**Statistical Issues on Conduct of Clinical Studies in Vulnerable Population**

Authors : Atul Juneja, Tulsi Adhikari

Affiliations: National Institute of Medical Statistics, Indian Council of Medical Research

Mailing address : NIMS(ICMR), Ansari Nagar, New Delhi – 110029.

Telephone numbers : 011-26588905, 011-26588725

Email address : [atul\_juneja@hotmail.com](mailto:atul_juneja@hotmail.com), [tulsi\_adhikari2003@yahoo.co.in](mailto:tulsi_adhikari2003@yahoo.co.in)

Competing interest and funding support : Nil

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**Abstract**

Vulnerable population is one of the important parts of our population which also need to be benefited from the results of clinical research. In view of their limited autonomy it may not be easy to conduct clinical research such as clinical trials in them because of ethical issues. When it is must to conduct clinical trial in this population, along with ethical considerations, some statistical issues may also be addressed to give the objectivity to the decision of conducting trials in this population, which is not in a position to convey their acceptance of participating in the trial independently. The paper discusses the issues in terms of sample size, type 1 error and effect size and analysis based on Intension to Treat or Per-protocol, before arriving at the decision of conducting a trial in vulnerable population.

**Key words :** Vulnerable population, effect size, clinical trial

**Introduction**

Vulnerable population are those groups of population who bear unequal burden of research because of their easy availability in the settings where the research is being conducted (1). This type of population includes prisoners, children, pregnant women and subordinate employees in an organisation. There is possibility of them being research participant under compulsion because of less autonomy. It is also expected from the research system that the benefits and risks are equally distributed among all sections of population and rights of vulnerable population are protected (2). There is obvious need to have well defined ethical principles which currently ICMR guidelines provide in India(3). This is based on the basic principles of respecting an individual under the conditions of limited autonomy because of mental health issues or being under pressure, such as prisoners etc. Hence it may be stated that the studies may be taken up in such population when it is must. This “must“ has to be defined or quantified. This is the process of further strengthening the ethical principles. In other words studies in vulnerable populations are justified only when a problem disproportionately affects the group (3).

The aim of this article is to address the issues of vulnerable population considering statistical aspects, so that an effort could be made to quantify the conditions under which the study. such as clinical trials, on vulnerable population is to be conducted. This includes the statement from the ethical guidelines “when a problem disproportionately affects the group(vulnerable population). It needs to be technically or statistically seen, what disproportionately means. It has been generally indicated in number of studies that due caution in designing studies and statistical issues may be considered before the studies in the vulnerable population are initiated (4). This article tries to address specific issues in research on vulnerable population which need to be seen in statistical perspective so as to help the study planners and program people to make decisions, based on some quantified facts.

**Statistical Considerations**

As mentioned above the studies on vulnerable have to be conducted only under essential conditions and to a limited extent i.e., on a limited sample size (1). When it comes to designing of studies relating to research, there is need to define the subjective issues in terms of objectivity and with defined magnitude such as sample size, effect size, error terms and analytic approaches involved and further cautions based on ethical principles if being conducted in vulnerable population. Hence we need to consider effect size9  before the study in such group is initiated.

The programme group should consider a defined threshold of effect size only beyond which the study should be indicative. This is indicative of substantial difference between the incidence/prevalence of heath condition in vulnerable population in question vis a vis general population. This quantification of effect size as arrived at from the experts would help programme managers to decide on issues of taking up studies in such population. In terms of statistics if the effect size is large the sample size would be less, maintaining other assumptions of type 1 and type 2 errors. This would endorse the principle of essentiality of research, that too, on a limited sample size from the ethical aspects.

It is also important that we do not miss on the likely substantial different between the two groups of study of which one being vulnerable population. Conventionally, magnitude of chance factor which is type 1 error is maintained at 0.05 or less so as to minimise the chance of wrongly rejecting the null hypothesis so as not to consider the effect size as significant. It is suggested that one may consider liberalising the type 1 error. In case of vulnerable population it would not be appropriate to miss on the real difference if it exists. This would obviously increase the chance of false rejection of the null hypothesis, thus compromising on true effect. This would help to provide enough opportunity for the effect size to be detected as significant and further contribute to lowering of sample size. However this cannot be considered as the rule of thumb and has to be discussed among the research group and along with statistician who is well familiar with the principles of clinical research such as GCP (Good Clinical Practice) before fixing the type 1 error for the analysis of the study (5,6). As regards type 2 error is concerned that can be maintained at 80% or 90% as being done for studies in general population.

When it comes to analysis it is suggested that analysis may be carried out both using per protocol and Intention to treat analysis. Considering the nature of the population (vulnerable) there could be more drop outs or information might have been difficult to elicit for instances, the participants with mental challenges. The approach of intention to treat may not be ideal. Hence the results of the analysis have to be seen with more cautious approach and could be discussed among the technical group which include the subject expert epidemiologist statistician and people associated with health delivery system before it is translated into action. This would all depend on the nature of health condition being studied.

**References**

1. The Belmont Report: Ethical Principles and Guidelines for the Protection of Human Subjects of Research(Internet).National Commission for the Proptection of Human Subjects of Biomedical and Behavioral Research 1979( Cited 2017 March10):Available from:.https://www.hhs.gov/ohrp/regulations-and-policy/belmont-report/
2. Report on Ethical and Policy Issues in Research Involving Human Participants Volume I (Internet). [NATIONAL BIOETHICS ADVISORY COMMISSION](http://www.onlineethics.org/34819/34837.aspx) (NBAC) (Cited 2017 March10).: Available from:https://bioethicsarchive.georgetown.edu/nbac/human/overvol1.pdf
3. Ethical Guidelines for Biomedical Research on Human Subjects. New Delhi: Indian Council of Medical Research; 2006.
4. Shivayogi P. Vulnerable population and methods for their safeguard. *Perspectives in Clinical Research(internet)*. 2013 (Cited 2017 March10); 4(1): 53-57.

Available from: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3601707/>

doi:10.4103/ 2229-3485.106389.

1. Hypothesis testing, type I and type II errors. Industrial Psychiatry Journal. 2009; 18(2): 127-131.
2. Banerjee A, Chitnis UB, Jadhav SL, Bhawalkar JS, Chaudhury S. Hypothesis testing, type I and type II errors. *Industrial Psychiatry Journal(internet)*. 2009 (Cited 2017 March10): 18(2): 127-131.

Available from: http://www.industrialpsychiatry.org/article.asp?issn=0972-6748;year=2009; volume=18;issue=2;spage=127;epage=131;aulast=Banerjeedoi:10.4103/0972-6748.62274.

1. Hanfried Helmchen, Kalle Hoppu, Günter Stock, Felix Thiele, Benedetto Vitiello, Arved Weimann. From exclusion to inclusion. Improving clinical research in vulnerable populations (Internet). 2014 Cited 2017 March 10 Available from : https://edoc.bbaw.de/opus4-bbaw/.../BBAW\_Vulnerable\_Populationen\_PDFA1\_b.pd Brandenburg Academy of Sciences and Humanities (BBAW), 2014. ISBN: 978-3-939818-45-8
2. Huberty, C.J. (2002) ‘A history of effect size indices’. *Educational and Psychological Measurement(Internet)2002* [cited 2017 march 10]: 62(2): 227-240.Available from http://journals.sagepub.com/doi/abs/10.1177/0013164402062002002