Components of a randomized clinical trial


The purpose of this paper is to discuss a number of components associated with the design, development and conduct of a randomized clinical trial (RCT). In a RCT, a patient is entered into a protocol in which therapy is randomly assigned. Thus, neither the patient nor the care provider have active roles in deciding treatment. The elements of informed consent were developed to ensure that the patient's interests are protected. The informed consent document serves as the cornerstone of a clinical study by introducing patients to the research protocol, informing them of their role as participants in the study, and educating them of their rights. Questions regarding ethics arise during all phases of a study. A study designed with insufficient sample size will provide inconclusive data, thus making participation in the study of limited to no value. Conversely, having patients enrolled in a RCT after data has proved superiority of an arm of the study postpones beneficial therapy for patients and society. Other ethical conflicts arise when subjects are recruited for clinical trials. Special care must be taken to avoid coercion in protected populations such as students, employees, the mentally challenged, and the indigent. Careful planning with adequate attention to consent form development can minimize problems and optimize patient care and research integrity.

Introduction

The randomized clinical trial (RCT) is a research design used to compare 2 or more forms of therapy. Four traits that distinguish a RCT from routine clinical care are; 1) a RCT is controlled (all subjects in the RCT are selected based upon stringent predetermined entrance criteria); 2) it is randomized (subjects are assigned to treatment groups by chance, independent of their individual characteristics); 3) the final outcome is established through statistical analysis (criteria are established for measuring differences amongst the 2 groups prior to initiation of the study, and the data are analyzed to determine if the preset level of significance is obtained); 4) most often, a double-blind technique is employed (neither the patient nor the examiner collecting data knows which treatment an individual received).

A vast range of ethical problems are encountered in conducting a RCT. Protecting the patient's rights to understand and approve their treatment is the most contentious issue in a RCT. Since each patient is assigned to a treatment group randomly and blinded, informed consent is critical. Through informed consent, the patient chooses to not know what treatment they will receive. Often, the patient replaces their right of choice with trust in the care provider. Thus, there is a major conflict for the care provider since they must suspend their own judgement in selecting treatment and providing care, and randomly and blindly provide the care in the research protocol. Proponents and protagonists for continued use of RCTs exist. Some argue that the entire process is so technological and dehumanizing that its use should be curtailed sharply (1), while others contend that the power of the RCT to identify the merits of therapies is so great that it would be unethical to introduce a new therapy without validation using a RCT (2, 3).

This paper will examine some obvious ethical problems encountered in RCTs. Specifically, ethical considerations in 1) designing, 2) recruiting and 3) terminating patient participation will be discussed. The role of informed consent in preserving the subject's rights without placing undeserved responsibilities on the practitioner will be discussed by review of the elements of informed consent. Further
information on other ethical problems presented by RCTs, as well as by other research designs, can be found elsewhere (4).

**Design of RCT**

**Formulation of null hypothesis**

The RCT is designed to test for significant differences between 2 or more therapies. Typically, these different therapies are considered to be equivalent, and statistical evaluation is done to prove or disprove this hypothesis. In statistical nomenclature, the hypothesis being tested is the null hypothesis.

The ethical justification for beginning a RCT requires, at a minimum, that the investigators be able to make an honest statement of no difference—that is a statement that there is no scientifically validated reason to predict that therapy A will be superior to therapy B. Further, there must be no therapy C known to be superior to either A or B unless there is good cause to reject therapy C, e.g., the population of research subjects will consist of either those in whom therapy C has been tried without success, or individuals who are aware of therapy C and, for reasons they consider important, have refused it.

The statement of the null hypothesis often creates ethical dilemmas for the health care provider. As an example, if a clinician has good reason to believe that a new therapy (A) is better than current therapy (B), he/she cannot participate in a comparative trial of therapy A versus therapy B. Ethically, the clinician is obligated to give therapy A to each new patient with a need for one of these therapies (5). Thus, the statement of the null hypothesis creates the following difficulties for the care provider:

(a) Requires the provider to suspend personal judgement that a particular therapy may be advantageous for a specific patient.

(b) Requires the provider to admit lack of awareness of which would be superior therapy.

(c) The provider's knowledge from preliminary data on new therapy may not support statement of equivalence.

(d) Placebo control thwarts the provider's desire to "do something".

Freedman proposed that the null hypothesis be replaced with a broader statement of clinical equipoise (6). He states that often the basic reason for conducting clinical trials is a conflict between standard therapy and a second therapy for which some evidence suggests equivalence or superiority. A RCT is justified if supporters for each therapy recognize that there is evidence to support the alternative therapy. "A statement of clinical equipoise is consistent with a decided treatment preference on the part of the investigators. They must simply recognize that their less-favored treatment is preferred by colleagues whom they consider to be responsible and competent."

Clinically, the care provider may recognize minor variations in a patient or the presentation of the disease that may challenge equivalency of 2 therapies for a particular patient. Thus, therapy may be intuitively superior for a particular patient. Although treatment of that patient with a specific therapy may seem appropriate, randomization will be destroyed. For this reason, inclusion and exclusion criteria must be developed as stringently as possible to ensure that treatment decisions do not provide unintentional bias.

As stated, preliminary data may present conflict. Poorly controlled pilot studies generate inadequate information that may inhibit the subsequent conduct of RCTs. For example, initial results may show that the new therapy (A) seems far superior to the standard (B); thus, the statement of the null hypothesis that justifies a comparison between A and B may be challenged inappropriately. Placebo-controlled RCTs are generally not begun until there is some preliminary evidence that the agent to be compared with placebo is more effective than placebo in bringing about the desired consequence. There are important practical reasons for this, not the least of which is that financial sponsors of RCTs do not wish to invest in agents that are not likely to be superior to placebo. Moreover, preliminary studies usually have been done to establish evidence of efficacy and to determine optimum dosing. Finally, when a RCT is begun, the investigators often have available information about the agents to be tested, which may often include clinical trials or data obtained in clinical practice in other countries. Thus, a significant body of information may refute the statement of equivalency between the two therapies. To avoid such problems, Shaw & Chalmers encourage the use of RCTs as early as possible in the course of testing a new therapy (5).

**Control groups**

**Placebo controls** – As noted earlier, a major ethical requirement for justification of a RCT is a legitimate statement of no difference. In a RCT investigating treatment of periodontitis in which a placebo is compared with an active agent, the administration of placebo must be viewed as a non-therapeutic procedure. Arguments that placebo administration in this situation is potentially beneficial for the patient-subject are generally not legitimate. Lasagna has said: "Too often the placebo-treated patients turn out to be the lucky ones in such a trial, 'deprived' only of a toxic and ineffective
chemical” (7). Such reasoning may be applicable at times when there is little or no preliminary evidence indicating the safety and efficacy of the active agent to be compared with placebo. In cases where efficacious therapy exists, the inclusion of a placebo (or no therapy) can be justified only with difficulty.

In the event that a particular placebo-controlled RCT has been justified, patients must be informed clearly of the perils of withholding active therapy. Criteria defining disease progression must be established and trigger exit from the study; an appropriate rescue protocol must be identified. To the extent that important preliminary evidence indicates efficacy of the active agent, there is an increased necessity to inform prospective subjects of the preliminary evidence and its implications. In those cases in which there has already been 1 RCT which rejected the null hypothesis, this, too, warrants disclosure. This assertion may appear inconsistent with recommendations that preliminary data developed during the conduct of a RCT should be withheld from subjects, but it is justified because the ongoing RCT has not undergone complete statistical analysis and must therefore be kept confidential.

**Alternative approaches to controls in RCTs**

According to FDA Guidelines (8): during all phases of clinical investigation the objective in using a placebo is to control the study adequately. It should be recognized that there are other methods of adequately controlling studies. In some studies, and in some diseases, the use of an active control drug rather than a placebo is desirable, primarily for ethical reasons. In some diseases or conditions where the natural course of the disease or the condition is predictable and in which objective measurements of therapeutic or prophylactic response can be made, carefully executed open studies may be compared to the historical data to provide acceptable evidence of efficacy. Some studies should be designed to ascertain the degree of safety and effectiveness of the investigational drug in comparison with one or more marketed drugs for the same indication.

Dose–response designs may be used for an agent that have gradations of therapeutic effects dependent upon the dose administered. In that study design, a high dose is compared against a modest dose of the drug. Such studies can be viewed as presenting the same ethical problems as placebo-controlled studies. If a 2 mg dose is compared against a 4 mg dose, 1 group or the other is either receiving an excessive or inadequate amount of the drug.

Cross-over placebo-controlled designs entail assignment of 1 group of patients to placebo and the other to active agent. Halfway through the study, the assignments are reversed; those who began taking placebo now receive active agent. At first glance, cross-over designs seem responsive to the ethical problems presented by placebo controls. No patient-subject is deprived more than any other of the benefits of the active drug. However all patient-subjects are assigned to placebo for one-half of the study.

The split mouth design can be viewed as a variation on the cross-over design. In the split mouth design, a quadrant, arch or half mouth is treated with one therapy, while the remaining areas are treated with another therapy(ies). It can be argued that the split mouth design incorporating a placebo-control deprives part of the mouth of therapy, but arguably provides potentially beneficial care to each patient. In periodontal therapies, other design issues must be addressed, e.g. active agents redistributing to other areas of the mouth, or non-treated areas may re-infect treated areas. Thus, split mouth designs involving placebo controls may be suboptimal for both scientific as well as ethical reasons.

Some studies of periodontal disease have used a run-in phase to determine areas of active breakdown, followed by active therapy to monitor elimination of disease activity. This approach has advantages since periodontal disease appears to be a site-specific, sporadic disease. Further, a run-in phase may be appropriate for minimizing overtreatment of disease. The negative aspects of a run-in protocol are the extension of time for starting the active phase of the study, and the increased costs of the RCT in terms of both time and money.

The literature on the ethics of RCTs most commonly discusses historical controls as an alternative to RCT. Thus, the placebo control data are derived from the experience of an institution with treatment of the disease in question accumulated prior to introduction of the new therapy. The study is then designed to compare a new treatment(s) to the historical control. Freireich & Gehan have provided an account of such alternative strategies (9). Variants on this approach involve the use of literature controls (control data derived from publications on the outcomes of treatment with the best available standard therapy) and the use of control data developed in the conduct of other clinical trials. The strongest defense for the use of historical controls can be made when the disease in question has a uniformly lethal outcome when untreated and for which there is no effective therapy. Thus, it is commonly argued that it would be unethical to establish a RCT designed to evaluate a new
Ethical issues in clinical trials

Treatment for rabies if there were any cause to predict that it might be effective in even a small percentage of cases (10). When the disease is not uniformly lethal, there may be heated arguments over whether it is more appropriate to use a RCT or historical controls. For example, McCartney has argued that the placebo-controlled RCT designed to test the efficacy of adenine arabinoside in the treatment of herpes simplex encephalitis was unethical in that the disease was known to be fatal in 70% of cases and there was no known effective therapy (11). His argument was rebutted by the investigators (12).

Current "standard of care" as a control

Research in periodontal therapy can be divided into 3 broad areas: prevention, arrest of active disease, and repair/regeneration of structure lost to disease. In each case, the consequence of placebo control or no therapy must be considered. In particular, the consequence of no therapy for gingivitis is reversible, while the consequence of no therapy for periodontitis is irreversible. Thus, the appropriateness of placebo controlled trials for arrest of active periodontal disease must be questioned. Ethically, an appropriate design for a clinical trial would seem to be the active agent compared to the corresponding standard of care (scaling/root planing and/or surgery) and to historical and/or literature controls. Using this design, agents can be evaluated for equivalency or superiority.

Randomization strategy

Prospective subjects of RCTs must be informed that their therapy will be chosen by chance. Although the therapies to be compared are considered medically equivalent by investigators, informed consent to randomization is imperative since the composition of risks and benefits is usually different. Moreover, patients implicitly believe that care providers will provide advice based upon their personal knowledge of the patient, his or her ailment, as well as all available therapeutics. If the state of relevant knowledge in therapeutics is such that choice of therapy by chance is justified this fact, of itself, should be disclosed. For supporting arguments for these statements, as well as an assessment of major counter arguments, see Levine & Lebacqz (13).

Chalmers et al. have reviewed RCTs of acute myocardial infarction therapies to determine the importance of blinding the randomization process (14). "Blinded randomization" was defined as "assignment prearranged at random and communicated to the investigator only after the patient had been accepted for the study and informed consent had been obtained". "Unblinded randomization" was defined as any study in which the patients could "be selected or rejected after the physician knew the treatment assignment". When compared with blinded randomization, unblinded randomization was associated with nearly double the frequency of maldistribution of at least 1 prognostic variable and nearly triple the frequency of differences in case-fatality rates between treatment and control group. "These data emphasize the importance of keeping those who recruit patients for clinical trials from suspecting which treatment will be assigned to the patient under consideration."

Patient accrual

Introduction of study - coercion

The potential for coercion exists in most encounters between a patient and the care provider. In the formal setting of a clinic, the potential for intimidation must be considered. Often, a patient's reasoning abilities are compromised due to the stress of illness and entry into an unfamiliar environment. A careful, non-threatening description of the study at initial presentation establishes trust, and allows the patient to better evaluate the merits of participation. Obviously, the best time for a patient to decline participation in a RCT is before enrollment.

Sample size

The size of a RCT is a significant ethical point of concern. The burden on the patient in any study must be carefully weighed. At first, it seems acceptable for a patient to participate in a small study with no risks. A study with insufficient sample size is a concern since it will provide incomplete or possibly misleading results. The results may then make full scale RCTs difficult to conduct due to bias introduced from the early, incomplete studies. On the other hand, RCTs with an excessive sample size are also a concern, since 1 group of patients in the study are typically being given an inferior therapy, while the general population (not in the RCT) is being denied the results of the trial. Resources are available that provide full descriptions of statistical analyses, including Type I and II errors, and tests for calculation of sample size. A general understanding of statistical analyses together with competent statistical support personnel are critical to any RCT.

The problems associated with patient enrollment and sample size are succinctly summarized by Ellenberg:
Patient accrual is nearly always a problem in RCTs. The number of patients estimated to be available for a particular trial is often far greater than the number that appears to be available once the trial is underway. Low rates of accrual result in abandoned studies, studies with power so low as to limit the inferences that can be made, and studies that continue accrual over a long period that the treatments being compared may no longer be of interest by the time the study results are available (15).

**Population demographics**

*Institutionalized populations* – Patients enrolled in research studies within dental schools, VA hospitals, and government sponsored health clinics, must be protected from undue burden. Levine & Lebacqz (13) examined the issues of coercion and imposition of burden on individuals who are vulnerable or less advantaged as often occurs with treatment within institutions. Patients in VA hospitals, public health clinics or “free” clinics should be considered more vulnerable than other patients since they typically have limited options for obtaining health care. Private patients may choose another physician or, in most cases, another hospital setting if they prefer not to participate in a RCT. Veterans or financially compromised patients often cannot obtain care in the private sector since they will have to assume large financial burdens to do so.

*Elderly* – Advances in health care as well as other factors have significantly increased life expectancies. As new treatment modalities for the aged are created, this population will be expanding their consumption of health care services. With market expansion, attention to this population will increase. As with all RCTs, care facilities provide a population of convenience for study, but present all the potential for coercion inherent in institutions. The potential for paternalism and diminished autonomy must be recognized.

*Gender* – The issue of gender in human subject experimentation has been discussed extensively. Disproportionate risks and benefits by gender have existed. Excluding females from the risks associated with human experimentation has, in many cases also excluded them from the benefits of clinical studies. A classic example of this discrimination are studies that exclude women of child-bearing age. Because of this exclusion, a number of available therapies are denied to women since they were not included in the RCT which defined the application of the therapeutic agent. Recognizing this past discrimination, both IRBs and federal agencies are requiring that investigators provide convincing arguments for exclusion based upon gender.

*Ethnicity* – As with gender, exclusion based upon ethnicity must be thoroughly justified. In addition, cultural mores and language difficulties can complicate obtaining consent that is truly informed. If large numbers of a particular ethnic group are to be enrolled in a RCT, it is prudent to find recruiters and project managers of the same ethnicity which will ensure a shared understanding of cultural norms and voluntary, non-coerced enrollment.

**Risks of non-entry into RCT**

As previously described, patient accrual can become highly coercive. One perception that patients possess (particularly for patients receiving therapy within an institution) is that they have no alternative therapeutic option outside the scope of the trial into which they are being recruited. Thus, a critical component of informed consent is that the patient fully understands that they may refuse to participate in a RCT without affecting their continuing ability to receive care. This must be carefully delineated in all written consent forms.

**Benefit to patient by participating in RCT (tangible versus intangible)**

The extent to which participation in a RCT represents a burden or a benefit is often debated. Fried argues that there is one type of burden that is imposed by participation in most, if not all, RCTs: the subject is deprived of the relationship with a health care provider (1). In standard clinical therapy, the provider’s only professional obligation is to the wellbeing of the patient, uncomplicated by competing obligations to generate high quality data. In Fried’s words, the subject is deprived of the “good of personal care”.

There are ways to modify the RCT to circumvent the charges of compromised provider contact and other burdens associated with RCTs, particularly those conducted in institutional settings. Levine & Lebacqz suggested several modifications to counter-balance the burden of participation (13). First, the loss of the personal physician–patient relationship can be countered by involving a physician not associated with the RCT on the treatment team for each patient. Secondly, patients can be given the option of personal care or participation in the RCT, thus increasing their range of options to a level similar to that enjoyed by private patients. Patients in an institutional setting who refuse participation might be referred for personal care to a general care facility, a teaching facility, or some other facility. Finally, a judgement that participa-
tion in a RCT is a burden or a benefit is a value judgement, and it is possible that the patients' value judgements might differ from those of investigators or Institutional Review Board (IRB) members. When in doubt as to whether a prospective subject population considers itself disadvantaged or whether it considers participation in a RCT more of a benefit or a burden, community consultation may be helpful in resolving the uncertainties (4).

In recent years the importance of consultation with the community has gained wide acceptance, particularly in RCTs in the field of AIDS research. The community is consulted not only to determine whether participation would be a burden or a benefit, but also to assist in the design, recruitment and conduct of RCTs (16).

**Burden or benefit?**

Survey research by Cassileth et al. provides interesting insights into whether prospective subjects consider participation in RCTs burdensome and, if so, who should shoulder such burdens (17). These surveys were conducted in the aftermath of a series of newspaper articles that gave high visibility to reports of misconduct and abuses in clinical research. Respondents, who were assured anonymity, included 104 patients with cancer, 84 cardiology patients, and 107 members of the general public. Responses were similar regardless of subgroup or demographic considerations.

Of the respondents, 71% said patients should serve as subjects, giving as their primary reasons their belief that such service provides an opportunity to increase scientific knowledge and could result in benefit to others. When asked what their main reasons for participation in medical research would be, 52% responded that it would help them get the best medical care available. However, when asked which patients get the best medical therapy, 36% reported that it was those patients who were treated by private physicians who knew them, 13% said participants in medical research, 25% said there was no difference, and an additional 25% reported that they did not know.

Mattson et al. surveyed the attitudes of actual participants in two large-scale RCTs (18). In their view, the advantages of participation in a RCT outweighed the disadvantages since a large majority said they would volunteer for similar studies in the future. Among the advantages identified by these subjects were additional medical monitoring and information, opportunities for second opinions, and reassurance and support received from RCT staff. Each of these advantages was rated as more important than actual feelings of physical improvement. Some subjects claimed altruistic motivations and a few pointed to the availability of some free services. There was a low frequency of perceived disadvantages, consisting largely of transportation problems and clinic waiting times.

**Termination of study**

Cowan has cited the statistical components that must be considered in determining if a RCT should be terminated prematurely (19). A RCT should not be continued longer than necessary since subjects enrolled in the group receiving the less advantageous therapy will be harmed. Further, other patients with the same disease who are not enrolled in the RCT will be deprived of the more advantageous therapy. Conversely, premature termination of a RCT may mean that data adequate to establish the safety and efficacy of the test therapies may never be developed. Thus, rules for stopping a RCT should be developed prior to initiation of the trial. An attempt should be made to anticipate all possible contingencies.

A significant ethical question involves disclosure to subjects of preliminary data which reflects trends in safety and efficacy that have not reached statistical significance (20). For example, should the results be disclosed that therapy A seems superior to therapy B when the level of significance reaches 0.07, when the pre-set level for statistical significance was 0.05? Obviously, if 0.07 becomes accepted, then why not accept 0.10? Disclosure of the emerging trend would almost certainly disrupt the RCT. Many subjects would decline further participation in the RCT in order to gain access to what seemed to be the more advantageous therapy.

Veatch concludes that there are 4 possible solutions (20):

1. “Nondisclosure of preliminary data because the subject would not want to know”. This solution is unacceptable since most reasonable subjects would want to have information they consider important to their well-being.
2. “Nondisclosure of preliminary data because benefits to society outweigh subjects’ rights”. Generally, the subjects’ rights are held at the highest level, making this option also unacceptable.
3. “Insistence on full disclosure”. This solution would almost certainly render impossible any continuation of the RCT.
4. “Consent to incomplete disclosure”. This is the generally accepted position on the problems of emerging trends and preliminary data.

As discussed in the development of the null hypothesis and clinical equipoise, the purpose of a RCT is to disprove the hypothesis of equivalency
between 2 or more therapies. Until this difference is proved statistically, the 2 therapies must be considered to be equivalent. The scientific community has chosen arbitrarily to say that something is true when the probability is less than 0.05 that it could have occurred by chance. This choice, although arbitrary, reflects a consensus developed among scientists, statisticians, those responsible for developing federal regulations in relevant fields, and others. Although some argue that the significance level should be set lower, with disclosure at p < 0.1 or p < 0.2, the existing regulations supported by scientist remains at p < 0.05.

The consent process is used to educate prospective subjects about the null hypothesis to be tested in the RCT. Subjects should be informed that the RCT has been designed so that neither the investigator nor the subject will be aware of superiority of one therapy until the arbitrarily pre-selected criteria of significance are achieved. Thus, by giving consent to participate in the study, the prospective subject is accepting the concept of equivalency of therapy until the standards of proof agreed upon by the community of professionals proves differently.

Data monitoring committees

Data monitoring committees are often used in large-scale, multicenter RCTs and are charged with the task of monitoring data collected during the RCT. Their specific task is to determine if the trial should be modified or discontinued, or whether the consent procedures should be altered (21). This committee is independent of the investigators and subjects, and their deliberations are secret until a change or termination is warranted. As previously stated, this committee is critical for terminating a study when statistical significance is noted between treatment arms.

The data monitoring committee can serve an important task by maintaining clinical equipoise for the providers involved with the RCT. They can monitor the data for patient safety and statistical significance, while the confidential nature of their findings will prevent introduction of bias to the investigators. The dilemma for care providers who have knowledge of emerging trends is that they will be faced with the conflict of permitting some of their patient-subjects to continue to receive what appears to be inferior therapy (22, 23).

Obsolescence of RCT due to new knowledge

All individuals involved with a RCT must monitor new information that may alter the paradigms associated with treatment of the disease studied in the trial. This point is particularly relevant for multiyear trials as new information on the disease process under study becomes available.

Informed consent

The informed consent process is designed to educate potential research subjects about the research study being conducted and to inform them as to their involvement in the project if he/she agrees to participate. Through this educational process, it is intended that the patient will fully understand what will/may happen to them in the study thus allowing them to choose self-determination of care outside the research arena or participation in a randomization process for choosing treatment.

This consent process is important because patients differ in their values and preferences and may find the quality of life offered by 1 or the other treatment to be as important to them as the possible outcome. Although 2 treatments may be medically equivalent in terms of life expectancy, they may be vastly different in terms of the value that the prospective subject attaches to the quality of life that he or she may enjoy while awaiting the outcome.

A dramatic illustration of this was a RCT comparing radical mastectomy with wide excision in the treatment of early breast cancer (24). The 2 treatments were judged to be potentially medically equivalent in terms of outcome measures such as life expectancy and probability of recurrence of cancer. However, one of the treatments was, to quote the investigators, of a "mutilating character". Consequently, from the perspective of the patient-subjects, the two approaches to therapy could not be considered equivalent.

Another purpose of the informed consent is to decrease the burden on the investigator, allowing the patient to knowingly assume some of the risks involved with human experimentation. A good example is enrollment of a patient in a placebo controlled trial studying treatment of a disease that produces irreversible damage; e.g. periodontal disease and hypertension. If the patient gives informed consent, he/she understands that criteria have been established that will precipitate his/her exit from the study if the disease progresses, but also accepts the possibility that further damage produced by the disease process may be irreversible.

Elements of informed consent

A number of different issues should be addressed during the informed consent process. Some institutional review boards suggest that these elements be covered in the consent form using an outline format.
with headings to clearly identify the purpose of each element.

Although all elements may be necessary for some studies, specific elements may be irrelevant for a particular trial. Each element must be reviewed when constructing a consent form to verify that the document educates and informs the patient about the study, and clarifies what their participation will entail. Every effort must be made to write the consent form such that a person with a 6th grade reading comprehension will understand.

**Invitation to participate in a research study** – The patient must be informed that they are being asked to participate in a research study, and that their participation is voluntary. They must understand that they can refuse to participate or that they may withdraw from the study without any effect on the services they would receive if they did not participate in the study.

**Purpose of study** – The purpose of the study should be accurately described in lay terms. There should also be a statement of the number of patients involved in the study.

**Alternative treatments** – Any alternative therapies should be described, and a disclosure of the benefits and risks of the alternative therapy should be included.

**Description of their involvement in study** – The procedures used in the study should be described. The consent form does not need to give great detail about procedures that will be done as part of standard of care, but it must be made clear how the subject’s treatment/care will differ from standard care. Also, any use of experimental drugs or devices, or new treatment methods must be clearly stated. Finally, if it is possible that significant new findings from other studies may become available that might affect the subject’s willingness to continue participation, the subject should be told that this information will be provided.

**Time commitment** – The amount of time that the subject will devote to the study should be specified, along with a statement of how this time commitment will differ from the time involved in standard care.

**Mechanism for orderly withdrawal from study** – In some studies, it could be injurious or impossible for the subject to abruptly withdraw from a study. It may be deleterious to stop taking a drug without going through a tapering dose phase-out period. Another example would be recovery of a non-resorbable membrane. The patient must have a second surgical procedure to remove the membrane, even though they wish to withdraw after the first surgical procedure. Therefore, in these studies, a procedure for what would be done if the patient wished to withdraw from the partially completed study must be described.

**Termination of participation** – Circumstances develop in some cases where the investigator may need to terminate patient participation regardless of the patient’s wishes. Two examples are withdrawal of the financial sponsor and termination of the study because interim analyses show statistical significance. The patient should be informed of these circumstances in the informed consent.

**Benefits** – A statement should be made of benefits to study subjects and to others.

**Risks** – A description should be given of any anticipated discomforts and risks and their likelihood of occurrence. When appropriate, a statement should be included that there may be unforeseeable risks.

**Compensation for injury** – If there is a risk of injury, a description of provisions for treatment and compensation should be included in the consent form. In addition, a statement should be included that injuries should be reported to the investigator and to the IRB. If there are no provisions for compensation/treatment in the event of injury, many IRBs require specific wording that compensation is not available, but treatment facilities are available, just as they are to the community in general.

**Financial considerations** – A specific statement of any free drugs/services should be made, including the length of time participants will receive them. A statement of any additional costs that the subject might incur from participation should be included. Also, any reimbursement for expenses and compensation for participation should be described. If compensation is dependent upon completing certain portions of the study, the schedule of payment should be given. Also, the level of compensation must be evaluated carefully to determine that it is not coercive.

**Confidentiality/anonymity** – In protocols labeled as “sensitive”, the subjects have a condition or history that they would not wish to be known by others. For example, illegal drug use, sexual practices, etc. In these protocols the only acceptable identifier is the study code number, and personal identifiers must be masked from the sponsor’s representatives.
Identifiers other than study code number must be masked for all studies. If the sponsor wishes to retain confidential follow-up information, the sponsor must form a written and signed agreement with the IRB that the information can only be removed from a sealed envelope upon approval of the IRB. If the study is neither sponsored nor under the purview of the FDA, a description of access to identifier and the mechanism for maintaining confidentiality/anonymity must be provided.

Specific wording for protocols involving sponsors and the FDA is generally required by each IRB. This wording has been developed to cover the above issues.

Contact person for further information about study – The name and telephone number of the principal investigator should be provided in addition to a statement that the investigator will answer any questions regarding the study.

Final statement – Immediately before the signature lines for the informed consent, the subject should be asked to make sure that all of their questions have been answered. In addition, a statement should be included that they may direct questions regarding rights as a research subject to the IRB office, and that they will be given a copy of the consent form. Finally, there should be a statement that they are agreeing to participate by signing the document.

Summary

The role of the RCT in the future is unclear. The logistics of conducting a multicentered trial has escalated the costs of new agents in terms of both time and money. In many cases, the decision to conduct a RCT is made on the potential profitability of the product/agent under test. Whatever the reasons credited for conducting an RCT, the research must be adequately designed to protect both the subjects involved in the study, as well as humankind from erroneous data.

References