



NHMRC Centre for Research Excellence
in Therapeutics

Annual Report 2006

Department of Epidemiology & Preventive Medicine



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Director's report

The CCRE in Therapeutics was established in 2003 and provides a national resource for the evaluation of new and existing drugs. The CCRE works closely with other units in the Department, including Cardiovascular Epidemiology, Clinical Pharmacology and Biostatistics. Professor Henry Krum is Director, and Associate Professor Chris Reid is Associate Director.

2006 was a year of substantial progress and activity within the CCRE in Therapeutics with the major foci of activity in the areas of multi-centre clinical research, registry activities and pharmacoepidemiology.

In the area of clinical trials, an exciting development has been the funding of the large ASPREE study which has now commenced in Australia. This is a study of >20,000 patients testing whether aspirin is beneficial (or otherwise) in elderly patients with regard to cardiovascular disease and cognitive function as well as other outcomes. Following on from major NHMRC funding, there has been substantial cash and in-kind support from Bayer and a formal NIH application has been invited and submitted.

Other multi-centre investigator initiated trials performed through CCRE Therapeutics in 2006 include the HAT, CHAT and HOPE 3 studies. Furthermore, Professor Myles has initiated his major NHMRC sponsored ATACAS study, of tranexamic acid and aspirin under our umbrella as well as the ENIGMA II study.

A rapidly expanding focus of CCRE activity has been that of registries, particularly those to do with drugs and therapeutic procedures, such as PCI. The MIG registry has exploded in activity with over 4,000 patients receiving PCI currently documented. Important and novel data have been extracted from this dataset.

Dr Danny Liew has led activities in the area of pharmacoepidemiology, particularly looking at cost-effectiveness and modelling of drug therapies such as statins, aspirin and anti-obesity agents. Dr Kathlyn Ronaldson is investigating causes of clozapine-induced myocarditis.

In concert with the expanded CCRE research activity has been the establishment of a dedicated community based clinical trials facility at our Caulfield site. This facility is ideal as a hub for multi-centre studies and community-based chronic disease trials. This site is the location of our large cohort studies including the ANBP2 follow-up study and SCReening Evaluation of the Evolution of New Heart Failure (SCREEN-HF) study.

An important component of CCRE Therapeutics' activity has been the training of young clinicians in clinical research methods. Drs Will Kemp and Hendrik Zimmet have been our first Transitional Fellows. Both have subsequently received competitive scholarship support to continue their studies. Dr Maros Elsik, a cardiologist from Sydney, is also undertaking PhD studies with us and has received NHMRC/NHF scholarship support.

The CCRE in Therapeutics has very rapidly become a favoured training ground for young clinical researchers, as attested to by the large number of inquiries regarding future training opportunities within the institution. We very much look forward to 2007 as a year of further expansion.



Above, staff from the CCRE

Background

In 1997, the Centres of Clinical Excellence in-hospital-based research program was initiated by the Federal Government. 2002 saw the extension of this activity to include Centres of Clinical Research Excellence (CCRE). The Department of Epidemiology and Preventive Medicine was successful in establishing a CCRE in Therapeutics and Clinical Research under the direction of Professors Henry Krum, John McNeil, Andrew Tonkin, Andrew Forbes, Paul Myles and Flavia Cicuttini.

Mission Statement

To improve clinical outcomes at the individual and community level through the use of evidence, based on high quality clinical research.

Organisational structure



Collaborations

External

- Dept of Medicine, St Vincent's Hospital, Melbourne
- Centre for Human Drug Research, Netherlands
- INCITE International Phase II Cardiovascular Group
- Baker Heart Research Institute, Melbourne
- Hanoi Heart Institute, Vietnam
- McMaster Cardiovascular Research Centre, Canada
- Central Drug Research Institute, Lucknow, India
- George Institute, Sydney
- GRAND Cardiovascular Trials Collaboration
- Clinical Trials & Evaluation Unit, Royal Brompton Hospital, London, UK

Dept of Epidemiology & Preventive

- Hemostasis Registry
- ANZICS Registry
- Centre of Research Excellence in Patient Safety

Researchers



Professor
Henry Krum

Professor Henry Krum is Director of the Centre for Clinical Research Excellence in Therapeutics. He is also a physician at the Alfred Hospital in Melbourne and heads Clinical Pharmacology at Monash University and the Alfred Hospital. His interests lie with heart failure and hypertension, and his work spans the fields of basic, clinical and applied sciences. Prof Krum has been a member of many International Steering and Executive Committees for major clinical trials in the area of cardiovascular pharmacotherapy. He currently leads a number of multi-centre investigator-initiated trials testing cardiovascular therapeutic strategies.



Associate Professor
Chris Reid

Associate Professor Chris Reid is the Associate Director of the CCRE Therapeutics and an epidemiologist with a background in exercise physiology. He has extensive experience in management of large-scale clinical studies and data registries, and was Study Director for the 2nd Australian National Blood Pressure Study. His research focus in recent years has been in the area of evidence-based management for primary and secondary prevention of cardiovascular disease. Associate Professor Reid directs the Data Management area of CCRE Therapeutics, and is chief investigator on a number of large-scale longitudinal clinical studies and patient registries.



Professor
John McNeil

Professor John McNeil is a clinical pharmacologist and epidemiologist who heads the Department of Epidemiology and Preventive Medicine at Monash University. Professor McNeil provides CCRE Therapeutics with leadership and expertise in the application of epidemiology to the study of drug efficacy, safety and cost-effectiveness. He leads CCRE Therapeutics' Translational Research program and has research interests in studies of drug safety and epidemiological modelling.



Professor
Andrew Tonkin

Professor Andrew Tonkin has a long-standing interest in clinical research particularly in the area of cardiology. Professor Tonkin is Director of the National Heart Foundation of Australia and Adjunct Professor in Preventive Cardiology at Monash University. Professor Tonkin's expertise lies in the field of design and analysis of small-scale and large-scale randomized therapeutic trials.



Professor
Flavia Cicuttini

Associate Professor Cicuttini heads the Clinical Diagnostic and Chronic Diseases Unit within the Department of Epidemiology and Preventive Medicine, Monash University. Associate Professor Cicuttini has research interests in the development and validation of clinical outcome measures in clinical studies, especially in the development of methods for quantifying disease progression in degenerative joint disease.



Professor
Paul Myles

Professor Paul Myles is the Director of Anaesthesia and Perioperative Medicine at the Alfred Hospital, and Professor of Anaesthesia at Monash University. Professor Myles is involved in a number of large multi-centre trials aiming to improve outcomes after surgery and anaesthesia. These include an investigation of nitrous oxide in anaesthesia (the ENIGMA Trial), and aspirin with or without tranexamic acid in coronary artery surgery (the ATACAS Trial).



Professor
Andrew Forbes

Associate Professor Forbes provides biostatistical expertise and professional leadership to CCRE Therapeutics. He worked in the pharmaceutical industry in the US, before joining Monash University to head one of the largest biostatistical units in Victoria, in the Department of Epidemiology and Preventive Medicine.



Dr Danny Liew



Dr Andrew Ajani

Dr Danny Liew is a clinical pharmacologist whose research interests lie in pharmacoepidemiology and pharmaco-economics. His work involves translating evidence from clinical and population-based studies for application to clinical and public health practice and health policy.

Dr Andrew Ajani is Director of Coronary Care at the Royal Melbourne Hospital. Dr Ajani's research interests lie in interventional cardiology and he is the convener of the Melbourne Intervention Group, who have established a large registry of coronary interventional procedures managed through the CCRE Therapeutics Data Centre.



Professor Frank Rosenfeldt

Professor Frank Rosenfeldt leads the Cardiac Surgical Research Unit at the Alfred and Baker Medical Research Unit. Professor Rosenfeldt has research interests in nutritional supplementation and cardiac function. His research is aimed at improving the success of procedures such as cardiac bypass and angioplasty.



Dr John Amerena

Dr John Amerena is a cardiologist at Geelong Hospital and senior academic in the Department of Clinical and Biomedical Sciences at University of Melbourne. Dr Amerena has broad research interests in clinical cardiology, and particular interest in coronary artery disease and hypertension management.

Dr Robyn Woods is a senior NHMRC Fellow at the Howard Florey Institute with research interests in cardiovascular physiology and the pathophysiology of cardiac natriuretic peptides. Dr Woods is the Executive Officer for the ASPREE study.



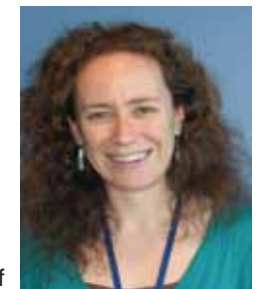
Dr Robyn Woods

Mr Adam Meehan is the Data Manager for CCRE Therapeutics and his expertise lies in the management of large epidemiological research databases and the implementation of state-of-the-art Health-IT technology.



Mr Adam Meehan

Dr Alice Owen is a Research Fellow with CCRE Therapeutics and a physiologist with research interests in cellular lipid composition and oxidative stress in cardiovascular disease, obesity and diabetes.



Dr Alice Owen

Mr John Varigos is a pharmacologist with extensive experience in the management of Phase 1 to Phase 4 clinical trials. He has managed studies in a variety of indications but has a special interest in the treatment of cardiovascular disease. He has worked as Clinical Research Manager in pharmaceutical companies and Australian Director and Clinical Operations Manager for a large multinational CRO. He is a member of the International Steering Committee and Australian National Coordinator for the Oxford University based ISIS studies and the McMaster University based Cardiovascular Collaboration.



Mr John Varigos

Dr Kathlyn Ronaldson was secretary of the adverse drug reactions committee for the medicine regulator in New Zealand and then Australia before joining the Department of Epidemiology and Preventive Medicine in November 2005. Her research interest is using epidemiological methods to investigate drug safety.



Dr Kathlyn Ronaldson

Operational Review

CCRE Therapeutics can divide its core strengths into three main areas; Clinical Trials, Clinical Informatics and Pharmacoepidemiology.

Clinical Trials

Home Automated External Defibrillator Trial (HAT)

In the past 3 decades, advances in the understanding of the resuscitation of cardiac arrest victims have provided opportunities to strengthen the links in the chain of survival. But despite this, survival has remained poor. The time interval from collapse to attempted defibrillation is the most important determinant of outcome. The chance of survival decreases on average by approximately 10-15% for every minute that elapses prior to attempted defibrillation.

The development of the automated external defibrillator (AED) provided the possibility to decrease the interval from collapse to defibrillation by enabling persons outside the traditional emergency medical services response system who are typically not trained in rhythm recognition to deliver life-saving therapy.

There are 31 Hospital HAT research sites located around Australia who have recruited 1466, (21%) of 7000 patient population, thus enabling the study to report on the use, attitudes and health outcomes relating to the use of AEDs relevant to the Australian setting.

The study has enrolled 7,000 patients who have been hospitalised in the past with an anterior myocardial infarction (heart attack) along with their spouse or companion (14,000) individuals from 180 hospital based HAT research Sites located in Australia, the United States, United Kingdom and New Zealand.

The dedicated HAT study personnel have supported approximately half of all participating patients and their families, to recognise sudden cardiac arrest, to use the AED first, and then call emergency services (000). The remaining 50% of participants have been taught to call emergency services first (000) and then to apply the cardiac resuscitation skills which they have been taught as part of the study. The study will evaluate the two different training methods and report on the best method to save the lives of patients following cardiac arrest.

The HAT study, which is funded by the National Institutes of Health (NIH), United States, will be completed on the 30th September 2007 and reported in March 2008 at the American College of Cardiology, Chicago, US.

Chronic Heart failure Assisted by Telephone study (CHAT)

A randomised trial of telephone support for chronic heart failure patients at high risk of rehospitalisation funded by the NHMRC and the Medical Benefits Fund. Chronic heart failure is a major public health problem in Australia. This project is implementing the first Australia-wide randomised clinical trial of telephone support for CHF patients provided by trained nurses to enable patients and their families to maintain their health in as stable a manner as possible, in their homes. This strategy has significant implications for providing equity of access for rural and remote Australians.

Over 400 patients have thus far been randomized in CHAT.

UNIVERSE Study

Despite the widespread use of statins in cardiovascular disease, it is not known whether these agents are of benefit in patients with established chronic heart failure (CHF). The UNIVERSE study is examining the effect of statins on ventricular remodelling, an important surrogate for clinical outcomes in CHF. The study compares a high dose of rosuvastatin (40mg/day) versus placebo additional to best practice background therapy. The results were presented at the American College of Cardiology Meeting in 2006 and will be published in J Cardiac Failure in 2007.

CHABLIS Study

The CHABLIS study compares the addition of angiotensin receptor blocker (ARB) versus an increase in ACE inhibitor dosage in patients with systolic chronic heart failure currently receiving low to medium dose ACE inhibitor. Although ARBs have been found to be useful in heart failure it is not established whether this utility is merely on the basis of increasing renin angiotensin system blockade which can also be achieved by an increase in ACE inhibitor dose. Therefore these two strategies have been compared head-to-head in CHABLIS with the end-point of brain natriuretic peptide being used to assess efficacy of these strategies.

The study has now recruited approximately 100 patients and will be presented at the Cardiac Society of Australia and New Zealand meeting in 2007.

ATACAS Trial

The ATACAS (**A**spirin and **T**ranexamic **A**cid in **C**oronary **A**rtery **S**urgery) study was established to answer a clinically important question: Should aspirin or tranexamic acid, or both, be used in people having heart bypass surgery? The trial is funded by a project grant from the NHMRC.

The trial commenced in May 2006, with the first patient being randomised at the Alfred Hospital, Melbourne. There are currently five centres (Monash Medical Centre, Geelong Hospital, Austin Hospital, St Vincent's Hospital and the Alfred Hospital) actively recruiting patients, with a further six sites awaiting ethics approval (Flinders Medical Centre, Royal Perth Hospital, Royal Adelaide Hospital, Escorts Heart Hospital India, Singapore General & Queen Elizabeth Hospital Hong Kong.) To date there have been 173 patients recruited to the trial. Further details of the trial can be found at www.atacas.org.au.

In January 2007 the New England Journal of Medicine published the results of an observational study by Mangano et al. The study included 4374 patients undergoing cardiac surgery and suggested that aprotinin, an antifibrinolytic drug, was associated with serious thrombotic complications. They concluded that there is a definite need for randomised controlled studies to answer the clinically relevant question: Are there safer and cheaper treatment alternatives to aprotinin.

Patients treated with aspirin (which is common in those needing heart surgery) have increased bleeding during and after surgery. Thus it is routine practice in most cardiac surgical centres around the world for aspirin to be stopped about one week before surgery.

However, a study published in the New England Journal of Medicine in 2002 found that patients who received aspirin early after their heart surgery had a lower death rate, as well as less heart attacks, stroke, and kidney failure. The authors believed that these beneficial effects could have occurred because aspirin prevents thrombosis (blood clots) in the blood vessels supplying the heart, brain and kidneys. Could it be that, although aspirin may cause more bleeding, there is a net benefit because of less thrombosis?

Another drug, tranexamic acid, is sometimes used to reduce bleeding after heart surgery. It works by blocking the clot breakdown that occurs early after heart surgery. This reduces bleeding, and the need for a blood transfusion. Importantly, there is some published information to suggest it is particularly effective in patients on aspirin. But we do not know whether or not tranexamic acid increases the risk of thrombosis (heart attack, stroke).

Clinical Informatics and Data Management

Bosentan Patient Registry (BPR)

The Bosentan Patient Registry (BPR) is a drug registry project established in association with the Pharmaceutical Benefit Scheme. Over a three year period, the BPR has been following the health of Australians who are using the drug bosentan (Tracleer™) for treatment of pulmonary arterial hypertension. The BPR completed enrolment of participants in mid-2007 and final follow-up is currently underway. The information collected by the BPR will provide a better understanding of health outcomes for this patient group and will inform research into the use and effectiveness of bosentan in Australia. This unique registry was established in cooperation between Actelion Pharmaceuticals Australia, CCRE Therapeutics (Monash University) and the Pharmaceutical Benefits Advisory Committee.

Melbourne Interventional Group (MIG)

The Melbourne Interventional Group (MIG) is a collaborative project of interventional cardiologists practicing at 8 major public and private hospitals in Victoria - The Alfred, Royal Melbourne, Austin, Box Hill, Western, Frankston, Geelong and Peninsula Private - and the Centre for Clinical Research Excellence, Department of Epidemiology and Preventive Medicine, Monash University.

The database documents demographic, clinical and procedural characteristics of consecutive patients undergoing PCI, and permits analysis of those characteristics at 30 days and 12 months (and potentially longer-term follow-up), via the use of case report forms developed specifically for the registry. At 30-day and 12-month follow-up, hospital admissions and standard major adverse cardiac events are documented (MACE, i.e. death, myocardial infarction, target-lesion and target-vessel revascularisation). Re-hospitalisation is also documented. Additionally, we collect information about ongoing medication therapy and the development of heart failure. Since June 2004 (until April 2007), 6322 PCI procedures have been enrolled in the registry.

The potential benefits of an Australian PCI outcomes database are multiple. It is likely that information gathered and analysed would be of interest to cardiologists, cardiac surgeons, hospital cardiac units, hospital quality assurance and finance

departments, state and federal governments, health insurance funds, industry and, most importantly, patients. To date, four manuscripts have been published with several more nearing completion. The group has presented abstracts at national and international cardiology meetings.

Australian Rheumatology Association Database (ARAD)

The Australian Rheumatology Association Database, better known as ARAD, is an Australia-wide registry of people with arthritis. CCRE Therapeutics provide data management for the registry, which is an initiative of the Australian Rheumatology Society. ARAD is a longitudinal study of the long term effects of arthritis and its treatments in Australia. The registry uses patient completed questionnaires to collect information about disease history, medication history and quality of life information for patients receiving new biological agents for the management of rheumatoid arthritis. Over 150 Rheumatologists are actively involved in recruiting patients to the registry, with over 1600 participants enrolled in ARAD to date.

DECompressive CRAniectomy trial (DECRA)

Multi-centre prospective randomised trial of early decompressive craniectomy in patients with severe traumatic brain injury

In collaboration with the Alfred Department of Anesthetics (Associate Professor Jamie Cooper), CCRE Therapeutics has established the data collection and management system for this study on decompression head injury. The study tests the hypothesis that *early decompressive craniectomy* will improve long term neurological outcome in patients with severe traumatic brain injury and intracranial hypertension which is refractory to conventional management.

REACH

This study is an international prospective observational registry of subjects at increased risk of atherothrombotic events, and is coordinated in Australia by CCRE Therapeutics together with the Baker Heart Research Institute. The study is being conducted at 274 sites in Victoria, NSW, Queensland, SA and WA. The objectives of the study are to evaluate the long-term risk (yearly event rate) of atherothrombotic events globally, as well as in different population subgroups, compare outcomes within different subject profiles and define predictors of risk for subsequent events. 2873 participants were recruited Australia wide at baseline in 2004.

In 2006, 2745 participants were contacted for their 21±3 month follow-up. Information was collected, via telephone contact, regarding cardiovascular events and claudication questionnaires were administered. A proposal was accepted to continue follow-up of this group of participants for a further 12 months and 33 ± 3 months information will be collected in 2007. Baseline data for the global study was published in 2006 (*International Prevalence, Recognition, and Treatment of Cardiovascular Risk Factors in Outpatients With Atherothrombosis: JAMA. 2006;295:180-18.*)

Hepar-P Project

CCRE Therapeutics is providing data management for the HEPAR-P Study, a study being conducted by the Malaysian Liver Foundation.

The HEPAR-P Study is a randomised double-blind placebo-controlled trial of an anti-viral phytopharmaceutical for chronic Hepatitis B infection. The study is being conducted in Malaysia, and the CCRE Data Centre is providing a range of clinical data management services including development of case record forms for fax receipt of data, patient randomisation and enrolment via IVRS (Interactive Voice Response System), and data collection and management.

Australian Resuscitation In Sepsis Evaluation (ARISE)

The Australian Resuscitation In Sepsis Evaluation (ARISE) Study was a multi-centre observational study of early resuscitation techniques in patients with severe sepsis undertaken by the Australia and New Zealand Intensive Care Society (ANZICS) Research Centre during 2006-2007. CCRE Therapeutics has been responsible for CRF and database design, data management and reporting for this study. The success of the ARISE Study has led to further research collaborations with ANZICS commencing in 2007.

Sentinel Surveillance Study

The Sentinel Study is a linked sentinel survey of chlamydia, HIV, syphilis and hepatitis C in Victoria developed by the Burnet Institute and undertaken in collaboration with the Department of Human Services Victoria, the Victorian Infectious Disease Reference Laboratory and the Melbourne Sexual Health Centre. CCRE Therapeutics is undertaking data management for this project that will be used to monitor HIV, hepatitis C and sexually transmitted infection incidence, prevalence, risk behaviour and testing patterns in order to inform and evaluate relevant public health strategies.

Predictors Influencing The Change in Health Status of Elderly in Community Care (PITCH)

PITCH is a prospective longitudinal observational study over 12 months for Bapcare (BC) clients located in Victoria on CACP, EACH and EACH (Dementia) packages of care. This study aimed at evaluating the current health status of BC clients, specifically looking at location and package type differences. In addition we aim to identify risk factors (predictors) associated with movement between packages of care and into alternative care settings. Initially 550 BC clientele were approached, 60% participated at baseline, 77% returned at 6 months and the 12 month data collection phase (the final phase) to end in October 2007. The study has provided aggregate baseline information to Bapcare about their client population and will continue to develop a dataset capturing health status change over time and potential risk factors. Among health status indicators include physical and mental functioning, emotional wellbeing, social support and caregiver strain. The study has the potential to impact the client in regard to better determining associated risk factors that lead to the need for higher levels of care, the service organisation in regard to better planning and targeting of areas which can be impacted, and broader service system in regard to informing future policies to do with aged care service delivery.

Pharmacoepidemiology

LIP-CON Project

This project aims to determine the effectiveness and cost-effectiveness of HMG CoA reductase inhibitors ('statins') and other lipid-lowering therapies prescribed for the primary and secondary prevention of cardiovascular disease in Australia. It involves systematic reviews and meta-analyses of the literature, as well as epidemiological and economic modelling.

Clozapine and Myocarditis Study

Clozapine is the most effective treatment available for treatment-resistant schizophrenia. However, its use is limited by adverse effects including myocarditis. The incidence of myocarditis is unknown, and most estimates have suggested a very rare adverse reaction, but a unit in Queensland found 8 cases in a cohort of 94 patients initiated on clozapine (8.5%).

Up to the end of 2006, the Australian Adverse Drug Reaction Advisory Committee had received 190 reports of myocarditis with clozapine, including 10 fatal cases. Since making contacts for the purposes of this study, we have become aware of 20 further cases, of which 3 have been fatal.

The purpose of the study is to identify risk factors which may be patient intrinsic (e.g. genetic, pharmacokinetic, immunological characteristics) or extrinsic (e.g. rate of dose escalation, concomitant therapy). The study has a case-control design and each case meeting the case definition is being matched to four controls started on clozapine at the same psychiatric unit in the same timeframe and taking it for at least 45 days. The objective is to include 200 cases and 800 controls.

Blood samples will be taken for genetic analysis. The targets of the initial analysis will be the HLA region of the DNA, where genetic predispositions to other drug hypersensitivity reactions have been identified, and the gene for the metabolising enzyme for clozapine, CYP1A2.

A follow-up of cardiac health of cases and controls is also intended in order to determine the long-term impact of clozapine-related myocarditis. Vital status and cause of death will also be documented.

Caulfield Clinical Trial Centre



In 2006 the CCRE in Therapeutics, Community Clinical Trial Centre based at the Caulfield General Medical Centre, Kooyong Road, Caulfield South was involved in a number of trials in collaboration with the Preventive Cardiology Unit, Baker Heart Research Institute. Activity at the Clinical Trial Centre (CTC) is focused around recruiting participants for a number of sponsor and investigator initiated trials. The participants for these trials are recruited from the general public via advertising and from General Practitioners throughout Australia who work in close collaboration with the DEPM.

Louise Shiel is the manager of the Caulfield based CCRE Clinical Trials Centre. She has extensive experience in both laboratory and clinical research, with qualifications in biochemistry/microbiology, computing and teaching. For the last 12 years she has managed sponsored and investigator-initiated trials, both in the Department of Epidemiology and Preventive Medicine, Monash University and at the Baker Heart

Research Institute. She has experience in all aspects of project management, research administration, data management and staff development.

Above from left Henry Krum, Louise Shiel, Chris Reid, Kimberley

ASpirin in Reducing Events in the Elderly (ASPREE)

The Clinical Trials Centre (CTC), Caulfield is the site of the National Co-ordinating Centre and the Victorian Regional Centre for the ASPREE study.

ASPREE is a large-scale, double-blind randomized placebo-controlled trial of aspirin in primary prevention in healthy elderly people. The primary research question is does low-dose aspirin have overall benefit in those aged 70 years and over, who do not have manifest cerebral, coronary, or peripheral arterial disease or dementia? The study will be conducted in general practices throughout Australia (and possibly the U.S., depending on funding success with the NIH) and will therefore represent the ageing population in urban and rural Australia. In ASPREE, 20,500 subjects will be randomised to daily 100 mg



enteric coated aspirin or placebo. Follow-up is planned for an average of 5 years. The trial methodology is based on the highly successful Second Australian National Blood Pressure Study (ANBP2) that was based in general practices in Australia with the practitioner as a co-investigator.

Low-dose enteric aspirin is potentially one of the most effective preventive agents for use in older subjects. It has the potential to extend the duration of the healthy active lifespan of elderly people by delaying the onset of cardiovascular disease, stroke and possibly dementia. These are the most common causes of physical disability and hospitalization amongst the elderly Australian population. If it proved effective the low cost of aspirin therapy would make it an affordable preventive agent for elderly populations in all countries.

From a clinical standpoint the size of the study may allow the identification of subgroups of patients in whom aspirin therapy is associated with particularly favorable or unfavorable ratios of benefit to risk. These may be useful in modifying prescribing guidelines in a way that ensures maximum safety. It will also provide 'raw material' for future modeling to estimate cost-effectiveness and explore likely effects of this and other similarly effective interventions on future medical service utilization.

SCREEN-HF

(SCReening Evaluation of the Evolution of New Heart Failure)

This is a prospective, cross-sectional cohort study designed to assess the utility and cost-effectiveness of brain natriuretic peptide (BNP) in the determination of LV dysfunction in patients at high-risk for this condition but without known cardiac dysfunction, symptoms of heart failure or previous diagnosis of either condition.

Studies have shown that BNP is a useful screen tool for heart failure during acute presentations of shortness of breath to the Emergency Room. Additional studies in General Practice have confirmed the ability of BNP testing to improve accuracy of diagnosis of heart failure in this setting. However, little is known about the peptide as a screening test for LV dysfunction in patients at high-risk for subsequent development of this condition and/or overt heart failure. To the knowledge of the investigators, this is the first study that addresses one of the key issues in utility of screening of high-risk patients for subsequent heart failure using a simple blood test.

The cost-effectiveness of such an approach has major implications for healthcare providers, particularly insurers.

Approximately 3500 participants will be recruited for this study. To achieve this recruitment it is estimated that about 10,000 HBA members over 60 years will be contacted by letter and

invited to be screened. Participants identified as having plasma levels in the highest 20% of NTproBNP will undergo further evaluation including echocardiography, ECG and further bloods for cardiovascular biomarker measurement. This study has now been approved by Alfred Ethics and recruitment commenced.

At the close of ANBP2, all subjects were asked for permission to be contacted in the future for on-going follow-up in regards to their health status. Over 95% of subjects provided written informed consent to be contacted. Since hypertension, myocardial infarction and diabetes together account for more than 80% of the population-attributable risk of heart failure, the ANBP2 population is an ideal one to review for the development of heart failure. These subjects are now to be contacted via mail out of questionnaires to enable a reliable estimate of the underlying prevalence of heart failure (HF) within an elderly hypertensive Australian population to be determined. The responses to the questionnaire will also allow us to determine the rate of progression from hypertension to HF in this elderly hypertensive population.

EPLILONG

Eplilong is a study examining a new compound that may assist people with insomnia. Specifically the study is investigating the efficacy and safety of eplivanserin on Sleep Maintenance Insomnia: in a 12-week Multicenter, randomized, double-blind, placebo-controlled study followed by an open treatment phase extension with eplivanserin for 40 weeks period. Recruitment for the study has been extended until June 2007.

LPL104884 & ILLUMINATE

Two trials, a short term phase IIb study sponsored by GlaxoSmithKline (GSK) and a long term outcome study sponsored by Pfizer, investigating two different and new classes of lipid lowering drug were conducted at the Centre in 2006. The GSK project was a multicenter study in subjects with stable coronary heart disease (CHD) or CHD-risk equivalent to examine treatment effects on circulating biomarkers associated with cardiovascular risk, safety and tolerability over 12 weeks. This phase IIb study was recruited and completed in 2006. The latter, multicentre, study sponsored by Pfizer was established to evaluate the combination of torcetrapib/ atorvastatin compared with atorvastatin alone on the occurrence of major cardiovascular events in subjects with coronary heart disease. This study began recruitment in 2005 and follow-up visits were conducted in 2006. The study was terminated early by the study sponsor, in December 2006, due to safety concerns.

VYTUL

Vytorin treating uncontrolled lipids

Vytul is a multi-centre, randomised, open-label study comparing the effectiveness and safety of treatment with Vytorin (ezetimibe and simvastatin) versus atorvastatin in patients with coronary heart disease and/or diabetes mellitus with uncontrolled lipids on statin therapy.

Evidence from epidemiological studies has confirmed that high serum cholesterol is a major risk factor for coronary heart disease (CHD). Results of both primary and secondary prevention studies have shown unequivocally that statins can reduce the risk of coronary mortality and morbidity.

The development of improved pharmacologic therapies and patient management strategies for the prevention of CHD is essential in order to achieve the expected benefits associated with pharmacotherapy. In order to allow more patients to obtain their targeted cholesterol levels, the introduction of a highly effective treatment which lowers LDL-C, increases HDL-C and has a good tolerability profile would be highly desirable.

A recent approach to cholesterol lowering is to combine complementary medications to achieve more effective control of LDL-C levels. The co-administration of the novel cholesterol absorption inhibitor ezetimibe and simvastatin may represent such a treatment.

Australian National Blood Pressure Study (ANBP2)

The Second Australian National Blood Pressure Study (ANBP2) Study was designed to determine if there was any difference in outcome (defined by total cardiovascular events and mortality) between patients randomised to anti-hypertensive treatment with an ACE-inhibitor versus diuretic-based regimen. It also examined risk factor prevalence, including diabetes. ANBP2 was conducted in general practices throughout Australia between 1995 and 1998. In total, 6083 subjects were enrolled in the study from 1594 general practices and followed for a median of 4.1 years.



Research Development and Training



As part of the research development and training component of CCRE Therapeutics' activities, scholarships and fellowships are available at the PhD and Post-doctoral level.

CCRE Therapeutics PhD Scholarships are awarded at two levels:

a) a bridging scholarship (three-year max) for those commencing clinical research who have yet to obtain independent funding from peer-reviewed grant giving bodies (eg: NHMRC, NHF, Vic Health, RACP, RACS).

b) a top-up scholarship (three-year max) for those undertaking clinical research and receiving a peer-reviewed fellowship.

CCRE Therapeutics Post Doctoral Fellowship:

The aim of this Fellowship is to provide new PhD graduates with the opportunity to undertake clinical research activities within CCRE Therapeutics in order to establish a base from which to successfully apply for independent post-doctoral research positions. The fellowships will be awarded for a maximum of three years.

Research Student Reports



Dr Dipak Kotecha, MBChB, MRCP

Thesis Title: *Evaluation of pulse wave tonometry and heart rate variability to assess cardiovascular risk in routine clinical practice (Alternative risk markers in coronary artery disease [ARMCAD study])*

Background: Estimating the risk of future cardiovascular events

such as death, stroke and myocardial infarction using traditional risk factors (such as age, gender, smoking, diabetes, hyperlipidaemia and hypertension) is well accepted in patients with and without existing cardiovascular disease. These estimates are based on a number of robust observational studies, including the original Framingham study. While these methods apply reasonably well on a population level their application to the individual patients is not always straightforward. In addition risk charts, such as those published by the Joint British Societies and American Heart Association may underestimate risk in certain groups, notably diabetics and patients of Indo-Asian background, whilst overestimating risk in others (by as much as 50% in some studies).

A number of variables including clinical, biochemical, and enzymatic have been evaluated to see if they add to conventional "risk-reduction" models such as Framingham and if so to understand if they may be used in routine clinical practice.

Aims: The aim of this study is to assess several known and a few novel risk-factors (heart rate variability, pulse wave analysis, high-sensitivity CRP and BNP) in high-risk groups. Analyses will include both a correlation with coronary angiography results

and a longitudinal cohort to study the incidence of coronary events.

ClinicalTrials link: <http://clinicaltrials.gov/show/NCT00403351>

Current Progress: Recruitment commenced October 2006: 170 patients enrolled at 4 centres in Melbourne.

Interim results of 70 participants to be presented at Cardiac Society of Australia/New Zealand Conference, August 2007.



**Dr Steven Haas, BPharm,
BPharmSci(Hons), MSHPA, MAEA,
MHBPRCA**

Thesis Title: *Pharmacotherapy:
Safety, Efficacy & Impact upon
outcomes of heart failure and
hypertension.*

Background: Heart failure and hypertension are extremely common ailments that are a major health burden affecting numerous

stakeholders in a number of ways – emotionally, physically and financially. Heart failure alone has been estimated to directly affect at least 300,000 Australians, with an incidence of approximately 30,000 Australians per year (est. 2001). Back in 1996-97, heart failure accounted for approximately 2% of all deaths in Australia and was responsible for about 0.8% of all hospitalisations. These figures are set to *increase* as the treatment for heart disease improves, life expectancy prolongs, and more people are identified as actually suffering from heart failure. This is further complicated by the lack of a universally accepted definition for heart failure, with clinical investigators and epidemiologists commonly at odds with one another. Caused by a myriad of conditions (including hypertension, myocardial infarction, valvular heart disease and myocarditis), the symptoms of heart failure are debilitating and classically consist of shortness of breath, extreme fatigue, sodium and water retention, and oedema. Males tend to be affected more than females, and over 10% of the population aged above 75 years of age are troubled by the condition.

Investigations undertaken: Two distinct areas of investigation were undertaken as part of the postdoctoral studies related to this thesis. The first area involved the utilisation of a statistical tool known as meta-analysis to investigate the effects of particular medications upon the conditions of heart failure and hypertension. Meta-analysis allowed us to summarise the current “state of play” with respect to certain clinical situations such as the role of beta-blocker therapy in diabetic heart failure patients and elderly heart failure patients, the effects of cyclo-oxygenase (COX-2) inhibitors on blood pressure as a

deleterious effect, and the promising effects of Coenzyme Q10 therapy in patients with hypertension.

The second area of investigation relates directly to pharmacoepidemiology with a particular focus upon the safety of medications. Areas of interest have included the incidence of clozapine-associated myocarditis amongst patients treated for schizophrenia, the incidence of cardiac valvulopathy amongst patients treated for Parkinson’s Disease with pergolide and cabergoline, and the uncertainty of long-term effects of statins in the treatment of high cholesterol and in heart failure patients in recent times.

Ms Helen Walls, BSc MPH(Hons)



Thesis Title: *Effectiveness, cost-effectiveness and equity of strategies to reduce the burden of obesity-related conditions*

The prevalence of obesity has increased dramatically in Australia, as elsewhere in the world, over recent decades. Obesity is now the cause of much morbidity and premature mortality, and has become a serious public health issue.

Our findings show that in Australia the shift towards excess body weight is not uniform across percentiles of body weight (also shown in NZ and the US). Examination of the changing body mass index (BMI) distribution shows that most of the increase is occurring at higher BMI percentiles (i.e., skewness is increasing). Furthermore, the shifts are not uniform across time or among sub-populations. The mixed pattern of shifting of the BMI distribution suggests strategies aimed at reducing the obesogenicity of the environment could be complemented with targeted strategies aimed at high-risk groups. But the most appropriate response is elusive, and controversial. The evidence base is for the most part small, narrow in approach, limited in impact, and lacking in cost-effectiveness and equity information.

This thesis will describe obesity trends in Australia and two countries overseas and discuss the implications for prevention; review literature on the relationship between body weight and mortality/morbidity; describe the relationship between body weight and selected health outcomes; and compare selected

'high-risk' strategies for obesity treatment with a relatively cost-effective 'population-based' obesity prevention strategy (reduction of TV advertising of energy-dense foods and drinks to children, as determined by the ACE-Obesity project) in terms of their impact on the burden of obesity-related disease, cost-effectiveness and their impact on equity considerations.

Ms Jessica Chellappah, BSc(Hons), MPH



Thesis Title:
Cardiovascular Risk Factors in Children and Young Adults – Current Status and Strategies for Prevention

Concept: Multiple studies of children have demonstrated clearly that systolic blood pressure, total and LDL-cholesterol, plasma insulin and obesity tend to cluster. A high likelihood exists that such cardiovascular risk factors present in obese children tend to track with age. Poor dietary habits

developed in childhood have been found to contribute to obesity in children, and continue into adulthood.

We aimed an intervention at children, whose dietary habits are in the process of being ingrained, hypothesizing that the long term benefits to adiposity and health overall would likely be optimized.

Research Plan: We took a study sample of 4 schools, Year 5 & 6s in 2006, from within the Southern Metropolitan region of Melbourne. Two private and two public schools were selected to participate and assigned randomly to intervention and control groups (total of 370 participants). We then determined the level of risk factors in participants in these schools (ie. blood pressure, body fat%, BMI, Blood lipids), and subsequently providing serves of fruit in the classroom daily, in intervention schools only over 3 months, together with healthy eating information. We then monitored the change in the extent of risk factor prevalence in both intervention and control groups at the end of the 3 months.

In addition, we assessed the children's dietary choices and their possible associations with family behavioural patterns, using questionnaires.

Results:

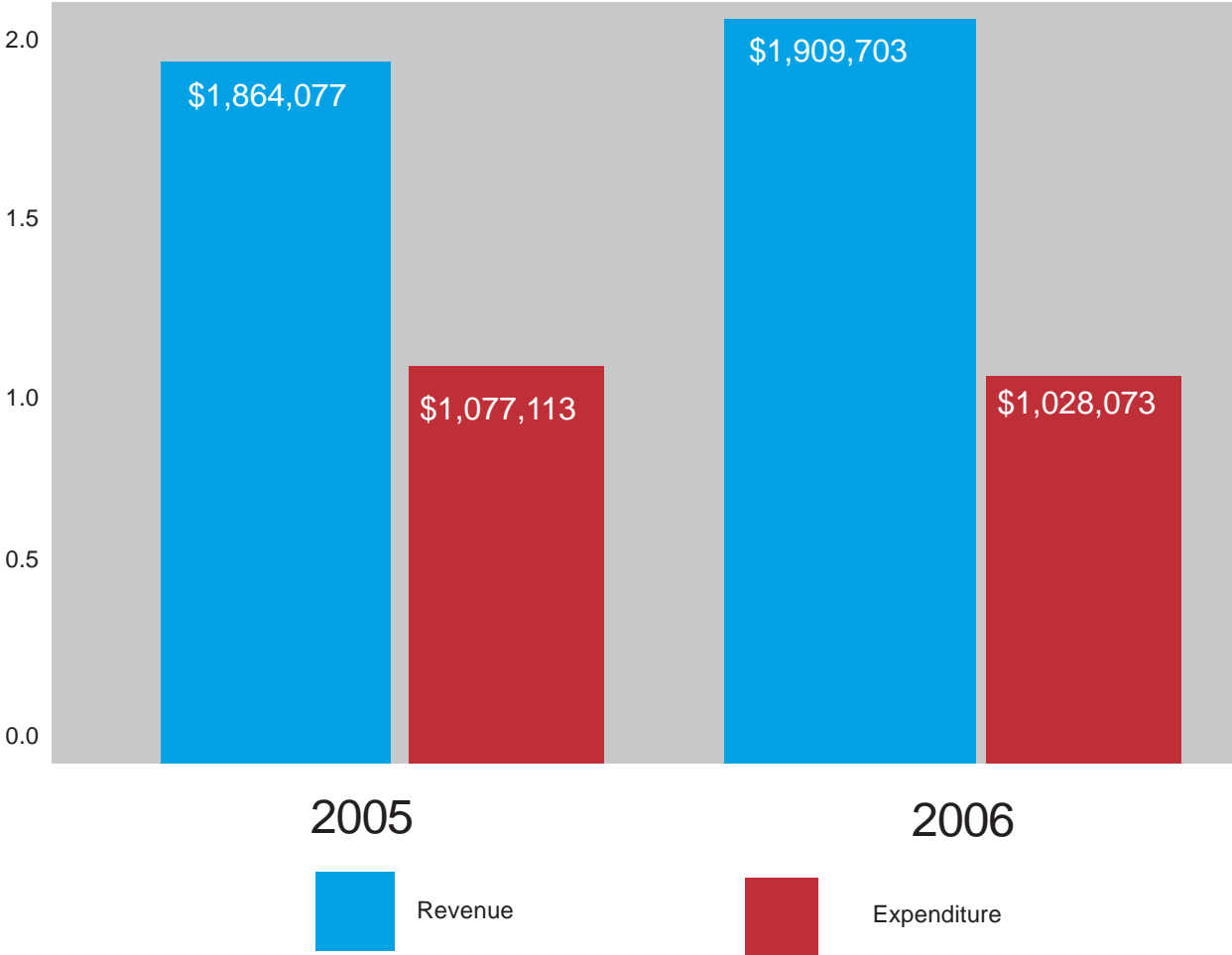
Some of our primary findings have shown that -

- a) Attitudes towards daily consumption of fruit were improved and sustained following exposure to the intervention.
- b) That children from intervention schools exhibited improved cardiovascular risk factor prevalence and dietary choices over the intervention period, as compared to controls.
- c) Improved dietary choices and risk factor prevalence had an association with family socio-demographic data.

Conclusion: Due to the overwhelming positive response from the schools involved, we are looking to expand out to involve more schools in the long-term.

Financial Report

The Centre of Clinical Research Excellence in Therapeutics continues to sustain growth with an income of almost \$2,000,000 for both 2005 and 2006. With this continued sustainability the CCRE Therapeutics has placed itself in an excellent position for further continued growth following the final year of NHMRC CCRE funding in 2007.



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