

# Newsletter

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May 2005

Volume 2, Issue 1

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Welcome to the first edition of the MRSC newsletter for 2005. In this edition we have articles on Statistics "Clinical Trials Focus", Cochrane Review News, Mater Research Register and the John P Kelly Research funding results for 2004.

We welcome any letters to the Editorial Team. 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 Stout at: Anne-Maree.Stout@mater.org.au or phone 3840 1591.

## WHAT'S NEW

**Mater Research Register** – The Mater Research Register is now launched. The Research Register is a mechanism to enable "Mater" researchers, clinicians or managers to access comprehensive information on research studies carried out across the Mater complex. The Research Register is located on the Mater Intranet Home Page under Applications. Refer inside the Newsletter for more information.

**MRSC Internet Site** In response to popular requests and with the realisation that most busy staff conduct their research at home and have difficulty being connected to the Mater Intranet, the MRSC now has an Internet site. The website address is <http://www.materrsc.org>. Researchers can visit this site to access evidence-based, research related tools and additional copies of our newsletter.

**Statistical Tools** – MRSC has developed statistical tools for sample size programs covering a wide range of research models.

### **"Remark" Software – SAVE DATA ENTRY TIME!**

The MRSC has recently purchased software which allows scanning of questionnaire data into a data management program. The "Remark" package (Remark Office OMR Version 5.5 for Windows) creates scannable documents, such as a questionnaire and then, once completed by the study participant, scans the document to produce a data file. Although scanning is subject to error, we found less error than when data is manually entered. Refer inside the Newsletter for more information.

**The Newsletter is 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.**

## EVIDENCE BASED PRACTICE & COCHRANE REVIEWER TRAINING COURSES

The Mater Research Support Centre has developed and will be conducting an Introduction to Evidence Based Practice Course (26<sup>th</sup>-27<sup>th</sup> May 2005) and an Introduction to Cochrane Systematic Review: Protocol Development Course (28<sup>th</sup> May 2005).

**When/Where:** Courses commence at 9:00am Thursday 26<sup>th</sup> May and will be held at Mater Health Services, South Brisbane in the Whitty Conference Room.

### **Course Content:**

- The principles of evidence-based practice
- The role of Cochrane Collaboration, Joanna Briggs Review, and clinical practice guidelines
- Research design and introductory statistics
- How to define and frame a research question
- How to locate the best evidence to answer clinical questions
- How to appraise the evidence for validity and clinical relevance
- How to apply and evaluate implementation of evidence
- Protocol development for a Cochrane systematic review

### **Registration:**

A registration fee of \$110 (incl. GST) for Mater staff participants applies to the Evidence Based Practice Course. No fee applies to the Cochrane Reviewer Training Course.

### **Invited Speakers include:**

#### **Prof David Henderson-Smart**

David is a Neonatologist at the Royal Prince Alfred Hospital; Director of NSW Pregnancy and Newborn Services Network and the Centre for Perinatal Health Services Research; Associate Editor of Evidence Based Paediatrics and Child Health; and

Australasian Coordinator of the Cochrane Neonatal Review Group.

#### **Dr Sepher Shakib**

Sepher is the Director, Clinical Pharmacology, Royal Adelaide Hospital, Adelaide SA. Author of the database 'Auditmaker' – a clinical audit tool for helping clinicians to set up a clinical audit database.

#### **Ms Dell Horey**

Dell has a Masters degree in clinical epidemiology; is the Australasian coordinator for the Consumer Panel of the Cochrane Pregnancy and Childbirth Review Group and review author and editor in the Consumer and Communication Review Group; her PhD thesis on information giving and decision making in pregnancy and childbirth has recently been accepted.

#### **Prof Chris Del Mar**

Chris is the Dean of Health Sciences and Medicine at Bond University; Coordinating Editor of the Cochrane Acute Respiratory Infections Collaborative Group; Editor of the research section of the Australian Family Physician; and an assistant Editor for the journal Evidence Based Medicine.

### **Who Should Attend?**

Research clinicians: medical, nursing and allied health professionals, managers and educators from all health care disciplines that are looking for a practical introduction to evidence based health care with a focus on the translation of research into clinical practice and/or those interested in undertaking a Cochrane systematic review.

For registration forms or further information, please contact:

MRSC Administration on (07) 3840 1591  
or email: [Sharon.Egan@mater.org.au](mailto:Sharon.Egan@mater.org.au)



*Recent Cochrane Review from Mater Researchers supported by the Mater Research Support Centre****Atosiban for women in preterm labour***

Mater researchers Dr Helen Liley and Vicki Flenady are part of a team of four reviewers (including: Dr Dimitri Papatsonis, Amphia Hospital Breda, Netherlands and Dr Stephen Cole, Royal Women's Hospital, Victoria) who have recently completed a Cochrane systematic review of "Oxytocin receptor antagonists for inhibiting preterm labour" for the Cochrane Pregnancy and Childbirth Review Group. Katie Welsh from the MRSC assisted the team in literature searching and reference management for the review.

***Review summary***

Recently, oxytocin receptor antagonists have been proposed as effective tocolytic agents for women in preterm labour to postpone the birth with less severe side-effects than other tocolytic agents.

Meta-analysis of six randomised trials, with a total of 1695 women was undertaken. Compared with placebo, the use of atosiban did not reduce the incidence of preterm birth or improve neonatal outcome. In one trial (583 infants), the use of atosiban, when compared with placebo, was associated with an increase in infant deaths at 12 months of age (relative risk (RR) 6.15; 95% confidence intervals (CI) 1.39 to 27.22). However, there were significantly more women randomised to atosiban before 26 weeks of gestation in this trial, which may have influenced this result.

When compared with betamimetics, atosiban was not superior in terms of tocolytic efficacy and resulted in an increase in the numbers of infants born less than 1500 gm (RR 1.96; 95% CI 1.15 to

3.35, two trials of 575 infants). However, atosiban was associated with less maternal drug reactions requiring cessation of treatment (RR 0.04; 95% CI 0.02 to 0.11, number needed to treat 6; 95% CI 5 to 7, four trials and 1035 women).

***Conclusions***

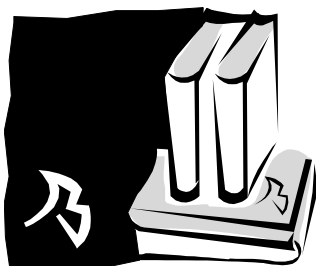
Although atosiban resulted in fewer maternal side-effects than other tocolytic drugs (betamimetics), no benefit was shown in delaying or preventing preterm birth and atosiban was associated with more infant deaths in one placebo controlled trial. The finding of an increase in infant deaths in one placebo controlled trial warrants caution.

These findings are in contrast to a recent Cochrane review<sup>1</sup> showing that the tocolytic agent nifedipine resulted in better neonatal outcome in addition to less severe maternal side-effects than betamimetics. No head-to-head comparison of atosiban and nifedipine has been undertaken. Atosiban is more costly than nifedipine and requires an intravenous infusion whereas nifedipine is administered orally.

Clearly, further well designed randomised controlled trials of tocolytic therapy are needed. However, based on the results of this review any such trial should have a placebo arm to allow appropriate interpretation.

It is expected that the review will be published in Issue 2 of The Cochrane Library due out in June 2005, which can be accessed via [www.thecochranelibrary.com](http://www.thecochranelibrary.com).

<sup>1</sup> King J, Flenady V, Coles S, Thornton S. Cyclo-oxygenase (COX) inhibitors for treating preterm labour (Cochrane Review). In: The Cochrane Library, in press. Chichester, UK: John Wiley & Sons, Ltd



### *Different Phases Of Trials - Phase II Studies*

The introduction of new drugs or treatments into clinical use is accompanied by many hazards and risks. Consequently, four phases to introduce new drugs or treatments have been defined which minimise these risks. Although these phases are used mostly by pharmaceutical companies during the development of new drugs, they do represent good principles to follow when a new drug or therapeutic regime is introduced into clinical use.

Phase I studies are designed to test whether a drug or treatment has an observable therapeutic effect and whether there are hazards or side effects associated with its use. Dosage and method of administration are also determined during this phase.

Phase II studies are designed to test whether the therapeutic effects are promising enough for the treatment to be tested against ones that are currently being used.

Phase III studies are controlled trials where the new treatment is compared with a placebo or the current treatment to test whether the new treatment is preferable.

Phase IV studies, often called post marketing studies, are large scale multi-centre studies to test the general acceptability of the treatment, and to detect and follow up uncommon side effects.

#### ***Phase II studies***

Phase II studies are undertaken to assess the effectiveness of a new drug or a new treatment in patients with a disease or condition and to evaluate common short-term side effects and risks associated with its use. Therefore, the main purpose is to determine whether a drug or treatment shows enough promise to progress to Phase III. Phase II studies are typically well controlled, closely monitored and for ethical and economical reasons, conducted in a relatively small number of cases.

The study is designed so that treatments with poor efficacy or frequent unacceptable side effects can be detected early, so that the study can be terminated and the treatment abandoned. If the treatment is not abandoned, then sufficient cases will have been accrued so that a reasonable assessment of the effect size for the treatment can be determined.

Phase II studies were developed to fill the needs of evaluating treatments where the key outcome to be evaluated is the success or failure of a treatment (i.e. a binary outcome). The statistics are therefore based on the percentage or number of cases that respond or do not respond to the treatment.

For example, a common response variable is tumour response to cytotoxic agents. Complete response (CR) means total disappearance of all evidence of tumours. Partial response (PR) means more than 50% reduction in total size of measurable tumours. However, the exact criteria for PR and CR can vary with the trial and also the type of cancer. Short response duration may mean little or nothing in terms of long term patient survival, but long term responses can indicate some patients are getting a major benefit.

For ethical and economic reasons, phase II studies are designed to minimise the number of cases required. This is achieved by designing the study into two stages. The first stage focuses on identifying those treatments that will not meet the standard of response required, so that the study can be terminated and the treatment abandoned as early as possible. If the response to treatment is promising enough then the study goes into the second stage where the effect size (scale of response) can be more precisely determined. All two stage designs are therefore special examples of a broad class of drug screening procedures to screen treatments for promising results to enter future phase III comparative randomised trials.

#### ***Types of phase II designs***

Statistically, phase II trials typically test the null hypothesis  $H_0: p \leq p_0$  that the true response rate of the treatment under consideration is less than some level ( $p_0$ ) that would be deemed too low for further consideration. Two designs for phase II which have been developed for monitoring binary outcomes are described below:

***Gehan's two-stage design*** is used to test whether a drug or treatment is successful in terms of the number of favourable responses. Dividing the study into two stages minimises the number of cases. The sample size for the first stage is determined according to a minimum requirement of efficacy. Once the first stage is completed, the sample size of the second stage is calculated which is dependent on the number of responses during the first stage. If no responses are observed in the first stage, subjects are not recruited for the second stage.

The advantage of this procedure is that a relatively small number of cases are used to determine the total size of the trial and in so doing, the minimum size of the trial that can lead to robust conclusions can be achieved. A disadvantage of this procedure is that the final time and resource requirement cannot be known until the end of the first stage.

**Simon's two-stage design** is the most commonly used procedure and is an improvement on Gehan's design. Although it is also in two stages, the sample sizes for both stages are determined at the start of the trial.

Two parameters are used to design Simon's procedures. The first is the maximum tolerable failure rate, or the percentage of cases that failed to respond, above which the treatment will be deemed not worth pursuing. The second is the minimum success rate hoped for, or the percentage of cases that respond, above which the treatment will be accepted as efficacious. From these two parameters, the number of cases to be tested in both stages is determined.

The first stage is used mostly to detect early those treatments that have a response rate below that which is tolerable, so that the trial can be terminated immediately and the treatment abandoned. In stage one the number of required successful responses is defined and as soon as these are available the study can move to the second stage. Should the number of successful responses fall short of that required at the end of stage one, then the trial is terminated and the treatment abandoned.

In stage two the accumulated number of required successful responses is defined, and as soon as this is reached, the trial can be terminated and the treatment considered worthwhile to enter into phase III trials. The treatment is considered not worth pursuing and abandoned if the number of successful responses falls short of that required at the end of the second stage.

#### **Additional technical issues**

In Simon's design, one specifies both the desirable and undesirable response rates required. The usual type I error (alpha) is the false positive rate in accepting a poor drug and the type II error (beta) is the false negative rate in rejecting a good drug. Several designs may satisfy the requirements of the specific type I and type II error probabilities. Therefore, Simon proposed two different criteria to find a good design among them. First, the optimal design achieves the minimum expected sample size.

Second, the minimax design seeks the minimum total sample size first and then achieves the minimum expected sample size (EN) for this fixed sample size. In the optimal design, the probability of early termination (PET) is high when the true response probability is equal to the undesirable rate. The minimax design is useful when the patient source is limited, such as a rare cancer or a single institution trial.

#### **Example**

We wish to have a phase II evaluation of a new cancer drug and feel that if its efficacy is below 15% then it should be abandoned, but if its efficacy is 40% or better then it should be compared with the current treatment in a phase III study. Using an alpha of 0.05 and power of 0.8, the results are as follows.

Maximum rejection proportion = 0.15  
Minimum acceptance proportion = 0.4

r1	n1	rTot	nTot	EN	PET
1	9	5	19	8.9	0.5995
1	7	6	25	8.2	0.7166

For the optimal design,  $n1 = 7$  cases are needed for the first stage and  $25 - 7 = 18$  cases for the second stage. If the number of responses are less than or equal to  $r1 = 1$  then the study is terminated after the first stage is complete. Otherwise, the second group of 18 cases is recruited and a total greater than 6 responses would be required to claim efficacy.

The minimax design requires  $n1 = 9$  cases and  $19 - 9 = 10$  cases for the first and second stage respectively. If there are  $r1 = 1$  or less responses in the first stage or  $rTot = 5$  or less responses at the end of the second stage, the drug or treatment is rejected. In this design the minimax design requires six fewer cases overall, but statistically has a greater expected sample size as compared to the optimal design.

Other design examples and further discussion of phase II procedures can be seen in the statistics sections on the Mater Research Support Centre intranet website or on the internet at <http://mater.obg.cuhk.edu.hk> under sample size calculations for one group.

#### **Reference:**

Simon, R. (1989) Optimal two-stage designs for Phase II trials. *Controlled Clinical Trials*, 10, 1-10.

Machin, D. Campbell, M. Fayers, P. Pinol, A. (1997) *Sample size tables for clinical studies*, 2nd edn. Blackwell Science, Oxford.

## MATER RESEARCH REGISTER

### *Register Ready for Registration of Researchers and Research*

There is now a mechanism for researchers, clinicians and managers to access information on research being undertaken across the Mater campus. The Research Support Committee (RSC) (a committee of the Mater Board) in its meeting on 19<sup>th</sup> May 2004 decided to establish a Research Register for the Mater.

With completion of Phase 1, the Mater Research Register is now available for registration of researchers and research. Phase 2 of development is currently underway which will see the incorporation of Human Research Ethics Committee submission requirements, progress reports and publications.

It is anticipated that the Register will enhance research capabilities and the quality of research by providing a comprehensive, accurate and up-to-date source of information on all research projects, researchers and publications being undertaken at Mater Health Services.

#### ***Research Register policy***

The Mater Research Register policy has been developed by the RSC and includes the need for all Mater research to be registered prior to commencement.

The RSC will oversee the Research Register and has established a Research Register Committee to provide overall management for the Register supported by a secretariat at the Mater Research Support Centre (MRSC).

#### ***How to register and view information in the Register?***

The Research Register is now available on the Mater intranet. Researchers are able to input and output information via the intranet. With the approval of the Chief Investigator, a subset of information on the Research Register will be available for all Mater staff.

***Researchers are now invited to register.*** Please go to the Mater Intranet under: Applications/Administration/Research Register  
**or (<http://172.30.20.28/rsc/home/default.asp>)**

*Detailed instructions on how to register are available on the Research Register. For further information or help on how to register, please do not hesitate to contact the MRSC on ext 1591.*

## **‘REMARK’ SOFTWARE – SAVE DATA ENTRY TIME!**

The MRSC has purchased software which allows scanning of questionnaire data into a data management program. The “Remark” package (Remark Office OMR Version 5.5 for Windows) creates scannable documents, such as a questionnaire and then, once completed by the study participant, scans the document to produce a data file. Although scanning is subject to error, we found less error than when data is manually entered. Scanned data should be cross-checked with the original questionnaire but even with this additional checking, the process is quicker than manual data entry.

The MRSC recently used the software to manage data from a survey on smoking at the Mater

Mothers' Hospitals. A four page questionnaire was completed by 600 participants. The process of formatting the questionnaire, scanning the completed questionnaire and cross-checking took approximately 16 hours.

The MRSC offers to the Mater Community the use of this software at our offices in Aubigny Place. Various options are available. Your Department can book in to use the computer/software or our Administration staff can format your document to “Remark” capability.

If this sounds like a service which would be of interest to your area, please contact MRSC on ext. 1591.

## SUCCESSFUL APPLICANTS - J P KELLY RESEARCH FUND, 2004

The John P Kelly Fund was established in 1982 to promote and support research activities on the Mater campus. The John P Kelly Research Committee (JPKRC) was set up to allocate these funds under the following principles:

- The process of allocation should be fair, open and transparent
- The principles of allocation should be recommended and the procedures endorsed by the Research Support Committee
- In addition to scientific merit, the clinical relevance, the encouragement of research, the opportunity for teaching and the promotion of the Mater mission should be considered.

To assist the JPKRC to carry out its role, MRSC was assigned to act as the JPKRC Secretariat. In this role MRSC acted as the daily communication interface between applicants and the JPKRC and carried out administrative duties in relation to the allocation process.

To facilitate a fair, open and transparent process, the MRSC set up the [John P Kelly Research Committee website](#) on the Mater Intranet. This enabled the Mater community to have immediate access to application documents, the application timetable and decisions made by the JPKRC Committee.

The MRSC would like to congratulate the following successful recipients of the Kelly Research Fund for 2004.

Name of Applicant	Name of Study	Amount Given
<b>Major projects from experienced researchers</b>		
Vicki Flenady	Antenatal detection of the fetus at risk of unexplained stillbirth using customised fetal growth centiles.	\$14,952
Dr Paul Devenish-Meares	Women and Induction of Labour Dilemma Trials	\$24,000
Associate Prof Timothy Florin	Measuring thioguanine nucleotides in well characterised inflammatory bowel disease (IBD) patients receiving standard thiopurine therapy with a view to improving outcomes.	\$9,060
<b>Beginner and Seeding projects</b>		
Judy Hough	Determination of differential effects of 3 positions on lung function in ventilated neonates	\$8,000
Jacqueline Jauncey-Cooke	A comparative survey measuring the impact of mechanical ventilation on the paediatric ocular surface	\$4,863
Associate Prof Robert Cincotta	Progesterone for Preterm Labour trial	\$8,000
Dr David Watson	Perinatal ultrasound project	\$5,000
Dr David Serisier	Evaluation of sputum induction for the development of reliable surrogate outcome markers in cystic fibrosis	\$4,313
<b>Education, Equipment and Infrastructure</b>		
Vicki Flenady	Evidence Based Practice Course	\$5,812
Prof Derek Hart	Animal Surgery Support Equipment	\$8,000
Dr Honey Heussler	Ambulatory Monitoring: Paediatric Sleep Unit	\$8,000

## FUNDING GRANTS SOON TO CLOSE

### **Heart Foundation Fellowships Call for Applications (2005)**

For: Career Development, Postdoctoral and Overseas. The closing date for applications is 5 pm, Friday 27 May 2005. Further details can be found on the Website:

<http://www.heartfoundation.com.au/index.cfm?page=150>

### **John P Kelly Research Committee**

Applications for the John P Kelly Research Committee funding for 2005 are now open. Applications close 31 May 2005. For more information please go to the Mater Intranet, click on "Departments" and then John P Kelly Research Committee.

### **Kidney Health Australia (*Seeding Funding*)**

Kidney Health Australia provides funds of up to \$15,000 for an optional maximum of two years. Seeding funds are awarded to assist the development of new research ideas, to form solid preliminary data to the point where they can be submitted to the NHMRC (or other) funding body for full funding. Closing date 30 June 2005.

<http://www.kidney.org.au>

### **MS Research Australia (*Seeding Funding*)**

**Purpose:** To broaden the scope of its support for research relevant to multiple sclerosis, the MSRA wishes to promote research into rehabilitative and other aspects of the disorder.

Applications are invited for small grants (up to \$10,000 plus GST for one year only) to 'seed' the earliest stages of new research efforts, e.g. the application may be for funding of a pilot study to be carried out before the project grant application is submitted. Closing date 5 September 2005

## UPCOMING CONFERENCES AND SEMINARS

### **ARSC Annual Scientific Congress**

**30<sup>th</sup> May to 1<sup>st</sup> June 2005**

Sydney Convention Centre, Sydney, NSW

<http://www.arcs.com.au>

### **Mater Child and Youth Mental Service**

**11<sup>th</sup> Annual Conference**

**1<sup>st</sup> – 2<sup>nd</sup> June 2005**

Brisbane

Grief, Trauma and Clinical Models for the Future

[www.kidsinmind.org.au](http://www.kidsinmind.org.au)

### **General Practice and Primary Health Care Research Conference**

**26<sup>th</sup> to 28<sup>th</sup> July 2005**

Adelaide

Getting Research Right for Policy and Practice

[www.phcris.org.au/events](http://www.phcris.org.au/events)

### **5th International Conference on success and Failures in Telehealth**

**4<sup>th</sup> – 5<sup>th</sup> August, 2005-05-12**

Brisbane

[www.uq.edu.au/sft](http://www.uq.edu.au/sft)

### **AHRDMA 15<sup>th</sup> Annual Scientific Meeting**

**20<sup>th</sup> - 21<sup>st</sup> October 2005**

Melbourne

<http://www.ahrdma.com.au/>

### **NSW Aboriginal Health Research Conference**

**18<sup>th</sup> & 19<sup>th</sup> October, 2005**

Sydney

Partnerships for Aboriginal Health Research

<http://www.ihr.org.au/criahconference2005/>