EDITORIAL

Sampling and Sample Size in Clinical Research – A Scientific and Ethical Imperative

Gogtay NJ[1], Thatte UM[1]

In 1992, Lau J and colleagues performed a cumulative meta-analysis (techniques which make it possible to study trends in effects that enable the investigator to identify the first time a treatment difference in outcomes between two interventions becomes statistically significant at a chosen level) of thrombolytic therapy for myocardial infarction [MI]. They analyzed the use of intravenous streptokinase as thrombolytic therapy in 33 trials conducted between 1959 and 1988 for acute MI [versus no therapy or placebo]. They found a statistically significant reduction in mortality with the use of streptokinase.[1] More importantly, this significance was achieved as early as 1973 after the enrolment of 2432 patients in only eight trials. The remaining 25 trials added another n = 34542 patients with their only contribution being narrowing the 95% confidence intervals with little or no impact on the odds ratio seen after the completion of the first eight trials.

However, the concept of synthesis of studies using meta-analysis was first proposed as early as 1976[2] and there were 20 trials in MI after 1976 that enrolled a sample size of n = 33618 patients amongst them. One could thus argue that all these studies after 1976 were unnecessary and possibly caused untold harm to those who consented to participate in them. At least half of these patients were thus subjected to an excess risk of mortality in the absence of streptokinase. Impact of streptokinase would have been obvious by 1973.[1] How patients are enrolled in a study (sampling) and how the *minimum number* needed to be enrolled to answer a specific research question (sample size) are crucial aspects of all studies and particularly randomized controlled trials (RCTs) as these are not just scientific but also ethical imperatives.

In the current issue of the journal,[3] Khatri N and colleagues have evaluated reporting of sample size and sampling considerations in articles in different specialities of Medicine, Surgery, Obstetrics and Gynecology, Pediatrics and Pharmacology in the year 2017 taken from PubMed Central. In each specialty, one high impact (≥2) and one low impact factor (<2) journal were chosen. The n = 264 original research articles evaluated by them consisted of 55 interventional and 209 observational studies. The authors found an overall poor reporting of both elements, with interventional studies ranking slightly better than observational studies though the difference was not statistically significant.

Both the study and the findings are not entirely novel. Poor reporting of sample size has been noted by authors in both qualitative[4] and quantitative research[5] elsewhere in literature. In addition, the rationale for using the value of greater than or lower than 2 for the impact factor cut off, whether the impact factor was the one assigned by Thompson Reuters, whether it was a two or five year impact factor, the choice of PubMed Central [which is a repository] rather than Medline or EMBASE [which are indexes] to identify journals and the rationale for choice of the disciplines chosen have not been addressed in the methodology. Also, in Table 1, where the authors have discussed sample size elements and sampling considerations, they have alluded to the method of randomization in the same column as sampling strategy. Randomization refers to treatment allocation by chance rather than choice to minimize selection bias whereas sampling is essentially how the sample was selected – whether probability based or non-probability based.[6]

The findings by Khatri N and colleagues do however remain relevant. Why is reporting sample size important to the science of the paper making it a very crucial element for the reviewer/editor to assess prior to publication and the reader to consider after publication? Too small a sample yields unreliable results, while an overly large sample demands is not only unethical but also utilises a great deal of time and resources. Appropriately calculated sample sizes are needed for the final statistic to be accurate and reliable, as these findings will be extrapolated to a larger population and used by policy makers for formulating guidelines.

Another important aspect addressed in this paper, often not paid adequate attention to by authors, reviewers and editors is the technique of sampling. If a sample is to be selected, regardless of the method, it is important that the individuals selected are representative of the whole population.[6] Although there are several different sampling techniques available, they can be broadly divided into two groups: probability (random) sampling and non-probability sampling. In the former, we start with all eligible individuals from which a sample is selected and each individual has an equal chance of being selected. Although more time consuming and expensive, this enables generalisation of results. In the latter, some individuals do not have a chance of being selected. Therefore, while cheaper and more convenient, there is a risk of being a non-representative sample which would lead to non-generalisable results. Thus, reporting sampling strategy is as important as reporting the sample size and its elements.

Considering that Khatri and colleagues have taken the elements of sampling and sample size reporting from the STROBE statement and the revised CONSORT guidelines that were published in 2008[7] and 2010[8] respectively, the problem of their poor and inadequate reporting persists beyond a decade post publication.

[1]Department of Clinical Pharmacology, Seth GS Medical College and KEM Hospital, Mumbai, Maharashtra

This problem is not unique to just what has been studied by Khatri and colleagues but has also been seen with other elements of the two guidelines and in core clinical journals like the Lancet, British Medical Journal and the New England Journal of Medicine.[9,10] These core clinical journals like several Indian journals are signatories to the International Committee of Medical Journal Editors (ICMJE) guidelines and endorse many of these.[11] Why then does the problem persist? There could be several reasons – First the author who sends his work for publication may not be aware of these guidelines. Second, a peer reviewer may or may not be similarly aware, or if aware may be too beleaguered to check which elements are missing and leave this aspect to be addressed by the author and editor. At the editorial level, endorsement of the guideline by being a signatory or having them on the home page of the journal's website may seem enough. The publications team may or may not have training to look for missing elements. For Indian biomedical journals that do not have full time staff and where the focus is on bringing out the journal on time, this aspect of adherence to guidelines may not be high on the list of priorities.[12]

Can we then, at all, find a solution to this problem? One potential solution could be a strict enforcement at the level of the peer reviewer and editor with rejection in the absence of adherence. This carries with it the risk of the journal/editor being considered draconian. Another solution could be prominent displays in the author dos and don'ts section on the journal's homepage and training workshops by the journals to improve awareness. None of this will however address the core problem and that is an attitudinal shift on the part of authors to consistently and conscientiously adhere to guidelines that now exist for practically any study that is reported including case reports.[13] In the editorial hierarchy, above the authors, both peer reviewers and editors need to be tenacious in ensuring adherence no matter how difficult and time consuming the task may be. The quality of studies that we publish drives the quality of evidence with which we treat our patients. We thus owe it to our patients not only to adhere to the various reporting guidelines, but also start with them at the stage of formulating the research question so that the protocol and in turn the final published manuscript contain all the requisite elements indicative of a good quality study that is not just well reported, but also actually well done.

References

1. Lau J, Antman EM, Jimenez-Silva J, Kupelnick B, Mosteller F, Chalmers TC. Cumulative meta-analysis of therapeutic trials for myocardial infarction. *N Engl J Med* 1992; 23:327:248-54.
2. Glass GV. Primary, secondary and meta-analysis of research. Educ Res 1976; 5:3–8.
3. Tripathi R, Khatri N, Mamde A. Sample Size and Sampling Considerations in Published Clinical Research Articles. *J Assoc Physicians India* 2020; 68:14-18.
4. Vasileiou K, Barnett J, Thorpe S, et al. Characterizing and justifying sample size sufficiency in interview-based studies: systematic analysis of qualitative health research over a 15-year period. *BMC Med Res Methodol* 2018; 18:148.
5. Martin J, Taljaard M, Girling A, Hemming K. Systematic review finds major deficiencies in sample size methodology and reporting for stepped-wedge cluster randomised trials. *BMJ Open* 2016; 4;6(2):e010166.
6. Gogtay NJ, Thatte UM. Samples and their Size: The Bane of Researchers (Part I). *J Assoc Physicians India* 2016; 64:66-69.
7. von Elm E, Altman DG, Egger M, Pocock SJ, Gotzsche PC, et al. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. *Lancet* 2007; 370:1453–1457.
8. Schulz KF, Altman DG, Moher D; CONSORT Group. CONSORT 2010 statement: updated guidelines for reporting parallel group randomized trials. *Ann Intern Med* 2010; 1;152:726-32.
9. Liampas I, Chlinos A, Siokas V, Brotis A, Dardiotis E. Assessment of the reporting quality of RCTs for novel oral anticoagulants in venous thromboembolic disease based on the CONSORT statement. *J Thromb Thrombolysis* 2019; 48:542-553.
10. Susvirkar A, Gada P, Figer B, Thaker S, Thatte UM, Gogtay NJ. An assessment of the compliance of randomized controlled trials published in two high impact journals with the CONSORT statement. *Natl Med J India* 2018; 31:79-82.
11. Satyanarayana K, Sharma A, Parikh P, Vijayan VK, Sahu DK, Nayak BK, Gulati RK, Parikh MN, Prati PS, Bavdekar SB, Sreehari U, Sahni P. Statement on publishing clinical trials in Indian biomedical journals. *J Postgrad Med* 2008; 54:78-9.
12. Gogtay NJ. Reporting of Randomized Controlled Trials: Will it ever improve? *Perspect Clin Res* 2019; 10:49-50.
13. https://www.equator-network.org/, accessed on 3rd February 2020.