CHALLENGES IN ACUTE AND CRITICAL CARE RESEARCH

Ethics approval, patient consent

Small sample size

Informed by: National Academies of Sciences, Engineering, and Medicine. (2018). *Improving Health Research on Small Populations: Proceedings of a Workshop*. Washington, DC: The National Academies Press. doi: https://doi.org/10.17226/25112.

THE NEED FOR PROSPECTIVE CLINICAL STUDIES

- "The government are very keen to amass statistics. They collect them, add them, raise them to the nth power, take the cube root and prepare wonderful diagrams. But you must never forget that every one of these figures comes in the first instance from the village watchman who just puts down what he damn pleases." Josiah Stamp (1929)
- The clinicians who are entering data are not necessarily concerned about research data needs

ETHICS APPROVAL
PATIENT CONSENT

ETHICS AND CONSENT IN ACUTE AND CRITICAL CARE RESEARCH IN NSW

- An important ethical principle in research involving humans is a fair distribution of the benefits of participation in research
- So that patients unable to consent themselves can still benefit from research NSW HRECs recognise delayed consent
- Approval from the NSW Civil and Administrative Tribunal (NCAT) is also required for *clinical trials* which seek to involve patients unable to consent

ETHICS AND CONSENT IN ACUTE AND CRITICAL CARE RESEARCH IN NSW

- NCAT legislation was designed with people with disabilities in mind
- NCAT cannot recognise a delayed consent mechanism
- NCAT can only recognise

  PROSPECTIVE consent by person responsible

  (guardian, spouse or partner, carer, relative or friend)

  PROSPECTIVE consent by NCAT
- This can render an otherwise ethical clinical trial infeasible in NSW

ETHICS AND CONSENT IN ACUTE AND CRITICAL CARE RESEARCH IN NSW

- Legislation is currently under review by the Law Reform Commission
- NCAT recently reviewed a number of it's decisions on clinical trials in acute and critical care patients in order to provide a pathway forward…

  A study that involves a placebo arm is not necessarily a *clinical trial*

  Standard practice comparison of treatments (where either arm of the trial would be suitable) is not a *clinical trial*

ETHICS AND CONSENT IN ACUTE AND CRITICAL CARE RESEARCH IN NSW

- New or experimental treatment not yet widely accepted by peer professionals is a *clinical trial*
- Any uncertainty, the Ministry Office of Health and Medical Research and Legal Branch is more than happy to provide advice and assistance
- NCAT is not an appropriate or helpful avenue of escalation
- Highlight in your HREC and SSA applications that your study is not a *clinical trial* as defined by NCAT to avoid NCAT caveats on your approval

SMALL SAMPLE SIZE

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SMALL SAMPLE SIZE – WHAT IS SMALL?

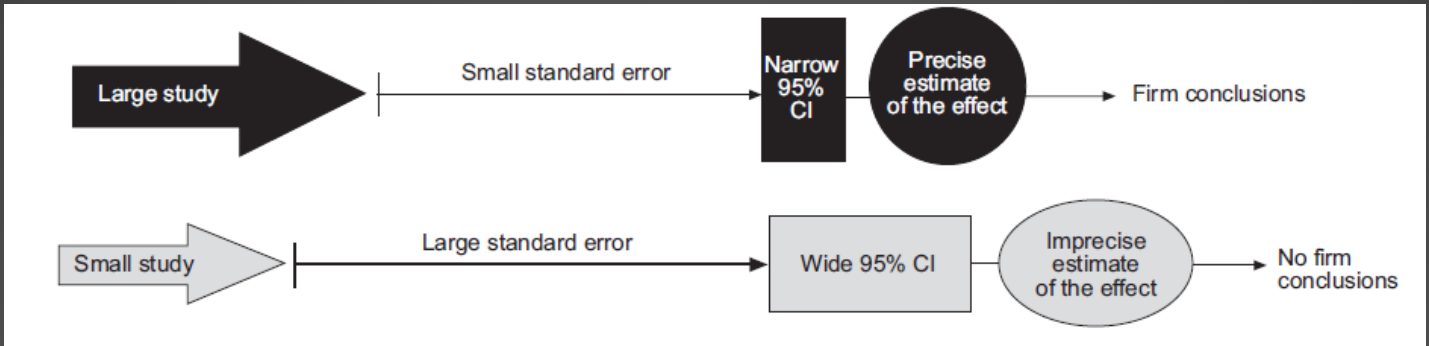
If the sample size makes any of these problematic, then the sample size is "small"

- Researchers want a situation in which the outcome of the data analysis is not highly influenced by one or two cases
- Researchers want valid estimates of parameters and standard errors
- The relationship between the final sample size and the "size" of the effect to be determined should be appropriate

SMALL SAMPLE SIZE – WHAT IT ISN'T

- Sometimes a sample is small because of constraints such as a small population or insufficient resources
- Other times a sample is small but a researcher could have done better with more time and effort
- Because small sample data analyses require compromise, it is difficult to justify those situations when it would be possible to do better

WHAT IS THE PROBLEM WITH SMALL?



Eur Respir J 2008; 32: 1141–1143

- Small sample sizes result in tests with low statistical power
- The statistical power of a test is the probability that it will correctly reject the null hypothesis when the null hypothesis is false (that is, the probability of not committing a type II error or making a false negative decision)
- The probability of committing a type II error is referred to as the false negative rate (β), and power is equal to 1 – β

WHAT IS THE PROBLEM WITH SMALL?

- Low statistical power reduces the chance of detecting a true effect, undermining the purpose of scientific research
- Low power also reduces the likelihood that a statistically significant result reflects a true effect
- Consequences of low statistical power include overestimates of effect size and low reproducibility of results
- Unreliable research is inefficient and wasteful and therefore, unethical
- Sample size must be justified in your ethics application

FINITE POPULATION CORRECTION

- In a small sample situation, particularly when sample size is constrained by population size, one potential approach for increasing the power of a statistical test is to use the finite population correction (fpc)
- Sampling fraction f=n/N where n is the sample size and N is the population size

FINITE POPULATION CORRECTION

- If f=1, then there is a census and no sampling error, (though there could be error from other sources)
- As f approaches 1 the sampling error in estimating the population parameter reduces
- An f approaching zero, however, reflects the usual situation in which the size of the sample is small relative to the size of the population
- When f is greater than .05 the power of statistical tests can be improved through use of the finite population correction factor,

$$fpc = \sqrt{\frac{N-n}{N-1}}$$

FINITE POPULATION CORRECTION

- If researchers know they will be operating in a small population context and inferences are desired only on that population, fpc can be used to estimate the sample size needed to achieve a certain level of power
- Standard power tables can be used to determine the appropriate sample size (n) for an infinite population
- The sample size adjusted for a finite population can then be computed

$$n_a = \frac{n}{1+\frac{n-1}{N}}$$

FINITE POPULATION CORRECTION

If the usual required sample size is 150 for a very large (infinite) population but the population size is 200, the adjusted sample size to achieve the same level of power is 150/(1+((150-1)/200)) or 86

If the usual required sample size is 50, but the population size is 200, the adjusted sample size is 50/(1+((50-1)/200)) or 41

FINITE POPULATION CORRECTION

- There are inferential limitations associated with using fpc that may or may not matter depending on the goals of the research
- It allows inference about the state of this population (the 200 referred to above) at the time of the sampling
- It does not support inference about another population that may be like this one, nor does it represent this population at any other point in time
- Useful for clinical audit studies

DESIGN AND MEASUREMENT QUALITIES THAT OPTIMISE RESEARCH

- General test statistic e.g. *t*-test = the ratio of a parameter estimate to its standard error
- If the goal is to detect a significant effect (i.e. obtain a large *t* value) there are two ways in which the test statistic can be increased
  - increase the parameter estimate
  - decrease the standard error

DESIGN AND MEASUREMENT QUALITIES THAT OPTIMISE RESEARCH

- *Increasing the parameter estimate*
  - Given the limitations on statistical power for a given treatment, it might be difficult to demonstrate an effect on the desired long-term outcome.
  - However, there may be more proximal outcomes that relate to behaviour change. It may be known that these behaviours ultimately translate into differences in the outcome of greatest interest.
  - The study may be better powered to detect an effect if the researcher focuses on those proximal outcomes.

DESIGN AND MEASUREMENT QUALITIES THAT OPTIMISE RESEARCH

- *Decreasing the standard error of the parameter estimate*
  - The standard error depends on sample size, reducing as the sample size increases. Thus, recruitment and retention are critical
  - Use all data in an analysis, even if the data from some participants is incomplete
    - There are many accessible methods of dealing with missing data that create the possibility for leveraging the data that have been provided. Examples include multiple imputation and model-based methods.

DESIGN AND MEASUREMENT QUALITIES THAT OPTIMISE RESEARCH

- *The statistical analysis itself*
  - Consider two different models: a simple one, with only x1 and y and another multiple regression that includes x1 and y and other auxiliary variables (covariates) that help explain the variation in y
  - Including covariates in the model that really do account for some of the variation in y, reduces the standard error of the estimate of the coefficient on x1, increasing the power of the test
  - While these covariates may cost in terms of degrees of freedom, they may substantially reduce the error term in the equation, the denominator of the test statistic
  - This increases the likelihood of detecting an effect without really changing the estimate itself

BAYESIAN METHODS

- At the heart of Bayesian methods is that everything that is known about a parameter before observing the data (*the prior*) is combined with the information from the data itself (*the likelihood*), resulting in updated knowledge about the parameter (*the posterior*)
  - More might be learned if small randomised experiments were embedded in a project to learn something generalisable - look for a chance to randomise and do little experiments
  - The prior information can stem from a meta-analysis, previous studies with comparable research populations, a pilot study, experts, or a range of other sources
  - Will require specialised statistical support

SOME REFERENCES THAT MAY ASSIST

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THANK YOU