The Randomized Controlled Trial: An Ethical Victory or Dilemma for Biomedical Research?

By Andrea Dumbrell

Since gaining acceptance from the late 1940s as exemplifying the gold standard of clinical reporting, the medical community has disputed the ethics of Randomized, Controlled Trials or RCTs (Friedman et al., 1996; Hellman and Hellman, 1991; Passamani, 1991). The rationale behind using RCTs is based on sound evidence that they reduce the potential for biased results within a study, and improve strategies for preventing and treating a wide variety of medical conditions and diseases (Elwood, 2000; Moher, 1993). Indeed, as modern pharmaceutical research continues to develop potential therapies, the RCT has flourished as the preferred method of evaluating the efficacy of new drugs and procedures. However, key components of RCTs present the opportunity for ethical inquiry (Beauchamp and Childress, 1994; Elwood, 2000). In this article, current arguments in favour and in criticism of randomization, informed consent and placebo use in RCTs will be presented.

Randomization refers to the process of assigning participants to either intervention or control groups of an RCT. It can be single-blinded (where only a physician or investigator is aware to which group a participant has been assigned), or double-blinded (where neither the physician nor the participant are aware to which group the participant has been assigned). Double-blinded studies are preferable, as they reduce the potential for bias on behalf of the investigators (Elwood, 2000). An investigator's preconceived ideas regarding possible outcomes will have little effect on the response of the participants, since he or she does not know the arm of the study in which the participant is taking part. Although it can never be totally eradicated, an effectively blinded, randomized trial substantially minimizes the possibility for bias in the results of an RCT (Beauchamp and Walters, 1999; Friedman et al., 1996).

Notwithstanding, randomization does present an ethical challenge. Inherent in the process of randomization is the concept of clinical equipoise, in which there is a "state of genuine uncertainty regarding the comparative merits of treatments A and B for a population P" (Freedman, 1996). In other words, no arm(s) of the RCT should be considered preferable in terms of efficacy of treatment. This requirement is considered ethically problematic by many physicians, especially in the case of RCTs dealing with terminal illness; illness for which there is no known cure, such as AIDS or advanced cancer (Beauchamp and Childress, 1994; Beauchamp and Walters, 1999). Here, a new treatment has the potential for effectiveness against a terminal disease, yet the control group must be assigned to either a placebo or a possibly less effective treatment (Friedman et al., 1996; Hellman and Hellman, 1991). Interest groups and physicians concerned with compassion for such patients put forth the argument that participating in a RCT may present the individual's only opportunity to receive the possibility of beneficial medication (Schuklenk, 1998). The fact that accepting this argument would require altering the present, historically supported means of legitimizing new drugs compounds the ethical difficulties of randomization, particularly in the case of terminal illness.

Another keystone feature of a RCT is the informed consent of the participant. Informed consent dictates that the individual has the right to choose whether or not to join a study based on a full disclosure of its methods, treatments, method of randomization, possible side effects and risks (Beauchamp and Walters, 1999; Beauchamp and Childress, 1994; Passamani, 1991). Presumably, if the potential participants possess this knowledge, they can make a reasonable judgement as to whether they should consent to participate in the study (Friedman et al., 1996). The Declaration of Helsinki, which outlines the principles of ethical

The Cloning Revolution

By Zain Kassam

Currently, human cloning has not been proven clinically viable; however, the importance of exploring the ethical and social concerns surrounding it transcends any specific cloning technique. (Robertson, 1998). This is because the genetic modification revolution is moving faster than ever before, and ethics are often being left to the backburner in pursuit of pushing human knowledge to its limits. It is during these times that steps must be taken to ensure that the public and government is well educated before hasty and uninformed decisions are made. Logical risk assessment, and not heated emotion, should be used in making any important decision. As a new and controversial science, human cloning may have potential benefits, but the detractors of cloning have wrongfully dismissed this area of study for erroneous reasons instead of the realistic dangers it may presents to society.

It is important to understand the nuclear somatic transfer (NST) cloning technique that has caused a great deal of concern in order to get a basic and general understanding of the positives and negatives that can be attributed to this process. This procedure entails grafting an adult human somatic diploid nucleus into a human ovum where its original nucleus has been removed. (Pence, 1998). For this cloning technique to be completely successful a number of intricate transformations would have to occur, for example the fusion of the somatic nucleus to the modified ovum and differentiation of the adult cell nucleus in its new environment. (Kassirer and Rosenthal, 1998). Furthermore, the new cell must have the ability to divide into daughter pluripotent stem cells, which can differentiate into specific tissue (Kassirer and Rosenthal, 1998). A number of these steps have been successfully executed on animals in the laboratory, and it should be noted that this human cloning technique could facilitate the growth of a duplicate specialized cell or an entire organism depending on the alterations in culture. (Wade, 1998).

continued on page 21

biomedical research practices involving human subjects, clearly states,

> In any research on human beings, each potential subject must be adequately informed of the aims, methods, anticipated benefits and potential hazards of the study and any discomfort it may entail. He or she should be informed that he or she is at liberty to abstain...or withdraw his or her consent to participation at any time.

As common sense would thereby suggest, informed consent is an essential ethical aspect of the patient's right to autonomy and self-determination when participating in a clinical study.

Nevertheless, there are a number of scenarios in which the common notion of informed consent may present serious ethical concerns. The study of vaginal microbicide effectiveness-trials by Ramjee et al. in 2000 illustrates one such example. Efficacy (phase III) trials were conducted on female sex workers in Thailand and South Africa in order to determine the effectiveness of a gel in preventing HIV and STD; however, as the study progressed, it was clear that a high level of illiteracy and a minimal level of schooling among the participants severely impaired the possibility that they fully understood the nature and possible side-effects of the study. Due to a considerable difficulty or inability to comprehend the study's potential consequences; for example, since the placebo gel and possibly the active gel would not protect participants against HIV or other STD contraction, the participants' consent to take part in this study could hardly be considered "informed". The concept of informed consent is also compromised when patients may not be in a position to give fully voluntary consent, as in the case of some psychiatric disorders, for example (Lavori and Sugarman, 2000). Returning to the previously stated excerpt from The Declaration of Helsinki, patients with impaired mental faculties due to various types of disease also present a substantial challenge to the tenets of informed consent. In both of these scenarios, one must consider the difficulty of ensuring that the participants in a study are truly informed in their consent to participate in a clinical trial.

An investigator's preconceived ideas regarding possible outcomes will have little effect on the response of the participants

In addition to randomization and informed consent, the use of a placebo, a pharmacologically inert substance, is a typical feature of a RCT (Beauchamp and Walters, 1999; Beauchamp and Childress, 1994; Friedman et al., 1996; Hellman and Hellman, 1991). When a new treatment becomes available for phase III trials, its effectiveness must be compared against a non-treatment or control arm. This control group is commonly administered a placebo, either on its own or in conjunction with established therapy for the condition (Lavori and Sugarman, 2000). The placebo is used in order to blind the participants — and in double-blind studies, the investigators as well — to the knowledge of whether they are in the active treatment arm of a study (Bok, 1974). Without a placebo, the potential for biased results greatly increases (Elwood, 2000). By comparing the active treatment group with a placebo group, the possibility of a statistically significant difference in the new therapy can be evaluated with much greater certainty.

Despite the placebo's pharmaceutically inert composition, ethical issues are raised by its use in RCTs. Many articles have recently tackled the ethical implications of conducting placebo-controlled trials with HIV infected participants (Mann and Tarantola, 1996; Walters, 1988). Following Fischl et al.'s 1987 study on the efficacy of AZT (azidothymidine, or zidovudine) on patients with HIV/AIDS, the drug became the only known therapy that decreased the frequency of opportunistic infections due to the virus. Given this evidence, it was considered standard therapy, as any studies on the disease after 1987 would be compelled to use AZT as a control treatment. As recently as 1998, however, placebo-controlled trials for AZT were being conducted in Thailand and other developing countries, despite the decade-old knowledge of the short-term effectiveness of AZT (Beauchamp and Walters, 1999). The use of placebos as a control arm when there is an established, beneficial therapy as an alternative contravenes the ethical conduct of clinical trials as dictated by the Declaration of Helsinki. In addition to this example, some see the use of placebos as deceptive on the part of the investigator (Bok, 1974). According to Bok, the use of placebos in experimentation is based on a breach of the concept of informed consent because the patient is not informed as to the exact substances in the placebo. Placebos are "intrinsically misleading", to the point that informed consent is impossible. These and other similar examples suggest that the routine use of placebo-controlled trials may not be appropriate for some RCTs.

Given the ethical controversy that surrounds these three aspects of RCTs – randomization, informed consent and placebos – it is clear that shortcomings still remain in today's standard methods of clinical reporting. As many articles on bioethics have described, much of this debate is based on conflicting theories of morality. RCTs are a unique and laudable attempt to balance the Kantian values of human dignity and rationality with the utilitarian idea of the "greatest good for the greatest number" (Hellman and Hellman, 1991). Clearly, an appreciation for the complexity of the ethical consequences of these philosophies is essential when investigators are designing RCTs. As the examples in this article suggest, RCTs provide results with admirable clinical accuracy, but modern medical considerations like terminal disease and international efforts in medicine demand a constant re-evaluation of the appropriateness of such methods of experimentation.

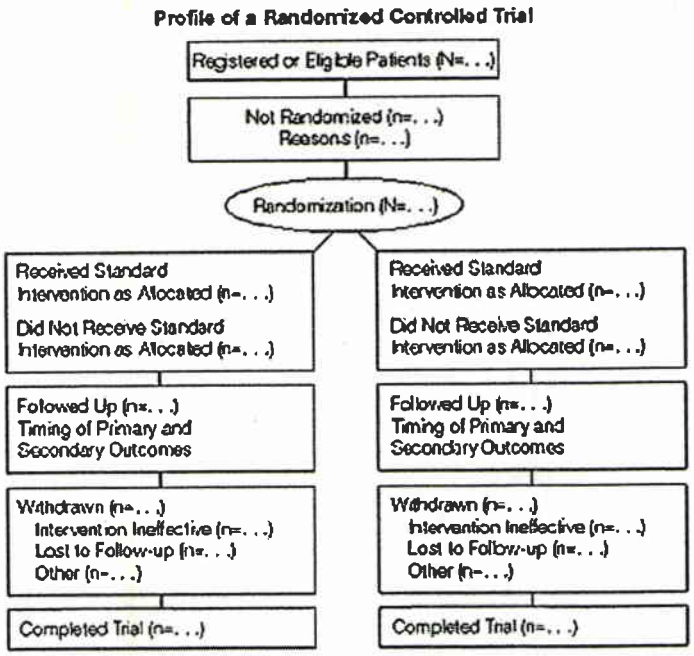

Figure 1:
A flow diagram representing the standard composition of a randomized controlled trial (RCT). Although accepted almost universally as the most reliable method of clinical reporting, the RCT still contains significant ethical obstacles.