

GUIDELINE FOR REPORTING NEGATIVE STUDIES IN BIOMEDICAL JOURNALS

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BACKGROUND

Negative studies are those where the in which authors fail to reject the null hypothesis after statistical analysis or in negative studies, authors typically conclude that there is “no significant difference” between the interventions for measured outcomes. There may be two important consequences of published negative study, one that the intervention is considered as non-effective and hence is not given to the patients and secondly the researcher is discouraged to further work in same area for the same objectives as it has already been proved that the intervention is not effective.^[1] Same is applicable for observational epidemiological studies where authors want to find the association or prognosis etc. Looking to the impact of a published negative study and its importance to ascertain that the study should be methodologically very strong for intended conclusion and the parameters needed to evaluate a negative study for validity should be reported adequately in published study.^[2] We have done a study on reporting of various parameters in negative studies published in Indian Medical Journals (Under communication) and on the basis of that study and other also studies published which were published in Indian as well as western journals to suggest a guideline for reporting of negative studies. This suggested guideline should be read in conjunction to other existing guidelines for superiority, equivalence trials and observational studies.^[3,4] Few other important issues which are not adequately highlighted in already existing guidelines are mentioned in this guideline. As majority of published article follow IMRAD (Introduction, Materials and Methods, Results and Discussion) hence the whole text is divided on the basis of these headings.

TITLE

The Title written or mentioned should be in neutral form, it should not have definitive statements (positive or

negative). Many time clinicians and researcher make opinion based on the title they have read during the scanning of the content of the journal without properly reading or critically analyzing the published article, thus the title if neutral will prevent this bias.

There is also a bias existing in the mind of reviewers and editors regarding negative studies. If title is negative or positive it will induce bias on the outset of reading the paper.^[5] This will be prevented if neutral title is used. It is already been mentioned that the nature of title may induce some bias in the mind of readers and so it is called as “fleshy title bias”.^[6]

The Title should also contain in itself the study design and nature of study like pilot study/preliminary observations etc. This will provide at least some information on the quality of study. Just by looking at the title reader will come to know whether the study design is robust or not? (Clinical trials in comparison with observational studies or full study Vs pilot study)

ABSTRACT

As initial opinion/assessment of study is done by reading abstract hence abstract should provide clear and overall information of full text without any selective reporting. It is usually observed that abstracts do not provide sufficient information of the study and more of the emphasis is usually given on the positive findings. Sometime a positive subgroup analysis is given more wattage than negative primary endpoints.^[7,8]

Abstract should contain sufficient methodological information and the results should be mentioned on the basis of primary and secondary endpoints in sufficient detail without any selective reporting of only positive findings. Study design like superiority, equivalence, non-inferiority, observational etc. should be mentioned in sufficient detail.

INTRODUCTION

In the introduction aims and objective of the study should be clearly mentioned. It should reflect whether the aim is to show superiority or equivalence? Primary and secondary endpoint should be mentioned and if there is any plan of subgroup analysis then it is also to be mentioned.

We have observed that in many published negative studies primary aim was to show superiority but when authors failed to reject null hypothesis then they claim equivalence which is totally inappropriate as equivalence cannot be claimed on the basis of superiority design.^[1,2] Hence in the introduction, intention of authors regarding superiority/inferiority should be clearly mentioned. If the study is preliminary or pilot in nature then reason for this should also be mentioned.

MATERIALS AND METHODS

The design of the study mentioned should be in an accepted terminology. We had observed that many different terminologies were used for study designs in the published negative studies which caused lots of confusion. Design of the study should be mentioned in accepted terminology either as per the journal instructions or laid down by some international agencies like centre for evidence based medicine.^[9] In the case of clinical trials superiority/equivalence/non-inferiority should be mentioned.

Sample size calculation should be mentioned in detail as per the study designs.^[10] All components of sample size calculation should be mentioned with justifications. In case of sample size of non-inferiority or equivalence design appropriate sample size formula based on confidence interval should be used.^[11,12] One of the most important reason for getting no significant difference is less power of the study. Hence sample size calculation should be done with adequate power and that should be reported in the published article.

RESULTS

We had observed many selective reporting of results mentioned in the published negative studies. Many at times it was observed that though primarily or logically most important endpoint is not significant difference between two groups but author tries to show the superiority of intervention based on secondary endpoints or some subgroup analysis which is inappropriate.^[13] We

suggest that writing the results should be based on the endpoints in a specified order. Result of primary endpoints should be mentioned first irrespective of negative or positive outcomes followed by secondary endpoints in order of logical sequence of clinical importance. Subgroup analysis should be reported after the secondary endpoints. Author should report both positive and negative in neutral way giving equal weight age to both. As mentioned in other guidelines both P values and confidence interval should be reported.

Table-1: Guideline for reporting of negative studies

Title	<ul style="list-style-type: none"> Title should not be positive or negative, it should be neutral. Title should preferably have a study design. If the study is a pilot study/preliminary observation then it should be mentioned in the title.
Abstract	<ul style="list-style-type: none"> An Abstract should give enough information about the study design. There should not be any selective reporting of results. Positive and negative findings should be explained in equal detail as per the endpoints.
Introduction	<ul style="list-style-type: none"> Aim of the study (superiority/equivalence/non inferiority) should be clearly mentioned in the introduction.
Materials and Methods	<ul style="list-style-type: none"> Study design should be mentioned in accepted terminology. Design of the trial should be clearly mentioned (Superiority trial, non-inferiority trial, equivalence trial) All components of sample size calculation should be reported. Sample size calculation should be done on the basis of study designs (superiority/non inferiority, equivalence). Justification of effect size should be mentioned. Power should be clearly mentioned. Data conversion should have justification.
Results	<ul style="list-style-type: none"> Results should be in logical manner based on primary and secondary end points. Equal weight age should be given to positive and negative outcomes. Both P values and confidence interval should be reported. Selective subgroup analysis showing positive results should not be highlighted over the negative results obtained in primary endpoints.
Discussion	<ul style="list-style-type: none"> Limitations which may lead to negative findings should be highlighted adequately Post hoc power should also be reported.
Conclusion	<ul style="list-style-type: none"> Non-significant P value should not be used to show equivalence. Definite statement about the ineffectiveness of intervention should not be given based on non-significant P values.

DISCUSSION

Reasons for non-significant results should be explained in detail including any bias, if present or any methodological issues. Limitations of the study like inadequate power or small sample size etc should also be mentioned. If the designed study with large sample size is needed for further exploration of issue then it is also to be mentioned. In our study on negative studies published in Indian Medical Journals it was visualized that limitations were not mentioned in many articles.

CONCLUSION

Main conclusion should be based on primary endpoints and not on secondary endpoints or subgroup analysis. Non-significant P values measured in superiority design should not be considered as measure of equivalents. In our study on negative studies published in Indian Medical Journal and also in some other studies it was observed that author concluded on the basis of non-significant P values that both interventions are equal, which is totally a wrong concept.^[1,2] Conclusions should be based on the data of the study and should not be concluded on the data of other published studies.

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