

ETHICAL ISSUES IN RANDOMIZED CONTROL TRIALS: A REVIEW

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Abstract

Randomized Control Trials (RCTs) are scientific experiments that are used to investigate the effectiveness of various interventions in the field of Medicine and public health. As a result of complexity of the process, even the competent individuals are not able to understand the process of randomization with anticipated consequences associated with it. There is rise in trend of research and conduct of RCTs in developing countries; hence, there is a need to review all ethical issues confronted by the researchers during conduct of such trials. An Online literature search was carried out in April 2015 to May 2015 from Google Scholar, BioMed Central Ethics and PubMed using the key term "Trials", "Randomized Control Trials", "Ethical issues" and various synonymous terms from the titles of the articles. This resulted in 25 articles. Following, which these articles were scrolled down, and all articles with ethical issues encountered with different type of trials, were included. Avoiding the duplication of issues, 13 articles were finally selected for review. From the review narrates that ethical issues of patient autonomy, informed consent, therapeutic misconceptions, state of equipoise for individuals, clinicians and researchers, controversies between placebo and active control orthodoxies, design biases, role of gate keepers, benefit verses risk assessment and protection of vulnerable groups are the important ethical issues highlighted by various researchers. There can be issues related to some surgeries, early cessation of RCTs due to some apparent benefits and conduct of trials in third world countries. It is imperative that institutional review boards should consider all such issues during ethical assessment of such trials.

Keywords: Benefit verses risk assessment Institutional review board (IRB), Randomized Control Trials (RCTs), vulnerable groups.

1.Introduction

Randomized Control Trials (RCTs) are scientific experiments that are used to investigate the effectiveness of various interventions in the field of Medicine and public health. RCTs and systematic reviews of many of these trials are considered to be the best body of evidence for judging the effectiveness of interventions. [1]These trials can be aimed to assess the impact of interventions at individual level or at cluster levels. The intervention tested in the trial can be medical and pharmaceutical interventions or surgical interventions. In all these types of trials, process of Randomization, which is conducted to minimize the bias, acts as the backbone of the trial. Randomization may involve assignment of individual participants into intervention and control arms or sometimes, cluster of people in both groups. Despite being experiments producing one of the highest body of evidence, RCTs are confronted with various general ethical issues as faced by any kind of research as well as few specialized problems specific to RCTs like harms associated with the use of placebo or controls. Moreover,

issue of informed consent is also very important. As a result of complexity of the process, even the competent individuals are not able to understand the process of randomization with anticipated consequences associated with it. There is rise in trend of research and conduct of RCTs in developing countries; hence, there is a need to review all ethical issues confronted by the researchers during conduct of such trials.

2.Methodology of Review

An Online literature search was carried out in April 2015 to May 2015 from Google Scholar, BioMed Central Ethics and PubMed using the key term "Trials", "Randomized Control Trials", "Ethical issues" and various synonymous terms from the titles of the articles. This resulted in 25 articles. Following, which these articles were scrolled down, and all articles with ethical issues encountered with different type of trials, were included. Avoiding the duplication of issues, 13 articles were finally selected for review.

3.Findings of The Review

Following is the brief review of ethical issues associated with Randomized control trials highlighted in various articles:

a. Kodish et al in 1990, examined two case studies i.e. first Zidovudine trial in which AZT was given to intervention group (n = 145) and placebo to control group (n = 137). After termination of trial at 27 week, all participants were offered AZT. The second study was National Surgical Adjuvant Project for Breast and Bowel Cancers (NSABP) study of segmental mastectomy. In this study, outcomes of patients with breast cancer were assessed for three-treatment groups i.e. segmental mastectomy with and without radiation and total mastectomy. They highlighted that in first study, critiques identified that freedom of the patients to make voluntary choices was overridden and individuals only participated because AZT was only available in the trial. In second study, there was less enrolment by treating physicians owing to concerns related to physician patient relationship, issues of informed consent, conflicts of interest between physician as researcher and clinician and their personal responsibility towards their patients. To cater for these, author recommended that legitimate ethical and scientific concerns of the clinical investigators and patients should be incorporated in the policy. Moreover, physicians should enroll patients only if they cannot judge preferability of any arm for the patient. (Clinical equipoise). Moreover, RCT may be modified according to preference of the patient for either arm[2].

b. Sara J L Edwards in 1998 highlighted perspectives of general public and health care professionals regarding ethics of trial after conducting a review of various Randomized Control Trials. Author highlighted that many times the doctors do not take the informed consent seriously. Secondly, large numbers of participants enter even the phase III trials with the motives of self-interests rather than Altruism. Ethical aspect is whether they have any realization that the medicines used for intervention are routinely available and they can be deprived of this treatment being in control arm. It also illustrated that many physicians are still ready to enter their patients in the trial even if they are not in a state of equipoise and have clear preference for any one arm of the trial. Regarding participants' behavior, it was found that their willingness and consent rates dropped with an increase in awareness regarding the preliminary data so rights of the participants for informed consent and participation willingness conflict with each other. It was also emphasized that patient's autonomy is compromised because of the desperation for treatment freely available through trial that compels the person to participate. [3]

c. Sara J L Edwards in 1999 also elucidated ethical issues related to design and conduct of cluster trials. It highlighted that in individual cluster trials, autonomy is important while in case of cluster-cluster trials, utilitarian welfare of cluster is of utmost importance but clarity is required on ways of defining the best interest

of the group. It should include concepts of equity, expected utility and distributive justice and trust within the cluster should be build up by consultations with members. The procedural safeguards should be present according to risks of cluster interventions. Informed consent should be taken from individual participants in Individual cluster trials while in cluster-cluster trial, the intervention is given to whole cluster and individuals are not independent so guardian can consent for entry of participants into trial as well as intervention. In addition to this authority, it is also imperative that guardians should sign their duties regarding the trial. [4]

d. Emanuel and Miller in 2001 illustrated the ethical issues associated with Placebo controlled trials. According to them, Placebo controlled trials are stuck between the two Orthodoxies. One is Placebo Orthodoxies depicting that placebo should be used unless there is a risk of death or permanent morbidity while the active control Orthodoxies that prohibit the use of placebo if there is an effective treatment available. They proposed a middle ground that placebo controlled trial should first be judged on scientific and methodological criteria i.e. high placebo response rate, waxing – waning course of disease, partly effective available therapies or low frequency of condition leading to requirement of enrolment of large people for trial. After evaluation on methodological grounds, it should be assessed on strict ethical criteria that there should not be more likelihood of research participants to die, have irreversible morbidity, severe harm or discomfort. Moreover, Institutional review boards must ensure presence of adequate safe guards to minimize the harms like exclusion of participants with increased risk of harm, minimal essential time period of placebo exposure for scientific validity, careful monitoring of patients, use of salvage medicines and stringent exit criteria for the participants with adverse events.[5]

e. Fries and Krishnan in 2004 studied the issues related to principle of Equipoise and design bias. Equipoise, also called uncertainty principle is a central ethical principle declaring that subject can only be enrolled in the trial if there is uncertainty about the benefit likely to incurred from one arm of the trial or other. They studied various industry sponsored RCTs to identify the trials where criteria of Equipoise was met, identified reasons for deviations, examine concept of design bias and they tried to develop some other ethical strategies that give subjects more autonomy and cater for their safety. They studied that every trial's results were in favour of sponsor so it can be predicted that Equipoise was violated. Moreover, there was element of design bias to increase scientific efficiency of the trial with less cost and number of subjects. They highlighted that there were conceptual and ethical issues associated with Equipoise because it does not allow the researcher to consider potential social benefits or risks to the patients. It implicitly encourages the researchers for negative studies by limiting the expected differences between different arms and ignores the principles of autonomy and social benefits. Based on all this study, researchers suggested two principles for RCT, first being "reasonable positive expected value" which declares that patients accept trial on the basis of expected value of pooled outcome of the trial verses outcome after declining the trial and it does not depend upon the outcome of individual arms. Second principle is patient autonomy; in which patient can decide enrolment in trial based on full factual review of expected outcomes. Sometimes on principle of Altruism, despite minimal increase in own risk, patient may enroll for value of social progress. Based on study of these principles, they suggested that principle of equipoise with inappropriate design must be abandoned due to its neglect towards patient autonomy; safety and potential benefits to the society and alternative principles like reasonable positive expected value and autonomy should be considered. [6]

f. Donner and Klar in 2004 studied the issues of informed consent in cluster randomized control trials. In

case of these trials, it is not possible to take informed consent from every individual as clusters comprise of large communities and intervention may be a media campaign. In such cases community leaders, elected and appointed official can act as surrogates on behalf of community. Therefore, the concept of guardians and gatekeepers is important. It should be informed to Institutional review board that how the issues of participant's consent are addressed and what was the timing of the informed consent. [7]

g. Mueller et al in 2007 described the ethical issues associated with early stopping of the trials and informed consent. It is becoming more common that trials are stopped on some apparent benefit from the study. According to the authors, early stopping of the trial is unethical because there is a tendency of these trials to overestimate the effects of an intervention. By study of other trials that were continued despite initial success, the results were different. Regarding informed consent, it can only occur with prerequisites of voluntariness and competency of the participants for decision-making and necessitates that any change during the trial should be communicated to participants. If the trial is stopped early after informing participants regarding preliminary results with knowledge of superior treatment, the equipoise will be lost and patients will invariably choose superior treatment. If trial continues after informing patients, the blinding will be lost and patients may cross over to other arm or leave the trial. Solution based on this study is that large number of events should accumulate before interim examination of data by data monitoring committee and enrolment should continue to ensure consistency of the trends. This methodology should be included in protocol at the time of registration and communicated to all the participants of the trial. In addition, journals should demand investigators regarding justifications for early stopping of trial. There should be consideration towards context of illness and treatment while deciding for early stopping of the trial because for toxic and expensive treatment, adverse consequences of overestimating the effect and early stopping can be grave. In context to these issues, we should understand the biases associated with early stopping of trial, have stringent stopping rules and take into account the adverse impacts likely to incur as a result of these overestimated effects.[8]

h. Nishimura et al in 2013 conducted a systematic review of RCTs and evaluated interventions that were designed to improve the process of informed consent for the research participants. They highlighted that in a large proportion of cases there is little understanding of the procedure by participants while giving consent. In context of rapid expansion in research like genetic research, bio-banking etc., it is imperative that the informed consent processes should be stringent and flawless. Quality improvement measures have been undertaken to improve the designs of the consent forms, information contained in them with use of multimedia tools and counseling. Main aim of all the measures was simplification of consent form and improvement in understanding of potential participants. These interventions showed a mixed impact on improving the participant knowledge. The Meta-analysis demonstrated improved understanding and outcomes with the modified consent forms and extended discussion. Secondly; Multimedia interventions are not significantly effective but can help in long-term knowledge retention. This may help to keep the participant in picture and by considering himself to be partner in the research process, he may remain voluntarily in the trial. Studies involving quiz may be effective but data on these is not much to draw effective conclusion. There should be cost effective guidelines for informed consent so that researchers and organization can implement them while conduct of trials. [9]

i. Jyotirmoy Sarker in a review article, in 2014, presented the ethical issues of Randomized Control Trials. Author highlighted that few ethical issues must be catered for before conduct of Randomized control trial. First, there should be a state of Equipoise i.e. doubt regarding one course of action or other. No coercion should

be used for selection of the participants. Sufficient information should be provided to the participants for understanding of the trial and provision of informed consent. Expected benefit of the study should outweigh the risk and there should be continuous monitoring of the risk. There should be no element of therapeutic misconception i.e. participant should clearly understand the difference between the trial and the treatment. In last, the trial should be bias free and there should be no conflicts of interest. These issues should also be assessed by the IRB before review of the trial. [10]

j. Rogers et al., in 2014, illustrated ethical issue linked to Placebo Controlled Surgical Trials used for assessing the efficacy of surgical interventions. Placebo control surgical trials are even more controversial than medicinal trials. The opponents oppose the trials because of risks to the participants like pain and scarring while proponents highlight the necessity of the trial because by any other method, it is difficult to find out that apparent benefit is because of intervention or placebo effect etc. Author narrates that because of nature of surgical interventions and surgical placebo effect, it is justified to conduct Placebo controlled surgical trials when there are minimum risks, outcomes are subjective and there is no other comparison group. To strengthen the ethical assessment of placebo controlled surgical trials, there should be structured consultation with relevant community regarding risks and benefits of the trial and therapeutic misconception should be addressed through use of educational material that can make things understandable for participants. Moreover, ethical considerations should incorporate position of non-surgeon clinicians who are involved in dealing with these participants. [11]

k. Marcia in an editorial in 1997 discussed another perspective of ethics encountered due to conduct of RCTs in third world countries. After highlighting the Tuskegee study, the author narrates that the research in third world seems more attractive to researchers because of better funding and less regulations in those countries. Mostly, these are those studies that cannot be conducted in own countries due to regulations and ethical issues, hence are conducted in third world. She discusses that, for control groups, the “standard care” should be best local available care in that underdeveloped country or best possible care available in country that is sponsoring the trial. She emphasized that it is imperative that research community should re-strengthen the commitment towards highest ethical standards irrespective of place of trial. Moreover, sponsoring agencies should also support and enforce those standards instead of violating them. [12]

l. Karlawish and Pack in 2001 in an editorial also highlighted ethical issue of deceiving the patients and informed consent based on study of Randomized and Placebo-Controlled Trials of Continuous Positive Airway Pressure (CPAP). In these studies, for testing the efficacy of nasal CPAP, two placebos were used; sham CPAP and placebo capsules. The investigators informed study subjects that placebo capsule might alleviate their problem while in reality they were not doing that. Main ethical issues in these trials were deception and withholding of information. In case of deception, there is violation of full informed consent because the subject is denied of disclosure of complete facts needed for informed consent. They illustrated that deception can only be appropriate if it is required for new knowledge and in this case full debriefing of the research subjects should be done after completion of the trial and efforts should be made that participants benefit from the knowledge gained by the trial. Finally, they recommended that definitive trials should be done to see the appropriate comparison groups and any justification of necessity of deception to produce valid and valuable knowledge.[13]

m. Weijer et al in 2011 conducted a systematic analysis of ethics of Cluster RCTs and raised many ethical issues associated with these trials. They highlighted that Cluster trials are required to be conducted when nature of intervention is such which requires implementation for whole cluster like mass media messages, training of

health professionals. Moreover, when investigator wishes to minimize the effect of contamination or to study impact at both individual and cluster level. They identified various ethical issues posed by cluster trials e.g. who should be counted as research subject in cluster trial esp. when intervention is on one person and outcome is assessed on other like training of health professionals and assessment of knowledge level of community. Secondly, who should give informed consent? They highlighted that individual indirectly impacted by study intervention cannot be declared as research subject so there is no need for their informed consent. Moreover, informed consent may be waived off if research poses no or minimal risk, has no effects on rights of subjects and there is no other option available to carry out research and debriefing of the subjects. Moreover, issue of informed consent from health worker is also important. Third issue was that clinical equipoise apply to Cluster trials or not and researcher have ethical obligation to provide more than usual care to research subjects and to stop trial if intervention appear unsafe or unusually effective. Fourthly, how to determine that benefit of the trial outweigh the risk. Fifth issue is that how vulnerable groups should be protected in cluster trials and finally who are the gatekeepers and what are their responsibilities. Moreover, how the balance can be maintained by these gatekeepers between individual and cluster interests. [14]

4.CONCLUSION

Findings from the review narrates that ethical issues of patient autonomy, informed consent, therapeutic misconceptions, state of equipoise for individuals, clinicians and researchers, controversies between placebo and active control orthodoxies, design biases, role of gate keepers, benefit verses risk assessment and protection of vulnerable groups are the important ethical issues highlighted by various researchers. In addition, there can be issues related to some surgeries, early cessation of RCTs due to some apparent benefits and conduct of trials in third world countries. It is imperative that institutional review boards should consider all such issues during ethical assessment of such trials.

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