Jilin Daxue Xuebao (Gongxueban)/Journal of Jilin University (Engineering and Technology Edition)
ISSN: 1671-5497
E-Publication: Online Open Access
Vol: 43 Issue: 11-2024
DOI: 10.5281/zenodo.14208007

THE ROLE OF CONFIDENCE LEVEL IN CLINICAL SIGNIFICANCE TEST

ELSAYIR, H.A.
Department of Mathematics, Al-Qunfudah University College, Umm Al-Qura University, Mecca, Saudi Arabia. Email: hamusa@uqu.edu.sa, habibsayiroi@Yahoo.com

Abstract

The confidence interval (CI) is a crucial tool for reporting research data because it not only provides insight into the effect size and its range but also offers information about potential clinical significance. When determining a point estimate, there is always some uncertainty due to sampling error, and a confidence interval can help measure this uncertainty. Unlike the p-value, which does not indicate the magnitude of an effect or its associated error, the CI allows researchers to assess the precision of an effect size, which should be reported with confidence intervals to provide a clearer understanding of the findings. Confidence intervals help evaluate likely effects and determine whether an intervention may have clinical relevance. In contrast, the p-value simply informs us whether to reject or accept a null hypothesis based on statistical significance, without providing information about the strength of the relationship. It is essential to mention that the proper interpretation of a CI depends on the context in which it is analyzed.

Keywords: Confidence Level; Sample Size; Significance Test; P Value; Clinical Significance. Treatment Effect.

1. INTRODUCTION

In clinical research, researchers often use sampling method to make inferences about the sampled population. However, because of random variation, estimates from one sample may differ from those in another. Confidence intervals (CIs) help address this uncertainty by providing a plausible range of values for the true parameter in the population, assuming the sample is representative. Biomedical research typically uses samples to infer population parameters through confidence intervals (CI), which provide a range of values around a sample estimate. Modern clinical trials, including superiority, non-inferiority, and equivalence studies, increasingly rely on CI rather than P values for conclusions.

In this article, we'll discuss what confidence levels are, their role in statistical analysis, and the impact on decision-making, especially in clinical and medical research.

Much literature about confidence intervals and related issues was found .James & Richard (2007) have developed a Bayesian based approach for computing the desired sample size for a case-control study with misclassified data. In an article titled "sample size determination. Gwowen Shieh (2013) discussed sample size requirements for interval estimation of the strength of association effect sizes in multiple regression analysis .Hazra A (2017) presented a brief descriptive guide to calculations regarding confidence intervals. Hopkins(2018) presented a spreadsheet using two new methods for estimating sample size for study designed to make an inference about real-world significance, based on acceptable uncertainty defined either by the width of the confidence interval or by error rates for a practical decision arising from the study. Aimed to develop and present rigorous approaches for sample size calculation using a real-world case study, the presented approach of Karissa M. et al (2019), which presented a

Jilin Daxue Xuebao (Gongxueban)/Journal of Jilin University (Engineering and Technology Edition)
ISSN: 1671-5497
E-Publication: Online Open Access
Vol: 43 Issue: 11-2024
DOI: 10.5281/zenodo.14208007

guidance for sample size computations for retrospective burden of illness studies, was methodologically rigorous and designed for practical application in real-world retrospective chart review studies. Schober P& Vetter TR (2020) briefly discussed the confidence intervals in clinical research aimed at making inferences about the population from a drawn sample. Sharma et al (2020) article covered different formulas of sample size calculation for different types of variables measured in distinct study designs, namely descriptive, epidemiological, comparative, and interventional research studies. The article by Wei Q. and Yin P. (2022) focuses on constructing a confidence interval for vaccine efficacy against COVID-19 using a fixed amount of events design. It presents five different methods and evaluates their performance based on three criteria: two-sided coverage probability, non-coverage probability at the lower tail, and the expected width of the confidence interval. Sharma PK, Yadav M.(2024) concluded that from a utility point of view and like other statistical tools confidence interval approach does have several advantages as well as disadvantages. The rest of this paper is as follows: Section 2 is devoted to CI in clinical test, factors affecting its width and its calculation procedures. Numerical illustrations have been done in section 3, followed by results discussion in chapter 4 and conclusions, which have been reached research in chapter 5.

2.1. CI in clinical significance test

In clinical research, the confidence level plays a crucial role in significance testing as it determines the degree of certainty with which researchers can infer results about a population from a sample. The confidence level, often set at 95% or 99%, indicates the probability that the true population parameter lies within the confidence interval (CI) derived from the sample data. There is a strong connection between CIs for effect size estimates and hypothesis testing. For instance, if the 95% CI for an effect size does not include the null hypothesis value that indicates "no effect" (e.g., an odds ratio of 1), it corresponds to a "statistically significant" result at an alpha level of 0.05. Beyond just determining statistical significance, the CI provides insight into the potential size of the treatment or exposure effect, helping assess the clinical relevance of the findings. Here is how it impacts significance testing:

1. **Relationship with the P-value**: In a significance test, the confidence level complements the P-value, which indicates whether the observed effect in a sample is statistically significant.
2. **Determining Precision**: Higher confidence levels (e.g., 99%) result in wider CIs, offering more certainty but reducing the precision of the estimate.
3. **Clinical Decision Making**: The confidence level helps clinicians assess not only whether an effect is statistically significant but also its potential range of effect sizes.

2.2. CI Calculation Procedures

To calculate a confidence interval, three key components are required, the sample statistic (e.g., the sample mean), the standard error of the statistic and the desired confidence level.

Jilin Daxue Xuebao (Gongxueban)/Journal of Jilin University (Engineering and Technology Edition)
ISSN: 1671-5497
E-Publication: Online Open Access
Vol: 43 Issue: 11-2024
DOI: 10.5281/zenodo.14208007

The number of standard errors depends on the z-statistic or t-statistic that corresponds to the desired confidence level. The critical value, or z value, is determined by the desired confidence level and is based on the properties of the standard normal distribution. For confidence levels of 90%, 95%, and 99%, the corresponding z values are 1.65, 1.96, and 2.58, respectively. The standard error is influenced by both the sample size and the variability of the variable under study.

Calculating the CI for the mean is straightforward, with the formula being:

$$CI = Sample\ mean \pm z\ value \times Standard\ error\ of\ the\ mean \ldots\ldots [1]$$

Sample mean ± z value × (Standard deviation/√n)

For example, to calculate the 95% CI of the mean, the z value used would be 1.96.

Here's what each component represents:

- **CI (Confidence Interval)**: The range within which the population mean is expected to lie, based on the sample mean and chosen confidence level.
- **Sample Mean (x̄)**: The average of the sample data.
- **±**: Indicates that the confidence interval has both an upper and lower bound.
- **z-statistic**: The z-score corresponding to the confidence level, representing the number of standard deviations from the mean.
- Standard Error: Standard Error = s / √n.

Several formulas for sample size evaluations are introduced for different situations (see I, Glen D. (1992) and Sharma et al (2020)).

The margin of error "E" is the maximum difference between the sample mean $\bar{x}$ and the population mean μ, then following Elsayir HA and Alkhairy IH (2024):

$$E = z_{\alpha/2}\left(\frac{\sigma}{\sqrt{n}}\right) \ldots\ldots\ldots\ldots [2]$$

$Z_{\alpha/2}$ is the critical value, for the area in the standard normal distribution.

After rearrangement of this formulae we get:

$$n = \left(\frac{\sigma z_{\alpha/2}}{E}\right) \ldots\ldots\ldots\ldots [3]$$

The above formula is used when σ is known and determination of the sample size necessary to estimate, with a confidence of 1- α, the mean value μ to within ±E. However, when sample size n >30, σ can be replaced by S, the sample standard deviation. If $n \leqq 30$, the population must be normally distributed with known population standard deviation σ to use the above formula. Hence formulas were developed to help determining an optimal sample design depending on these two constraints. Let n_h bet the sample size selected for stratum h, S_h is the standard deviation of stratum h, and c_h is the direct cost to sample an individual element from stratum h, based on optimal allocation when a

Jilin Daxue Xuebao (Gongxueban)/Journal of Jilin University (Engineering and Technology Edition)
ISSN: 1671-5497
E-Publication: Online Open Access
Vol: 43 Issue: 11-2024
DOI: 10.5281/zenodo.14208007

stratified sampling is used, the optimal sample size for stratum h would be given by: stattrek (2020).

$$n_h = n\left[(N_h S_h)/(\sqrt{C_h})\right]/[\Sigma(N_i S_i)/(\sqrt{C_i})] \ldots\ldots\ldots [4]$$

where, n and N_h is total sample size and the population size for stratum h respectively. The summation ∑ is across all of the strata; *i* represents one of those strata.

Based on Neyman allocation, the desired sample size for stratum h would be: Stattrek (2020).

$$n_h = n[(N_h S_h)]/[\Sigma(N_i S_i))] \ldots\ldots\ldots [5]$$

The sample size n can be reached after solving for n.

As in the case of study that can involve dichotomous variables responses or measurements (i.e., the measurements in form of rates or proportions), a relatively simple formula can be used to determine the required sample size. Suppose r_c be the number of observation outcomes (such as sex (male or female, disease, death)) in the control group, and r_e is the outcome in the experimental group. Following Ralph B. Dell et al (2002) we can define:

$$P_c = r_c/N_c \ ; \ P_e = r_c/N_e \ \ldots\ldots\ldots.. [6]$$

where r_c and N_c represent respectively the number of events and the total number of elements in control group or group c, and r_e, N_e for the experimental group or group e. Then the underlying hypotheses will then be:

$$H_0: (P_c - P_e = 0); \text{ against} : H_1: (P_c - P_e \neq 0)$$

The needed null hypothesis test H_o can be used to obtain the sample size formula. Thus, given estimates for p_c and p_e, sample size n for each group can be computed as:

$$n = (C \ (P_c Q_c + P_e Q_e) + \left(\frac{2}{d}\right) + 2, \quad \ldots\ldots [7]$$

where $q_c = (1 - p_c)$; $q_e = (1 - p_e)$; and $d = |P_c - P_e|$. d is the positive difference between p_c and p_e,C is a constant that depends on the values chosen for α and β.

2.3. Sample Size & Confidence Level

A confidence interval is a range of likely or plausible values of the population characteristic of interest, Kalinowski and Cumming G (2018). Confidence intervals, the usual choice is 95% (with 90% and 99% in certain situations) usually take the form:

(Point estimate) ± (Margin of error).

The simplest method for constructing the width of confidence level is the precision approach, in which you use the standard deviation (or an estimate) and your desired margin of error (the half width of your confidence level) as in the following formula:

$$n = (Z\sigma/W)^2 \ldots\ldots. [8]$$

Jilin Daxue Xuebao (Gongxueban)/Journal of Jilin University (Engineering and Technology Edition)
ISSN: 1671-5497
E-Publication: Online Open Access
Vol: 43 Issue: 11-2024
DOI: 10.5281/zenodo.14208007

n is the number of elements, σ is the standard deviation of the population, *Z* is the *Z* score for the confidence level. Confidence intervals are used to estimate sample sizes as follows: Let us be interested in the population mean, the total number of subjects required (n) is:

$$n = 4Z^2{}_\alpha \ S^2/W^2 \ \ldots\ldots [9]$$

where S is the variable standard deviation, W is the width of the confidence interval, and z_α is a value from the normal distribution representing the confidence level. We can rewrite the equation as:

$$n = (Z_\alpha \ S/E)^2 \ \ldots\ldots [10]$$

where E is the “margin of error” (half the width, W) which can be rewritten as:

$$n = (2 \ S/E)^2 \ \ldots\ldots [11]$$

The 95% confidence is approximated to be equal to 2 for z_α (instead of 1.96). When interest is in a population **proportion**, the total number of subjects required (n) is:

$$n = \frac{4Z^2{}_\alpha P(1-P)}{W^2} = (\ Z_\alpha/E)^2 P(1-P) \ \ldots\ldots [12]$$

where P is the expected proportion of the characteristic of interest. Consider P= 0.5. Then we get:

$$n = 1/E^2 \ \ldots\ldots [13]$$

Which can also be rearranged be:

$$E = \frac{1}{\sqrt{n}} \ldots\ldots [14]$$

So, doubling the sample size only reduces the margin of error without much improvement in precision for doubling of the effort.

2.4. *P* values, confidence intervals, and magnitude of effects

When calculating the p-value, we start by assuming there is no real difference between the two treatments (this is known as the null hypothesis). Next, we determine the likelihood of observing the difference we’ve seen purely by chance, assuming the null hypothesis is true. This likelihood is the p-value. Essentially, the p-value represents the probability of seeing effects as large as those in the study if there is no actual difference between the treatments. If the p-value is small, it suggests the findings are unlikely due to chance, leading us to reject the null hypothesis (the assumption that there's no difference). On the other hand, if the p-value is large, the observed difference could plausibly be due to chance, and we do not reject the null hypothesis. However, this doesn’t mean we accept the null hypothesis; rather, we cannot make a definitive conclusion without further investigation. In short, the p-value helps assess whether the findings are "significantly different" or "not significantly different" from a reference value, which in trials typically reflects "no effect."

Jilin Daxue Xuebao (Gongxueban)/Journal of Jilin University (Engineering and Technology Edition)
ISSN: 1671-5497
E-Publication: Online Open Access
Vol: 43 Issue: 11-2024
DOI: 10.5281/zenodo.14208007

3. Numerical Illustrations

In this section, we present numerical analysis for confidence interval and the related issues such as sample size and effect size. Some illustrations for some statistical tests were introduced in table (1), where the required sample size is determined according to desired tolerance for some specified parameters.

Table 1: Required sample size from a population with 95% and 99% confidence level

Estimated population size	Margin of error					
	Confidence level 95%			Confidence level 99%		
	5%	2.5%	1%	5%	2.5%	1%
100	80	94	99	87	96	99
500	217	377	475	285	421	485
1,000	278	606	906	399	727	943
10,000	370	1332	4899	622	2098	6239
100,000	383	1513	8762	659	2585	14227
500,000	384	1532	9423	663	2640	16055
1,000,000	384	1534	9512	663	2647	16317

In large populations, the variability within the sample becomes more representative of the population, so further increasing the sample size yields diminishing returns in terms of improving the accuracy of the estimates. A larger sample size is required when aiming for a lower margin of error or a higher level of confidence. This is because increased precision (smaller margin of error) and greater confidence in the results demand more data to reduce uncertainty. However, when the estimated population size is very large (e.g., greater than 100,000), the sample size does not increase significantly beyond a certain point.

From table (2), the sample size required is determined to estimate the mean of a normal distribution the standard deviation of the normal distribution assumed to be equals 2, then 7 subjects are to estimate the mean to within 2 with 95% confidence. The table shows that the required sample size is determined to estimate the standard deviation of normal distribution.

Then 193 observations are required to estimate sigma to within 0.2 with 95% confidence. Similarly, it is obvious from the table that the sample size required to estimate the proportion of a binomial distribution is determined. Then 1068 observations are required to estimate the proportion to within 0.03 with 95% confidence, assuming the proportion is around 0.5. The rest of the table contents can be interpreted in the similar way.

Jilin Daxue Xuebao (Gongxueban)/Journal of Jilin University (Engineering and Technology Edition)
ISSN: 1671-5497
E-Publication: Online Open Access
Vol: 43 Issue: 11-2024
DOI: 10.5281/zenodo.14208007

Table 2: Required sample size for some parameters (95% confidence)

Parameter to be estimated	Desired tolerance(delta)	Required sample size	Comments
Normal mean	+/-2	7	Assumed sigma = 2
Normal sigma	+/ - 0. 2	193	
Binomial proportion	+/ - 0.3	1068	Assuming the proportion is 0.5
Poisson rate	+/ - 0.5 (rate=5)	77	
Difference between two normal variances	+/ - 0.5	9 for each sample	Assumed sigma= 5 with group
Ratio of two normal variances	+/ - 0.5	68	
Difference between two binomial proportions	+/ - 0.1	193	Mean proportion= 0.5
Difference between two Poisson rates	+/-1	77	Mean rate =10
Difference between several normal means	+/-1	12	No. of means =3 Assumed sigma= 1

Tables (3) and Table (4) shows required sample size for a given population with allowable difference and variance estimate (for different Confidence levels, 95% and 99% successively.

A confidence interval estimates plausible values for a population parameter, not the sample. If we repeatedly sample from the population, 95% of the confidence intervals will contain the true population parameter. The population parameter is fixed, but the width of the interval varies with each sample.

A 95% confidence interval (CI) does not imply that 95% of the sample data fall within that interval. Instead, it is an interval estimate for plausible values of the population parameter, not the sample data. While it's tempting to interpret a 95% CI as the range within which the population parameter lies with 95% probability, this is not entirely accurate. The true population parameter is fixed, but the width of the 95% CI varies depending on the random sample.

If we were to take repeated random samples of the same size from the population, each would generate its own 95% CI. However, only 95% of those intervals would contain the true population parameter. Thus, a single CI does not guarantee that it captures the population parameter, but across many samples, 95% of such intervals would.

Jilin Daxue Xuebao (Gongxueban)/Journal of Jilin University (Engineering and Technology Edition)
ISSN: 1671-5497
E-Publication: Online Open Access
Vol: 43 Issue: 11-2024
DOI: 10.5281/zenodo.14208007

Table 3: Find Confidence Interval: 95% (99%) Confidence Level

Sample size	Population size	Percentage	Confidence level
1(1)	1(1)	1(1)	N A N(N A N)
1(1)	2(2)	1(1)	19.5(25.67)
5(5)	5(5)	1(1)	0(0)
5(5)	10(10)	1(1)	6.5(8.56)
5(5)	30(30)	5(5)	17.74(23.35)
5(5)	50(50)	10(10)	25.2(33.17)
10(10)	50(50)	10(10)	16.8(22.11)
10(10)	100(100)	10(10)	17.33(23.34)
10(10)	500(500)	20(20)	24.57(32.34)
30(30)	1000(1000)	20(20)	14.1(18.57)
100(100)	1000(1000)	50(50)	9.3(12.24)
100(100)	10000(10000)	50(50)	9.75(12.84)

Table (4) displays sample size for a given confidence level and population size (N) where table (5) also displays the confidence level for an increasing amount of sample size and population size. One way to bridge the gap between statistical significance and clinical relevance is by reporting confidence intervals (CIs).

The confidence interval provides both an estimate of the true value and its range of uncertainty. For instance, a 95% CI corresponds to a significance level of 0.05 in hypothesis testing, while also offering insight into the potential true effect size. A confidence interval (CI) for a measure of treatment effect indicates the range within which the true treatment effect is likely to lie, based on certain assumptions.

In contrast, a p-value assesses whether the observed trial results could have occurred by chance, assuming no real difference exists between the new and old treatments, and that the study was properly conducted.

The effect size is introduced in table (5) Column1) where alpha=0.05; and power=0.95). Effect size (ES), sample size, and significance level affect power. The number of effect size must be from 0.001 to 10. The effect size conventional amounts are small =0.20, medium=0.50, and large=0.80.

Confidence intervals are generally preferred over p-values because they provide a range of possible effect sizes that are consistent with the data. On the other hand, p-values offer a threshold for determining whether results are "statistically significant" (usually with a cut-off of $p < 0.05$).

Jilin Daxue Xuebao (Gongxueban)/Journal of Jilin University (Engineering and Technology Edition)
ISSN: 1671-5497
E-Publication: Online Open Access
Vol: 43 Issue: 11-2024
DOI: 10.5281/zenodo.14208007

Table 4: Calculate Power Sample size

Population Size	Confidence Interval % (95)	Margin of Error	Sample Size
100	95	1	**99**
100	95	0.5	**100**
1000	95	0.5	**975**
1000	95	1	**906**
10000	95	1	**4900**
10000	95	0.5	**7935**
10000	95	0.1	**9897**
1000	95	0.1	**999**

If the 95% confidence intervals for outcome estimates in different groups do not overlap, it indicates a statistically significant difference between the groups. However, even if there is a small overlap in the CIs, the difference might not be clinically meaningful, regardless of the p-value. Reporting confidence intervals thus moves the interpretation beyond a simple judgment about the role of chance, offering a more quantitative assessment of the biological effect.

Table 5: Effect size, Sample size &Power (Alpha=0.05; Power=0.95)

Effect size (ES)	Delta(Δ)	The Critical value ( )	Sample size(n)	Power
0.001	3.605	1.960	51978840	**0.950**
0.100	3.606	1.960	5200	**0.950**
0.200	3.608	1.962	1302	**0.950**
0.300	3.613	1.964	580	**0.950**
0.400	3.622	1.967	328	**0.950**
0.500	3.623	1.971	210	**0.950**
0.600	3.649	1.976	148	**0.952**
0.700	3.671	1.982	110	**0.953**
0.800	3.666	1.989	84	**0.952**
0.900	3.711	1.997	68	**0.955**
10.00	**10.000**	**4.303**	**4**	**0.993**

Jilin Daxue Xuebao (Gongxueban)/Journal of Jilin University (Engineering and Technology Edition)
ISSN: 1671-5497
E-Publication: Online Open Access
Vol: 43 Issue: 11-2024
DOI: 10.5281/zenodo.14208007

4. DISCUSSION

When interpreting this in a clinical context, it's helpful to consider potential outcomes at both ends of the confidence interval. For example, if the patient experiences the most conservative outcome—an improvement of 6 letters—would this be as meaningful to the patient as the most optimistic outcome of 10 letters? If the clinical significance of the treatment effect remains similar whether considering the bounds of the confidence interval, there is greater confidence that the treatment will be meaningful for the patient.

However, if the potential benefit appears significantly different when comparing the lower and upper bounds, it may lead to more caution in interpreting the expected benefits of the treatment.

The conflict between clinical importance and statistical significance is a key concern in biomedical research. Clinical importance is primarily determined by the effect size, which reflects the actual magnitude of change or difference observed. On the other hand, statistical significance, often represented by the p-value, merely indicates whether a difference exists in terms of probability, without addressing the practical relevance of that difference.

5. CONCLUSION

It worthwhile to remember that the concept of the confidence interval was introduced to deal with statistical inference results derived from subset of a population. Medical and clinical researchers must consider several important factors when interpreting evidence. In this article, we aim to offer practical insights into key methodological principles that can aid in clinical decision-making.

While P-values are a small part of interpreting study results, a more thorough understanding is gained by also evaluating treatment effects and their associated confidence intervals. The magnitude of the effect is typically expressed as the mean difference between groups for continuous outcomes.

These measures reflect the observed effect quantified in the study comparison. Moving away from a simple binary interpretation of "significant" versus "not significant" encourages a more nuanced evaluation. Instead of solely focusing on statistical significance, the emphasis should be placed on critically assessing the clinical relevance of the observed effect.

This approach provides a more meaningful understanding of the study’s results. In summary, the confidence level in clinical research ensures a balance between precision and certainty, guiding the interpretation of significance tests and their implications for patient care and clinical outcomes.

Conflicts of Interest

The author declares no conflicts of interest regarding the publication of this paper.

Jilin Daxue Xuebao (Gongxueban)/Journal of Jilin University (Engineering and Technology Edition)
ISSN: 1671-5497
E-Publication: Online Open Access
Vol: 43 Issue: 11-2024
DOI: 10.5281/zenodo.14208007

References

1) Gautret P, Lagier JC, Parola P. Hydroxychloroquine and azithromycin as a treatment of COVID-19: results of an open-label non-randomized clinical trial. Int J Antimicrob Agents. 2020 article in press. [PMC free article] [PubMed] [Google Scholar].

2) Elsayir HA and Alkhairy IH (2024). Estimating the Sample Size for Epidemic and Medical Research. American J Sci Edu Re: AJSER-181.

3) Gwowen Shieh (2013). Sample size requirements for interval estimation of the strength of association effect sizes in multiple regression analysis. *Psicothema 2013, Vol. 25, No. 3, 402-407*doi: 10.7334/psicothema2012.221.

4) Habib Ahmed Elsayir, Factors Determining the Power of a Statistical Test for the Difference between Means and Proportions, *American Journal of Mathematics and Statistics*, Vol. 8 No. 6, 2018, pp. 171-178. doi: 10.5923/j.ajms.20180806.02.

5) Hazra A.(2017). Using the confidence interval confidently. J Thorac Dis. 2017 Oct; 9(10):4125-4130. doi: 10.21037/jtd.2017.09.14. PMID: 29268424; PMCID: PMC5723800.

6) Hogan CA, Sahoo MK, Pinsky BA. Sample Pooling as a Strategy to Detect. Community Transmission of SARS-CoV-2. JAMA. 2020. doi:10.1001/jama.2020.5445.

7) Jack Virag. The role of confidence levels in statistical analysis. Last updated: Thu Apr 04 2024. https://www.statsig.com/blog/confidence-levels-in-statistical-analysis.

8) Kalinowski P, Lai J and Cumming G (2018). A Cross-Sectional Analysis of Students' Intuitions When Interpreting CIs. *Front. Psychol. 9:112. doi: 10.3389/fpsyg.2018.00112*.

9) Keaven Anderson & Qing Liu (2014). Optimal Adaptive vs. Optimal Group Sequential Design. Merck Research Laboratories. BASS X1.

10) Lenth RV. Some practical guidelines for effective sample size determination. [Last accessed on 2017 Jul 10]; Am Stat. 2001 55:187–93. Available from: http://www.jstor.org/stable/2685797. [Google Scholar].

11) Paul H. Lee. Sample sizes in COVID-19–related research. CMAJ April 27, 2020 192 (17) E461; DOI: https://doi.org/10.1503/cmaj.75308.

12) Phillips, M.R., Wykoff, C.C., Thabane, L. *et al.* The clinician's guide to *p* values, confidence intervals, and magnitude of effects. *Eye* 36, 341–342 (2022). https://doi.org/10.1038/s41433-021-01863-w.

13) Schober P, Vetter TR. Confidence Intervals in Clinical Research. Anesth Analg. 2020 May, (1305):1303, doi.10.1213/ANE.0000000000004731.PMID;32287136.

14) Sharma PK, Yadav M. Confidence Interval: Advantages, Disadvantages and the Dilemma of Interpretation. Rev Recent Clin Trials. 2024; 19(1):76-80. doi: 10.2174/0115748871266250231120043345. PMID: 38099533.

15) Stamey, J. and Gerlach, R. (2007). Bayesian Sample Size Determination for Case-control Studies with Misclassifiation. *Computational Statistics & Data Analysis Volume 51, Issue 6, Pages 2982-2992.*

16) *Stattrek (2020). Neyman allocation, Retrieved from: http:/stattrek.com/lesson6/sampleSizestrataaspx.*

17) *Ying Lau, Sai Ho Wong, Ling Jie Cheng, Siew Tiang Lau. Exploring experiences and needs of perinatal women in digital healthcare: A meta-ethnography of qualitative evidence .International Journal of Medical Informatics. Volume 169, 2023, 104929, ISSN1386-5056, https://doi.org/10.1016/j.ijmedinf.2022.104929.*