes the likelihood of a full comparison between the experimental group and the control group is presented in Figure 2.

In this design, addicts are randomized to three groups, and the study period is divided into two phases of 6 months each. In group A, the experimental group, informed consent is obtained. This group will receive heroin in addition to standard treatment during both phases. Group B is a control group in which informed consent will not be obtained until just before the end of phase 1, and in phase 1, these addicts receive standard treatment as usual. At the end of phase 1, the effects on health and psychosocial behavior in group A will be compared with those in group B. To obtain the necessary data for that comparison in group B, just before the end of phase 1 group B is offered heroin provision during phase 2. We assume that almost all addicts will give their consent because of the

attractiveness of receiving heroin. Group C is a control group for the effects on criminal behavior during phase 1 and phase 2. In this group, personal encounters with the addicts are not necessary for the effect measurement, and no informed consent will be asked. At the end of the follow-up period or shortly thereafter, the investigators will provide police and court authorities with the names of the addicts belonging to groups A, B, and C. The authorities will link these names to their files of criminal activities. Finally, the authorities will report back to the investigators only descriptive criminal statistics (means, standard deviations, etc.) on the group level (A, B and C) within the follow-up period. Because only a small percentage of the criminal activities are registered in police and justice records, control group C needs to be larger than the other groups. In addition, group C will be followed longer.

Phase 1 is the most important phase of the study, as a comparison of the effects on health and psychosocial behavior can be measured at the end of it. Phase 2 serves different purposes. First, the effects on criminal activities will be measured at the end of phase 2. Second, at the end of phase 2, it is possible to perform follow-up measurements regarding health and psychosocial behavior in groups A and B to determine the stability of the effects, if any. Finally, the results of the statistical analyses of phase 1, and policy decisions based on these results, can be available halfway through phase 2. So, a time-gap in the care for addicts who participated in the trial can be avoided.

Ethical considerations

In clinical medicine, both the Zelen design and the traditional design have been the subject of ethical scrutiny and controversy.⁹ In both designs the physician-patient relationship can be adversely affected because of the physician's preference for one of the treatments.¹³ However, in the traditional design, this relationship may be under even greater pressure because patients know that treatment allocation is purely a matter of chance.¹⁴ In addition, sometimes, complex information must be given about the treatment options and procedures. There are indications that patients cannot absorb all important information given in an informed-consent procedure.¹⁵ Thus, the objective of an informed-consent procedure is often imperfectly realized.¹⁶ In the Zelen design no consent is obtained in the control group, and some ethicists questioned to what extent data can be used without informing this group.¹⁷ However, as Zelen noted, this does not differ from the use of aggregated data routinely collected in registries at clinical departments and care facilities.¹⁸

In discussions with colleagues and ethicists we have noticed that the Zelen design may arouse strong emotions, sometimes to the extent that reflective thinking is replaced by reflexive denunciation and rejection. We hope that our

essay is convincing that there are strong validity arguments in favor of the Zelen design in a heroin provision trial. Note that methodological rigor and ethics are related issues. In this field of study, it can hardly be ethically justifiable to re-employ the previously used designs, which have been repeatedly shown to yield results that are probably invalid but at any rate unconvincing.³⁻⁶ We must balance the methodological advantages against the disadvantage that we cannot inform the control group about their apparent participation. It is tempting, however, to define "study participation" as "being subject to follow-up from the moment of randomization." Although this definition may apply in the traditional randomized trial, other study designs, whether experimental or nonexperimental, may actually use or require other definitions. Consider an example from nonexperimental epidemiological studies. Using a questionnaire, an investigator collects data on antihypertensive drug use in a group of people. After the data collection is over, the idea of a control group emerges. The investigator decides to use general population data with which to compare his or her data. Should we conclude that the general population participated in the study from the very start? What if a random sample from the general population was asked also to complete the investigator's questionnaire; from which point in time would this sample be participating in the study?

Returning to the heroin provision trial, Figure 3 shows the outline of an alternative study design in which, in several cities, all eligible heroin addicts (for example, badly integrated ones) in the care provider's files are identified. One could imagine that in some cities, far more eligible addicts are identified than needed for the trial. So, of all eligible addicts, a random sample will receive, after giving informed consent, heroin provision during phase 1. At the end of phase 1, a second random sample is taken from the group of eligible addicts who were not included in the first sample. All addicts in the second sample will be traced and asked for their consent to participate in phase 2, in which they will receive heroin provision after a baseline measurement. The baseline measurements in the second sample will be used for comparison with the measurements at the end of phase 1 in the first sample. We would argue that the second sample (control group) does not participate in the study until the moment they consent to baseline measurements and heroin provision. In fact, that there may be more eligible addicts available than needed is not crucial to the argument, but for some, this may enhance the idea of sampling only a fraction for inclusion in the trial. It struck us that some colleagues and ethicists rejected our plan for a heroin trial when we presented it as a Zelen design, whereas they judged the plan as elegant when we presented it as shown in Figure 3. This might imply that the chances of support and funding of projects that require a Zelen concept may increase if presented as we did here.

Figure 3. Alternative study design. *Broken line* denotes standard care.

Conclusion

We have focused on the use of the Zelen design in a heroin-provision experiment in badly integrated long-term addicts. However, we think that our design considerations have a wider applicability. In this final section, we describe these considerations more generally.

The Zelen design as an alternative for the traditional randomized design should be considered if: (a) the experimental intervention is highly attractive for all potential participants, and (b) the control group will receive standard treatment. If these conditions are met, the choice between the two designs depends on weighing the loss of validity due to selective dropout and non-compliance in the control group against the potential loss of precision due to not performing a baseline measurement. In most situations, exact numerical data on the correlation between baseline and end measurements will not be available. The use of the Zelen design precludes blinding of participants who receive the experimental treatment. Sometimes, the traditional as well as the Zelen design involve ethical problems. In our opinion, both designs are ethically justifiable and should not be rejected on a priori grounds.

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Members of research ethics committees accepted a modification of the randomized consent design

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Abstract

Objective The use of randomized consent designs has been subject of methodological and ethical controversy. In most Western countries, research ethics committees make the decision whether a randomized consent design can be applied. The purpose of the study is to assess to what extent a randomized consent design and a modification of this design is accepted by research ethics committees, in terms of ethics, health law and methodology.

Study design and setting A postal survey was conducted among members of research ethics committees in the United Kingdom, and in the Netherlands, with professional competence in ethics, (health) law, methodology or clinical practice.

Results In both the UK and in the Netherlands, the modified randomized consent design appears to be statistically significantly more acceptable than the randomized consent design, with respect to ethical and judicial aspects. The overall rejection rate of the randomized consent design was 66% in the UK and 59% in the Netherlands. However, the modified randomized consent design was rejected by 47% and 41% in the two countries, respectively.

Conclusion the modified randomized consent design appears to be more acceptable than the randomized consent design. To increase consistency in the way research ethics committees handle study protocols, a discussion about the use of randomized consent designs appears necessary.

Introduction

In 1977, Marvin Zelen proposed a randomized consent design in which eligible patients are randomized and informed consent is sought only in those who are assigned to the experimental group.¹ Normally consent is sought from all eligible patients before random treatment assignment. However, physicians often have difficulty to invite patients to participate in clinical trials because of anticipated problems with obtaining informed consent. In Zelen's randomized consent design this problem is avoided.^{1,2} A serious methodological drawback of this Zelen design is that withdrawal from the experimental group after the informed consent procedure may bias the estimate of the true treatment effect.³⁻⁵ In addition, many ethicists and health lawyers opposed the design arguing that the participants are randomized without prior consent, and that those in the reference group are not even aware of their involvement in a study.^{6,7} To meet this concern a variant of the randomized consent design was introduced in which informed consent is sought in both treatment arms after randomization.^{2,8-11}

Today the use of a randomized consent design is still controversial. For example, Zelen's consent design is not acceptable to the British Medical Research Council and current US federal guidelines also preclude its use.^{3,12} In recent years, a BMJ debate about informed consent that included ethical problems in using randomized consent designs, roused the emotions¹³⁻¹⁷ and authors have summarized the pros and cons of these designs.¹⁸⁻¹⁹ Also in the Netherlands, opinions differ strongly on the use of the Zelen or pre-randomization design.²⁰ Again, the most prominent counter-argument was that participants are not aware of their entry into a study or to be randomized. To refute this argument, a modified randomized consent design was proposed in which the reference group members are sampled at the end of the study period allowing them to enter the study after giving consent (see Figure 1b). In this way, the ethical objection that the reference group members were not aware of being included in a study should be met without losing the methodological advantage of the randomized consent design where attractive treatments are concerned²¹ (for more details see the method section).

The main purpose of the present study is to compare a randomized consent design to the proposed modification thereof with respect to their acceptability in terms of ethics, health law and methodology. In addition, we wanted to examine whether differences in acceptability exist between the United Kingdom and the Netherlands, which differ greatly with respect to their statutory regulations concerning medical experiments.

Methods

Context

In most Western countries, research ethics committees consisting of members with professional competence in ethics, health law, methodology, or clinical practice make the decision whether a randomized consent design can be applied. However, between countries, the statutory regulations vary widely. For example, in the Netherlands, the procedure of reviewing health related research proposals has been standardized in the Medical Research Involving Human Subjects Act (WMO).²² This act stipulates that any research ethics committee should include an ethicist, a (health) lawyer, a methodologist and a clinician. In the United Kingdom, there is no law comparable with the Dutch WMO and arrangements for reviewing the ethics of local and multi-center research are described in Health Service Guidelines of the National Health Service (NHS).^{23, 24} The central office for research ethics committees lays down rules for the composition of a research ethics committee.²⁵ A committee should contain a mixture of experts and lay members. The expert members should have expertise in methodology, ethics, clinical practice or in statistics relevant to research or pharmacy. At least one third of the members shall be laypersons.

Study design

In November 2000, we mailed questionnaires to 240 traceable local research ethics committees (LREC) and multicenter research ethics committees (MREC) in the United Kingdom, including the central office for research ethics committees (COREC). In the Netherlands, we mailed the questionnaires to the 77 registered medical ethics committees (local research ethics committees), and to the central medical ethics committee (CCMO). The questionnaire described a fictitious study on the provision of heroin to long-term heroin addicts, which met three preconditions for the proper use of a randomized consent design²¹, namely, 1) the experimental intervention cannot be blinded and is very attractive (in which situation full prior consent would evoke contamination, and differential non-compliance and dropout in the reference group); 2) no personal measurement(s) are necessary until informed consent is obtained; and finally, 3) the reference group receives standard treatment ('usual care'). A randomized consent design with informed consent for effect measurements in the reference group, indicated as randomized consent design (Figure 1a) and the modified version, indicated as modified randomized consent design (Figure 1b), were explained as feasible design options for this study.

Figure 1a. Randomized consent design

Figure 1b. Modified randomized consent design

In the randomized consent design, addicts are randomized to two groups. In the experimental group informed consent is sought after randomization. This group receive heroin in addition to standard treatment. The addicts in the reference group receive standard treatment. Therefore, at the end of the study the effects on health and psychosocial behavior in the experimental group would be compared with those in the reference group. At the end of the study, the reference group would be asked for their consent to participate in a subsequent study in which they will receive heroin in addition to standard treatment. We expected that almost all addicts would give their consent because of the attractiveness of receiving heroin. The baseline measurements for the subsequent study will be used as the effect measurement for the first study.

In the modified randomized consent design, all eligible heroin addicts in the care providers' files are identified. A random sample will receive, after having given informed consent, heroin in addition to standard treatment. At the end of the study period a second random sample is taken from the original group of the eligible addicts who were not included in the first sample. All addicts in the second sample will be extensively traced and asked for their consent to participate in a subsequent study in which they will receive heroin in addition to standard care.

The questionnaire consisted of questions about ethical, judicial and methodological acceptability of the randomized consent design and the modified randomized consent design on a three-point scale: acceptable, not acceptable, do not know. Furthermore, the participants were asked to indicate their preference for one of the designs from an ethical, judicial and methodological viewpoint and an opportunity was offered to give short comments. Through the secretary of the

research ethics committees, four members of each of the 240 ethics committees in the UK and the 78 ethics committees in the Netherlands with professional competence in ethics, (health) law, methodology or clinical practice, were asked to fill in the questionnaire. All the committees received a reminder after 6 to 8 weeks, including a second copy of the questionnaire. We presented our study protocol to the research ethics committee of the Maastricht University hospital, which concluded that no formal approval was required as it concerned a postal survey.

Statistical Analysis

Proportions between groups were compared with a Chi-square test and the comparison of proportions for paired data were made using McNemar's test. Equality of proportions was tested with a binomial distribution. To test null hypotheses a significance level of 0.05 (two-sided) was used.

Results

With four participants in each committee the maximum number of participants that could be achieved in the United Kingdom was 960. However, the questionnaires for 9 committees were undeliverable and were returned by post and 2 committees had merged, leaving 920 potential participants of which 337 (37%) responded. Of these, 11 responders did not cross off any of the questions, leaving 326 (35%) analyzable responses. In the Netherlands, the maximum number of participants was 312. However, 14 committees registered at the central medical ethics committee had not judged any study protocol in the year 2000 and we assume that these committees were not operational. Of the 256 potential participants, 136 (53%) responded. Here, three responders were excluded from the analysis because they completed only one or two answers, leaving 133 (52%) responders.

Table 1 presents the acceptability of the randomized consent design and the modified randomized consent design to responders in the United Kingdom and in the Netherlands with respect to the ethical, judicial and methodological aspects. In the UK and in the Netherlands the modified randomized consent design appeared to be statistically significantly more acceptable than the randomized consent design, with respect to ethical and judicial aspects. In the UK, the methodological acceptability of the randomized consent design is statistically significantly greater than the acceptability of the modified version.

Table 1. Ethical, judicial and methodological acceptability and overall rejection of the randomized consent design and a modified randomized consent design among 459 members of British and Dutch research ethics committees.

	Randomized consent design N (%)	Modified randomized consent design N (%)	P-value of the difference*
<i>United Kingdom (N=326)</i>			
Ethical acceptability	111 (34) †	189 (58)	P<0.0001
Judicial acceptability	86 (26)	115 (35)	P<0.0001
Methodological acceptability	165 (51)	138 (42)	P=0.006
<i>The Netherlands (N=133)</i>			
Ethical acceptability	61 (46)	82 (62)	P<0.0001
Judicial acceptability	45 (34)	69 (52)	P<0.0001
Methodological acceptability	56 (42)	47 (35)	P=0.10
<i>Overall rejection ‡</i>			
United Kingdom (N=326)	216 (66)	152 (47)	P<0.0001
The Netherlands (N=133)	78 (59)	55 (41)	P=0.001

* McNemar's test.

† As both designs could be acceptable with respect to one of the aspects, the sum could exceed the total number of responders.

‡ The overall rejection is determined if a responder rejected the design with respect to at least one of the three aspects (ethical, judicial, methodological).

To determine an overall rejection rate, we assumed that the research protocol under a committee's review would be rejected if a responder rejected the design with respect to at least one of the three aspects. For both designs, the overall rejection is higher in the UK than in the Netherlands, but the differences are not statistically significant.

Table 2 presents the preferences for the randomized consent design or the modified consent design in responders who accepted both designs with respect to the ethical, judicial and methodological aspects. The preference of the modified design is higher than that of the randomized consent design, but not to a statistically significant degree.

Table 2. Distribution of preferences for the randomized consent design or a modified randomized consent design among members of British and Dutch ethics committees who deemed both designs acceptable.

	Both designs acceptable	Preference randomized consent design N(%)	Preference modified randomized consent design N (%)	p-value of the difference*
<i>United Kingdom (N=326)</i>				
Ethical	90	33 (37)	22 (24)	P=0.18
Judicial	74	15 (20)	20 (27)	P=0.50
Methodological	107	45 (42)	28 (26)	P=0.06
<i>The Netherlands (N=133)</i>				
Ethical	58	14 (24)	27 (47)	P=0.06
Judicial	42	11 (26)	17 (40)	P=0.34
Methodological	39	12 (31)	17 (44)	P=0.46

* Equality of numbers was tested with a binomial distribution.

In table 3 remarks are summarized of 154 (47%) British and 71 (53%) Dutch responders, who used the opportunity in the questionnaire to give comments.

Table 3. Summary of comments of 154 (47%) British and 64 (48%) Dutch responders.

Remarks *
- The information to make an informed judgment, (especially for real assessment of ethical aspects) is insufficient (12, 4).
- Irrespective of the design, the control group receiving standard care has the right to know and consent to their participation in research (39, 13).
- In the randomized single consent design the control group receiving standard care has the right to know and consent to their participation in research (24, 4).
- Both designs appear to contravene the General Medical Council Guidelines or the WMO (3, 4).
- The randomized single consent design appears to contravene the General Medical Council Guidelines or the WMO (3, 2).
- Provision of heroin in the intervention group is an inducement to the informed consent and therefore not correct (10, 6).
- Provision of heroin to the controls after the study could be perceived as a reward for having unknowingly given up their right to be informed (4, 5).
- It is unethical to provide a (dangerous) drug like heroin in a trial (13, 1).
- The effect measurement is not reliable because participants are under the influence of the narcotic drug (3, 0).
- In the modified randomized consent design there will be problems with tracing the eligible patients in the control group after the study to participate in the subsequent study (8, 3).
- The results of the study will be biased because in the modified consent design study groups are selected differently, informed consent is required at different times (18, 11).
- Researcher has access to confidential information without consent of the study participants (11, 1).
- There is no difference between the two designs and they are equal in terms of ethics, law and methodology. (12, 10).

* The numbers of British and Dutch responders that made that specific remark, respectively, are indicated in parentheses.

Discussion

The overall rejection rate of the randomized consent design by members of research ethics committees was 66% in the UK and 59% in the Netherlands. The modified randomized consent design was rejected with 47% and 41%, respectively. This suggests that the modified version of the design is more acceptable than the randomized consent design. In particular, the modified randomized consent design appears to be more acceptable than the randomized consent design with respect to ethical and judicial aspects. In both countries, the differences between the acceptability of the designs are highly statistically significant.

Our study has several limitations. The response rates were low (37% and 53% in the UK and the Netherlands, respectively). In a comparable UK postal study the response rate was 51% and this is consistent with many postal surveys.²⁶ In another UK postal study the authors could not calculate the response rate because of the variation in the number of local research ethics committees during one year.²⁷ In our study, we did not find one obvious explanation for the low response rate. Some responders complained that the central office for research ethics committees had not formally approved the study. Furthermore, in the UK, the composition of committees is not regulated by law and therefore it is not clear whether all four competencies were present. Unfamiliarity with the randomized consent design and the description of the fictitious study that may have been too condensed may have caused non-response. Finally, as indicated by several responders' remarks, our example of a very attractive intervention, i.e. the provision of heroin, might have triggered negative emotion and may have precluded members of committees to participate. Nevertheless, the results of our study are an indication of how a substantial proportion of participants judges about the acceptability of the presented study designs.

As far as we know, this is the first study on the acceptability of specific designs or study protocols among research ethics committee members. Therefore, we have no reference for our findings. Although a lot of comments (see table 3) concerned the provision of heroin as an unacceptable intervention, we will not discuss this item, as the study protocol was only a vehicle to demonstrate the use of the randomized consent design.

We think that the patients in the reference group would undergo the same procedures in the randomized consent design as in the modified consent design. This is also indicated by some of the responders in their remarks. So, if there are ethical or judicial objections because of infringement on the rights of the participating patients, they hold for the randomized consent design as well as for the modified design. Furthermore, regardless whether the randomized consent design or the modified version is used, the interpretation of the results would be identical. From this we concluded that there is no essential difference between the two designs with respect to ethical, judicial or methodological aspects. The

difference is only on paper. Consequently, in our opinion, both designs should be equally acceptable. However, in this study a statistically significantly higher proportion of responders rejected the randomized consent design than did the modified randomized consent design. The increased acceptability of the modified design is also shown in the comparisons of the acceptability on ethical and judicial grounds. This suggests that ethical and judicial arguments play an important part in the decision whether to accept the randomized consent design or the modified randomized consent design. Anyway, the results of our survey show various points of view with respect to the acceptability of the randomized consent design or the modified version.

To increase consistency in the way research ethics committees handle study protocols, an open discussion about the pros and cons of the use of randomized consent designs is important. Our survey may be instrumental in achieving such discussion leading to consensus, for instance by means of a Delphi consensus technique²⁸ or to reach another form of understanding, in compliance with the ethical principles of the Declaration of Helsinki.²⁹ This would be very important since, apart from ethical acceptability per se, it would not be a satisfactory situation if investigators would formulate essentially similar study designs in a different way for the mere purpose of making a better chance for ethical approval.

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Indications and requirements for the use of pre-randomization

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Abstract

Background Although in effectiveness studies the conventional randomized trial, in which informed consent is obtained in all participants before randomization, is the first choice, this design is not the panacea for all research questions. To counter contamination problems pre-randomization designs might be an alternative. Pre-randomization implies that the randomization takes place prior to seeking informed consent and consequently pre-randomization designs are controversial among ethicists, health lawyers, methodologists, and clinicians. The reticence to use these designs is undeserved, provided that the proper requirements and indications will be applied.

Objective Guidelines for the optimal application of pre-randomization designs are presented. For this purpose, designs in which pre-randomization is used are outlined, methodological considerations to choose between conventional designs or pre-randomization designs are described, and relevant ethical and judicial aspects are discussed.

Conclusion In specific situations, based on well-defined indications and requirements, pre-randomization designs have an essential contribution to achieve evidence-based medicine. Banning pre-randomization a priori implies that effectiveness of many public health and medical interventions cannot be studied. Therefore, every design should be based on a balance between maximizing the potential for patient autonomy and minimizing the bias caused by contamination. Although general rules are important, an independent group of experts, like members of research ethics committees should decide whether this balance is acceptable.

Introduction

Nowadays, evidence-based medicine is widely propagated as the reference for good clinical practice. This development involves a critical appraisal of a widening range of public health or clinical interventions. As a consequence, the need for patient related research is growing as is demonstrated by the increasing number of scientific publications. In effectiveness studies the conventional randomized trial will always be the design of first choice. However, the conventional design in which informed consent is obtained in all participants before randomization, is not the panacea for all research questions because information in the reference group about the experimental intervention could lead to serious protocol violations. Therefore, in the last two decades several investigators applied pre-randomization to counter this contamination problem, questioning the absolutism of the conventional design.¹⁻³ The term *pre-randomization* implies that the randomization takes place prior to seeking informed consent.

Because of this deviant informed consent procedure the position on pre-randomization of medical ethicists, health lawyers, methodologists, and clinicians remains to be controversial and varies from total unacceptability to acceptance under specific conditions.⁴⁻¹¹ Unsurprisingly, there is controversy both between and within Research Ethics Committees (REC) about when, or even whether, these designs are admissible.¹²

Pre-randomization is also applied in apparently less controversial designs in which clusters, like primary care practices or schools, rather than individuals are randomized and obtaining informed consent from the participants after randomizing the clusters is inevitable. Another situation in which pre-randomization is used is in patients who are unable to give informed consent because of a reversible process of disease, like comatose or psychiatric patients who may be able to give consent after a period of convalescence.^{13, 14} Whether the latter is justified and in which circumstances a temporary proxy consent may be used, is a complex issue and the ethical and judicial ramifications are discussed elsewhere.¹⁵⁻¹⁸ This type of application of the pre-randomization design is beyond the scope of this article.

In this article we derive general guidelines for the optimal application of pre-randomization designs. Prior to this, different types of pre-randomization are outlined and an overview of methodological differences between conventional designs and pre-randomization designs is given. In the last section, ethical and judicial considerations concerning trials and informed consent are described.

Pre-randomization designs

In 1977, Marvin Zelen introduced the randomized single-consent design.^{19, 20} The key characteristic of this design is that patients are randomized *before* informed

consent is sought. The patients allocated to the experimental treatment group are approached by the investigator or clinician for informed consent. However, the patients randomized to the reference group are given the (best) standard treatment but are not approached for informed consent. The reason to introduce this design was to avoid problems associated with persuading clinicians to enter patients into clinical cancer trials.^{20, 21} To overcome ethical concerns, the randomized *double-consent* design as counterpart of Zelen's *single-consent* design was introduced.²⁰⁻²⁴ In this design, patients are initially offered the treatment to which they were randomized, but informed consent is sought in all patients, irrespective of treatment arm. Usually, a version of the double-consent design is used in which participants in the reference group are informed about their own treatment only and information about the alternative treatment is withheld. Seldom, patients in both treatment groups are fully informed about all major aspects of the trial.¹²

Box 1. Definitions of key concepts used in this paper

Pre-randomization design: study design in which randomization precedes the seeking of informed consent (synonyms: Zelen design, randomized consent design).

Individual randomization design: study design in which each participant is randomly assigned to a treatment group. The number of random assignments equals the number of participants.

Cluster randomization design: study design in which the unit of random assignment is a group or a social unit. The number of random assignments is smaller than the number of participants. Examples of clusters are counties, postal code areas, hospitals, or primary care practices.

*Single-consent design**: pre-randomization design in which informed consent is sought in the experimental group only, mentioning the use of a reference group (Zelen's proposal of 1977).

*Incomplete-double consent design**: pre-randomization design in which informed consent is sought in the experimental group, mentioning the use of a reference group and in the reference group, not mentioning the use of the experimental group.

*Complete-double consent design**: pre-randomization design in which informed consent is sought in the index group and in the reference group, mentioning the use of the other comparison group.

*Single-delayed consent design**: a single-consent design in which the participants in the reference group are sought for informed consent at the end of the study (if required for an end measurement with a personal contact).

* Although it is possible not to mention the use of a reference group in the experimental group or even inform the participants in the experimental and reference group only at the end of the study. As these variants are rarely needed, no distinct definitions are added.

Cluster randomized trials are becoming increasingly important in health care research, public health research, and general practice research.^{1, 25, 26} In cluster randomized trials clusters of people, or intact social units, rather than individuals

are randomized to an experimental or reference group and outcomes are measured on individuals within these clusters.²⁷ Cluster randomized trials use pre-randomization which means that clusters are randomized before cluster members are approached for informed consent.^{28, 29} The decision about the participation of a particular cluster in the trial is sometimes taken before randomization, by a person who is assumed to represent the participants,³⁰ and participants may consent individually to the treatment offered within their cluster after randomization.^{30, 31} Box 1 shows the definitions of key concepts that we use in this paper.

Methodological issues for conventional designs and pre-randomization designs

General issues

Clinical trials should provide information about the relative magnitude of effect(s) of an experimental intervention on (disease) outcome as compared to some reference intervention(s) or policies. This information is ultimately obtained by comparing the outcomes of interest between the study groups. The difference thus calculated may be explainable by different mechanisms. First, it could be the result of the experimental intervention. Second, it could be the result of bias. Briefly, bias may result from differences in the (joint) distributions of prognostic indicators between the two study groups at baseline, differences in the frequency with which effective co-interventions were applied during the study period, and differences in the way the outcomes were measured. Finally, chance may always explain the findings, however unlikely given a small *p*-value or another statistical measure of the precision of the estimate. Thus, the internal validity (scientific quality) of any study is inversely associated with the number of ways the findings can be interpreted. Ideally, a study allows only one interpretation, namely, that the experimental intervention explains the differences found. An appropriate study design is a prerequisite to achieve this goal.

The two most important maneuvers used in clinical trials are randomization and (different forms of) blinding. Randomization is intended to make the study groups prognostically comparable at baseline. Blinding aims to keep participants, caregivers, and/or those who measure outcomes unaware of treatment allocation. This is important when it can be expected that knowledge about the intervention or even the fact that randomization occurred, may change behavior of participants, caregivers, and/or may influence those who measure outcomes in a way that will disturb the comparability of the study groups.

In general, the most important types of protocol violations that seriously can endanger the internal validity of a study are dropout and non-compliance. We define a dropout as a randomized participant whose outcome measurement is not obtained and, as a consequence, cannot be included in the analysis of outcome, or

a ((few) well chosen) value(s) for this measurement is substituted or imputed. When the average outcomes of the dropouts differ between the treatment groups the validity of the results is violated. We define a non-complier as a participant who deviates from the protocol with respect to his/her allocated treatment by refusing the allocated treatment altogether, taking the allocated treatment in a way that negatively affects its effect, or by taking alternative and effective treatment. Non-compliance influences the contrast between the study groups, and, even in an intention-to-treat analysis, causes biased results. Most of the time, non-compliance dilutes the intended contrast and will thus cause underestimation of the true treatment effect(s). Furthermore, as non-compliance can, in principle, be measured and sometimes adjusted for, it generally seems a somewhat less serious threat to internal validity than dropout.

Protocol violations in conventional designs and pre-randomization designs

Especially participants who are dissatisfied with their treatment allocation may decide to withdraw or stop their full participation (dropout) thereby possibly causing irreparable selection bias. Dissatisfaction may also lead to non-compliance because participants seek other treatments, which, if effective, may cause between-group incomparability at the level of co-interventions, which is difficult to deal with data-analytically. Finally, dissatisfaction may have a negative attitude to the outcome measurement(s) and may lead to incomparability that cannot be adjusted for. One solution for this problem is blinding and the need for blinding is determined by the extent to which the aforementioned mechanisms render the study's findings open to more than one interpretation.

One way of blinding participants is the use of a convincing placebo or sham procedure. However, with some interventions the use of a placebo or sham procedures is infeasible since they would have to mimic peculiar (physiological) effects that are inseparable from the effect of the experimental treatment. Think, for example, of a trial on heroin provision, an attractive intervention, in which using a placebo is impossible. In this case pre-randomization could be an alternative to maintain the internal validity of such a study.

The influence of the use of pre-randomization on a study's internal validity as compared with the conventional design is elaborated by means of Figure 1. This Figure shows the occurrence of the different types of protocol violations and non-participation for the conventional design and the single-consent design (Zelen's original proposal). Non-participation in the trial and/or protocol violations may occur due to factors related to the experimental treatment, the reference treatment, or due to factors unrelated to the treatments. These are factors related to the burden of the effect measurements, or to the randomization procedure, or factors based on random processes like emigration et cetera. These factors are explained in the legend to Figure 1.

Figure 1. Factors causing protocol violations and non-participation in a conventional design (left panel) and in a single-(delayed) consent design (right panel) as defined in Box 1.

Legend to Figure 1.

Factors causing non-participation and/or protocol violations in a trial

E: Factors related to the experimental treatment include inconveniences due to complications, side effects and extra efforts associated with the experimental treatment. The (eligible) participant may anticipate (any of) these inconveniences (dangers) and refuse co-operation at the patient recruitment procedure (**E1**) or experience (any of these) effects during the trial and decide to become a non-complier and/or drop out completely (**E2**).

In case of an attractive experimental treatment E1 and E2 will be negligible small in a single-consent design and will not bias the results.

R: Factors related to the reference treatment include the expected attractiveness of the alternative, that is, the experimental treatment. The eligible participant might refuse co-operation at the patient recruitment procedure (**R1**) or, in the case of a conventional design, take a chance on a desirable outcome of the randomization procedure but withdraw if s/he is allocated to the reference group (**R2**).

In case of an attractive experimental treatment, the protocol violations of group R2 could considerably bias the results of a conventional design.

M: Factors related to the burden of the effect measurements during and at the end of the study. This also can be anticipated at the including procedure (**M1**) or during the trial (**M2**). These factors will be balanced between the treatment groups.

P: Factors related to the randomization procedure, for example because of a general aversion to lotteries.

X: Random processes causing withdrawal such as emigration, traffic accidents, family affairs et cetera.
These factors will be balanced between the treatment groups.

In the pre-randomization design (Figure 1, *right panel*), all eligible participants are randomized and thus included in the study. In the conventional design (Figure 1, *left panel*), potential participants get the opportunity to refuse participation prior to randomization. In contrast to the protocol violations related to the treatments, those protocol violations caused by the burden of the effect measurements or random processes will be balanced between the treatment groups in both designs. In the case of an attractive experimental treatment, contamination in the reference group could lead to search for an alternative treatment, and/or refusing cooperation, or withdrawal and in this way considerably bias the results of a conventional design. In the pre-randomization design we expect that this contamination is avoided and consequently protocol violations will be negligible. In this design, the effect measurement in the reference treatment group could lead to contamination if an individual approach is necessary. Individual measurements at the start or during the trial would reveal the purpose of the study and cause protocol violations. One way to overcome this problem is to obscure the purpose of the trial but that would be ethically and judicially questionable. If no individual *baseline* measurements are necessary, another approach would be to find a way to persuade the participant to comply with the outcome measurements at the end of the study. In this case the informed consent procedure in the reference group is delayed (single-delayed consent design, see Box 1).

Thus, methodologically the pre-randomization design seems preferable when an attractive experimental treatment is involved, the reference is the standard treatment, the use of a sham procedure or placebo cannot be used, and possible contamination caused by outcome measurements may be prevented.

This also applies for trials in which the information given during the informed consent procedure could be (a part of) the intervention, like for instance a health promotion trial. The knowledge or awareness of this intervention would also have the (intended) trial effect in the reference group and could influence the behavior of the participants in the reference group. For instance, investigating the effect of education about healthy food, is only possible if the reference group is not alerted. In a screening trial on breast self examination to early detect breast cancer, individual randomization and informed consent in all participants would alert the

participants in the reference group. As a consequence a part of these participants would perform breast self-examination or search for alternatives like a referral to the radiologist and in this way affect the contrast between the study groups.

Knowledge about the experimental intervention could have (partly) the same effect as intended in the experimental group. If the intervention consists of giving information with a negligible burden for the participants, for instance additional information about dietetics in a standard health education program for students, a design in which incomplete informed consent (see Box 1), or even no informed consent is obtained in all participants might be methodologically attractive.

Guidelines for the use of pre-randomization designs

The diagrams shown in Figure 2 can support making an optimal choice between the different types of pre-randomization designs. A prime issue in selecting a study design is the level of the intervention. If each participant is randomly assigned to a treatment group, an individual randomization scheme may be used. If the intervention is only feasible at an aggregated or clustered level, such as school classes, hospitals or primary care practices, the unit of random assignment is a cluster. Depending on the level of the intervention, a diagram offers guidance.

Furthermore, if in Figure 2 serious protocol violations are anticipated, but cannot be avoided, consider not conducting the study.

Ethical and judicial considerations

In a clinical trial there is a balance between individual and collective ethics.^{32, 33} 'Individual ethics' implies that each patient should receive that treatment which is thought to be most beneficial for his condition. This is the clear aim of good clinical practice in which the patient and his clinician decide together on the best course of action. Usually, the clinician proposes the therapy on the basis of his knowledge and experience, with appropriate acknowledgement of the patient's wishes.

'Collective ethics' is concerned with societal benefit. By achieving medical progress as efficiently as possible, future patients may benefit from superior therapy. Exclusive adherence to collective ethics is unacceptable as it implies that clinical trials can be conducted while ignoring the needs of the participants and solely complying with scientific and statistical principles. Some authors instinctively pay exclusive attention to individual ethics. Adoption of this attitude implied that properly designed clinical trials could not be performed. We would thereby lose our best tool to tell effective and ineffective medical treatment apart. In randomized double-blind trials patients should be unaware of the treatment allocation. A commitment to individual ethics only, would appear contradictory to any use of randomization, blinding and placebos.

Figure 2. Diagrams for the use of pre-randomization designs.

Legend to Figure 2.

Node A: If serious protocol violations (see Figure 1) are anticipated in the reference group that may be avoided by blinding the participants in this group, go to **B**. If blinding is not necessary, use the conventional design.

Node B: Can using a placebo in the reference group prevent protocol violations? If not, a pre-randomization design might be a solution for the blinding problem, go to **C**. Otherwise use a conventional placebo controlled design.

Node C: Is a cluster assignment a solution for blinding the participants for the alternative treatment? If not, go to **D1**. If so, go to **D2**.

Node D & D1 & D2: If a baseline measurement is required and this information cannot be obtained by a register or data collected routinely, a personal contact with the participant is necessary. In this case the participants in the reference group have to be informed about the reason for this measurement without alerting these participants with the knowledge about the experimental treatment: i.e. the incomplete double consent design.

The most widely accepted ethical code for medical research is the Declaration of Helsinki.³⁴ In addition, in most countries legislation and/or guidelines are promulgated for the application of informed consent procedures in clinical trials.³⁵⁻³⁷ Many lawyers interpret these guidelines as prohibiting research with individuals if informed consent or consent by proxy is not or not fully sought. Others accept not obtaining informed consent in very specific cases as conceivable or at least as not explicitly excluded by law.

To protect the individual autonomy an eligible person at trial inclusion should be enabled to weigh the likely pros and cons of participation and infringement of his private interest against potential benefits for society. However, the goal of informed consent is often imperfectly realized as sometimes complex information must be given about the treatment options.^{38, 39} The informed consent procedure has been the subject of ethical and judicial debates.^{8, 40-44} Special attention is given to circumstances in which informed consent is not obtained.¹⁵⁻¹⁸ First, the eligible person may be unable to give consent in case of minority or in case of specific neurological or psychiatric disorders. Another circumstance occurs in cluster randomization trials in which an informed consent procedure at the level of those who undergo the intervention would require a great deal of disproportional, logistical effort and the intervention does not infringe on someone's private interest. A third condition appears when a regular informed consent procedure would endanger the trial's internal validity (as described in the previous section). In pre-randomization designs one may distinguish between different informed consent procedures ranging from no information to full information (see Box 1). Which of these options should be considered in a study protocol should be determined by weighing methodological requirements against the ethical principle of an individual's autonomy and being completely informed in advance.

If a baseline measurement is not required, also a single consent design, in which the participants in the reference group are not informed, could be an option. If a measurement with personal contact at the end of the study is necessary, inform the participants in the reference group and ask their consent at the end of the study: i.e. the single-delayed consent design. If the experimental intervention involves only a minimal burden for the participants a design without informed consent could be an option.

Conclusion

In general, the usefulness of pre-randomization in study designs is undervalued. However, based on well-defined indications and requirements, pre-randomization designs may be essential to evidence-based medicine. Banning pre-randomization *a priori* implies that information about the effectiveness of important public health and medical interventions will not be forthcoming. A number of effective interventions will not be introduced because of the lack of evidence. Furthermore, the use of established, (possibly) ineffective interventions will be continued without evidence of net benefit.

In our opinion, every design should be based on a balance between maximizing the potential for patient autonomy and minimizing the bias caused by contamination. The combination of varieties of research questions and contexts, in which a study has to be conducted, necessitates a tailor-made design. In every

design proposal the investigator searches for a balance between optimal methodology, using for instance our guidelines as proposed in this article, and his/her personal assessment of ethical implications. As this balance cannot be fully reached by formulating general rules, the final decision whether this balance is acceptable, should be made by independent group of experts, like members of a research ethics committee.

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General discussion

Introduction

This chapter discusses the findings of the study and focuses on general aspects. Specific points of interest have been dealt with in the discussion sections of the respective chapters.

Implications for research: methodological guidelines for ethical research

Clearly, evidence-based medicine is the reference for good clinical practice, health care, and public health. Patient related and public health effectiveness studies serve this purpose and by far the majority of these studies use a conventional randomized study design. However, the conventional design is not the panacea for all research questions and investigators become aware that pre-randomization could be an alternative under strict conditions.

In general, pre-randomization is justified if the following conditions are met¹: the study has a clinically relevant objective; it is likely that the study will lead to important new insights; a valid evaluation of the effects is impossible using a conventional randomized design; the informed consent procedure bears no potential harm to participants; at least usual care is offered to participants in the reference group; and the approval of an independent research ethics committee.

The findings of our study show that, methodologically, pre-randomization is useful when an attractive or preferable experimental treatment is involved, the reference is the standard treatment, the use of a sham procedure or placebo cannot be used, and using pre-randomization can minimize bias caused by contamination. Besides, in case of a single-consent design the choice depends on weighing the loss of validity due to selective dropout and non-compliance in the reference group against the potential loss of precision due to not performing a baseline measurement.

In particular, the starting point for conducting a trial is to obtain an optimal comparison of the outcomes of interest between the study groups. For this purpose, regardless of the study objective, the investigator must assess the likelihood that contamination will spoil the experimental contrast. Randomization and different forms of blinding are important in clinical trials to achieve internal validity, but these maneuvers must not be used as 'standard rituals'.^{2, 3} Methodological guidelines, as presented in chapter 6, may lead the investigator to an appropriate study design, in addition to which the protection of the autonomy of participants and causing no harm or burden to them is the ethical guide.

An interesting viewpoint on blinding study participants is described by Rothman and Michels.^{4, 5} In the spirit of the most recent (Fifth) Declaration of Helsinki they contended that the use of placebo controls in clinical trials is generally unacceptable (this is unethical) when standard therapies or interventions

are available for a particular patient population. Against the background of this statement our guidelines, described in chapter 6, may lead to a suitable study design. If there is no high risk of serious contamination that necessitate blinding a conventional design is the best choice. Otherwise a pre-randomization design might be an alternative for ensuring blinding the study participants for the alternative treatment.

Anyhow, based on well-defined indications and requirements, pre-randomization designs have an essential contribution to evidence-based medicine. Banning pre-randomization designs implies that knowledge about the effectiveness of many public health, medical, and clinical interventions will not be available. A number of potentially effective interventions will not be introduced because of the lack of evidence. Furthermore, the use of established, (possibly) ineffective intervention, like alternative medicine or quack remedies, will be continued without evidence that the benefit prevails the harm.

The critical contribution of an independent group of experts, like members of research ethics committees, in the approval of study proposals is essential to protect health care and public health now and in the future.

Research ethics committees as ethical and methodological watchdogs

Research ethics committees or another independent groups of experts, are important instruments to preclude arbitrariness and to prevent too much personal influence of investigators, ethicists, lawyers, methodologists, and physicians on the acceptance of a study proposal. Therefore, independence of review is an important element of good research governance.

Our survey on the acceptability of randomized consent designs (chapter 5) demonstrates that members of research ethics committees make a well-balanced judgement about the acceptance and rejection of randomized consent designs. Pre-randomization in individually randomized trials is acceptable for many members of research ethics committees if the study design is presented in an ethically well-considered way. Although the differences between members and between committees are substantial, some variation in the judgement of study proposals may be acceptable. However, inappropriately high variability can impede the progress of research.⁶ On an international level this problem is obvious since countries clearly differ in their requirements for approval by a research ethics committee for an identical study.⁷

In spite of the secrecy that still surrounds research ethics committees and their decision making,⁸ it seems that members of research ethics committees do not shut the door for a discussion about the usefulness of controversial designs like pre-randomization designs. Guiding for such a discussion must be the balance between methodology and ethics, on which every design must be based.

The ethics of informed consent: the right information at the right moment

The most influential source of guidance in the design and implementation of ethical research in human beings is the Declaration of Helsinki. This declaration and derived national, and local laws, and guidelines, must not be conceived too much as a straitjacket of all sorts of regulations. Regulations must give trialists the opportunity to balance methodology and ethics in the design and implementation of a trial.

In addition to worthwhile study objective and good methodology informed consent is fundamental to the ethics of conducting trials and it is viewed as the key to respecting study participants' autonomy. Respecting this means that informed consent should not be an end in itself, but a means to protect the individual and to guarantee the right of autonomy (chapter 2). On the other hand, physicians who conduct research are using the patients as a means to an end. Their goal is no longer solely the wellbeing of the patients. They are also, perhaps primarily, committed to creation of generalizable knowledge. If so, the goal of ethical guidelines might also be the acknowledgement of this conflicting interest.⁹ Besides, the ultimate importance of informed consent is violated by the view that complete, specific consent in full detail is an illusion,¹⁰ the question to what extent informed consent is required and in what form remains open,¹¹ and both the timing of the informed consent procedure and the content of the informed consent are still part of an (ongoing) discussion.¹²⁻²⁴

In pre-randomization designs, cluster or individually randomized, there is a broad variation of informed consent procedures, ranging from full consent in all participants in all study groups to no consent at all.

The informed consent procedure in pre-randomization designs differs from the procedure in a conventional design in an essential way. Pre-randomization implies that participants are not asked to consent to (their) randomization, but only to undergoing treatment(s) and effect measurement(s). This is one of the major objections against pre-randomization in an individually randomized trial because participants in the reference group are unaware of their participation in the trial, participation in the reference group would not be voluntary, and participants in the reference group cannot willfully withdraw from the trial. However, a fundamental question is whether these participants, who receive standard treatment, are subjects whose autonomy is violated only because they are randomized. We take the position that autonomy is respected and no burden or harm is caused as long as a personal approach for measurements is not necessary. There is no question that informed consent is required by such a personal approach for baseline and effect measurements (if not yet routinely available), as we demonstrate in chapter 4 by means of a fictitious heroin-provision experiment.

Pre-randomization designs were rarely used, sometimes underused, and often badly designed

In our systematic literature search (chapter 3) we define pre-randomization designs with individual randomization as randomized consent designs. Since Marvin Zelen introduced his single-consent design in 1977, the randomized consent design has been rarely used in published research. We detected 50 studies until 2002. Besides, for the majority of the studies the use of a randomized consent design was unjustified because the most important protocol violations, namely, non-compliance and dropout, seriously endanger the internal validity of the studies. In these studies the use of a randomized consent design was not restricted to avoid contamination, but, among other things, also to avoid problems expected with the randomization procedure. This seems not to be a valid reason to preserve the internal validity of a study (chapter 6).

In a review of recent cluster randomized trials published in three general and leading medical journals from 1997 to 2002, the authors identified 42 potentially eligible trials.²⁵ They reviewed 36 trials and concluded that cluster trials are vulnerable to the risk of bias at cluster level, and at individual level. According to the authors, some cluster randomized trials may not have taken adequate precautions to guard against threats to the internal validity of their design. Like others,^{26, 27} they argue for amending the CONSORT statement to allow for the special methodological circumstances of cluster trials. The statement includes a checklist of items that should be included in the trial report and is already available for individually randomized trials.

It is remarkable that, in the literature, cluster randomized trials raise less ethical objections than individual randomized trials that use pre-randomization.^{1, 28} Both designs use pre-randomization, but cluster randomized trials are discussed methodologically²⁹⁻³² rather than ethically.³³ Perhaps this difference could be explained by the nature of the intervention. Trials randomizing clusters have become particularly widespread in the evaluation of non-therapeutic interventions, including lifestyle modifications, educational programs, and innovations in the provision of health care. When the intervention is of minimal or no impact on the individuals concerned, the investigator and the research ethics committee may handle less stringent conditions on ethical requirements. On the other hand, as shown in chapter 3, the subject of randomized consent designs, in which individuals are randomized, changed over years from medical to behavioral interventions. In spite of this, these designs are still being ethically criticized, even if they are well designed methodologically.

Because of the reticent use of pre-randomization in study designs, it might be possible that pre-randomization designs are currently underused or have been underutilized. Interesting in this matter is the statement that the Zelen design or single-consent design may be the best choice for a heroin provision experiment, as

described in chapter 4. In 1998 a conventional randomized controlled trial started in the Netherlands investigating the effectiveness of prescription of heroin added to regular methadone treatment.^{34, 35} Using a randomized consent design could have prevented some methodological shortcomings, like the partly improper inclusion of eligible addicts, and non-balanced non-compliance and dropout between the experimental and the reference groups. Unfortunately, it is unlikely that the opportunity to prove this statement will occur.

Pre-randomization needs a reappraisal

In general, a renewed interest for pre-randomization in study designs could contribute to a better quality of scientific research, and evidence-based medicine. For this purpose, ethical, methodological, and judicial requirements must be discussed without prejudices, but based on valid arguments. This thesis may contribute to this discussion.

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Summary

In Chapter 1 the topic of this thesis is introduced. The cause for this thesis was a discussion in the mid-Nineties in the Netherlands about the usefulness and ethical acceptability of pre-randomization in medical research. Triggered by the conviction that pre-randomization is useful in specific circumstances and against the background that it is often rejected on invalid grounds, the present study into the applicability and acceptability of pre-randomization in study designs was started.

Marvin Zelen first described the use of pre-randomization in study designs in 1977. The essence of this design is that potential participants are randomized before informed consent is obtained. This sequence is contrary to the conventional design in which informed consent is prior to randomization. Interventions in pre-randomization designs can be applied in individuals or on the level of units, or clusters. Besides, after randomization, giving information about the intervention, and obtaining informed consent, can be done only in the experimental group (the so called single-consent design) or both in the experimental group and in the reference group (the so called double-consent design).

Ethical principles for conducting scientific research are formulated in the Declaration of Helsinki and a sound informed consent procedure for participants entering a trial is one of the major tools to respect participants' autonomy. Nowadays, (bio)medical research projects involving human subjects must be reviewed by a research ethics committee and in that way study participants' rights are being protected.

Chapter 2 explores the history and principles of informed consent. Since World War II, a variety of protective measures have been introduced for persons receiving medical care or being involved in scientific research. The concept of informed consent has been accepted as a standard. In experimental therapeutic research, informed consent still causes controversies; individual benefit being weighed against general benefit. In various types of observational research for many ethicists informed consent is becoming an absolute precondition to participate in a study. Observational epidemiological research on the basis of existing data is endangered. Both the Declaration of Helsinki and the Personal Registration Act state that, under certain circumstances, it may be possible to deviate from the requirement of obtaining individual informed consent. A medical ethics committee could then give permission for such a research project. Informed consent should not be an end in itself, but a means to protect the individual and to guarantee his/her right to autonomy. Insisting on informed consent in situations where autonomy is respected and no harm or burden is caused, seems to defy the purpose of informed consent.

Chapter 3 gives a comprehensive overview of the use of randomized consent designs (i.e. pre-randomization designs) since 1977. Three types of randomized consent designs are distinguished, ranked according to the extent to which participants are informed about treatment options. Databases were searched for eligible studies and data were extracted on country of study conduct, year of commencement, area of medicine, type of design, reason(s) for use, details on approval by a research ethics committee, the index and reference intervention, nature of endpoints, and details on data collection. Furthermore, for each trial, the rates of non-compliance and loss to follow-up were registered by treatment arm. The three types of randomized consent designs were compared as to differences between the rates of non-compliance and loss to follow-up in the separate trial arms. The number of trials in which a randomized consent design was used is very small ($n=50$); over the years a shift from medical to behavioral type of interventions was seen. In 22% of the studies problems expected with the randomization procedure was reported as the main reason for using a randomized consent design. In 65% of the studies the non-compliance in the index group is larger than in the reference group. In the majority of the studies the use of a randomized consent design was unjustified and the use of these designs should be restricted to studies in which contamination is otherwise unavoidable.

Chapter 4 illustrates the use of a randomized consent design (Zelen design) by means of a fictitious heroin-provision experiment in badly integrated long-term addicts. Compared with the traditional design, the Zelen design probably reduces non-compliance and dropout considerably, thus increasing validity. Depending on the study population, the Zelen design may reduce study precision. However, in a trial aimed at badly integrated addicts the Zelen design can be conducted without loss of precision because baseline measurements will only weakly correlate with effect measurements. The Zelen design as an alternative for a conventional randomized design should be considered if: (a) the experimental intervention is attractive for all potential participants, and (b) the reference group will receive standard treatment. If these conditions are met, the choice between the two designs depends on weighing the loss of validity due to selective dropout and non-compliance in the reference group against the potential loss of precision due to not performing a baseline measurement.

Additionally, the ethical problem of studying participants without their consent was solved by a slight modification of the Zelen design in which the sampling of a reference group is postponed.

The acceptance of this modified randomized consent design and Zelen's randomized consent design by members of research ethics committees in the United Kingdom, and in the Netherlands is studied in chapter 5. In a postal survey

the fictitious heroin-provision experiment was used as a vehicle to demonstrate both randomized consent designs.

In both the UK and the Netherlands, the modified randomized consent design appears more acceptable than the randomized consent design, with respect to ethical and judicial aspects. The overall rejection rate of the randomized consent design was 66% in the UK and 59% in the Netherlands. However, the modified randomized consent design was rejected by 47% and 41% in the two countries, respectively. To increase consistency in the way research ethics committees handle study protocols, a discussion about the use of randomized consent designs appears necessary.

Chapter 6 presents guidelines for the optimal application of pre-randomization designs. For this purpose, designs in which pre-randomization is used are outlined, methodological considerations to choose between conventional designs or pre-randomization designs are described, and relevant ethical and judicial aspects are discussed. In specific situations, based on well-defined indications and requirements, pre-randomization designs have an essential contribution to achieve evidence-based medicine. In general, every design should be based on a balance between maximizing the potential for patient autonomy and minimizing the bias caused by contamination. Although general rules are important, an independent research ethics committee should decide whether this balance is acceptable.

Chapter 7 reflects on the main findings and addresses some general issues concerning the acceptability and applicability of pre-randomization in study designs. In general, pre-randomization is justified if the study has a clinically relevant objective, it is likely that the study will lead to important new insights, a valid evaluation of the effects is impossible using a conventional randomized design, the informed consent procedure bears no potential harm to participants, at least usual care is offered to participants in the reference group, and the study protocol is approved by an independent research ethics committee. This study shows that, methodologically, pre-randomization is useful when an attractive or preferable experimental treatment is involved, the reference is the standard treatment, the use of a sham procedure or placebo cannot be used, and using pre-randomization can minimize bias caused by contamination. Besides, in case of a single-consent design the choice depends on weighing the loss of validity due to selective dropout and non-compliance in the reference group against the potential loss of precision due to not performing a baseline measurement.

Banning pre-randomization designs implies that knowledge about the effectiveness of many public health, medical, and clinical interventions will not be available. A number of potentially effective interventions will not be introduced because of the lack of evidence. Furthermore, the use of established, (possibly)

ineffective intervention will be continued without evidence that the benefit prevails the harm.

In general, pre-randomization needs a reappraisal and for this purpose ethical, methodological, and judicial requirements must be discussed without prejudices, but based on valid arguments. This thesis may contribute to this discussion.

Samenvatting

Hoofdstuk 1 beschrijft de aanleiding voor het schrijven van dit proefschrift en introduceert het onderwerp. De aanleiding is terug te voeren naar discussies, onder andere in de vakliteratuur, over de bruikbaarheid en de daarmee samenhangende ethische toelaatbaarheid van pre-randomisatie. Bij de meest toegepaste manier van onderzoek, waarbij twee of meerdere groepen worden vergeleken, worden potentiële deelnemers geïnformeerd over het onderzoek, waarna toestemming voor deelname wordt gevraagd (informed consent). Daarna worden de deelnemers op basis van loting (randomiseren) toegewezen aan een van de onderzoeksgroepen. Pre-randomisatie draait dit principe om: potentiële deelnemers worden eerst gerandomiseerd over de onderzoeksgroepen en daarna wordt aan de experimentele groep, of aan alle groepen toestemming gevraagd waarbij meestal geen informatie wordt gegeven over de andere groep.

Het meest bekende onderzoeksdesign waarbij pre-randomisatie wordt toegepast is in 1977 door Marvin Zelen geïntroduceerd. Dit design is bekend als het Zelen design. Hierbij wordt na randomisatie alleen aan personen in de experimentele groep toestemming gevraagd. De andere vormen van pre-randomisatie waarin na randomisatie aan alle deelnemers in verschillende variaties toestemming wordt gevraagd, zijn ontworpen om tegemoet te komen aan ethische bezwaren. Pre-randomisatie wordt ook gebruikt indien interventies op groeps- of clusterniveau worden uitgevoerd en dientengevolge deze clusters worden gerandomiseerd in plaats van individuen. Voorbeelden van clusters zijn scholen, wijken, huisartspraktijken en gezondheidszorgvoorzieningen.

Essentieel bij de opzet van een onderzoek is de zorgvuldigheid waarmee *proefpersonen* worden geïnformeerd en toestemming voor deelname wordt gevraagd. Dit is in alle gevallen noodzakelijk indien de autonomie van de persoon in het geding komt, of lichamelijke, emotionele of sociale schade kan worden berokkend. Om proefpersonen te beschermen is in ethische codes, zoals de Verklaring van Helsinki, vastgelegd waaraan wetenschappelijk onderzoek moet voldoen. Experimenteel onderzoek waarbij mensen worden betrokken kan niet worden uitgevoerd zonder toestemming van een onafhankelijke commissie. In Nederland zijn dit de medisch ethische toetsingscommissies, die bij wet zijn ingesteld. In het buitenland bestaan vergelijkbare commissies, zij het op basis van andere wet- of regelgeving.

In hoofdstuk 2 wordt nader ingegaan op de geschiedenis en de betekenis van informed consent. Sinds de Tweede wereldoorlog zijn allerlei beschermende maatregelen getroffen voor mensen die medische zorg ontvangen, of worden betrokken in een wetenschappelijk onderzoek. Steeds vaker werd geïnformeerde

weloverwogen toestemming (informed consent) ingevoerd als standaard. In het experimenteel therapeutisch onderzoek zorgt informed consent nog steeds voor controversen, waarbij het nut voor het individu tegenover het algemene nut wordt geplaatst. Ook bij alle vormen van observationeel onderzoek lijkt informed consent een dermate absolute eis te worden, dat epidemiologisch onderzoek op basis van bestaande gegevens onmogelijk dreigt te worden. Volgens zowel de Verklaring van Helsinki als de Wet persoonsregistratie is het onder bepaalde omstandigheden mogelijk af te wijken van het vragen van individuele informed consent. Toestemming voor onderzoek zou dan gegeven kunnen worden door een commissie van toezicht of een medisch-ethische commissie.

Informed consent dient geen doel op zich te zijn, maar een middel tot bescherming van proefpersonen en waarborging van het recht op autonomie.

Hoofdstuk 3 gaat in op het vóórkomen van pre-randomisatie in gepubliceerd onderzoek sinds de introductie van deze wijze van opzet van onderzoek door Marvin Zelen in 1977. Door middel van systematisch zoeken in veel gebruikte literatuurbestanden werden slechts 50 studies gevonden waarbij pre-randomisatie werd toegepast. Over de jaren heen verschoof de toepassing van medische interventies (vooral bij oncologische trials) naar gedragsmatig interventies (zoals bijvoorbeeld advies over een andere levenswijze). In éénvijfde van het aantal studies waren verwachte problemen met randomiseren de reden om pre-randomisatie toe te passen.

Bij de 50 gevonden onderzoeken werd nagegaan in hoeverre de proefpersonen afweken van de afgesproken richtlijnen (non-compliance) en hoeveel percent van de deelnemers hun deelname stopten, waardoor geen metingen konden worden gedaan (loss to follow-up). Zowel non-compliance als loss to follow-up kunnen het resultaat van een onderzoek negatief beïnvloeden en de interpretatie en daarmee de toepasbaarheid van de resultaten bemoeilijken. Het blijkt dat in de meerderheid van de studies de mate van non-compliance en loss to follow-up groter is in de experimentele groep dan in de controle groep. Dit is opvallend omdat pre-randomisatie juist is bedoeld om non-compliance en loss to follow-up te voorkomen, vooral in de controle groep, ervan uitgaande dat vanwege de aantrekkelijkheid van de interventie de proefpersonen in de experimentele groep graag (blijven) meewerken. De conclusie lijkt gerechtvaardigd dat in de gevonden studies het toepassen van pre-randomisatie niet de juiste keuze is geweest.

Hoe pre-randomisatie wel verantwoord kan worden toegepast wordt beschreven in hoofdstuk 4. De toepasbaarheid van pre-randomisatie (Zelen design) wordt geïllustreerd aan de hand van een fictief onderzoek naar de effectiviteit van het verstrekken van heroïne aan langdurig verslaafde en verloederde druggebruikers. Bij een dergelijk onderzoek is het geven van een placebo niet mogelijk en is een

andere vorm van blinding aangewezen. Het Zelen design is bruikbaar voor een dergelijk onderzoek omdat het verstrekken van heroïne kan worden gezien als een aantrekkelijke interventie en uitval en non-compliance in de controlegroep kan worden vermeden omdat deze deelnemers niet worden geïnformeerd over de interventie. Daarnaast is aan de voorwaarde voldaan dat de controle groep de best beschikbare standaardbehandeling krijgt en een beginmeting niet noodzakelijk is.

Om tegemoet te komen aan vooral ethische bezwaren tegen het Zelen design, wordt in dit hoofdstuk een alternatief design gepresenteerd dat methodologisch gelijk is aan het Zelen design, maar waarbij de steekproeftrekking voor de controlegroep wordt uitgesteld. Onderzoekers en ethici die we beide designs ter beoordeling voorhielden vonden het alternatieve design meer acceptabel dan het Zelen design.

Dit gegeven was aanleiding het Zelen design en het alternatieve design ter beoordeling voor te leggen aan leden van medisch ethische toetsingscommissies. Dit onderzoek wordt beschreven in hoofdstuk 5. Een enquête werd gestuurd naar alle medisch ethische commissies in Nederland (77) en in Groot-Brittannië (240). Leden die deskundig waren op het gebied van de ethiek, (gezondheids)recht, methodologie of klinische praktijk werd gevraagd of ze het Zelen design en/of het alternatieve design ethisch, juridisch en/of methodologisch acceptabel vonden. De beoordeling vond plaats aan de hand van een fictief heroïne-verstrekkings-experiment, zoals beschreven in hoofdstuk 4. Zowel in Nederland als in Groot-Brittannië bleek het alternatieve design wat betreft ethische en juridische aspecten meer acceptabel dan het Zelen design. Naar onze mening is er geen methodologisch verschil tussen beide designs en zouden beide designs gelijk beoordeeld moeten worden. Blijkbaar spelen vooral ethische en juridische argumenten een rol bij de beslissing of pre-randomisatie toelaatbaar is. Om meer consistentie te krijgen in de beoordeling van onderzoeksprotocollen door medisch ethische toetsingscommissies is een discussie aangewezen waarbij aan de hand van de voor- en nadelen van pre-randomisatie consensus wordt bereikt, bijvoorbeeld door middel van een Delphi consensus techniek. Het lijkt onwenselijk dat onderzoekers in essentie gelijke onderzoeksdesigns op een andere wijze formuleren met als doel meer kans te maken op goedkeuring door een medisch ethische commissie.

In hoofdstuk 6 worden richtlijnen gepresenteerd voor de juiste toepassing van pre-randomisatie. Hierbij wordt onderscheid gemaakt tussen pre-randomisatie waarbij individuele proefpersonen een interventie krijgen en pre-randomisatie waarbij de interventie op clusterniveau plaatsvindt. In het eerste geval worden individuen gerandomiseerd en in het andere geval clusters zoals schoolklassen, ziekenhuizen of huisartspraktijken. Belangrijk bij de keuze tussen een conventioneel design en

pre-randomisatie designs zijn methodologische overwegingen, waarbij wordt nagegaan wat de invloed is van non-compliance en loss to follow-up op de wetenschappelijke kwaliteit (interne validiteit) van het onderzoek. De mate waarin deze aantastingen van het protocol (door contaminatie) kunnen optreden kan blinding noodzakelijk maken. Blinding zorgt er voor dat proefpersonen, onderzoekers en degene die de effecten meten niet weten welke behandeling is toegewezen. Als het risico op contaminatie laag wordt ingeschat, of als het gebruik van een placebo kan zorgdragen voor blinderen, dan is een conventioneel onderzoeksdesign te overwegen. In andere gevallen kan het gebruik van pre-randomisatie voor de juiste blinding zorgen en kan aan de hand van een stroomschema worden bepaald welk soort pre-randomisatie design bruikbaar is.

Daarnaast zijn ethische en juridische overwegingen van belang bij de opzet van onderzoek. Enerzijds behoort een proefpersoon/patiënt de best mogelijke behandeling te krijgen, anderzijds draagt een proefpersoon/patiënt bij aan de vooruitgang van de (medische) zorg. Dit respectievelijk individueel- en collectief ethisch belang dient in evenwicht te zijn. De manier waarop de informed consent procedure wordt uitgevoerd en het moment waarop informed consent, al dan niet, wordt gevraagd is tevens onderhevig aan de juiste afweging. In elk onderzoeksdesign moet worden gezocht naar de juiste balans tussen het maximale behoud van de autonomie van de proefpersoon en het minimaliseren van de vertekening van de resultaten veroorzaakt door contaminatie. Of in een onderzoeksprotocol deze balans wordt gevonden, is ter beoordeling aan medisch ethische toetsingscommissies.

Hoofdstuk 7 gaat in op de belangrijkste bevindingen. Pre-randomisatie is toepasbaar als de onderzoeksvraag relevant is, de resultaten kunnen leiden tot belangrijke nieuwe inzichten, het onderzoek niet kan worden uitgevoerd met een conventioneel design, de deelnemers in de controlegroep tenminste de standaard zorg krijgen en het onderzoeksprotocol is goedgekeurd door een medisch ethische toetsingscommissie. Tevens tonen de bevindingen aan dat methodologisch gezien pre-randomisatie is aangewezen indien de experimentele interventie aantrekkelijk is voor de deelnemers, blinding op een andere manier niet mogelijk is en het gebruik van pre-randomisatie de vertekening van de resultaten, veroorzaakt door contaminatie, kan minimaliseren. Zodoende kunnen pre-randomisatie designs een essentiële bijdrage leveren aan de ontwikkeling van het evidence-based (be)handelen. Het uitbannen van pre-randomisatie zou betekenen dat gegevens over de effectiviteit van veel medische- klinische- en openbaar gezondheidszorginterventies niet beschikbaar komen. Potentieel effectieve interventies blijven onbekend en mogelijk ineffectieve interventies kunnen blijven bestaan vanwege het ontbreken van bewijs van werkzaamheid. Daarom is het van belang dat medisch ethische toetsingscommissies door de beoordeling van

onderzoeksprotocollen de gezondheidszorg en de volksgezondheid blijven beschermen. Dit onderzoek toont aan dat deze commissies discussies over minder conventionele designs, zoals pre-randomisatie designs, niet uit de weg gaan.

In algemene zin verdient de toepassing van pre-randomisatie in onderzoeksdesigns een herwaardering om zodoende bij te dragen aan een betere kwaliteit van wetenschappelijk onderzoek. De discussie hierover dient vrij te zijn van ethische, juridische en methodologische vooroordelen. De inhoud van dit proefschrift kan aan deze discussie bijdragen.

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Curriculum Vitae

Ron Schellings was born on April 7, 1958 in Maastricht, the Netherlands. After completing secondary school he studied psychiatric nursing, followed by social psychiatric nursing at the Academy of Health Care in Sittard. He obtained his degree in 1982 and worked at the Academic Anxiety Center (psychiatric hospital Vijverdal, Maastricht) for seven years. From 1989 until 1992 he worked at the Consultation bureau of Alcohol and Drugs Limburg. After studying economics at Maastricht University in 1988-89, he started studying Health Science at the same University. He graduated in 1992 and worked as a researcher at the department of Epidemiology of Maastricht University, where he was involved in a study on substitute care for long-term psychiatric patients, and in the protocol development for a heroin-provision experiment. This project laid the foundation for the subject of this thesis. Besides working at the department of Epidemiology, he worked at the Institute of Psycho-Social and Psycho-Ecological Research (training program for older adults with mental retardation) and the department of Medical Sociology (Alcohol and Drugs Monitoring). Since 1999 he works as an inspector of health care at the Health Care Inspectorate of the Public Health Supervisory Service of the Netherlands. He is in charge of mental health care and since 2004, in particular, of the forensic psychiatry.