Nested Consent Design for Clinical Trials

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Background: Since random treatment allocation is hardly understood by the majority of patients, a new ‘nested consent design’ for clinical trials is proposed.

Proposed design: The design consists of a two-step enrollment of study subjects. The first step is the enrollment of participants into a follow-up study, where consent to be subjects involved in the follow-up is obtained. The second step is the enrollment of randomly sampled eligible participants into a new treatment group. After the explanation of (1) treatment mode, (2) additional burdens associated with the proposed treatment and (3) expected effects and possible adverse events, written informed consent is obtained. Those who reject participation and those who are not allocated into the new treatment are treated by standard care. Endpoints are set to be the same for all follow-up study participants whether allocated into the new treatment or not, and follow-up is carried out in the same manner. Analyses are performed between those allocated to the new treatment and those non-allocated on an intent-to-treat basis.

Example: Although not a clinical trial, this design was applied in a smoking cessation program at Aichi Cancer Center Hospital for first-visit patients who answered in a questionnaire survey that they were smokers. Out of 1330 necessary participants, 324 were enrolled in the follow-up study during the first three months of enrollment.

Conclusions: The design was found to be feasible for prevention trials, and possibly for clinical trials to compare a new treatment with a standard treatment. There seems to be no ethical difference between this design and the one-arm study design.

Key words: study design – informed consent – intervention – smoking cessation program

INTRODUCTION

The concept of informed consent in medical care has been developing in many countries. This is especially so in the USA, where experiments on humans such as ‘radiation experiments’ and the ‘Tuskegee syphilis experiment’ were conducted (1), where malpractice lawsuits are highly prevalent under the jury system (2), where the expensive health care system makes a great difference in access to medical care between the insured and uninsured (3), and where health care for minorities is a serious problem (4). It is easily understood why informed consent is emphasized and regulated by law (5) to standardize its process in the USA.

In randomized clinical studies, this concept has been similarly introduced, and strict regulations have been adopted in the USA (6). All participants of clinical studies must be informed and submit a written consent form before their participation, whether a new treatment or a standard one is proposed. Additionally, in randomized studies, explanation of the randomization mechanism is required before patients’ participation. As a result, Zelen’s randomized consent design (7), in which randomized assignment to treatment is conducted before obtaining consent for the treatment, cannot be adopted. Avoiding the randomized consent design is wise in the USA to protect medical researchers engaged in clinical trials, in view of risk management (8).

In phase I or II studies, eligible patients are asked to participate in the trial, sequentially or arbitrarily at the doctors’ discretion. In most cases, the doctors’ discretion for patient selection is socially acceptable, because doctors must fulfill certain additional requirements, and because after the invitation into clinical trials, more than standard medical care is provided. Patients invited to the trials have the proposed treatment regimen explained to them, as well as standard treatments, but not necessarily why they are actually sampled. The eligible patients who are not selected by doctors in charge of the trial are not given the chance to participate. It is not regarded as socially unethical, except in cases such as human immunodeficiency virus/acquired immunodeficiency syndrome; HERPACC, Hospital-based Epidemiologic Research Program at Aichi Cancer Center
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New Treatment Group in the Follow-up Study

The second step is the enrollment of certain participants into a new treatment group. The endpoints of the new treatment group must be the same as in the above follow-up study. The definition of eligibility criteria should be narrower than that for the above follow-up study. A defined proportion of participants are sampled for the new treatment group randomly from all participants who meet the eligibility criteria. Those not sampled can compose a comparative reference group. For the participants allocated into the new treatment group, the following information is provided: (1) mode of new treatment, (2) additional burdens associated with participation in the new treatment group and (3) expected effects and possible adverse events associated with the treatment. The subjects should be informed that they are allocated randomly into the new treatment group. Those who accept the new treatment are enrolled in the new treatment group after giving their written informed consent. Those who refuse the new treatment remain as participants of the follow-up study.

Fundamental Participants’ Rights

The participant’s right to withdraw from participating in either or both the follow-up study and/or new treatment should be respected, although the information obtained prior to withdrawal belongs to the researchers unless a special reason is given. The privacy of the participants should not be invaded, and consent must be obtained under circumstances where participation is not enforced in any way. In addition, ethical aspects of the study should be examined by an independent committee to prevent inappropriate new treatment.

Analysis

To evaluate the effects of adopted intervention(s), comparisons should be made between the ‘allocated into new treatment group’ and ‘non-allocated’, on an intent-to-treat basis (9). It should be noted that the difference in endpoints between the allocated and non-allocated is diluted when the percentage of those who participate in the proposed new treatment group decreases, resulting in the need for a larger sample size (10).

Analysis on the non-allocated group and follow-up study participants ineligible for the second-step enrollment can be conducted similarly to an ordinary follow-up study.

Application for a Smoking Cessation Follow-up Study

Since no clinical trials by this design have been started, an ongoing study of smoking cessation is introduced as an example. There are few studies in Japan that report a smoking cessation rate among patients after a hospital visit, while several studies have been published in other countries (11-13). Accordingly, a program on smoking cessation was started at Aichi Cancer Center Hospital on September 16, 1997, after obtaining the permission of the Ethics Committee of Aichi Cancer Center (No. 13-11). The entry of participants was planned to be completed in September 1998.

Subjects of the follow-up study are first-visit patients to the hospital, who participate in a lifestyle questionnaire survey
named HERPACC (Hospital-based Epidemiologic Research Program at Aichi Cancer Center) (14), and who answer in the questionnaire that they are current smokers. They are invited to participate in a one-year follow-up study to examine their change in post-visit smoking habit. The following are explained before obtaining written consent: 1) this study aims to measure the spontaneous smoking cessation rate after hospital visit, 2) two questionnaires concerning current smoking habit will be mailed to you, one at two months after participation and the other at one year after, 3) there will be no disadvantageous treatment in hospital care in case of no participation, 4) no contact after the one year follow-up, and 5) participants’ privacy is never invaded’.

Before sending the first questionnaire, half of the eligible participants aged 30-69 years are randomly sampled, after stratification by sex and age (10 years age group). For those sampled, they receive the questionnaire with one additional phrase: ‘We will provide a simple smoking cessation program conducted by means of a free booklet and telephone interviews, for the participants who wish to quit smoking’. (This question is added only for half of the participants randomly selected.) To those who answered ‘I am interested in the program’, an informed consent form, an explanation of the program schedule and a copy of the ‘Quit Smoking Self-help Guide’ edited by Drs Nakamura and Ohshima are sent.

The program consists of three telephone interviews. The first is for assessing participants’ stage of readiness to change the habit (stage 1: being aware of the harm of smoking; stage 2: being able to analyze own smoking habit; and stage 3: preparing for smoking cessation), and determination of the date of quitting if possible. The second is at one week after the pre-determined date of quitting, and the third at four weeks after the pre-determined date, for the purpose of supporting non-smoking. If the participants wish to withdraw from the program, no contact is made thereafter.

The second questionnaire is sent to all the participants in the follow-up study, including those who attend the smoking cessation program. No responses are regarded as being current smokers. The smoking cessation rates are compared between the allocated and non-allocated aged 30-69 years, according to the intent-to-treat basis.

We assumed the smoking cessation rate to be 20% for the participants of the program and 3% for the rest. When 20% of those randomly allocated into the smoking cessation program actually wish to participate in the program, the smoking cessation rate among the allocated as a whole decreases to 6.4%, requiring 479 per group (958 in total) under the condition of statistical power 80% and significant level for one-sided test 5%. In this hospital, the first-visit patients comprise 20% cancer patients and 80% non-cancer patients, and those aged 30-69 years represent about 90% of those patients. It was assumed that about 70% of the first-visit smokers would participate in the follow-up study. Accordingly, to examine the difference in the smoking cessation rate among the non-cancer first-visit patients, 1330 participants from 1900 first-visit smoker patients were required.

It was found that 324 out of 400 smokers (81%) participated in the follow-up study during the first three months of the study from September 16 to December 22. Those aged 30-69 years numbered 270, and 134 participants were randomly assigned to the intervention group. Out of 80 participants of the intervention group to whom the first questionnaire (the two-month-later survey) was sent until one week before December 22, 20 (25%) responded that they were interested in the smoking program. This participation rate seemed to make it possible to enroll the required number of patients in one year.

**DISCUSSION**

**STUDY DESIGN AND ETHICAL PROBLEMS**

Several study designs have been proposed concerning the mode of informed consent in randomized controlled trials. In the conventional design, information on randomization is provided before study entry. Those who agree to random assignment to one of the proposed treatments can enter the trial. This process is sometimes very tough for the participants, especially for patients with a serious disease (15,16). To avoid the cruelty of the obeying process, Zelen proposed a new design named prerandomization or randomized consent design (7); it is called more specifically single-consent design when consent is sought only for one group allocated into a new therapy, and double-consent randomized design when both groups of patients are asked to accept the treatment allocated (6). Zelen’s design was used by several clinical trials (17-20), and an intervention trial for cancer prevention (21). Since patients who accepted randomization in the conventional design were very limited in many trials, another study design, named ‘comprehensive cohort study’, has recently been proposed, in which those not accepting the randomization are similarly followed up (22). The cohort consists of randomized groups and non-randomized groups; in the latter groups, patients or their physicians choose the preferred treatment. By means of the comparison between results from randomized groups and non-randomized groups, the external validity of the results observed in the randomized groups could be examined. Of these designs, the conventional design has been adopted by protocol in almost all randomized clinical trials, although the practice of informed consent reportedly differed in many cases from the protocol description (23).

In addition to the toughness for patients of the conventional design, the following inconsistency poses difficult problems in practice at the bed side, at least in Japan. In the case of comparison of two standard treatments, physicians’ arbitrary treatment choice is made for patients outside clinical trials, while a strict informed consent process in the conventional design is required for the patients’ enrollment. In the case of a new drug phase II study, arbitrarily selected eligible patients have a chance to be provided the new drug. In the following phase III conventional randomized study of the same drug, patients selected arbitrarily by doctors in charge are to be informed of the randomization mechanism of treatment allocation.

The informed consent process of the conventional design may be ethical on some occasions, but not always ethical from the patients’ perspective. It is often the case that the proposal of a trial with the randomized process and the detailed explanation process exhausts patients, and the explanation may cause a psychologically difficult situation and even bring a nocebo effect (the opposite effects of placebo) (24), resulting in no participation in
the trial, which is truly a waste of energy for both patients and doctors, leaving only an avoidable discomfort. When regarding ethics applicable to patients, it is clear that the patient’s situation should take priority. The ethical consistency solely in the framework of clinical trials (17,18) is sometimes meaningless, even though the consistency is indeed useful to protect protocol makers or biostatisticians who live separately in each clinical trial and have no responsibility for actual medical care. Although the randomized consent design has been criticized in the USA (25), study groups in Europe support the design (20,21,26).

In the proposed ‘nested consent design’, a new treatment such as new drug therapy before approval of the authorities concerned is proposed for the randomly selected patients. In ordinary settings, it is hard to criticize the discretion of researchers on how the patients are selected, because the patients have no right to request such a new treatment. It is analogous that doctors participating in a phase II study can choose subjects from eligible patients at their discretion. In addition, there are no additional ethical problems in comparison with the phase II studies, in terms that not all follow-up study participants are invited to receive a new treatment, and that the non-selected participants are not necessarily informed of the sampling.

When ethics in clinical trials are considered, the points are the content of treatment, information provision on the treatment as well as available alternatives, and consent to participate in the treatment without enforcement. The sampling or allocation design itself does not violate the human rights in usual clinical trials. Objectively promising standard health care is promising or standard from the patients’ view, independent of the investigators’ research intent or participant selection process. However, when objectively harmful substandard health care is conducted, the investigator’s research intent and subject selection process should be examined to determine the degree of responsibility for the misconduct.

STATISTICAL ASPECTS

There are no differences in statistical aspects between this design and Zelen’s single-consent design. The aspects have been discussed in several papers (6,17,18). Masking of the allocated treatment is not possible for these designs, so both designs are applicable for clinical trials in which placebo or nocebo effect on endpoints is negligible. An increase in refusal rate for the new treatment dilutes the difference in effectiveness between the groups compared, resulting in the need for a larger sample size. Accordingly, a promising treatment acceptable for patients should be selected as a new treatment. The former is a common requirement for open trials, and the latter for the conventional design in principle.

A design similar to the ‘nested consent design’ may previously have been adopted in epidemiological studies, when the informed consent in medical research was not a serious point for discussion. In that sense, our proposal may actually not be the first. However, the full description of this design as one entity gives a source for further discussion on the study design of clinical trials or intervention trials.

Acknowledgments

The authors are grateful to Mr Erick C. Uebels for English manuscript preparation. This work was supported in part by a Grant-in-Aid for Cancer Research (9-5) from the Ministry of Health and Welfare of Japan.

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