

Bias in a Randomized Controlled Trial and how these can be Minimised

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Keywords: Randomized controlled trial; Treatment; Efficacy

Randomized Controlled Trial, involving random assignments of participants to interventions, is seen as gold standard to study the effectiveness of an intervention, and has been the most powerful method of research for centuries, with the first recorded clinical trial dated back to 600 B.C by Daniel of Judah [1]. While Sir Bradford Hill is known to be the pioneer of modern day clinical trials for his study on treatment of tuberculosis, it was the French study on treatment of pneumonia by P. C. A. Louis which really marked the beginning of major advances in clinical trial [2,3].

The term "RCT" is often used to describe randomized controlled trial to distinguish between comparing groups with the group not receiving treatment, and others comparing multiple treatment groups with each other. Randomized controlled trial is the most accurate method to measure the relationship between an intervention and desired outcome and to assess whether the treatment in question is cost effective and makes the difference in quality of life. The numbers of randomized clinical trials have grown in recent past, is now accepted as rule of thumb or gold standard to base clinical decisions for "evidence-based medicine, "and considered to be "the most powerful tool in modern clinical research" [4].

Randomized clinical trials are now fundamental to assess clinical efficacy in medical sciences. Randomized clinical trials can be classified according to (i) intervention types; explanatory and pragmatic trials, efficacy and effectiveness trials, and phase I, II & III trials (ii) exposures to intervention; parallel trials, crossover trials and trials with factorial designs (iii) number of participants included in the study; from n-1 to mega-trials, fixed size and sequential trials (iv) awareness of participants and investigators about the intervention being assessed; open trials, single blind trials, double blind trials and triple and quadruple-blind trials and (v) whether the study participant's preference has been taken into consideration in the design of the study; Zelen design, comprehensive cohort design, and wennbergs design [5].

Despite its preference among health care professionals, for the potential to control bias right from the beginning of the study, randomized controlled trials are not immune to bias. Bias is defined as "opinion or feeling" favouring one side in an argument over other or one item in a group or series; predisposition; prejudice [6]. In health sciences research, bias is defined as systemic deviation of results or conclusion from the truth due to systematic error in research methodology [7-9]. Other than bias, confounding factor, which is some aspect of subject and chance is a random error associated between an intervention and outcomes, have significant impact on the interpretation and general is ability of the results of a research project [7]. Bias in a randomized controlled trial can occur in a study design, planning stages, during the course of the trial, and bias that occur during the publication and dissemination of the trial.

Pre-Trial and Design Bias

Randomized controlled trials can be subject to a strong ethical bias, if the concept of "clinical equipoise" or "uncertainty principle" is not met during the planning stages and design of the study project. The

concepts of clinical equipoise requires a state of genuine uncertainty on part of a research investigator regarding the comparative intervention merits of each arm in a clinical trial. As this may lead to an insuperable obstacle to an ethical commencement of a clinical trial, now there is a general understanding, that this concept of clinical equipoise is satisfied if there is inconclusive agreement among the experts that no treatment is superior to other, and not necessarily on part of individual investigator [10]. In order to reach this agreement, a study was conducted to establish as how much clinical equipoise can be disturbed to ascertain the ethical credibility of a clinical trial. It has been argued that if 70% of experts favour one treatment over the other, half of participants would prefer to receive that treatment rather than being exposed to an intervention trial, and would render any human trial unethical [11].

Randomized trials are expensive, requires a lot of resources, and most randomized control trials to assess the efficacy of treatment interventions are funded and sponsored by pharmaceutical industry. This conflict of interest may then be attributed to systemic flaws in design of the study to generate favourable outcomes. Among 61 industries sponsored clinical trials to assess the efficacy and effectiveness of sponsored drug with their comparators, 100% favoured the sponsored drug and superior to the comparator [12]. Contrary to this most public funded randomized control trials met the general principal of uncertainty, while 74% of industry-sponsored clinical trials favoured the new intervention, and this financial conflict of interest has been noted to be widespread [13-15].

In industry sponsored trials, in most cases, the outcomes would have been established before initiating the clinical trials and during the drug development process, so there is a strong likelihood of design bias, thus moving away from the fundamental principal of clinical equipoise [16]. During the drug development processes, a promising outcome has been found as pharmacological studies, pharmacokinetics studies, animal studies, initial studies in human would have been undertaken, before the drug is subjected to expensive randomized controlled trial, and thus most likely to be designed for success.

This potential conflict of interest leads to a pre-determined flaw in the designed process. There is an ongoing debate, as whether design design bias is a good thing or bad thing. Is it ethical to subject human being to major risks without preliminary studies? Is it ethical to subject human being to drug toxicity, once the promising outcome has been established during drug development process? Is ethical to conduct randomized clinical trials for financial interest or prove one drug superior to the comparator?

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Received June 11, 2015; Accepted March 05, 2016; Published March 12, 2016

Citation: Gul M (2016) Bias in a Randomized Controlled Trial and how these can be Minimised. J Psychiatry 19: 357 doi:10.4172/2378-5756.1000357

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These industry-sponsored industry sponsored clinical trials have been dubbed as double-edge sword, and leading to strained relationship between academician and pharmaceutical sector [16]. It is understood that clinical trials are expensive, but moving away from industry sponsored trials to public funded clinical trials, would reduce drugs cost in long term, and would eliminate the incentive and the opportunity to conceal harmful side effects of drugs or exaggerated effectiveness, and public funded trials can be conducted at a lower cost than industry sponsored trials [17].

Selection bias

Even with highly sophisticated randomized method to allocate participants into different treatment arms, randomized control trials are not immune to selection bias, which can be introduced by the investigator (sampling bias) and by the study participants (response bias).

There will always be a reason for participant's attraction towards a trial or refusal to participate in clinical trials, which could make it difficult for the outcomes to be then generalized. This is because the informed decision to participate in a clinical trial happens before the randomization process. This preferential participation or non-participation can be seen as types of "response bias".

Selection bias also occurs on part of investigator or recruiter's prior to knowledge of participant's condition or co-morbid conditions which may either skewed the data with promising outcomes or in other direction. This "diagnostic purity bias" is common in randomized control trials. It has been found that investigator prior knowledge of patient may exaggerate the new intervention if randomization is not adequately concealed, with one study showing inadequate concealment may exaggerate the new intervention by an average of 40% to their competitor [18,19].

Furthermore an apparent random sample can be biased, as recruitment from registers, telephone directories; health care data base would exclude those who are not registered for one reason or another, thus making selection bias unavoidable. In addition to this sometime allocation concealments are confused with blinding, as random sequence generation and allocation concealment together constitute randomization, in order to minimise selection bias. The selection bias can be further reduced by process called "Stratification", which is to group the sample according to important characteristics to ensure these are equally distributed among the trial arms. "Minimisation" is another process, alternative to stratification, to ensure allocation ratio across trial arms. Although this is not a truly random process, but if performed properly with care, it minimise the selection bias. Another method to reduce selection bias is a procedure called block randomization to ensure similar numbers of participants are allocated to each arm of clinical trial.

In order to enhance the clinical significance of a trial, Quadruple-blind trial, although expensive would further reduce the selection bias. In Quadruple-blind trial, all four parties, including the patient, the clinician-caregiver, the outcome assessor, the statistician, are all blind what the patient received [20].

Publication bias

It is the randomized control trials, which received more criticism for publication bias than other research methods. It has been known that studies with positive results are more likely to be published compare to the ones with negative outcomes [21,22]. Failure to publish or not have been accepted for publication has been found not to be a random event, and were known to be influenced by the outcomes of a study.

Studies with promising outcomes as well those funded by industry were preferentially published over studies with negative results [23,24]. It has been found that external funding leads to higher probabilities of successful publication, but Elm et al. found that the probabilities of publication decreased with commercial funded studies, with government studies more likely to yield statistical significant result and published [21,22,25-27].

It has also been noted that research with statistical significance takes less time to get published, compare to the studies without statistical significance, and this "time lag bias" may raise further speculation about the validity of the study as early evidence could have been exaggerate [26,28,29].

It has been noted studies with positive results are more likely to be published in English journals [30]. There is also a speculation that trials associated with renowned academician and famous institutes are more likely to be published than trials originates elsewhere. Clinical trials originate from developing countries are less likely to publish in high impact journal.

Among many reasons described by the investigators for not publishing their trials were clinically insignificant results, statistically insignificant results or the results were not important or interesting [31]. Submission was also noted to be another aspect of publication bias, and it has been found it was more of failure to write up and submitting the trial results rather than rejection of a submitted manuscript and no evidence of publication bias were found once trial were submitted to a journal [32,33].

Compulsory registration of clinical trials, setting up clinical trials registers at international, national and regional level, detailed protocol of clinical trials, detailed and explicit description of intervention, outcomes measurement and statistical analysis plan, should be able to eliminate publication bias. Any changes to outcomes, missing data, needs to be explained.

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