ETHICAL ISSUES OF RANDOMIZED CONTROLLED TRIALS

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ABSTRACT: Clinical trials involve the application of different medical interventions on human participants. Randomized controlled trials involve different groups of human subjects undergoing different clinical interventions. This process ensures bias free subject allocation which leads to a way to statistically establish the research result. Strict ethical guidance is necessary from selection of participants to the analysis of trial results. Without proper guidance the trial participants would be subjected to unethical experiments. Before starting the randomized controlled trials the investigators must meet all ethics issues. The institutional review board (IRB) must check whether all ethical demands are met or not before permitting the research.

key words: randomized clinical trials, ethics, clinical research

INTRODUCTION: A randomized controlled trial is an experiment that is designed to check the effectiveness of a medical intervention by comparing it with another medical intervention in a control condition. Intervention is not restricted to treatment only, it includes all sorts of clinical manipulations offered to the trial participants that may affect their health[1]. During a randomized controlled trial the participants are assigned to separate groups to compare different treatments. The trial participants are assigned randomly, i.e. they are not given any chance to choose a group. The groups should be similar in some extent so that the different interventions can be compared easily. Before starting the trial the researcher should establish the necessity of the comparison. Some researchers considered randomized controlled trials as the most powerful tool in modern clinical research[2] while some others consider randomized controlled trials to be the best of all research designs[3]. The probable reason behind this is to equalize other possible causes that may affect the result of a research. This helps to attribute the difference in result between the two groups to the applied clinical interventions. Thus it ensures the validity of the research outcome.

METHODS: This is a review article done during research ethics course of Bangladesh Bioethics Society in collaboration with National Institutes of Health, Bethesda, Maryland, USA through video conferencing on September 25 through November 11 of 2013. The search was confined to Google search and pubmed published articles. Key words was 'RCTs, ethical issue and clinical research'.

IMPORTANT FEATURES OF RCTS: RCTs are very useful in determining the causal relationship between different interventions and their results. This is due to some salient features of RCT that differentiates it from other clinical trials. The participants are randomly allocated to various treatment groups. Both the participants and the researchers are sometimes uninformed about which treatment is given to which patient. Even both the groups are treated in the same manner. This method of keeping both the trial and control group uninformed about their treatment is called 'double-blind' test. The aim of the randomized control study is to measure the difference of a targeted outcome

between the trial and controlled group[4]. Sometimes large population is needed for conducting RCTs to establish statistical significance of the result.

ADVANTAGES OF RANDOMIZATION: Randomized controlled trials are advantageous in various ways. Proper randomization is very important to make a clinical research outcome authentic. Randomized clinical trials can cancel any chance of bias during selection of participants. In case of blind test both the investigators and patients are unaware about the type of treatment. RCTs establish that the significant differences in research outcomes are due to the difference in interventions only[5].

PROCESS OF RANDOMIZATION: Randomization of patients to different control treatment groups can be done by following two different steps. Appropriate implementation of these interrelated steps is necessary for authentic randomization. At first we have to generate a random allocation sequence. This sequence should use arbitrary numbers. Random number list can be used. Computer programs that can generate arbitrary numbers are available now. The next step is the implementation of concealed allocation sequence. For achieving this goal, a central trial coordination centre should be established. The drugs should be coded before dispensing. There should be a way of monitoring the drugs that are being used for trial purpose[6].

ETHICAL ISSUES REGARDING RCTS: One of the biggest drawbacks regarding RCT is that it needs to follow a lot of ethical guidelines. This is time consuming and sometimes may affect the validity of the trial significantly. Though a lot of enthusiasts advocate for RCTs many important aspects of health care cannot be subjected to a RCT for ethical issues. Before conducting a RCT we must ensure that there is equipoise i.e. there should be a doubt about whether one course of action is better than another [7].

When there is a chance that one group of the study patients is going to get the better treatment than the other a question arises about the ethical basis of that trial. RCTs are designed when there is enough uncertainty about whether the new treatment is better than the existing one or not. This balance is known as equipoise. Without establishing this equipoise we should not go for any randomized clinical trials. Both of the groups should have the equal possibility of getting the better treatment before starting the treatment.

Thus for meeting the ethical demands a randomized controlled trial must ensure:

- Free and independent choice of the participant without coercion
- Provision of informed consent of the participants
- Maximum benefit with minimum risk
- Equal opportunity for all to participate in the trial
- There is no therapeutic misconception in the mind of the participants
- Bias free trial in case of industry funded research

Free and independent choice of the participant: There should be no coercion or any sort of undue influence for taking part in the research. Those who are willing to participate should know that they can withdraw from the program anytime in the future if they wish. They should also be informed that they can refuse the offer to participate in the

program if they want. The total process should be free from any sorts of undue influence that may motivate the patient to participate in the program[8].

Provision of informed consent of the participants: Informed consent means the free consent of the participant about taking part in the trial. The investigators must provide sufficient information enough information about the possible risks and benefits. The objective of informed consent is to protect both the investigator and the participant. This ensures that the investigator has not deceived the participant. The researcher should ensure that the subject of the research has given the informed consent in written format. They should be given sufficient time to consider the proposal. The participant should sign at the end of the form[8].

Maximum benefit with minimum risk: In case of studies where the risk of harm exceeds the 'minimal' level it is necessary to establish that the expected benefit outweighs that risk distinctively. A study will be ethical only when the benefit clearly offsets the possible risk factors. The Helsinki Declaration[9] and the CONSORT Statement[10] stress a favorable risk benefit ratio. The Declaration of Helsinki states that, "All medical research involving human subjects must be preceded by careful assessment of predictable risks and burdens to the individuals and groups involved in the research in comparison with foreseeable benefits to them and to other individuals or groups affected by the condition under investigation. Measures to minimize the risks must be implemented. The risks must be continuously monitored, assessed and documented by the researcher." Physicians may not be involved in a research study involving human subjects unless they are confident that the risks have been adequately assessed and can be satisfactorily managed[9].

Therapeutic misconception in the mind of the participants: Therapeutic misconception refers to the misunderstanding in the participants mind about the difference between clinical trial and treatment. Some participants believe that the trial is a part of their treatment and if they do not agree with the trial they will not receive their treatment properly. This was first discussed by Paul Appelbaum *et al.* in 1982[11,12,13].

Bias free trial in case of industry funded research: Clinical trials are frequently conducted under the collaboration of pharmaceutical industry with researchers. In those cases there is a possible chance of biased result. One of the most well-known examples of bias involves the selective serotonin reuptake inhibitor (SSRI) paroxetine (Paxil), an anti-anxiety medicine. The pharmaceutical company funding this research suppressed results from four trials that not only failed to show treatment effectiveness for off-label use of its SSRI among children and teens, but also showed possible increased risk of suicidal tendencies in this age group. In case of funding of drug studies by the pharmaceutical industry the research team must ensure that the industry will not affect the trial result to be biased for their benefit. The investigators who are involved in various steps of the research should clarify whether they have any industry ties or not. The IRBs must check for conflict of interest among the researchers.

CONCLUSION: Clinical trials are the primary means to evaluate the efficacy and safety of new drugs and other medical technologies. RCT is the 'Gold-standard' for clinical trials. RCT allows to check the efficacy of different interventions in groups with varying risk factors. Randomization eliminates the chance of investigator bias while selecting the participants for different groups. This method also checks whether the research outcomes are statistically significant or not. However, before designing a RCT the ethical issues should be clarified properly. The IRBs must check whether the research proposal meets all the regulatory and ethical demands or not.

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