Southern African Journal of Anaesthesia and Analgesia. 2021;27(6 Suppl 1):S53-56
https://doi.org/10.36303/SAJAA.2021.27.6.S1.2730
Open Access article distributed under the terms of the
Creative Commons License [CC BY-NC 3.0]
http://creativecommons.org/licenses/by-nc/3.0

South Afr J Anaesth Analg
ISSN 2220-1181 EISSN 2220-1173
© 2021 The Author(s)
FCA REFRESHER COURSE

Statistical issues in clinical research and linkage to other parts of the research process

I Maposa

Division of Epidemiology and Biostatistics, School of Public Health, Faculty of Health Sciences, University of the Witwatersrand, South Africa
Health Science Research Office, Faculty of Health Sciences, University of the Witwatersrand, South Africa
Corresponding author, email: *innocent.maposa@wits.ac.za*

Statistical issues in clinical research arise in many situations and at different stages of the research process. The purpose of this paper/opinion is to highlight the connections between different stages of a clinical research process with the statistical issues and how the challenges that may arise due to these issues may be mitigated. The paper also reflects on the ASA statement on misconceptions about p-values and how these can be addressed. The paper concludes by recommending that clinical researchers need some knowledge and understanding of basic statistical techniques. In addition, they would also benefit immensely from consulting with domain experts such as biostatisticians or statistical experts before embarking on their clinical research endeavours.

Keywords: statistical issues, clinical research

Introduction

Statistics is one of the many important components of a research process. Understanding statistics limits many potential errors in research and can even improve the chances of success. The following quotation highlights some of the realities in and amongst clinical researchers:

*"Less than a third of orthodontists (*clinicians*) today understand or can explain the meaning of a systemic review, a meta-analysis, prospective trials, cohorts, odds ratio, sample power, confidence intervals, specificity, null hypothesis, to name a few. Probably less than 10% can explain what PICO means. In light of this reality, when we can't analyze what we are reading or teaching, would not reading, analyzing and writing about EBP, Research Protocols or Clinical Trials augment a better future for a well-trained and molded orthodontist (*clinician*) of the 21st century? To a question that often surfaces when asked about whether a research or a literature search project should even be a part of a Masters' program that is training students for being clinicians and practitioners, my answer is simple. Research Methodology, Basic Biostatistics and EBPs are to a clinical science what 'grammar is to a language.' You might not surface it every day, but you still unknowingly need to understand and apply it well, if you need to use the language!"*[1]

The essence of the quote is that, as clinical scientists, there is merit in understanding the tools of research especially biostatistics which can work wonders in addressing your quantitative research questions. However, given the myriad of challenges clinical researchers face, the next key ingredient for successful research projects is to spend a good amount of time planning, consulting with research experts, and thinking critically about the project. Keep these five W's in mind whenever you are thinking of initiating a project: What? Why? Who? Where? When? And the how part then follows.[2] Biostatistics experts can help you with the how and sometimes the what and why.

This editorial piece reflects on some of the key parts of a research process that link directly to the statistical issues. Firstly, it reflects on the importance of research question clarity. Research question clarity should lead to clarity in aim(s) and objectives; secondly, the research methodology aspects and how they link to the research question, aims and objectives; thirdly, sample size issues, and then lastly, statistical analysis issues.

Research question clarity

All research starts with a point of inquiry. What is the problem of inquiry or research question and why is it necessary? The what question should be answered in an unambiguous single sentence, failure of which may indicate the research topic is too broad, ill-thought out or too obscure. How do you want to approach this inquiry, and how does an appropriate answer look like? As you ask yourself such questions, you will notice that the question becomes clearer and clearer. Once the question is clear, the different facets to the problem can then be explored by specifying SMART objectives. Objectives are a pathway to addressing a problem of inquiry. These answer to: What needs to be achieved ("measurable") for the research problem to be sufficiently and appropriately addressed? Do you have any hypotheses? How are these hypotheses captured in the objectives? If objectives are defined in a way that is not quantifiable or measurable, statistics will not help you!

Methods

There are two main research methodology paradigms, with the third a mixed approach. The two are the qualitative and quantitative inquiry. The two are different, each with its own strengths and weaknesses depending on the set objectives.

Qualitative approaches seek to get in-depth opinions from participants while quantitative research seek to generate statistics using questionnaires or secondary data. In clinical epidemiology, there are different quantitative research designs which in turn are applicable dependent on aims, hypotheses and objectives of the research study.

Research design(s)

In clinical research, our aim is to design a study that would be able to derive a valid and meaningful scientific conclusion using appropriate statistical methods that can be translated to the "real world" setting.[3] Before choosing a study design, one must establish aims and objectives of the study, and choose an appropriate target population that is most representative of the population being studied.

In epidemiological research, you can utilise the PICO/PECO/PICOT/PICOTS framework. PICO represents – (P)opulation, (I)ntervention, (C)ontrol/(C)omparator, (O)utcome. PECO represents – (P)opulation, (E)xposure, (C)ontrol/(C)omparator, (O)utcome. PICOT adds the time dimension and PICOTS adds (T)ime and (S)tudy design. What population is to be studied, what is the intervention or exposure, what is the control or comparator and what is the outcome of interest. Also, what study design is to be used and for what period should the study be. This framework gives clarity on many dimensions of the research including statistical analysis methods. Generally, the type of outcome determines how the sample size can be calculated and what statistical methods to be used for comparisons of outcome between groups and the type of models to be used for causal or association studies.

From an epidemiological standpoint, there are two major types of quantitative clinical study designs – observational and experimental. Experimental study designs are generally suitable for causal inference, whereas most observational study designs can be used to assess associations. Observational studies are further divided into cohort studies (prospective or retrospective), case-control studies and cross-sectional studies. There are special statistical and epidemiological methods that can be used with each or across all the study designs for optimal, efficient, and robust inference. Quantitative study designs generally entail data collection from a sizable sample. It is imperative for clinical researchers to know what they want to measure before data collection starts so they can collect all relevant data. Note that if you do not collect the values of variables of interest, e.g. confounding factors or exposures, you will not be able to account for them in the analysis.

Sample size issues

Clinical research, including clinical trials and surveys should be well designed. A critical component of good design of clinical research is determination of the number of patients or participants (a.k.a sample size) required by the investigation to adequately address the research question or objective. The formal statistical basis for sample size determination requires: a) the question or objective of clinical inquiry to be well defined; b) the most relevant clinical endpoint or outcome reflecting the objective to be identified; c) the specification of the smallest effect of clinical or experimental significance (a.k.a clinical difference or effect size) between groups in terms of the outcome that is clinically important to detect; d) specification of the desired power (generally, a minimum of 80% is sufficient) and significance level (generally 5%); e) estimates of the mean or proportion and variability of outcomes, and f) anticipated non-responds or dropout/attrition. This approach to sample size determination is normally referred to as "effect size" method and it is hypothesis-driven. In most clinical trials, where intervention and control groups are compared on some outcome of interest, the sample size is determined using this approach.[4]

There is, however, another approach, usually used in prevalence studies where the aim is to estimate prevalence and describe a target population. The approach is known as the "precision" method. This method of sample size determination requires: a) prevalence of condition in the population (based on expert opinion or literature) but if unknown, a 50% prevalence is generally assumed and gives an optimal sample size; b) desired margin of error or level of precision; and c) confidence interval (generally 95%).

Sample size must be determined for each clinical study; however, it is important to highlight that this determined sample size is only a minimum number that can power the study or give sufficient participants or patients to reach required minimum precision given the different assumptions. Thus, there is no universally correct value but a statistically robust process to determine the value. The smallest effect size of practical interest may be determined through consultation with one or more domain expert or literature. The smaller the effect size, the greater the number of observations that will be required. A biostatistician or statistical experts can assist with this, but there are many available platforms online to generate this number given the necessary parameters are available.

Statistical analysis issues

Quantitative data analysis can be performed in different statistical software, e.g. STATA, SPSS, SAS or R/RStudio and others. It is essential for clinical researchers to be familiar with one of the mainstream statistical software programs. Unfortunately, "*statistical software will no more make one a statistician than a scalpel will turn one into a neurosurgeon*".[4] Writing the statistical analysis section of the methods can be greatly enhanced if the aim, hypotheses and/or objectives are formulated in such a way that they are quantifiable, testable and are statistical in nature. This is where consultation with biostatisticians become essential. There is always a huge risk of stating untestable hypotheses and objectives, collecting disparate data unable to respond to objectives and then getting stuck with a biostatistician or statistical experts to work some magic to align data and objectives that are not reconcilable. *"Fancy statistical methods will not rescue garbage data." Course notes of Raymond J. Carroll [2001].*

The planning stage can help alleviate such inconveniences. Whenever in doubt, consult.

Quantitative data analysis requires some basic knowledge of statistical techniques. For study patients/participants description, clinical researchers should be familiar with descriptive statistical methods, including frequency counts or percentages for categorical variables and means or medians for continuous variables with their corresponding measures of variation, that is, standard deviations and interquartile range, respectively. Although descriptive methods are a useful starting point, clinical research usually goes further to ascertain associations and connections between variables. Bivariate analysis is generally performed and for association between categorical variables, the chi-square test or Fisher's exact test are used while the independent t-test or Mann–Whitney U test are used to ascertain differences between two groups on a continuous outcome. The independent t-test requires that the continuous variable is also normally distributed and variances in the groups are equal. The Mann–Whitney U test (a.k.a Wilcoxon rank sum test) is a non-parametric test and does not impose any assumptions on the distribution of the outcome hence a natural alternative when the assumptions are violated. There is also a dependent t-test which is used when the independence assumption between groups is violated. This occurs mainly in matched studies or before/after (pre/post) type of designs. These also have non-parametric equivalent tests. When groups are three or more, the analysis of variance (ANOVA) method is used to assess differences in means of the different groups. The Kruskal–Wallis test is a non-parametric equivalent of the ANOVA test. Mentioned here are only some of the statistical techniques that are mostly used to determine association and differences between variables and groups of variables. Due to the simplicity of the bivariate analysis methods, generally, these tests are not sufficient to give conclusive insights on the relationships of variables. The world is more complicated.

The next level of analysis requires adjustment of potentially "confounding" variables to ascertain the unbiased effects of the exposure variables of our interest. Domain experts can advise on what variables may be confounding for a relationship of interest. For example, cognitive ability in a general test can be confounded by age. Regression methods (a.k.a regression models) can be implemented to determine association or effect of exposures or interventions of interest while adjusting for other variables. A basic understanding of regression is essential for clinical researchers. This knowledge and understanding helps with the defining of quantifiable and testable hypotheses and objectives.

Results reporting

Strengthening the reporting of observational studies in epidemiology (STROBE)[5] is a very good reference on how clinical research studies can be reported. The authors suggest that some of the statistical aspects that need to be clarified in reporting include describing any efforts that the researchers took to address potential sources of bias. Explaining clearly, with all relevant parameter assumptions, how sample size was determined as well as reporting numbers of individuals at each stage of study and giving characteristics of study participants are other key elements. The studies should also report unadjusted estimates and confounder-adjusted estimates with their corresponding 95% confidence intervals. Reports should also discuss limitations of the study and how these were mitigated. Missing data should also be reported as well as accompanying sensitivity analysis.

P-values: What they tell us and what they do not tell us

A little bit about p-values myths and misconceptions and how to circumvent the challenges. Good statistical practice is an essential component of good scientific practice. The American Statistical Association (ASA), in their much-publicised statement on p-values, indicate that good statistical research practice should "emphasise principles of good study design and conduct, a variety of numerical and graphical summaries of data, understanding of the phenomenon under study, interpretation of results in context, complete reporting and proper logical and quantitative understanding of what data summaries mean". They also contend that the p-value was never intended to be a substitute for scientific reasoning. They note, in addition, that "over time, it appears the p-value has become a gatekeeper for whether work is publishable, at least in some fields" to which they observe that this practice encourages things like "p-hacking" and "data dredging" that emphasise the search for a small p-value over other statistical and scientific reasoning. To highlight some of the misconceptions and also address them, the ASA Board issued six principles and these are: a) p-values can indicate how incompatible the data are with a specified statistical model; b) p-values do not measure the probability that the studied hypothesis is true, or the probability that the data were produced by random chance alone; c) scientific conclusions and business or policy decisions should not be based only on whether a p-value passes a specific threshold; d) proper inference requires full reporting and transparency; e) a p-value or statistical significance, does not measure the size of an effect or the importance of a result; and f) by itself, a p-value does not provide a good measure of evidence regarding a model or hypothesis.

In light of these principles, the ASA suggest reporting effect size estimates and their confidence intervals among other solutions to mitigate the limitations of p-values.[6,7]

Conclusion

In clinical research, statistical issues transcend just the statistical analysis section but encompasses most of the aspects in a research process. From defining quantifiable hypotheses and objectives, to study designs, sample size determination, statistical analysis and through reporting. Knowledge of basic statistics is essential for clinical researchers to be able to minimise and eliminate statistical errors and issues in the process

of their research. The p-value should be treated with caution as a standard for guiding clinical decision-making processes.

Conflict of interest

No conflict of interest.

Funding source

This review report was not funded from any source.

Ethical approval

No ethics was required for this review.

ORCID

I Maposa https://orcid.org/0000-0002-3448-4096

References

1. Vaid NR. Application of evidence in teaching and clinical protocols: Do we still nurture the " ostrich mindset "? APOS Trends Orthod. 2014;4(1):1-2. https://doi.org/10.4103/2321-1407.125741.
2. Dawson C. Introduction to reseach methods. How To Content. 2013;53(9):1689-99.
3. Chidambaram AG, Josephson M. Clinical research study designs: The essentials. Pediatr Investig. 2019;3(4):245-52. https://doi.org/10.1002/ped4.12166.
4. Good PI, Hardin JW. Common errors in statistics (and how to avoid them). Wiley Onlin Library; 2006. p.1-269. https://doi.org/10.1002/0471998524.
5. Vandenbroucke JP, Von Elm E, Altman DG, et al. Strengthening the reporting of observational studies in epidemiology (STROBE): Explanation and elaboration. PLoS Med. 2007;4(10):1628-54. https://doi.org/10.1371/journal.pmed.0040297.
6. Americal Statistical Association. Statistical significance and p-values: provides principles to improve the conduct and interpretation of quantitative science. 2016. Available from: https://www.sciencedaily.com/releases/2016/03/160307092305.htm.
7. Greenland S, Senn SJ, Rothman KJ, et al. Statistical tests, P values, confidence intervals, and power: a guide to misinterpretations. Eur J Epidemiol. 2016;31(4):337-50. https://doi.org/10.1007/s10654-016-0149-3.