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Setting the Objectives and Hypotheses in Randomized Clinical Trials: Notices for Clinicians and Pharmacologists

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Abstract: Contrary to the sufficient availability of hundreds of papers on how to report randomized clinical trials, less attention is paid on details in design of randomized clinical trials specially on setting the objectives and hypotheses. This study aimed to discuss some aspects of setting objectives and hypotheses in randomized clinical trials. Interactively referring to several examples in literature, this study have discussed different details of setting objectives and hypotheses in randomized clinical trials and provided recommendations on how to do it the best it can be.

Key words: Randomized clinical trials, methodology, hypothesis, objectives

INTRODUCTION

Randomized clinical trials are considered as the cornerstone for clinical evidence. Randomized clinical trials are studies following a research method, in which the participants are randomly assigned, usually, as test or control groups to receive different interventions and finally to compare the results. Most often, the efficacy, safety and effectiveness of new drugs or new interventions are assessed in clinical trial studies. Randomized clinical trials are considered as the cornerstone for systematic reviews, evidence-based practice guidelines and the practice of assessing health technology (Sadeghi-Bazargani and Hajebrahimi, 2011). Randomized clinical trials are assumed to have a gold standard position in clinical research. However, a possibility that evidence from randomized controlled trials has not necessarily the value of a gold standard should also be considered (Gill *et al*., 1996). RCTs may be the top source of evidence after systematic reviews, however, there is a big lack of evidence yet. This may be due to problematic design and reporting of clinical trials as well as the low external validity. Contrary to the sufficient availability of hundreds of papers on how to report randomized clinical trials, less attention is paid on details in design of randomized clinical trials (Falagas *et al*., 2009) specially on setting the objectives and hypotheses. Our aim was to critically discuss some aspects of setting objectives and hypotheses in randomized clinical trials. Interactively referring to several examples in literature, this study is discussed different details of setting objectives and hypotheses in randomized clinical trials.

SETTING THE OBJECTIVES

The objectives of randomized clinical trials are usually defined to estimate important quantities to investigate a possible causal relationship between a treatment, or a preventive modality and a health related outcome. For instance Adalatkhah *et al*. (2011) wanted to know whether oral flutamide has a better efficacy in treating the acne lesions than the conventional therapy with cyproterone acetate/ethinyl estradiol combination after six months of treatment (Adalatkhah *et al*., 2011). They aimed to estimate Relative Risk (RR) and Number Needed to Treat (NNT) of obtaining a satisfactory result after treating moderate acne with flutamide when compared with conventional cyproterone therapy. Estimation is made sometimes for simple measures while sometimes complex measures, derived from mathematical methods, are estimated such that is done through astigmatism clinical trials in ophthalmology (Alpins, 2001; Sedghipour *et al*., 2012).

Other than estimation, selection can also be considered as an objective in a randomized clinical trial. Comparing five different doses of a drug, the objective could be to select the dose giving highest efficacy while providing high safety according to some given criteria. The researcher may also be interested in estimating the magnitude of the effect for each dose group or he/she

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may be interested in estimating the magnitude of difference in measures of outcome (safety or efficacy) among the compared doses. The estimation in clinical trials is not just limited to outcome variables, thanks to the availability of modern dose-response modeling techniques, the objective of a clinical trial may also be to estimate the critical dose of drug that increases the risk or benefit to a given magnitude. Such a dose in this example could be none of the doses predefined in trial comparison arms (Filipsson *et al*., 2003; Sand *et al*., 2008). Based on what discussed above, it is evident that several specific objectives can be defined in clinical trials. No doubt, several objectives will lead to several hypotheses and having several hypotheses necessitates defining multiple outcomes. Higher type I error is a known drawback of increasing the number of objectives; however, it is not the sole issue needing to be cared for, in this regard. Indeed, one of the specific objectives should be selected as primary specific objective of the study that will usually be followed by a defining a relevant hypothesis and measuring of an outcome known as primary outcome.

A clinical trial study usually has a general objective, which is set based on the core research question of the study. It should describe, in one or two sentences, the general purposes for which the trial is being proposed. It is usually an easy job to define the general objective which would be very similar to the title of the study. This general objective can be broken down to several specific objectives that would together achieve the overall goal of the research project. Specific objectives are steps towards or components of the general objective of the study. Defining the specific objectives, however, needs more skills and experience. Irrespective of the focus of this article, there are several characteristics to be considered when setting specific objectives either in research or management science. To make these easier to remember even a mnemonic known as SMART is proposed (Doran, 1981). In this mnemonic the letter "S" means specific. In setting an objective in clinical trials the researcher should be as much specific and unambiguous as possible. For example to determine the effect of drug X on treating Ischemic Heart Disease (IHD), is not specific enough. The drug X may affect the symptoms of IHD, quality of life, or its progress and outcomes like myocardial infarction incidence or survival. Each of these could even be more clarified. For example estimating survival function parameters to predict survival probability at any arbitrarily selected time point could be the focus in defining an objective for a clinical trial, while, estimating hospital case-fatality rate could be a different objective. Other letters of SMART mnemonic represent the terms measurable, attainable, relevant and time-framed.

What was discussed about specific objectives is common for all types of quantitative clinical studies. However, in randomized clinical trials the specific objectives are often prioritized to select one clinically important objective as the primary specific objective of the study. This objective will be the one that mainly determines the methodology and should be achieved with adequate statistical power. Piantadosi from Jons Hopkins school of medicine states in his book that There may be numerous secondary objectives employing different outcomes but the properties of the trial can usually be controlled for one primary objective (Piantaddosi, 2005).

The objectives of the International Subarachnoid Aneurysm Trial (ISAT) are presented here as examples of primary , secondary and tertiary objectives in a parallel clinical trial. It was a multi-center, randomized clinical trial that compared the efficacy as well as the safety of endovascular coil treatment with surgical clipping for the treatment of ruptured brain aneurysms; (Molyneux *et al*., 2002). The study defines the objectives as follows:

- **Primary objective:** To determine whether an endovascular treatment policy of acutely ruptured intracranial aneurysms compared with a neurosurgical treatment policy, reduces the proportion of patients with a moderate or poor outcome (Ranking grade 3-6) by 25% at one year
- **Secondary objectives:** To determine whether endovascular treatment:
- Is as effective as neurosurgery in preventing re-bleeding from the treated aneurysm
- Results in a better quality of life than neurosurgery at one year (Euroqol measure)
- Is more cost effective than neurosurgical treatment
- Improves the neuropsychological outcome at one year
- (some centres only)
- **Tertiary objectives:** To examine the longer term outcome over five years with specific reference to re-bleed rates

To determine the long-term significance of angiographic results.

SETTING THE HYPOTHESES

Referred to Lieberman (2001), a hypothesis is defined as a testable statement about a proposed relationship between two or more variables.

Hypothesis in medical research is referred to as an educational guess, nevertheless, due to ethical reasons and some other factors, not every educational guess is

allowed to be tested in clinical trials. Only a strong educational guess is recommended to be tested in clinical trials. In a clinical trial investigating a drug, a hypothesis can be referred to as a postulation, assumption, or statement that is made about the population regarding the effectiveness/efficacy and safety of the drug of interest (Chow *et al*., 2003).

Defining a hypothesis for a randomized clinical trial may be slightly different from other types of medical research. Based on the goal of study, three types of hypotheses are usually considered in designing a randomized clinical trial. Let's assume that in a parallel RCT, a new treatment (test protocol) is going to be compared to a conventional or comparison treatment (control protocol). The researcher may like to answer any of the three research questions forming three types of hypotheses as follows.

Equality hypothesis: This is a common type of hypothesis tested in medical research and nearly every medical researcher is familiar with it. Let's set a null hypothesis as H_0: $\mu_t-\mu_c = 0$ where μ_t is the mean outcome response for test treatment and μ_c is the mean outcome response for control treatment. Thus an alternative hypothesis would be H_1: $\mu_t-\mu_c \neq 0$. It is possible to apply such type of hypothesis to compare a test drug with placebo (Chow *et al*., 2003). In practice this example may be a bit tricky because it is indicative of a need for two-tailed testing of hypothesis that may be quite unnecessary when comparing a drug with placebo leading to unnecessary loss of statistical power of study. This is because our comparison intervention has been a placebo. Although, placebo effect is reported to exist for some types of outcomes, theoretically placebo is a substance without effective ingredients (Furukawa, 2002; Hrobjartsson and Gotzsche, 2001; Hrobjartsson and Gotzsche, 2003, 2004; Hajebrahimi *et al*., 2011). Thus, if by chance the researcher finds the placebo to be different from test drug and observes the placebo effect to be higher than drug, there is no sense in defending the efficacy of placebo and no physician will accept to prescribe placebo to treat a disease. Therefore, if an exacerbating effect is excluded for the test drug, to do a two-tailed test of hypothesis doesn't seem logical and a one-directional hypothesis will suffice as; H_0: $\mu_t-\mu_c = 0$ and H_1: $\mu_t-\mu_c \geq 0$ which ensures higher statistical power of study. This is not the sole issue to be considered in clinical trials. Suppose an instance where a new drug for severe obesity decreases the weight as little as 0.001 kg compared to control group after two months of treatment. So considering this tiny effect, rejecting the null hypothesis may not be a reasonable motivation to recommend the use of new drug. Such a problem leads to introduction of the term clinical significance versus the conventional statistical significance. As will be discussed presenting other types of hypotheses in clinical trials, a clinically meaningful difference needs to be incorporated in writing clinical trial hypotheses.

Superiority hypothesis: This type of hypothesis is usually considered when the researcher is interested to investigate whether the new treatment has better efficacy in test group patients compared to the comparison group. This type of hypothesis can be presented as; Test protocol>Control protocol. The mathematical presentation of a superiority hypothesis will be as; H_0: $\mu_t-\mu_c <= \delta$ and H_1: $\mu_t-\mu_c>\delta$ where δ is clinically meaningful difference.

This means that the hypothesis will be rejected if the test treatment has lower efficacy or even equal efficacy when compared with control protocol.

Non-inferiority hypothesis: The new treatment is at least as good as the conventional (standard) treatment. This type of hypothesis can be presented as; Test treatment> = Control treatment. A mathematical presentation could be as follows (Blackwelder, 1982):

$$H_0: \mu_c-\mu_t> = \delta \text{ and } H_1: \mu_c-\mu_t<\delta$$

Equivalence hypothesis: The new treatment is equivalent to the conventional treatment. In this type of hypothesizing, it is concluded that the difference between the test treatment and conventional treatment is of no clinical importance if the null hypothesis is rejected (Chow *et al*., 2003).

THE OUTCOMES

After setting the objectives and hypotheses it is time to define the variables and start measuring. What a researcher will measure to achieve an objective can be called an outcome. If the objectives and hypotheses are clearly written there would be no challenge to define the outcomes. It should be explained that outcomes are determined at subject level, whereas specific objectives are determined are at group level or better to say specific objectives are met by analyzing the aggregate of outcomes (Piantaddosi, 2005). For example outcome of a clinical trial study on diabetes treatment could be 30% decrease in serum HbA1c after three months of therapy, while the relevant objective could also be to determine proportion of patients achieving 30% decrease in serum HbA1c after three months of treatment. In a two-arm parallel RCT for instance, the objective could be to estimate number needed to treat for new drug compared to conventional treatment in decreasing serum HbA1c by 30% after three months of treatment.

Although, there may be many factors important in deciding which outcome to choose as primary among several possible ones, three most reasonable criteria are;

1-clinical importance of the outcome to be measured 2-objectiveness 3-magnitude of the effect predicted for the outcome. Based on the context and disease of interest, the objectiveness of the primary outcome can be cared for controversially. It is recommended to mention both types of subjective and objective outcomes in clinical trial reports if relevant (Hajebrahimi *et al*., 2011). Recent studies show that in most interventional studies patient-oriented and reported endpoints are more important than some independent objective measurements. As an example quality of life in end-stage cancer treatment may even be more important than death which is usually not preventable in such circumstances. Also in assessing a palliative therapy and some cases of rehabilitation therapy functional abilities of patients could be the most relevant outcome.

Personal experience and preference of researcher also plays a major role in choosing the primary outcome. Adalatkhah *et al*. (2011) as mentioned earlier, compared treating moderate acne with flutamide vs. conventional cyproterone therapy. The dichotomous measurement scale for primary endpoint assessment was defined as improvement from moderate to mild acne based on GAGS score. They also considered continuous ASI (Acne Severity Index) score, GAGS score and patient satisfaction as the secondary endpoints (Adalatkhah *et al*., 2011).

To provide some examples of possible outcomes and primary outcomes the authors have presented here some studies published in a medical journal during 2010-2011. As could be seen in Table 1, the number of outcomes assessed may be quite large in some studies that need to

Table 1: Some examples of possible outcomes and primary outcomes reported in clinical trials published in a medical journal during 2010-2011

Title	Measured outcomes	Primary outcome
Comparing analgesic effects of a topical herbal mixed medicine with salicylate in patients with knee osteoarthritis (Zahmatkash and Vafaeenasab, 2011)	Pain severity, morning stiffness and nightly pains were measured by visual analogue scale	Not defined
The effect of hydro alcoholic nettle (*Urtica dioica*) extracts on insulin sensitivity and some inflammatory indicators in patients with type 2 diabetes: A randomized double-blind control trial (Namazi *et al*., 2011)	Serum of inflammation markers (IL-6, TNF-α and hs-CRP) Insulin sensitivity was calculated with Katz formula	Not defined
Therapeutic effects of biguanide vs. statin in polycystic ovary syndrome: A randomized clinical trial (Navali *et al*., 2011)	Weight to hip ratio (WHR) body mass index (BMI) Abnormal periods Abnormal oral glucose tolerance test (OGTT) Acne C-reactive protein (CRP) Hyperinsulinemia Hirsutism score Follicle stimulating hormone (FSH) Luteinizing hormone (LH) Fasting blood sugar (FBS) Post-prandial blood sugar (PPBS) Serum insulin Insulin sensitivity index (ISI) Serum cholesterol Serum high-density lipoprotein (HDL) Serum low-density lipoprotein (LDL) Serum triglyceride Serum total and free testosterone	Not defined
Arthroscopically-assisted vs. open surgery in repairing anterior cruciate ligament avulsion (Barzegar *et al*., 2011)	The range of motion (ROM) of knees measured in degrees Amount of laxity (score) measured by arthrometer Difference reported after anterior drawer test (ADT) performed on both knees time of suture removal, duration of hospital stay, wound status, nonunion and return to previous work	Not defined
Effects of daily consumption of probiotic yoghurt on inflammatory factors in pregnant women: A randomized controlled trial (Asemi *et al*., 2011)	Fasting blood and anthropometric measurements Serum concentrations of TNF-α and CRP Complications	Not defined
Low dose vaginal misoprostol versus prostaglandin E2 suppository for early uterine evacuation: A randomized clinical trial (Mostafa-Gharebaghi *et al*., 2010)	The time to termination of gestation Spontaneous pregnancy termination Successful termination after 2 days Complications	The time to termination of gestation
Effects of oral clonidine premedication on haemodynamic response to laryngoscopy and tracheal intubation: A clinical trial (Talebi *et al*., 2010)	Systolic blood pressure heart rate	Not defined
The Influence of tourniquet use and timing of its release on blood loss in total knee arthroplasty (Yavarikia *et al*., 2010)	The total blood transfusion units	(The total blood Transfusion units)

be relevantly cared for during the design and analysis. Also noteworthy is that very few studies adhere to the CONSORT recommendation on reporting and clearly defining the primary outcomes. The authors recommend that both the reviewers and authors of the scientific journals including the international journal of pharmacology to take into account this important principal in clinical trials.

One last issue to be addressed is whether primary endpoint used by some researchers differs from primary outcome or not. Piantadosi states the preference on outcome rather than endpoint as "I prefer the term outcome because the occurrence of a particular outcome may not imply the "end" of follow-up or anything else for the subject" (Piantaddosi, 2005). Actually this is not the sole terminology application controversy in clinical trials and seems there is a need for future focused research in this regard. Through our ongoing research on controversies in clinical trial terminology, seems there are different understandings in this regard among the clinical researches.

DISCUSSION

Methodological reporting pitfalls can be considered as a comorbidity for all types of clinical research, however the situation is more important when it comes to clinical trials (Sadeghi-Bazargani and Mohammadi, 2012). Consolidation and methodological rigor are quite vital in design and report of randomized clinical trials. Setting hypotheses and objectives share a major role in this regard and should be carefully addressed while designing a randomized clinical trial. Otherwise, the efficiency of study or validity and applicability of results may easily be jeopardized. To prevent purposeful or un-purposeful misconduct or misreports of randomized clinical trials, strict standards and guidelines should be prepared and widely disseminated among clinical researchers. The authors of RCT articles should as well adhere to them. The hypothesis should clearly be stated in articles and scientific reports, so that reader can understand it and evaluate the process of hypothesis testing. Nonetheless, most writers underreport or don't report it in their articles and leave a difficult job for the reader to infer or guess what it had been. In order to make valid judgments while reading an article, the reader should be able to distinguish whether the hypothesis is a superiority hypothesis or other types. Some writers clearly state their type of hypothesis as superiority, non-inferiority or equivalence and it is strongly recommended to be clear in this regard (Adalatkhah *et al*., 2011; Enkling *et al*., 2007; Park *et al*., 2012). Nevertheless, It is not a general habit among the authors to report all necessary information in their randomized clinical trial papers. The statement known as Consolidated Standards of Reporting Trials (CONSORT) has been developed, updated and widely disseminated to help authors improve reporting of their controlled trials (Junker *et al*., 1996; Ross, 1996; Schulz *et al*., 2010). Hundreds of articles are published discussing CONSORT statement but, despite such dissemination of knowledge, majority of published RCT articles do not follow it (Falagas *et al*., 2009). One explanation for this among others could be that adequate attention is not paid at designing stage of an RCT study leading to purposeful or un-purposeful underreporting of design details the way recommended by the CONSORT statement.

So it is highly recommended that journals in different fields of clinical and pharmacological research encourage publishing on methodological aspects of clinical trials.

Summary of things to consider regarding hypotheses and objectives:

- Set the RCT general aim based on the core research question
- Break down the general aim into different specific objectives
- Follow the requirements of writing specific objectives, particularly; make them as specific, clear and measurable as possible
- Select one specific objective as the primary objective according to its clinical importance, relevance and efficiency
- Make clear whether the efficacy or effectiveness of a treatment has been measured
- Include a safety objective if reasonable (as it is most of the times)
- Write at least one hypothesis for each objective
- Decide on type of the hypothesis most appropriate for the study and report the details
- Define the best outcomes to be measured for each hypothesis
- Define the primary outcome based on primary objective of the study

Despite the consensus on choosing one primary outcome, there are situations in clinical or pharmacological research that the researcher is faced with large number of outcomes without reaching a reasonable logic to prioritize them for selecting the primary outcome. Having multiple outcomes or in a wider scope large number of variables to be modeled especially with a sample size is a major challenge in classical statistics. Application of newly presented statistical methods that lack some limitations of traditional latent variable based

methods like PCA, FA and PLS, to substitute classical statistical methods have put some light on finding better alternatives for classical methods or traditional latent variable based models as mentioned earlier. Orthogonal projections to latent structures may be a good option in this regard which is originated for the first time in chemometrics (Trygg and Wold, 2002) but has also opened its way into clinical research (Sadeghi-Bazargani *et al*., 2010; Sadeghi-Bazargani, 2011). A subtype of this model known as OPLS-DA may be acceptable for analyzing clinical trials (Bylesjo *et al*., 2006). Nevertheless the main drawback of these modern methods compared to classical statistical methods is that they are new and not well assessed through a wide spectrum of clinical research.

Also when more than one follow-up measurement is analyzed in a randomized controlled trial, there is no consensus how to analyze the overall intervention effect in a proper way (Lu and Tilley, 2001; Snapinn and Jiang, 2011). Several methods have been used by the researchers and we ourselves have used such methods as limiting the analysis to a cutoff time point and use of repeated measures ANOVA, that are well known to clinical and pharmacology researchers and we ourselves have used them mostly earlier through our research life (Iranparvar *et al*., 2006; Sadeghi-Bazargani *et al*., 2006; Mostafaei *et al*., 2009; Shakouri *et al*., 2009; Adalatkhah *et al*., 2007) or the use of more advanced methods like GEE and several variants of analysis of covariance models (Adalatkhah *et al*., 2011; Hajebrahimi *et al*., 2008) or even transposing the problem into a failure/success time scenario to apply semi-parametric and parametric survival methods (Mostafa-Gharebaghi *et al*., 2010; Savadi-Oskouei *et al*., 2010) are the solutions to managing repeated measures in clinical research especially the clinical trials. Such an issue although somehow related to the scope of this article, is recommended to be addressed in detail through future publications focusing on how to manage multiple outcomes in RCTs.

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