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Research Article

APPLICATION OF EPIDEMIOLOGIC PRINCIPLES FOR OPTIMIZING PRECLINICAL RESEARCH STUDY DESIGN

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ABSTRACT

The use of sound study designs for preclinical research is necessary to maintain the scientific integrity of the field of translational research. To exemplify the need of continuous training and monitoring of the adherence to study design principles for preclinical research, a systematic review of a subset of articles from a pediatric research journal which publishes preclinical research studies was conducted. The appropriate use of randomization, control group, sample size estimation and data analysis was reviewed and documented. The majority of the published research studies included in this review used appropriately two or fewer of four study design principles. With the recent focus on translation of biomedical research into individual and public health benefit, poor study design and inappropriate data analysis should not be acceptable for preclinical research. The integrity of translational science from preclinical studies to clinical to population studies must be protected by using sound study design principles.

Key Words: translational, study design, epidemiology

INTRODUCTION

The National Institutes of Health made translational research a priority; centers of translational research were formed and the Clinical Translational Science Award (CTSA) was launched in 2006. The translational process is the interface among basic science (preclinical), clinical medicine and ultimately public health or, in other words, bench to bedside to population. Appropriate and sound study design is critical for research inference and thus essential for translating preclinical data to humans.

Human subject clinical trial reports improved substantially since the 1960's when the lack of rigor was identified [1-2]. As addressed by London *et al*., the review of the methodological quality of preclinical studies (in-vitro studies and animal work) is not adequately addressed [3]. Preclinical research, in contrast with clinical research, does not regularly use methods to control bias, produce random treatment allocation, blind outcome assessment or account for missing data. As an example, Perel et al. conducted a review of animal experiments corresponding to human trials of treatment for head injury and acute ischemic stroke [4]. Their primary conclusion, "many studies in animal models are of poor methodological quality", is concerning. The translation of findings from poorly designed animal studies to clinical studies will not advance science. A review of emergency medicine animal research for the use of randomization and blinding found that animal studies that do not use either method are more likely to report a different between study groups than studies using methods for randomization and blinding [5]. Good quality study design and conduct are considerably important first steps for all types of research. Appropriate study design and sound methods are essential for translating preclinical data to humans and planning safe and efficient clinical studies.

Epidemiology is a discipline that easily functions in roles from cell populations to human populations. Using epidemiologic principles and methods to guide the design of preclinical research should be considered and implemented. Epidemiologic study designs are modeled using the concepts of scientific experimentation.

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The epidemiologic study design is based upon the principles that reduce variation by extraneous factors in comparison with the primary factors of the study [6].

In this paper, the use of sound study design principles for preclinical research is evaluated with a systematic review of articles published from April 2009 through March 2010 in the basic science investigation section of a peer reviewed, official journal of a pediatric society. The goal of the review was to describe the current venue of preclinical research reports of research methods and results.

MATERIALS AND METHODS

Articles in the basic science investigation section of journal issues from April 2009 to March 2010 were considered for inclusion in the review. Only preclinical studies (nonhuman), including the comparison of two or more groups and measuring an effect of a treatment or agent, e.g. experimental design, were included. Four principle components of study design were randomly selected from a list of study design methods and used to guide the review (Table 1).

The selected components were: randomization, concurrent control group, sample size estimation and data analysis plan. An index was created to assist scoring each article; the index ranged from 0 to 4. One point was assigned for each study design component determined *a priori* and included in the study design. Each study design index component was scored as a dichotomous variable, present or absent. Descriptive analysis techniques, both quantitative and qualitative, were used to describe the outcomes of the evaluation.

RESULTS

Fifty articles met the inclusion criteria for review. Of the total articles, 34 (68%) reported the use of a concurrent control group, 33 (66%) included an adequate data analysis plan, 20 (40%) included a description of an appropriate randomization scheme, and three (6%) estimated the necessary sample size for the study. The index score ranged from 0 to 4; only one study report included all four study design components of the index. The majority of the articles had an index score of 2 or less (Score=0, 6 (12%); Score= 1, 10 (20%); Score= 2, 23(46%); Score=3, 10 (20%); Score=4, 1 (2%)).

Qualitative assessment of the articles demonstrated potential misunderstanding of study design principles or misuse of study design terminology. Randomization, for example, was described with terms such as: “animals were divided into four groups”; “animals were randomly divided”; “animals were sorted into groups”; “animals were randomly assigned”; and, “half of the animals were placed into one group and the other half in a second group”. Plans for data analysis were included in some reports; however, often the methods were not appropriate for the design of the study or the level of measurement of the data. The *t* test was often inappropriately used to compare more that two groups at one time or a sophisticated, multivariate model was reported as being used for a basic data structure.

Negative outcomes were often the primary conclusions reported, i.e., “contrary to our hypothesis, the treatment has no significant effect”. The research, however, did not include adequate sample size to make such conclusions. Not establishing necessary sample size *a priori* places the research at risk of not having sufficient power to identify significant effects if in fact they do exist.

The inclusion of a section on limitations was rare. Several of the points highlighted above could have been explained via the discussion of the limitations of the study design used to address the research question. Such a discussion is valuable for the planning of future studies.

Table 1. Epidemiologic Study Design Principles for Preclinical Research

Principles	Randomly Selection for Evaluation
Allocation ratio	
Bias assessment	
Confounding/effect modification	
Control group	X
Data analysis plan	X
Matching	
Missing data accountability	
Post hoc exclusions	
Randomization	X
Reliable and valid assessments/measurements	
Reliable and valid outcome measurement	
Sample size	X
Subject selection	
Treatment masking	
Unit of Measurement (Single subject, Cluster)	

DISCUSSION

Of the fifty articles reviewed for the appropriate use of randomization, control group, sample size and plan for data analysis, only one article (2%) met all four criteria. Poor study design and inappropriate data analysis is not acceptable for human subjects research. With the recent focus on translation of biomedical research into individual and public health benefit, poor study design and inappropriate data analysis should not be acceptable for preclinical research. The principles of epidemiology and biostatistics and their contributions to sound study design are indispensable for biomedical research. 'Best practices' for study design and data analysis should be established in every biomedical research laboratory. The quality of the study design will determine the validity of the research. Bebarta et al.'s conclusion after a review of a series of animal studies presented at a national academic research meeting that animal studies that do not utilize randomization and blinding are more likely to report a difference between study groups than studies that employ these methods is alarming.[5] New knowledge and interventions are built upon a series of research endeavors; building upon invalid studies will not allow translational research to meet it goals.

This review of articles was not intended to be 'finger-pointing' at the journal which published the work. The articles used for this review were from research conducted in laboratories from around the world. The articles are generalizable to the current state of preclinical research reporting. As mentioned, the identified deficiencies may have been due to reporting inadequacies rather than weak research. Either way, the inclusion of epidemiology and biostatistics in the training programs of biomedical researchers and continued funding and support for this expertise to accompany biomedical research is necessary for the translation of sound preclinical research to the next step in translation.

The use of sound study designs and analyses followed by standardized reporting should help to reduce biased interpretation of results. Improvement in the reporting of human subject clinical trials can be attributed to the use of the Consolidated Standards of Reporting Trials (CONSORT) statement [7]. Equivalent standards for preclinical research should be established. A recent report by Kilkenny et al. with reference to the largest and most comprehensive review of published animal research undertaken to date, suggested the use of a tool such as the ARRIVE Guidelines [8]. The ARRIVE Guidelines consist of a checklist of 20 items describing the minimum information that all scientific publications should include. This checklist includes: number and characteristics of animals, details of housing and husbandry, and the experimental and statistical methods used (details of sample size, randomization, and data analysis). Evidence is not yet available to determine the effect, if any, upon the quality of animal research and subsequent research reports post-use of the ARRIVE Guidelines. Rather than waiting, it would behoove the preclinical research community to demand focus on the necessary components of a study design to result in valid data for addressing primary research questions. The integrity of translational science from preclinical studies to clinical to population studies must be protected by using sound study design principles.

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