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## Mater Research Support Centre Newsletter

Welcome to the fourth edition of the MRSC newsletter. The focus for this edition is on Stillbirth research at the Mater. In addition, we continue our series of articles on sample size, provide an update on Cochrane activities and in response to clinicians' requests provide articles in equivalence studies and data collection for trials.

We welcome any letters to the Editor. A word limit of 300 words applies for letters to the Editor and the MRSC reserves the right to edit or refuse to publish any submissions. Should you wish to submit a letter to the Editor, join our mailing list, or to contact any of our staff, please email: Anne-Maree at Anne-Maree\_Stout@mater.org.au or phone 3840 1591.

### WHAT'S NEW

#### **Want to do a Sample Size calculation?**

The Mater Research Support Centre has now over 75 web based applets on the Intranet for calculating sample size requirements. Included in the web page are also detailed explanation of the procedures, formulations, and examples for those who want more details.

#### **Taking the pain out of Data Entry**

Our OMC Remark Scanner software is now available for use by Mater researchers. To find out more please telephone our Centre on ext 1591.

The newsletter is now on the Mater Intranet – to download additional copies of our newsletter visit our Website via the Mater Intranet, clicking on “Departments”, Mater Research Support Centre, Information, News and then MRSC newsletters.

**Congratulations to our students Braiden Judd, Julie MacPhail, Maelle Morgan, Brodie Radford, Jill Tierney and Kiri Vaughan on their excellent University results. Well Done!**



The staff at the MRSC would like to wish you all a very safe and happy Christmas and New Year and look forward to working with you again in 2005.

The MRSC will be closed from Monday 27 December, 2004 until Sunday 9 January 2005.

## DATA COLLECTION FOR TRIALS

This article is in response to a request by clinicians to have access to information on the requirements when filling out data collection forms for studies. This is a brief overview on correct data collection and is by no means exhaustive in nature. There are specific international and national guidelines, standards and regulations which must be followed when completing data collection forms details of which can be accessed from our website.

### ***Study Procedure Manual***

Accurate completion of the data collection forms for any study is integral to successfully carrying out a clinical trial therefore a study procedure manual (this is in addition to the study protocol) should be prepared for every trial. The study procedure manual should include the Standard Operating Procedures (SOP) on how the documentation should be recorded, what to do with missing data, what forms need to be completed when etc. This is the research assistant's guideline on how to complete all the required data collection forms. Included in the manual should be SOP for the use of electronic systems, if applicable, including the maintenance of a security system that prevents unauthorised access to the data and adequate backup of the data.

Written trial documents should be kept in a locked room and/or filing cabinet. The Therapeutic Goods Administration (TGA) requires records to be retained by the sponsor for 15 years following the completion of a trial.

### ***Access of Data***

Ideally all trial data should be accessed from the primary source, which in a hospital setting is usually but not always the patient medical chart. Electronically stored, routinely collected data from administration and clinical databases can be used for collection of some data however studies have confirmed that the validity of routinely collected data is suspect, particularly in systems that are not under clinical and professional control. It is essential that if data is to be obtained from sources other than the admitting hospital this needs to be reflected on the consent form so that other institutions and clinicians have the patient's consent to release the required data.

There are two methods that data can be entered: paper data entry which is then transferred to a computer for storage and analysis and direct electronic data entry onto a computer.

### ***Accuracy of Data Collection Forms***

Paper based data collection forms which are then transferred to computer gives approx. 70 – 85% accuracy.

Online data entry onto a computer gives approx. 95% accuracy.

Double entry data entry onto a computer gives approx. 99% accuracy.

### ***Paper Data Collection***

For all data collection forms the person entering the data should sign and date the form. All entries should be filled out in black pen. There should be a signature log of those who are entering data and of those individuals authorised to make data changes and what data changes that particular person is permitted to make.

The use of 'Whiteout' or similar correction fluid products is not permitted and any change or correction to a data collection form must be dated, initialled and explained (if necessary) and should not obscure the original entry. The use of a signature log ensures that the person making the changes can be easily identified if necessary.

All boxes should be filled in. Boxes should not be left blank as it is then unclear if this value is zero, not applicable or missing data. If the question is not applicable then N/A should be documented by the question or a line should be placed through the question. For Australia all dates should be recorded as *dd/mm/yyyy* unless otherwise requested by the trial investigators. To ensure completeness of data all data entry forms should be checked by a second person.

### ***Computer Data Collection***

For electronic data collection forms the system must be designed to enable the person entering the data to sign and date the form and permit data changes in such a way that there is no deletion of previously entered data.

Researchers must be responsible for ensuring appropriate security for any confidential material, including that held in computing systems. Where computing systems are accessible through networks, particular attention to security of confidential data is required. Electronic data must be password protected.

Once again boxes should not be left blank – a value should be allocated to be placed in a box to signify that the question is not applicable. Another value should be allocated to signify missing data where the source data has been checked and the data is unable to be obtained. In this way when data analysis is performed it is easy to see which data has been verified as truly missing.

Data entry personnel should be given explicit instructions regarding the types of data changes they may make. Data should be transcribed as recorded on the paper data form even if it appears incorrect and then a query should be made regarding the data. In this way there is an audit trail from the original data records to the computer data file. 'On the spot' changes without verification lead to discrepancies between the original data records and the computer data file, thus leading to questions regarding the integrity and validity of the data. All data should be backed up at regular intervals.

Where possible computer systems should be programmed to recognise unacceptable data or errors or incomplete data. This enables immediate detection and correction of errors.

More information on data collection and management can be obtained from the MRSC website. The MRSC is happy to offer assistance and advice on the correct method of data collection and management for clinical trials. Please email Anne-Maree.Stout@mater.org.au.

#### *References:*

Hosking J, Newhouse M, Bagniewska A, Hawkins B. Data Collection and Transcription. *Controlled Clinical Trials* 16:66S-103s, 1995

McFadden E. Management of Data in Clinical Trials. 1998. New York: John Wiley and Sons.

National Statement 2000. Commonwealth of Australia. Canberra. AGPS. TGA. Note for Guidance on Good Clinical Practice (CPMP/ICH/135/95). Annotated with TGA Comments. 2000. Canberra. Department of Health and Aged care.

The National Privacy Principles in the *Privacy Amendment (Private Sector) Act 2000*  
[www.privacy.gov.au/publications](http://www.privacy.gov.au/publications)

## WHAT WE CAN DO TO HELP WITH YOUR RESEARCH DATABASE

Database development is an increasingly important part of MSRC services as more and more researchers have approached the centre for assistance.

The MRSC is currently providing database development services to 8 projects for different groups of researchers across the campus. MRSC has experience in developing both quick desktop solutions such as MS Access and Delphi databases and web-based solutions using the Mater intranet for research and audit activities.

It is quite usual for a researcher to use paper-based forms, Excel spreadsheets or a simple Access database to collect data at beginning of the research. However, as the research progresses, these means of data collection may become inadequate to satisfy the growing needs in term of complexity and capability, which, to some extent, may lower work

efficiency.

By analysing the requirements of the researcher, the MRSC can offer an optimal database solution tailored to individual needs. The MRSC can also tailor and modify existing database systems to meet the researcher's increasing needs.

In the short term, MRSC is able to support the development of small and simple databases in Access or Delphi and also relatively complex databases using web-based technology. It is our belief that research databases will, in the future, reside on web servers, with users interacting with these databases via a web page. Our approach is to deliver quick desktop solutions to satisfy the current need of data entry and progress the project to a web-based database which may take a longer time to implement.

## DEMONSTRATING EQUIVALENCE

In response to a number of queries, an overview of the statistics behind an equivalence study is provided here. We hope researchers find this helpful.

In most experimental procedures the objective is to find if a statistically significant difference exists between two treatments (comparative study). However, failure to detect this difference in treatments does not imply that they are equivalent. Usually all that has been shown is an absence of evidence of a difference. In addition, there may not have even been enough power to detect a clinically meaningful difference.

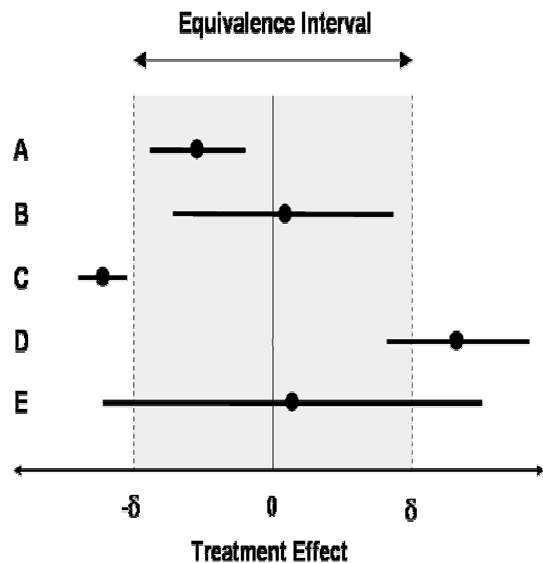
Testing for equivalence is useful to reveal whether a new treatment is clinically equivalent in efficacy to a standard treatment (equivalence study). Reasons for demonstrating equivalence is when the new treatment is likely to have fewer side effects, be more socially acceptable, cheaper or less time consuming than the standard but not necessarily more efficacious. To perform the equivalence test the investigator must be able to specify a minimum difference between treatments that will have no clinical, scientific or practical consequence.

In testing for equivalence it is not usually a serious error to claim that two treatments are significantly different, when in fact they are not. The consequence would be to keep the patients on the standard treatment. Thus the Type I error (probability of erroneously accepting equivalence) can be set quite large, sometimes 10% or 20%, instead of the usual 5% ( $p\text{-value} < 0.05$ ). Furthermore, the probability of erroneously concluding non-equivalence is called the Type II error and is typically set at 10% or 20% (i.e. power of 90% and 80% respectively). Power is the probability of concluding equivalence if it truly exists. However, if death is the endpoint and a new treatment presents fewer side-effects or less toxicity than the present treatment it is important to set a large power (95% or 99%).

The average difference between both treatments along with its 90% confidence interval is calculated when a trial is complete. The figure below illustrates this for experiments A to F. Equivalence may be concluded when the 90% confidence interval (Type I error of 5%) lies entirely within the predetermined equivalence interval.

Therefore, only experiments A and B have demonstrated equivalence. Experiment A illustrates that it is possible for the treatments to be significantly different and still lie within the equivalence range.

Also, experiment E shows that treatments can be neither significantly different nor equivalent. Another way to investigate equivalence is to use two one-sided tests, which is not discussed.



**Treatment A:** Statistically different and statistically equivalent

**Treatment B:** Not different and significantly equivalent

**Treatment C, D:** Statistically different and not equivalent

**Treatment E:** Not different and not equivalent

In practice, it is very important to know the correct sample size before commencing an equivalence study. Accruing the correct sample size will ensure both the Type I and power criteria are met for a particular equivalence interval. The sample sizes for an equivalence and comparative study are not identical. Equivalence studies generally require more cases. Sample size for equivalence studies can be obtained from the MRSC website. Click Departments from the Mater Intranet and go to Mater Research Support Centre (MRSC) and follow Utilities>Statistics>Quick index of programs>Sample sizes>SSiz 2 Groups.

For more information please contact:

Scott Pain (Statistician)

Phone: 3840 1587

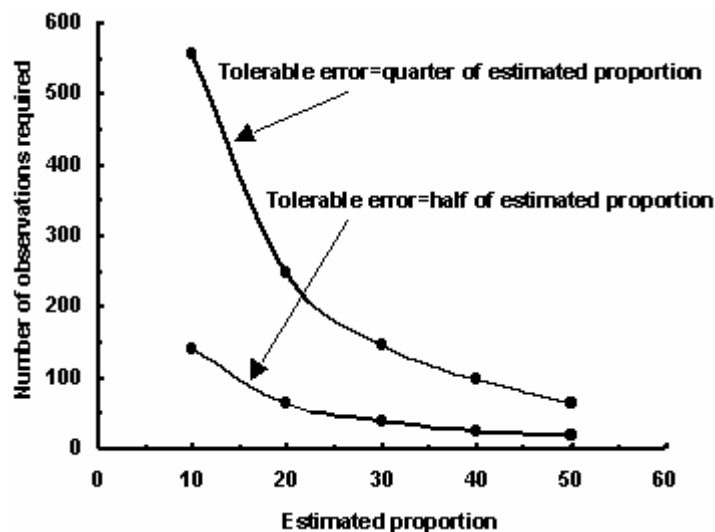
Email: [Scott.Pain@mater.org.au](mailto:Scott.Pain@mater.org.au)

This is the last in a series of three articles dealing with sample size calculations. The previous articles can be accessed on our website.

### *Sample size for estimating population proportion*

Researchers may want to know the proportion of a parameter in a population. Examples of this are complication rate of surgery, the proportion of people who would vote for a particular party, the readmission rate following discharge, and so on.

The sample size required depends on a complex relationship between the proportion anticipated and the 95% confidence interval of the tolerable error, as demonstrated in the following figure.



It can be seen that sample size increases where the anticipated proportion is low, and also if the tolerable error is narrow.

For example, we may anticipate the labour vote to be 45%, and we want to know if this is true, to an accuracy of +/- 5%. This will require a sample of 381 respondents in a survey.

On the other hand, we know that the perinatal death rate is around 1.5%, and we want to estimate it to an accuracy of +/- 0.5%. This will require a survey of 2271 births.

### *Sample size calculations for groups of unequal sizes*

A research model may have groups of unequal sizes, and a model of unequal group size may be when it is difficult to obtain sufficient cases for one of the groups. Sample size estimation for this situation consists of firstly estimating the sample size required for equal size groups, then adjust that number for the unequal size.

The formula is fairly straightforward. If  $N$  is the sample size needed in each of 2 equal size groups, and  $N_1$  is the number available in one of the group, then the number needed in the other group,  $N_2$  can be calculated as  $N_2 = 1 / (2/N - 1/N_1)$ . For example, if the sample size per group for two equal groups is 30, and only 25 cases is available for 1 group, then the number required for the other group is  $1 / (2/30 - 1/25) = 1 / (0.0667 - 0.0400) = 1 / 0.0267 = 37.5$  or 38 as a whole number. Please note that the minimum number for either group must exceed half of that required for equal size groups.

### *Sample size calculations for less frequently used types of parameters*

Different types of number will have different properties, probability distributions, and their own algorithm to estimate sample size requirement. However, the underlying principle is the same. A larger sample size is required for the more precise conclusions. If proportions are used, the sample size requirements are greater if the proportions involved are smaller.

Sample size calculations for counts of events (Poisson distribution), survival time, Receiver Operator Characteristics, and for non-parametric measurements all require their own sample size calculations. These have not been covered in this paper.

### *References:*

- Sokal RR and Rolf FJ (Ed. 2, 1981) Biometry W H Freeman and Co. NY ISBN 0-7167-1254-7. p263 for comparison of means and p766 for comparison of proportions.
- Robinson L, Neutons JJ (1987) Research Techniques for the Health Sciences. MacMillan p.366 for population parameters
- van Belle Gerald (2002). Statistical Rules of Thumb. John Wiley and Sons, New York. ISBN 0-471-40227-3. p. 45-46 for unequal groups

The Centre for Clinical Studies (CCS) and staff at Mater Mothers' Hospital have been actively involved in research and related activities aimed at reducing perinatal mortality with a focus on stillbirth. Support received from the MRSC has contributed to the achievements of the CCS. Funding received from SIDS and Kids Queensland and more recently the Perinatal Society of Australia and New Zealand (PSANZ) has enabled the establishment of the CCS as the coordinating centre for the PSANZ Perinatal Mortality Special Interest Group (PNM SIG). A number of activities have been successfully undertaken at the CCS working closely with the PNM SIG and are briefly outlined here.

### ***Perinatal mortality classifications***

The PSANZ classifications for perinatal death (Perinatal Death and Neonatal Death Classifications) and the accompanying Classification Guide (which provides a detailed description of the classification and case examples) were initially released in May 2003 and have recently been revised. The purpose of the PSANZ Perinatal Death Classification (PSANZ-PDC) is to identify the single most important factor which led to the chain of events which resulted in the death. The purpose of the PSANZ Neonatal Death Classification (PSANZ-NDC) is, in addition to the PSANZ-PDC, to identify the single most important factor in the neonatal period which caused the death.

The perinatal mortality classifications are available on the PSANZ PNM SIG website: [www.psanz.org.au](http://www.psanz.org.au).

### ***Perinatal Mortality Audit Guideline incorporating Psychological and Social Aspects of Perinatal Bereavement***

The Centre for Clinical Studies has been commissioned by the PSANZ PNM SIG to develop guidelines for perinatal mortality audit for Australia and New Zealand (ANZ). The intended audience for the guideline is clinicians providing care for mothers and newborns in hospitals in Australia and New Zealand, and all other parties with an interest in perinatal mortality audit and research. A number of clinicians across the Mater Complex have contributed to the development of the guideline namely: Vicki Flenady (Coordinator), Prof David Tudehope, Dr Glenn Gardener, Sue Jenkins-Manning, Deborah Jessop, Kylie Lynch, Jocelyn Toohill, Katie Waters and Prof Frank Bowling.

The purpose of the guideline is to enable a systematic approach to the investigation and audit of perinatal deaths across Australia and New Zealand to enhance the quality of information to:

- assist parents in gaining a better understanding of the cause of the death of their infant;
- assist parents and clinicians in the planning of future pregnancies including possible different management strategies;
- enhance the ability to undertake effective monitoring of strategies aimed at reducing perinatal deaths; and
- contribute to the body of knowledge to further reduce perinatal death.

It is hoped that implementation of the guideline will assist health care providers in undertaking high quality investigation and audit of all perinatal deaths, thus providing the best possible information on which to base discussion with parents, clinical audit and research aimed at reducing perinatal death.

The draft Perinatal Mortality Audit Guideline is available for comment on the PSANZ PNM SIG website [www.psanz.org.au](http://www.psanz.org.au).

### ***NHMRC funding for stillbirth research at the Centre for Clinical Studies***



Vicki Flenady and a team of investigators across Australia have recently received an NHMRC project grant to undertake a large population based epidemiological study on Unexplained Antepartum Fetal Death (UAFD) in Australia.

A group of clinicians and consumers within the PSANZ PNM SIG have commenced a collaborative effort to support and undertake research and related activities aimed at reducing the risk of UAFD (the ANZ Fetal Death Collaborative Group). This study forms the basis for this work within Australia.

The death of a baby before birth is a devastating event for the parents and families. In the vast number of these deaths, no cause can be found leaving no clues for parents and care providers struggling with decisions about future pregnancies and how the risk may be reduced for all women in pregnancy.

With decreasing perinatal mortality rates, the relative contribution of fetal death before the onset of labour

without an apparent cause (Unexplained Antepartum Fetal Death- UAFD) appears to be on the increase and now constitutes the most common “cause” of fetal death. In Australia, the rate of UAFD is approximately 2 per 1 000 births, contributing 30% to all fetal deaths. The rate of UAFD is over three times the current rate of Sudden Infant Death Syndrome (SIDS). Despite this, little research has been undertaken in this area.

The aim of this study is to determine the epidemiological characteristics of unexplained antepartum fetal death in terms of pregnancy risk, and the factors which can predict increased risk in the antenatal period. The study involves a case control study of 800 unexplained antepartum fetal deaths in three States of Australia and an analysis of information on all births in Australia which is routinely collected by Health Departments.

### ***Other planned studies on stillbirth at the Centre for Clinical Studies***

#### **Prospective data collection on stillbirths in ANZ**

Based on the recommended data collection in the PSANZ Perinatal Mortality Audit guideline for all stillbirths, the PNM SIG plans to invite hospitals in ANZ to participate in this prospective collection

which aims to improve quality of information on stillbirth for research and audit.

#### **Fetal Movement Intervention Assessment Study (Femina)**

##### *Who is the Femina collaboration?*

The Fetal Movement Intervention assessment (Femina) collaboration is an international, interdisciplinary collaborative effort related to reduced fetal movements (FM) in pregnancy.

##### *Content of proposed studies in Femina*

The Femina collaboration aim to study many aspects of reduced FM, its associations with outcome, and our ability to use increased vigilance and information about FM as a tool for improved quality of care, patient safety and perinatal outcomes.

The coordinators of the Australian and New Zealand component of this study are Vicki Flenady, Dr Glenn Gardener (MMH) and Dr Yogesh Chadha (RBWH).

For further details on stillbirth research at CCS, please contact Vicki Flenady on telephone 3840 1592 or via email [Vicki.Flenady@mater.org.au](mailto:Vicki.Flenady@mater.org.au).

## **COCHRANE REVIEW NEWS**

**Stop Press!** The Cochrane Library – the world’s best single source of evidence about the effects of healthcare is now available on Wiley InterScience. From 2 January 2005, subscribers will need to access the database through <http://www.thecochranelibrary.com>.

There is no actual log on button since the system automatically detects users with an Australian IP address, allowing seamless access to the full content of the Library from the homepage. Only those users that want to take advantage of more advanced features, such as saving searches and signing up for email alerts, are required to register for their own username and password.

If you are a Cochrane Library user familiar with the database offered previously via Update Software you will find much of the search and navigation functionality of the Cochrane Library on Wiley InterScience remains familiar. New users should find the interface intuitive and easy to navigate. For a comprehensive guide to using The Cochrane Library, a user guide is available at <http://www3.interscience.wiley.com/homepages/106568753/CochraneLibraryUserGuide.pdf>.

#### ***The Mater’s Latest Contribution to The Cochrane Library:***

##### Published Protocol:

- Cincotta R, Gardener G, Duncombe G, Flenady V, Dodd J. Antenatal administration of progesterone for preventing spontaneous preterm birth. The Cochrane Database of Systematic Reviews 2004, Issue 3.

##### Protocols submitted for Publication (awaiting editorial comment):

- Watson D, Koh G, Lawrence AM. Outpatient induction of labour for improving birth outcomes.

##### Reviews submitted for Publication (awaiting editorial comment):

- King J, Flenady V, Cole S, Thornton S. Cyclo-oxygenase (COX) inhibitors for treating preterm labour (Protocol for a Cochrane Review). The Cochrane Database of Systematic Reviews 2003, Issue 2.
- Papatsonis D, Flenady V, Cole S, Liley H. Oxytocin receptor antagonists for inhibiting preterm labour (Protocol for a Cochrane Review). The Cochrane Database of Systematic Reviews 2003, Issue 2.

## UPCOMING CONFERENCES AND SEMINARS

### ***Royal Brisbane & Women's Hospital Seminar***

**19 February 2005**

Royal Brisbane & Women's Hospital, Brisbane

"Practice, Protocols and Proof"

For further details email

anndrea\_flint@health.qld.gov.au

### ***New Frontiers in Neonatology. A Global Forum for Research and Science***

**28 February 2005-2 March 2005**

**Innsbruck, Austria**

"New Frontiers in Neonatology"

[www.ipokrates.org](http://www.ipokrates.org).

### ***Perinatal Society of Australia and New Zealand 9th Annual Congress***

**13-16 March 2005**

Adelaide Convention Centre Adelaide, South Australia

"Before and Beyond Birth"

### ***The IMPACT (Interdisciplinary Maternal Perinatal Australasian Clinical Trials) NETWORK***

**Saturday 12 March 2005 0900 hrs-1700 hrs**

PSANZ 2005 Conference Satellite Meeting

Women's and Children's Hospital, Adelaide

### ***Cochrane Work-In***

**Sunday, 13 March 2005 0900-1200 hrs**

### ***Perinatal Mortality Special Interest Group (PNM SIG)***

**Sunday 13 March 2005 0900 hrs-1200 hrs**

PSANZ 2005 Conference Satellite Meeting

Women's and Children's Hospital, Adelaide

### ***RANZCOG***

**10 – 13 April, 2005**

Hotel Grand Chancellor, Hobart, Tasmania

The meeting theme is "Delivering the Future" and reflects the need to address the issues facing our profession in terms of continuing to deliver a high standard of health care to women.

### ***Australian Neonatal Nurses Association Annual Professional Day***

**Sunday 13 March 2005**

Adelaide South Australia

Minimise the compromise

For more information visit [www.anna.org.au](http://www.anna.org.au)

## RESEARCH GRANTS SOON TO CLOSE

### **Queensland Nursing Council**

#### **Research Grants**

#### **What funding is available?**

There are three categories of research grants available:

- Novice researcher
- Experienced researcher
- Florence Chatfield Grant

#### **Special research grant for 2005**

QNC has received a donation from the former Institute of Practising Nurses to fund research aimed at "improving direct patient care". The money will be used to fund one or more special grants in the Novice or Experienced categories of this year's round of offerings.

**When to apply?** Applications open on 15 December 2004 and close on 28 February 2005

#### **More Information:**

[http://www.qnc.qld.gov.au/home/content.aspx?content=Grants,\\_Scholarships\\_&\\_Bursaries/Research\\_Grants](http://www.qnc.qld.gov.au/home/content.aspx?content=Grants,_Scholarships_&_Bursaries/Research_Grants)

#### **NHMRC Grants**

The NHMRC fosters medical research and training and public health research and training throughout Australia in accordance with the National Health and Medical Research Council Act 1992. Funding is provided on a competitive basis through the funding schemes advertised on this web site. Applications must be prepared and submitted in accordance with the requirements specified in the particular Funding Policy for each scheme, by the specified due date.

#### **More information:**

<http://www7.health.gov.au/nhmrc/funding/projects.htm>