NHMRC CLINICAL TRIALS CENTRE
THE UNIVERSITY OF SYDNEY

RESEARCH REPORT 2006–2007

The National Health and Medical Research Council Clinical Trials Centre conducts its own clinical trials, provides expertise and infrastructure for trials run by other groups, and undertakes research aiming to improve both the conduct of trials and the resulting clinical evidence.

Since 1988, when the CTC was set up as a research centre at the University of Sydney, over 60 000 patients have been randomised into its trials. Currently, around 40 active trials — in cancer, cardiovascular disease and neonatology — are being conducted in collaboration with networks of clinical investigators across Australia and elsewhere. The CTC has played a leading role in establishing some of these investigator groups, most recently the Cooperative Trials Group for Neuro-Oncology and the Australasian Lung Cancer Trials Group.

Trial investigators also participate in international collaborations to carry out prospective meta-analysis of data from concurrent clinical trials. For example, the NeOProM collaboration has been formed by five cooperating trial groups, involving over 5000 patients, with leadership from the CTC. Developments such as this increase the efficiency of research and the validity of its findings, resulting in benefit to patients throughout the world.

The CTC also has strong links and partnerships with government and nongovernment organisations and industry. Projects include capacity building for Australian health and research, reviews of evidence to assist government policy making, and methodological research.

The CTC's past research has served the Australian population well, particularly through reduced cardiovascular disease and deaths from heart disease and improved survival and better quality of life for patients with many types of cancer.

This report covers the CTC's achievements for the biennium, 2006–2007.

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FROM THE DIRECTORS

In 2006 and 2007, many research projects came to fruition in the publication or presentation of findings that will have direct application in improving the health of people in Australia and internationally. The CTC has become an important stakeholder in large-scale clinical trials research of genuine international significance to public health, with a major impact on practice worldwide.

Notable developments in the biennium were the strengthening and development of collaborative activities. An example is the initiative to help Australian clinician groups to initiate and conduct the next generation of trials in oncology. The CTC's staff, expertise, dedicated infrastructure, quality assurance, and new systems have allowed high-quality new trials answering important clinical questions to come into operation. With funding from the NHMRC, the CTC has developed new programs to assist Australian investigators wanting to undertake new trials. The 'outreach' program supports clinical investigators via our expertise and data management systems. We also offer infrastructure for cancer trials. A partnership with the Cancer Institute NSW aims to encourage investigator-initiated oncology trials through operational and statistical leadership.

The CTC has long been an advocate of prospective registration of clinical trials. The Australian New Zealand Clinical Trials Registry, established at the CTC in 2005, is concentrating on refining its data and accessibility, and is, linking into a worldwide system of registers. The number of trials registered increases steadily.

Major ongoing trials initiatives include: evaluating drugs, radiation, surgery and supportive therapies in early and advanced cancer; evaluating international differences in risk, care and outcomes of patients with acute myocardial infarction; and genetic and biomarker studies.

In oncology, recent achievements have included the early results of the Sentinel Node Biopsy versus Axillary Clearance (SNAC) trial, completion of the Zoloft's Effects on Symptoms and Survival Time in Advanced Cancer (ZEST), and publication of the results of the CO.17 trial in advanced colorectal cancer. A CTC study has helped to resolve the question of whether radiotherapy after mastectomy improves survival of patients with breast cancer. The analysis examined the differences in treatment in individual studies and took into account the variation in radiation dosage and target volumes, to find that radiotherapy does, indeed, lead to better survival at 5 and 10 years.

Further results with wide clinical application have been emerging from the large international diabetes trial, FIELD. The important finding that diabetes treatment with fenofibrate reduces the need for laser treatment for diabetic retinopathy was published in 2007. The earlier large cardiovascular trial, LIPID, continues in follow-up. Our results showing that the study treatment, pravastatin, continues to be safe and beneficial after many years are valuable for patients on long-term cholesterol-lowering therapy. The data from both these large trials continue to accumulate and to generate new research questions, an advantage of the CTC's multidisciplinary and collaborative approach to trial conduct. A current focus is the use of biomarkers to investigate patients' individual risk factors and susceptibility to treatment.

The PCAT Collaboration, a research group coordinated by researchers in the Netherlands, the United States and at the CTC, has undertaken several studies involving reanalysis of data to answer questions about treatments for patients with acute myocardial infarction. The group recently published an article analysing the effect of treatment delay, with implications for the care of these patients. Also, the Cholesterol Treatment Trialists' Collaboration, which is prospectively combining vast data from major international cardiovascular trials, presented new evidence on the beneficial effects of cholesterol lowering for people with diabetes.

Several new international collaborative groups for prospective meta-analysis of data from neonatal trials, which include the CTC's own trials, have been created, strengthening our expertise and extending our interest in this area.

An important ongoing activity of the CTC is systematic reviews of trials on clinical questions and reviews of new technologies. In addition to the ongoing reviews of new procedures for the Department of Health and Ageing, we have recently completed a series of reviews to inform the management of serious rare disorders at nationally funded centres. A recent review of published studies examined how to discuss dying with patients who have

advanced life-limiting illnesses, and led to Australian guidelines on doctor–patient communication in this area.

Underpinning all our clinical trials research are novel approaches to methods. The CTC's biostatistics team is central to advances in trials methodology. Our research team has developed prognostic models for individualised decision-making, novel methods for evaluating and integrating quality-of-life information, and more efficient and valid methods for trials research. We have instituted new strategies for minimising bias in systematic reviews and pioneered the use of prospective meta-analysis as the gold standard in combining trial results. Our work includes expository papers on trial design, outcome assessment, and new insights into the interpretation of trial evidence.

Following on the success of symposiums in 1999 and 2002, the CTC again hosted the International Clinical Trials Symposium, in Sydney in September 2007. Those attending were informed and also entertained by international keynote speakers and Australian trials leaders in a varied program, which included topics in the broad themes of partnerships in clinical trials, biological and genetic targeted therapies, special groups in clinical trials, trials in developing countries, and others. The three-day scientific program was supplemented by a day of didactic workshops.

The symposium was also the venue for launching the CTC's new book, *Interpreting and Reporting Clinical Trials*. CTC staff and their colleagues who wrote the book's chapters have elucidated the international CONSORT guidelines in a natural, readable way for clinicians and others learning about clinical trials.

As the CTC approaches its 20th anniversary, we can look back on having coordinated around 45 multicentre randomised trials involving many thousands of patients, achieved through establishing and supporting collaborative groups and playing a lead role in clinical trial initiatives. Their success has been due to the teamwork and efforts of the CTC staff and those in Australia and around the world who work with them. These activities have been generously supported by government, non-government and charitable bodies, industry and other sponsors.

JOHN SIMES
Director

Professor John Simes is the foundation director of the CTC and continues to direct all the CTC's activities. He is recognised internationally for his expertise in the fields of clinical trials and biostatistics and represents the CTC on many national and international committees. He has fostered clinical trials and clinical trial networks in cancer, cardiovascular medicine, thrombosis, neonatal medicine and surgery. He has played a leading role in many international trials that have led to major advances in health care and has for many years championed the need for evidence-based clinical research.

Professor Simes is also a specialist medical oncologist at Royal Prince Alfred Hospital.

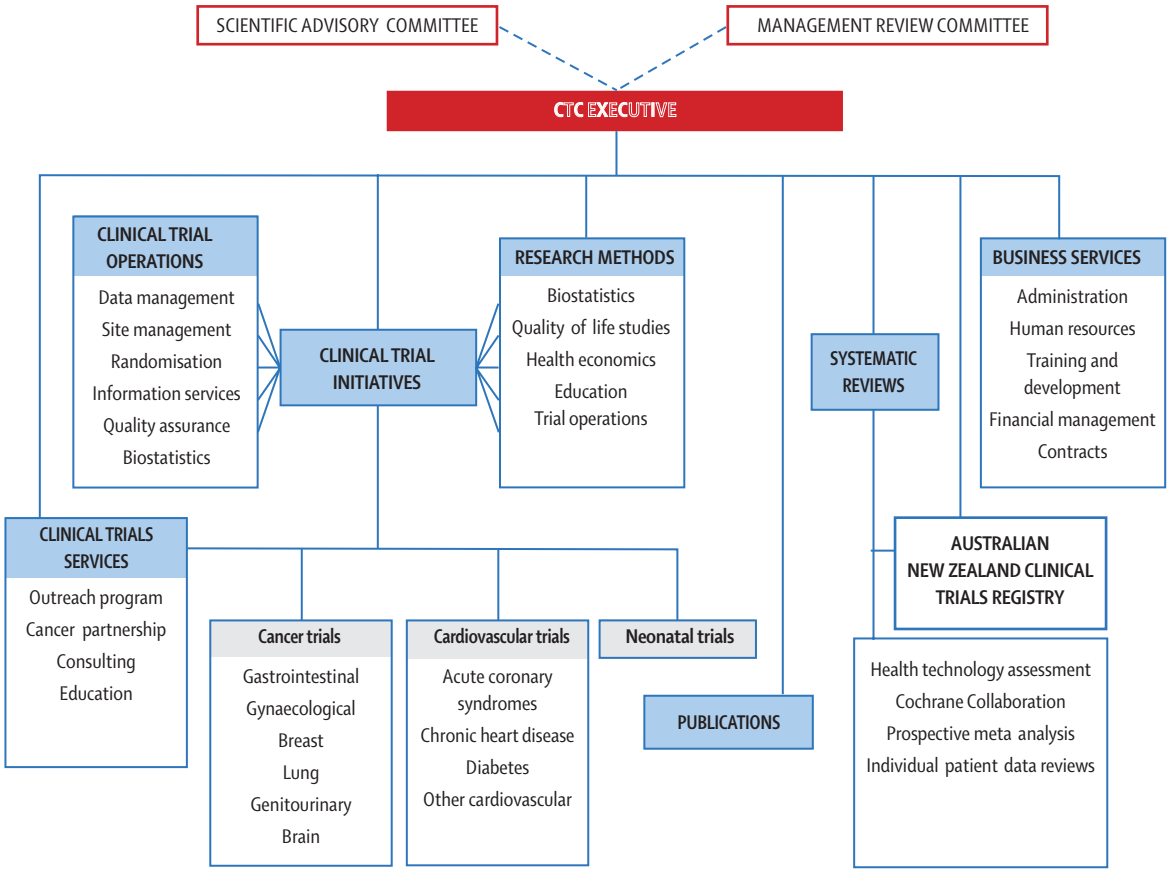
ANTHONY KEECH
Deputy director

Professor Keech, cardiologist and epidemiologist, co-directs the CTC research program. He a leading international figure in lipid and cardiovascular clinical trials and is chairman of the FIELD study on heart disease and diabetes. As a professor in the Department of Medicine at the University of Sydney, he initiates, coordinates, develops and teaches courses for medical and other postgraduate students. He also leads educational initiatives of the CTC, particularly in the Asia-Pacific region. In 2007, he was co-chair of the International Clinical Trials Symposium.

Professor Keech is also a practising consultant cardiologist at Royal Prince Alfred Hospital.

CTC EXECUTIVE AND ORGANISATION

CTC EXECUTIVE: Left to right: Anthony Keech (deputy director), Wendy Hague (clinical trials program director), Kim Russell-Cooper (general manager, in attendance) and John Simes (director).



BUILDING CAPACITY FOR CLINICAL TRIALS RESEARCH

NEW PROGRAMS TO SUPPORT CLINICAL TRIALS RESEARCH IN AUSTRALIA

Collaboration with Australian trials researchers

The CTC provides capacity for clinical trials is through support for Australian researchers setting up trials in areas of need. This activity is supported by an NHMRC Enabling grant, and:

- aims to ensure the highest quality of clinical trials research in new or high-priority health research areas, at all institutions throughout Australia.
- provides resources in clinical trials expertise and web-based clinical trials management systems to enable investigator-initiated clinical trials of public good.
- supports new trials, including trials in surgery, trials of current clinical practice, new health technologies, clinical management studies, and trials in palliative and supportive care and complementary medicine.

This grant has provided for the development of clinical trial procedures, web-based trials systems and cooperative group networks as platforms for multicentre trials to be initiated and undertaken in NSW and elsewhere.

The management committee for this venture comprises John Simes (chair), Wendy Hague, Val Gebski, Jenny Chow, Jonathon Craig from Westmead Hospital, Sydney (independent adviser), and Marissa Lassere from St George Hospital, Sydney (independent adviser). Its activities are overseen by the CTC's Scientific Advisory Committee.

Infrastructure funding for cancer research

SUPPORT FOR THE CENTRAL FUNCTIONS OF CANCER COLLABORATIVE GROUPS

The Australasian Gastro-Intestinal Trials Group (AGITG) and the Australia New Zealand Gynaecological Oncology Group (ANZGOG) are established research collaborations, coordinated at the CTC. They receive funding from various sources to undertake specific clinical trials to improve the treatment of people with cancer.

Their operations have been supported since 2005 by a continuing infrastructure grant from the Cancer Institute New South Wales, which has allowed them to strengthen their networks, expand their programs and improve the conduct of their trials.

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Wendy Hague
Clinical trials program director

Wendy Hague is clinical trials program director of the CTC and is primarily responsible for the successful conduct of the CTC's clinical trials and ensuring that trials systems, procedures and methods are of the highest standard.

Major achievements to date have been:

- increasing the number of sites participating in ANZGOG and AGITG trials in NSW, nationally and internationally
- promoting the development of new concepts and trials
- attracting funding from other sources to support individual trials and other infrastructure
- developing and implementing a quality assurance and audit program (p. 20).

PARTNERSHIP TO SUPPORT CANCER TRIAL OPERATIONS, BIOSTATISTICS AND AUDIT

Infrastructure for clinical trials is a key requirement for developing good quality clinical research.

The Cancer Institute NSW and the CTC have formed a partnership to provide investigators and collaborative groups in New South Wales with access to statistical and operational expertise, by means of a continuing grant.

Major achievements to date attributed in total or in part to this funding include:

- establishing cancer collaborative groups, including the research program of the Australasian Lung Trials Group (ALTG) (p. 22), setting up the Cooperative Trials Group for Neuro-Oncology (COGNO) (p. 22), and developing new trials through existing groups (for example, with the Australia and New Zealand Melanoma Trials Group (ANZMTG)
- supporting investigators in the design of new clinical trials
- education and training of new investigators in clinical trial methods and protocol development.

The partnership has supported 24 studies, which have evaluated novel therapies or the optimal use of existing treatments. It has contributed to the participation of centres across the state in clinical trials, with a resulting increase in the proportion of new cancer patients enrolling in trials — from less than 2% in 2003 to more than 5%.

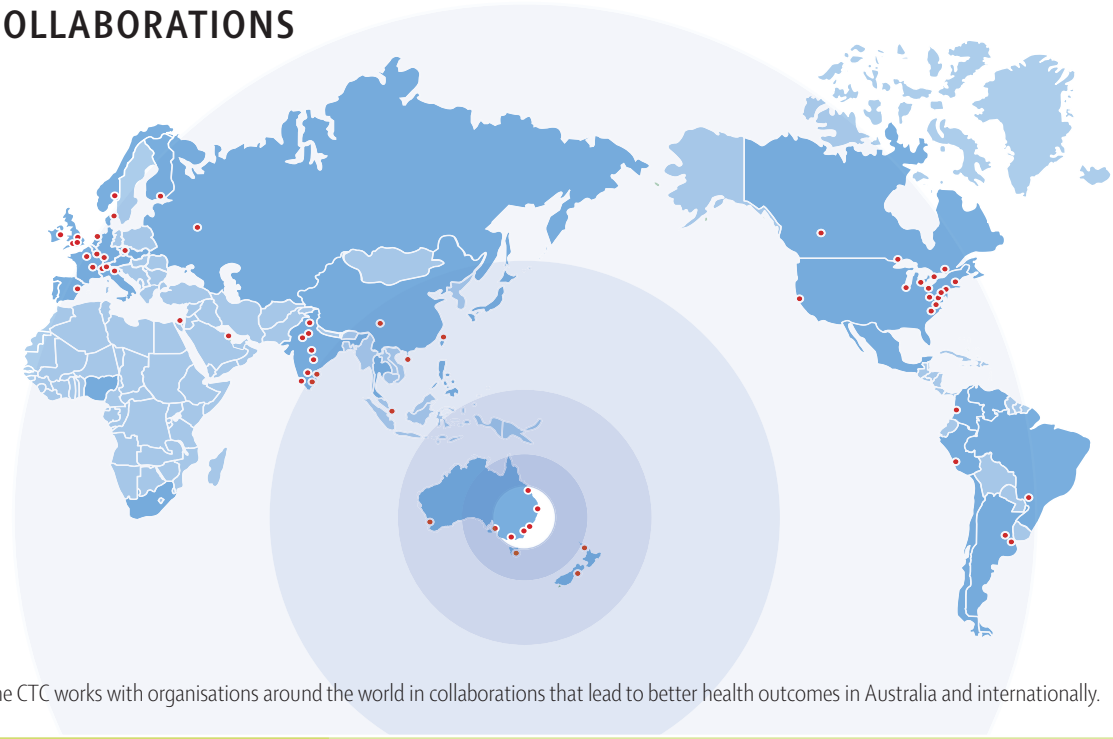
Operational services supported by the partnership include developing study outlines, protocols and materials for clinical trials; data systems development; local monitoring; internal quality assurance; project management support; and reporting and publications.

ANZGOG–AGITG CLINICAL TRIALS RESEARCH FELLOW

Corona Gainford, clinical trials research fellow and medical oncologist, manages the Cancer Institute NSW infrastructure grant which funds her fellowship. At the CTC, Corona is a clinical supervisor of cancer trials and participates in developing new concepts. She is the co-principal investigator of TRIPOD, a phase II trial of intraperitoneal chemotherapy for ovarian cancer (p. 20).

At the CTC, she teaches clinical trials staff and also teaches in the University of Sydney postgraduate medical program.

COLLABORATIONS



The CTC works with organisations around the world in collaborations that lead to better health outcomes in Australia and internationally.

Group	Nature of group	Activity
Australian New Zealand Breast Cancer Trials Group (ANZ BCTG)	Collaborative group for breast cancer trials: Australia, New Zealand International collaborations: International Breast Cancer Study Group (IBCSG), Breast International Group (BIG), International Breast Cancer Intervention Study (IBIS)	Statistical centre for group, including randomisation
Australian and New Zealand Germ Cell Tumour Study Group (ANZGCTG)	Collaborative group for testicular cancer trials: Australia, New Zealand	Coordinating centre
ASPIRE Study Group	Collaborative group for ASPIRE trial: Australia, New Zealand, United Kingdom, India	Coordinating centre
Australasian Gastro-Intestinal Trials Group (AGITG)	Collaborative group for gastrointestinal cancer trials: Australia, New Zealand International collaborations: NSABP (USA), ECOG (USA), EORTC (Europe)	Coordinating centre
Australasian Germ Cell Trials Group	Collaborative group for cancer of testes and ovaries	Coordinating centre
Australasian Society of Thrombosis and Haemostasis	Professional group undertaking thrombosis trials: Australia, New Zealand	Coordinating centre
Australasian Lung Cancer Trials Group (ALTG)	Collaborative group for lung cancer trials	Coordinating centre
Australia New Zealand Gynaecological Oncology Group (ANZGOG)	Collaborative group for gynaecological cancer trials: Australia, New Zealand International collaborations: Gynecological Cancer Intergroup (GCIG), International Gynaecological Cancer Intergroup (IGCI), Gynecologic Oncology Group (GOG),	Coordinating centre
Australian New Zealand Clinical Trials Registry	National register of Australian clinical trials	Coordinating centre
Australian universities	University members of Biostatistics Collaboration of Australia	Coordinating centre
Cochrane Collaboration	Collaborative group undertaking systematic reviews of trial evidence: international	Editorial base of the Cochrane Breast Cancer Group

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Group	Nature of group	Activity
Cholesterol Treatment Trialists' Collaboration (CTTC)	Collaboration of clinical trial groups studying cholesterol treatments: Australia, New Zealand, United Kingdom, United States, Italy	Coordination of meta-analyses in heart disease
Cooperative Trials Group for Neuro-Oncology	Collaborative group for lung cancer trials	Coordinating centre
Department of Health and Ageing	Government: Australia	Provide assessments of new technologies and other research services BCA: biostatistics education
European Organisation for Research and Treatment of Cancer	International collaborative group	Collaborator through Australian groups
FIELD Study Group	Collaborative group for FIELD diabetes trial: Australia, New Zealand, Finland	Coordinating centre
Flinders Medical Centre, Australia	Clinical and laboratory centre: Australia	Co-collaborator on VIGOUR trials
Gynaecologic Cancer Intergroup (GCIG)	International collaborative group	Collaborator through ANZGOG
Gynecologic Oncology Group (GOG)	International collaborative group	Collaborator through ANZGOG
Inhaled nitric oxide for preterm infants	Meta-analysis collaboration: Australia, United States, Canada	Collaborator
INIS Study Group	Collaborative group for INIS trial: Australia, New Zealand, United Kingdom	Regional coordinating centre
INSPIRE	Meta-analysis: ASPIRE and WARFASA (Italy)	Member
LIPID Study Group	Collaborative group for LIPID cholesterol-lowering trial: Australia, New Zealand	Coordinating centre
Medical Research Council (MRC)	Government, international	Collaborator
National Cancer Institute of Canada Clinical Trials Group (NCIC CTG)	Trials research group: Canada	Collaboration on cancer trials and meta-analysis
National Heart Foundation	Nongovernment organisation: Australia	Sponsor of the LIPID trial
National Perinatal Epidemiology Unit (NPEU), University of Oxford	Research institution: UK	Co-collaborator on the INIS neonatal trial
National Surgical Adjuvant Breast and Bowel Project (NSABP)	Collaborative group	Collaborator through Australian groups
NeOProM collaborative group	Meta-analysis collaboration	Coordinating centre
NSW Cooperative Oncology Group	Collaborative group: NSW	Coordinating centre for the group
Oxford Clinical Trials Office (OCTC)	Trials research group: UK	Cancer trials
PARIS collaborative group	Meta-analysis collaboration with representation from many countries	Co-coordinating centre
PreVILIG collaborative group	Meta-analysis international collaboration	Member
Primary Coronary Angioplasty versus Thrombolysis (PCAT)	Meta-analysis collaboration with representation from many countries	Co-coordinating centre
Prospective Pravastatin Pooling project	Collaborative group: Australia, New Zealand, United States, Scotland	Coordinating centre
Royal Australasian College of Surgeons	Professional society undertaking trials of surgery: Australia and New Zealand	Coordinating the SNAC trial in breast cancer with the RACS
VIGOUR group	Collaborative group for trials of heart disease: 40 countries	Data coordinating centre, Asia-Pacific Region; International statistical centre (HERO-2 trial)

Biostatistics Collaboration of Australia (BCA): training a new generation of biostatisticians

The Biostatistics Collaboration of Australia (BCA), administered at the CTC, was formed in 2001 to meet the need for well-trained biostatisticians in Australia. No single Australian university has the capacity to offer a comprehensive national postgraduate program in biostatistics. The BCA program, developed by academic statisticians from around the country, is a model of collaboration among universities: each university recognises the course units developed or taught by the other universities. Teaching by distance methods, initially necessitated by the widely dispersed faculty, is now seen to be a strength, because of its evidence convenience for working students.

Sarah Goodman-Jones, administrative officer, and Erica Jobling, executive officer, at the BCA coordinating centre.

The courses provide a sound mathematically based grounding in statistical methods with a strong emphasis on application to all areas of health and medical research.

The group recently developed an additional core unit, 'Probability and distribution theory'. Statisticians at the CTC contribute to the program by developing, coordinating and teaching various units of study, including 'Principles of statistical inference' (Adrienne Kirby, coordinator) and 'Advanced clinical trials and meta-analysis' (Peta Forder and Val Gebski, coordinators).

The BCA program has been re-funded by the Australian Government for a further five years, to 2010, providing partial support for the transaction costs incurred by the multi-university consortium model.

In 2007, 224 students were enrolled. By the end of 2007, over 100 had graduated.

www.bca.edu.au

PARTICIPATING UNIVERSITIES

Adelaide University (new in 2007)
Australian National University
Macquarie University
Monash University
Newcastle University
University of Melbourne
University of Queensland
University of Sydney

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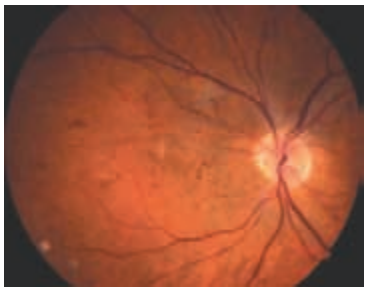
RESEARCH HIGHLIGHTS



Photograph of the retina, showing branching retinal blood vessels with microaneurysms and small haemorrhages.

RETINOPATHY SUBSTUDY

In a substudy of 1012 FIELD patients, serial photography was used to track the progress of retinal disease and the effects of fenofibrate treatment. Photographs were taken at baseline, 2 years, 5 years and the end of the study.

Patients on fenofibrate were less likely to have two steps of progression of retinopathy grade, macular oedema, or laser treatment. This was an exploratory finding requiring confirmation with a larger group of patients.

FIELD eye study

IMPORTANT CLINICAL IMPLICATIONS FROM NEW RESULTS OF THE FIELD TRIAL

The leading cause of vision loss among working adults in most countries is diabetic retinopathy (in which blood vessels of the retina become damaged, causing growth of new vessels, bleeding, or swelling at the back of the eye). While laser therapy is a successful treatment in preventing blindness, it sometimes causes ocular side-effects and reduces the visual field.

One of the studies in the Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) trial investigated whether the use of fenofibrate could reduce the rate of laser therapy in people with type 2 diabetes (p. 26). This multinational trial had 9795 patients aged 50 to 75 years from Australia, New Zealand and Finland.

Laser therapy was more commonly needed in patients with poorer blood glucose and blood pressure control and in those with other complications of diabetes. Fenofibrate reduced laser treatments for proliferative retinopathy by 30% and for macular oedema by 31%. These benefits of fenofibrate were apparent after only eight months into the five-year study.

The mechanism of the effect was not related to the concentrations of lipids in the blood, and may reflect anti-inflammatory or antioxidant effects of the drug. This finding is likely to have major clinical implications for the prevention of retinopathy and has led to great interest in the scientific community.

The study (with the retinopathy substudy) was published in *The Lancet* in 2007.

Right: Professor Anthony Keech, chief investigator of the international FIELD trial.

High points in gastrointestinal cancer research

CETUXIMAB IMPROVES SURVIVAL

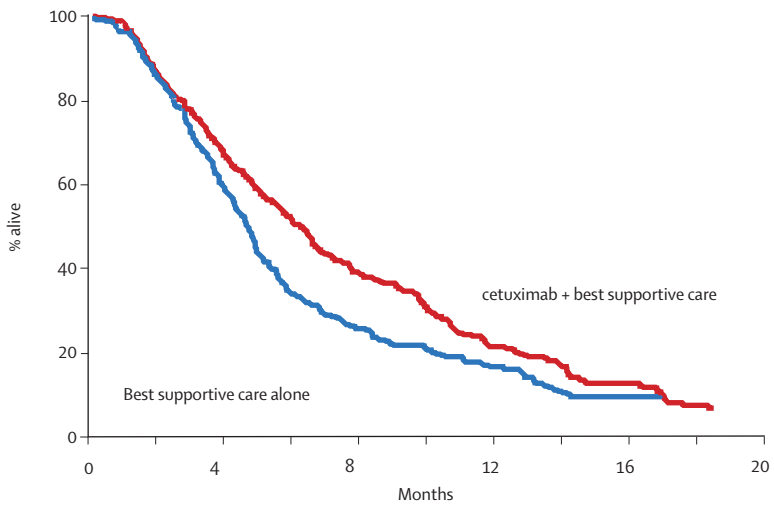
Results of the CO.17 trial were published in 2007 in the *New England Journal of Medicine*.

CO.17 was designed to determine how cetuximab affects the duration of survival and quality of life of very ill people with advanced colorectal cancer whose cancer has progressed after chemotherapy. Cetuximab is a monoclonal antibody which targets a protein on the surface of many cancer cells and some normal cells, inhibiting cell growth and leading to cell death.

Compared with supportive care alone, weekly treatment with cetuximab resulted in a statistically significant 23% improvement in overall survival. There was also a 32% reduction in the risk of disease progression. Patients treated with cetuximab also had less deterioration in quality-of-life scores.

The average improvement in survival was a result of the better survival of the minority of patients whose tumour responded to treatment. It is not yet known how these particular patients can be identified. However, one finding of the study was that patients in the cetuximab group had a high incidence of rashes, and those with worse rashes survived for longer. Rashes or hypersensitivity related to growth-factor inhibition could be investigated as a potential biomarker predicting patients most likely to benefit from treatment.

The trial was a study by the Australasian Gastro-Intestinal Trials Group in conjunction with the National Cancer Institute of Canada Clinical Trials Group (NCIC CTG). The CTC coordinated the CO.17 trial in Australia, New Zealand and Singapore.



MAX: COMBINATION TREATMENT COMPARED WITH A SINGLE DRUG FOR COLORECTAL CANCER

The MAX study is determining the optimal low-toxicity regimen for a broad range of patients with advanced colorectal cancer. The rationale for the treatment is a comparison of the standard chemotherapy, capecitabine, with capecitabine and a biological agent, bevacizumab, with or without mitomycin C. The study aims to improve the duration of survival without compromising quality of life.

Recruitment exceeded expectations in 2006. In spite of an amendment in August 2006 to increase the sample size from 333 to 450 patients, recruitment was completed, with 471 patients, in 2007.

This trial is significant as the first international oncology study led and coordinated by the AGITG and CTC. Although some patients will still be in follow-up over the coming months, early publications are emerging for major international conferences in 2008.

Val Gebski
Head of Biostatistics and first author of the radiotherapy study

Does radiation therapy improve survival after breast cancer?

An analysis of survival after breast cancer used published data and modern knowledge of treatment to resolve the controversy over whether radiation therapy improves survival. It was known that radiation therapy after mastectomy reduces the risk of recurrence of breast cancer, but its effects on overall survival had been less clear.

The CTC study first excluded previous trials in which the effects of radiotherapy were confounded by different types of surgery. Then, in an analysis of data from 36 clinical trials, the ingenious approach to answering the research question was to divide the trials into three categories: studies that used optimal radiation doses delivered to an appropriate amount of tissue; studies in which the dosage of radiation was too high or too low; and studies in which the amount of tissue treated was not adequate.

In the trials in which patients received well-targeted treatment, more patients who had had radiotherapy survived at 5 years and at 10 years. If the dosage or the area of tissue treated was not accurate, radiation did not make a difference to survival. The study's findings were considered to be the most plausible or realistic estimates of improved outcome associated with modern radiation therapy, which will assist doctors and patients in their decision making.

In their paper in the *Journal of the National Cancer Institute*, the authors recommended that postmastectomy radiation therapy now be considered for all patients at high risk.

ZEST: Depression and quality of life in advanced cancer

"Treatment with a selective serotonin reuptake inhibitor should be reserved for those with a proven indication."

— conclusion of the ZEST trial

Self-ratings of depression, mood, fatigue, and global quality of life are related to survival in advanced cancer.

The recently completed ZEST trial (Zoloft's Effects on Symptoms and Survival Time in Advanced Cancer) considered whether treatment with antidepressants might improve psychological wellbeing in patients with advanced cancer and consequently prolong their survival by helping them to cope better with their illness and treatment.

The trial used an established selective serotonin reuptake inhibitor — sertraline — in patients with advanced cancer who felt depressed, anxious, tired, or who had low energy, but who were not thought to have major depression.

ZEST began in 2001 with a planned sample size of 440 patients. After about 189 patients had been recruited, the first interim analysis showed that survival was shorter with sertraline, so recruitment was stopped. With further follow-up, the difference between the groups became less apparent, and was considered a chance finding.

For patients with advanced cancer who do not have major depression, sertraline did not improve wellbeing and did not improve survival.

This study had notable methodological strengths: its double-blind, randomised design (blinding was maintained after the interim results for the group were made available to clinicians and patients); the use of multiple, validated outcome measures; and enrolment of a broad cross-section of patients with advanced cancer; and excellent compliance. The results were published in *The Lancet* in 2007.

First results of the SNAC breast cancer trial

SNAC

The SNAC (Sentinel Node Biopsy versus Axillary Clearance) trial was the first large trial of surgical treatment of breast cancer in Australasia.

The trial aimed to ascertain whether biopsy of a few sentinel lymph nodes would reduce the side-effects — arm swelling, pain and disability — that often affect women who have had the standard treatment, full clearance of the lymph nodes. Recruitment was very fast, and 1088 patients enrolled over four years.

Results after 12 months of follow-up showed that women allocated to sentinel-lymph-node biopsy had fewer problems with arm swelling, movement, sensation and other aspects of quality of life than women allocated to routine axillary clearance. However, arm swelling was worse at one year than at six months, and longer follow-up is needed to see what happens in later years.

Clinical management based on sentinel-lymph-node biopsy was as accurate for diagnosis as axillary clearance, for women with single, small tumours. This underlines the importance of women attending for regular screening, so that cancers are detected as early as possible.

Follow-up in the SNAC trial will continue for at least 10 years.

"The RACS SNAC trial was the fastest recruiting cancer trial ever conducted in Australia.

This excellent result came about because of the collaboration of the women who participated, the investigators conducting the trial and their data management teams combined with the diligence of the staff at the NHMRC Clinical Trials Centre."

— SNAC chairman, Professor Grantley Gill

SNAC 2

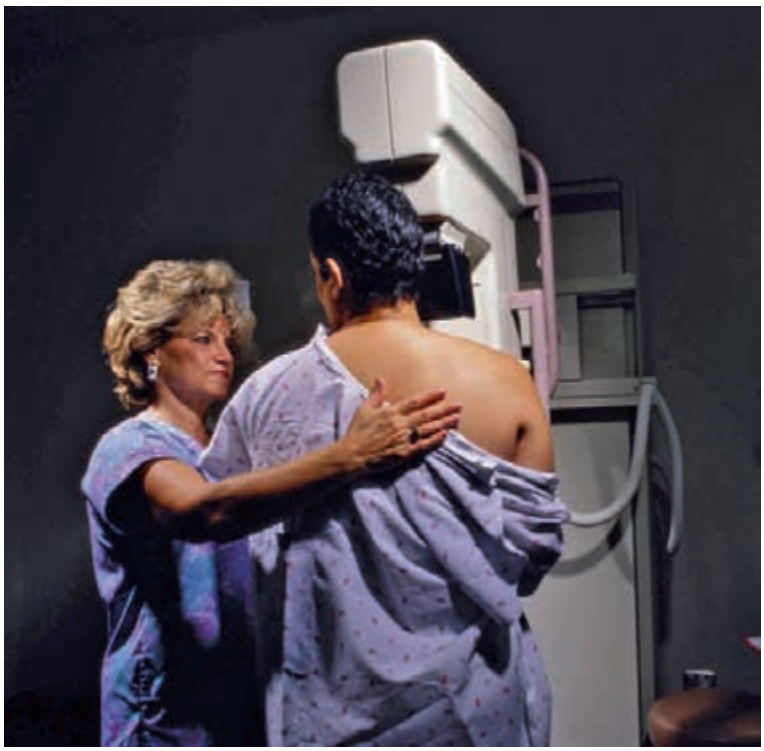
SNAC 2 is an extension of the SNAC trial, and began recruitment early in 2006.

It is investigating sentinel-node-based management of the axilla for a wider range of women, including women with multiple primary tumours in the same breast and women with large tumours. The trial will measure the risk of recurrence of the tumour, particularly in the axilla. Also, the diagnostic accuracy of sentinel-lymph-node biopsy is a particular focus.

FUNDING

The Royal Australasian College of Surgeons and the CTC have collaborated in conducting the SNAC trial, which has been funded by:

- MBF Australia, the Department of Health and Ageing
- National Health and Medical Research Council
- National Breast Cancer Foundation
- Scottwood Trust, New Zealand



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THIRD INTERNATIONAL CLINICAL TRIALS SYMPOSIUM

KEYNOTE SPEAKERS

Professor Doug Altman
Professor of Statistics in Medicine at the University of Oxford, and founding director of Oxford's Centre for Statistics in Medicine

Professor Robert Califf
Vice Chancellor for Clinical Research, Director of the Duke Translational Medicine Institute, and Professor of Medicine in the Division of Cardiology at Duke University Medical Center in Durham, North Carolina

Professor Paul Glasziou
Director of the Centre for Evidence-Based Medicine, Professor of Evidence-Based Medicine in the Department of Primary Health Care at the University of Oxford, and part-time general practitioner

Dr Richard Horton
Editor, Lancet Publishing Group

Dr Joseph Pater
Former director of the National Cancer Institute of Canada Clinical Trials Group

Following the success of the international symposiums in Sydney in 1999 and 2002, the CTC again hosted the International Clinical Trials Symposium, in September 2007.

Internationally recognised experts in clinical trials research were invited from Australasia, America and Europe to speak. Presenters and delegates came from 15 countries, representing 185 organisations. A diverse and stimulating program on topical issues was delivered via workshops, plenary sessions, invited presentations, free papers, focus groups and panel sessions. A popular event was the now-traditional symposium debate, where the panellists paraded their erudition and life experience on a knife edge of good taste to offer a new slant on clinical trials.

Representatives from academia, regulatory bodies, the pharmaceutical industry and health care organisations exchanged ideas on the practical aspects of undertaking clinical trials research and translating these trials results into improvements in clinical practice.

Some of the themes for the third symposium had arisen from questions raised in the second symposium. Others were current topics warranting exploration and discussion. Themes were: partnerships among government, industry and academia; frontiers in statistical methods, including adaptive designs; biological and genetic therapies; nonpharmacological technologies; and translating trials research into practice.

At the symposium, the NSW Office for Science and Medical Research announced seed funding for the development of a national curriculum in training in clinical trials management. The first project will be a course for senior clinical researchers to be held by the CTC and other Sydney research groups, in conjunction with Harvard University, early in 2008.

International Clinical Trials Symposium 2007

PRESYMPOSIUM WORKSHOPS

160 people attended the four presymposium workshops organised by the CTC and presented by CTC staff and invited experts.

1: Biomarkers and surrogate evaluation

Topics included real-world experiences in cancer trials, ethical issues to do with tissue banks and international collaborations, biomarkers as surrogates for clinical endpoints and systematic evaluation of surrogacy evidence in cardiovascular disease, HIV medicine and oncology.

2: Updates for clinical trial managers

The workshop covered recruitment and retention strategies from the perspectives of the coordinating centre and the sites, performing well at an audit, interpreting trial results, and resources for phase I trials.

3: Publications: getting your research published

The presenters were dominant figures in publishing and leading researchers, who led discussion on CONSORT guidelines, preparing manuscripts and the practice and interpretation of statistics.

4: Health technology assessment: interpreting trial evidence for policy decisions

Nonpharmaceutical trials and assessments present challenges. This workshop had sessions on conducting trials of surgery and clinical devices, decision analysis and Australian regulatory policies.

SPONSORS

Principal sponsor/partner: Department of Health and Ageing

Partner: National Health and Medical Research Council

Gold sponsor: New South Wales Department of Health

Silver sponsor: Office for Science and Medical Research

Supporting sponsors:
- Association of Regulatory and Clinical Scientists
- GlaxoSmithKline
- Roche

INTERPRETING AND REPORTING CLINICAL TRIALS

The CTC's popular new textbook was published in 2007 and launched at the International Clinical Trials Symposium.

Interpreting and reporting clinical trials: a guide to the CONSORT statement and the principles of randomised controlled trials, edited by Tony Keech, Val Gebski and Rhana Pike, covers the fundamentals of clinical trials. CTC staff predominate among the chapter authors.

The book has been well received by its target readers — clinicians, trial coordinators, students and others — meeting their needs for a readable but comprehensive compilation of up-to-date knowledge.

It explains and expands on the items of the CONSORT statement, the international standard for reporting clinical trials. Its contents include randomisation, blinding, sample size calculation, basic statistical methods, how to deal with subgroups, and the interpretation and generalisability of results, supplemented by checklists and case studies.

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IMPROVING QUALITY OF LIFE AND SURVIVAL IN CANCER

COLLABORATION AND LEADERSHIP IN ONCOLOGY TRIALS

The CTC has long-standing relationships with national cancer cooperative groups and is well represented in clinical trials initiatives in cancer. It has collaborated in over 60 cancer trials recruiting 10 000 patients in breast, oesophageal, gastric, colorectal and gynaecological cancers and melanoma.

In the province of the conduct of trials, the CTC covers the full range of responsibilities — from assisting in establishing new groups by creating a research governance structure and terms of reference, identifying important questions related to public health — through to large-scale trial operations in collaboration with the groups, for example, in concept and protocol development, randomisation, data collection, ethics and regulatory compliance, on-site monitoring and audit, and analyses and manuscript preparation.

As a member of existing international collaborations, the CTC has recently taken the lead as coordinating centre for international trials, for example, the MAX colorectal cancer trial in the United Kingdom, and the HOSTT cervix cancer study in Taiwan.

The CTC expects to continue its strong associations with the existing national cancer cooperative groups as part of a flourishing oncology program.

Kathleen Scott, *head of site management with* Burcu Vachan, *oncology program manager*.

ROLES OF THE CTC IN CANCER COLLABORATIVE GROUPS

NATIONAL CANCER COOPERATIVE GROUPS	CENTRAL OFFICE, INCLUDING TRIAL OPERATIONS	STATISTICAL OFFICE
Australasian Gastro-Intestinal Trials Group (AGITG)	CTC	CTC
Australia New Zealand Gynaecological Oncology Group (ANZGOG)	CTC	CTC
Australian and New Zealand Germ Cell Trials Group (ANZGCTG)	CTC	CTC
Australasian Lung Cancer Trials Group (ALTG)	CTC and Peter MacCallum Cancer Institute	CTC and Peter MacCallum Cancer Institute
Cooperative Trials Group for Neuro-Oncology (COGNO)	CTC	CTC
Australia New Zealand Melanoma Trials Group (ANZMTG)	Sydney Melanoma Unit and CTC	No central statistical centre.
Australian New Zealand Breast Cancer Trials Group (ANZ BCTG)	University of Newcastle	CTC (statistics and randomisation)

INTERNATIONAL CANCER COOPERATIVE GROUPS
National Surgical Adjuvant Breast and Bowel Project (NSABP)
National Cancer Institute of Canada Clinical Trials Group (NCIC CTG)
Gynaecologic Cancer Intergroup (GCIG)
Gynecologic Oncology Group (GOG)
European Organisation for Research and Treatment of Cancer (EORTC)
Oxford Clinical Trials Office (OCTO)
Medical Research Council (MRC)
Eastern Cooperative Oncology Group (ECOG)
European Study Group for Pancreatic Cancer (ESPAC)
Pan-European Trials in Alimentary Tract Cancer (PETACC)
Trans-Tasman Radiation Oncology Group (TROG)

ONCOLOGY SCHOLAR

Peter Grimison is a medical oncologist with a particular interest in the conduct of cancer clinical trials. He is the chair of the Accelerated BEP trial and has assisted the trials of the ANZGCTG.

He is a Cancer Institute NSW Scholar and holds an NHMRC Postgraduate Research Scholarship for PhD study on quality-of-life assessment in clinical trials.

ONCOLOGY EXECUTIVE COMMITTEE

Director of the CTC:
John Simes
Oncology co-director:
Martin Stockler
Clinical trial program director:
Wendy Hague
Oncology program manager:
Burcu Vachan
Head of biostatistics:
Val Gebski
Senior biostatistician:
Patrick FitzGerald
Clinical research fellow:
Corona Gainford

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The Australasian Gastro-Intestinal Trials Group

The CTC is the coordinating centre for the Australasian Gastro-Intestinal Trials Group (AGITG), which has an active network of clinical investigators across Australia and New Zealand. The AGITG has 560 members, mainly from Australia and New Zealand, but also from Canada, Singapore, United Kingdom, Hong Kong, Germany and the United States.

Since it began in 1991, the group has conducted 26 trials and recruited more than 2500 patients to investigator-initiated trials from over 65 sites. While recruitment increased from 356 in 2005 to 488 in 2006, 2007 saw 225 patients recruited to AGITG trials.

During 2007, trial activity remained strong, with a greater proportion of trials in active follow-up after closure and only one new trial opening. Preliminary work by the CTC is underpinning four AGITG-developed trials which will open to recruitment in 2008 and two international intergroup studies.

AGITG TRIALS

Trial	Participants	Interventions	Main outcome measures	Status
CURRENT TRIALS				
Da Vinci: Phase II trial of De Gramont schedule 5-fluorouracil and leucovorin plus irinotecan versus single-agent irinotecan in patients with previously treated metastatic colorectal cancer (AGITG study)	Patients with previously treated metastatic colorectal cancer	• irinotecan + 5-flourouracil + leucovorin • irinotecan	• toxicity • safety • quality of life • survival	Recruitment target: 100 **Recruitment: 88**
EORTC 62024: Gastrointestinal stromal tumours (GIST) expressing KIT receptor: adjuvant imatinib mesylate (Glivec) versus no further therapy after surgery (EORTC study)	Patients with fully resected gastrointestinal stromal tumour	• imatinib • no therapy	• survival • relapse-free survival • relapse-free interval	Recruitment target: 80 **Recruitment: 66**
ESPAC-3: European study of adjuvant chemotherapies in resectable pancreatic cancer (ESPAC study)	Patients with operated cancer of the pancreas	• surgery + 5-fluorouracil + leucovorin • gemcitabine • surgery	• survival • progression-free survival	Recruitment target: 150 **Recruitment: 133**
Quasar 2: Phase III study of capecitabine and bevacizumab as adjuvant treatment of colorectal cancer (OCTO study)	Patients with colon cancer treated by surgery	• capecitabine • capecitabine + bevacizumab	• disease-free survival	Recruitment target: 120 **Recruitment: 48**
TRIALS IN FOLLOW-UP				
ABC: Phase II trial of gemcitabine in fixed dose rate infusion compared with cisplatin in patients with biliary tract carcinoma (AGITG study)	Patients with inoperable biliary tract carcinoma	• gemcitabine • cisplatin	• tumour response • safety	Closed **Recruitment: 50**
ATTAX: Phase II study evaluating a weekly schedule of docetaxel with cisplatin and 5-fluorouracil or capecitabine (AGITG study)	Patients with advanced oesophageal or gastric cancer	• docetaxel, cisplatin, 5-fluorouracil • docetaxel, capecitabine	• tumour response	Closed. **Recruitment: 106**
ATTAX 2: Phase II study of cetuximab plus docetaxel in docetaxel-refractory patients (AGITG study)	Patients with advanced oesophageal or gastric cancer	• cetuximab + docetaxel	• tumour response	Closed. **Recruitment: 38**

Trial	Participants	Interventions	Main outcome measures	Status
CO.17: Phase III study of cetuximab and best supportive care versus best supportive care in patients with pretreated metastatic epidermal-growth-factor-receptor (EGFR-positive colorectal carcinoma) (NCIC CTG–AGITG study)	Patients with pretreated metastatic colorectal cancer with positive EGFR	• cetuximab + supportive care • supportive care	• survival • time to progression • response • quality of life	Closed. Recruitment: 252
Gofurtgo: Phase II study of fixed dose rate gemcitabine–oxaliplatin with 5-fluorouracil and radiotherapy to treat localised pancreatic cancer (AGITG study)	Patients with localised pancreatic cancer	• radiotherapy, gemcitabine and oxaliplatin	• tumour response • safety	Closed. Recruitment: 48
MAX: Phase II–III study to evaluate the role of Mitomycin C [mitomycin], Avastin [bevacizumab] and Xeloda [capecitabine] in patients with untreated metastatic colorectal cancer (AGITG study)	Patients with previously untreated metastatic colorectal cancer	• capecitabine • capecitabine + bevacizumab • capecitabine + bevacizumab + mitomycin	• toxicity • response • progression-free survival • quality of life	Closed. Recruitment: 471
C06: Oral uracil and ftorafur + leucovorin compared with 5-fluorouracil + leucovorin for patients with stages II and III carcinoma of the colon (NSABP study)	Patients with stage II or stage IIII adenocarcinoma, no metastatic disease and a life expectancy of at least 10 years (excluding diagnosis of cancer)	• 5-fluorouracil + leucovorin • UFT (tegafur and uracil) + leucovorin	• disease-free survival • survival • quality of life • prognostic significance of genetic and biological markers	Closed. Recruitment: 11
C07: 5-fluorouracil plus leucovorin compared with oxaliplatin with 5-fluorouracil + for the treatment of patients with stages II and III carcinoma of the colon (NSABP study)	Patients with resected stage II or stage III colon carcinoma	• 5-fluorouracil + leucovorin • 5-fluorouracil + oxaliplatin	• disease-free survival • survival	Closed. Recruitment: 134
EORTC 62005: Phase III study of two different doses of imatinib mesylate in patients with CD117-expressing metastatic or unresectable gastrointestinal stromal tumour (EORTC study)	Patients with metastatic gastrointestinal stromal tumour	• imatinib twice daily • imatinib once daily	• progression-free survival • survival • tumour response	Closed. Recruitment: 116
EORTC 40983: Phase III preoperative and postoperative chemotherapy with oxaliplatin + 5-fluorouracil + leucovorin versus surgery alone in resectable liver metastases of colorectal origin (EORTC Study)	Colon cancer with liver metastases	• 5-fluorouracil + leucovorin + oxaliplatin • surgery	• progression-free survival • survival	Closed. Recruitment: 35

NOTABLE ACHIEVEMENTS

MAX: The MAX study completed recruitment in June 2007 (p. 11).

Quasar 2: Quasar 2 is run internationally by the Oncology Clinical Trials Office (OCTO) at Oxford University, and opened in Australia and New Zealand in June 2007. In addition to the 35 sites in Australia and New Zealand, two sites in Hong Kong will join this study.

CO.17: The results were published in the *New England Journal of Medicine* in 2007 (p. 11).

ABC: The results were presented in 2007.

ATTAX and ATTAX 2: Results were presented at the American Society of Clinical Oncology meeting in 2006. The follow-on study, ATTAX2, reached full recruitment in 2007.

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Julie Martyn
ANZGOG associate program manager

Australia New Zealand Gynaecological Oncology Group

The Australia New Zealand Gynaecological Oncology Group (ANZGOG) was established in 2002 to improve gynaecological cancer treatment and outcomes through a cooperative approach. ANZGOG conducts its own clinical trials and participates in international collaborative trials. Australia and New Zealand have more than 30 trial sites. All the group's trials are coordinated from the CTC.

The final results from ANZGOG 0201, the first locally developed ANZGOG study, were published in *Gynecological Oncology* in 2007.

TRIPOD, a second ANZGOG phase 2 trial, opened to recruitment in 2007. TRIPOD looks at the feasibility of intraperitoneal delivery of chemotherapy for ovarian cancer. The New South Wales Cancer Council funds the central coordination costs and site payments.

Two international collaborative-group trials closed to recruitment in 2007, Calypso in September and EORTC Tarceva in December. The CTC is the international statistical centre for Calypso, and the analysis of toxicity data from the first 200 patients was presented at the European Society of Gynaecological Oncology meeting in October 2007.

Two Gynaecological Cancer Intergroup (GCIG) collaborative group trials will open in 2008. Symptom Benefit was developed by ANZGOG and endorsed by the international group. PORTEC-3 (Postoperative Radiation Therapy for Endometrial Carcinoma), also has a patient preferences substudy which was developed by ANZGOG.

TRIPOD HAS TWO INTERESTING SUBSTUDIES:

1. investigation of the biodistribution of chemotherapy drugs in the abdominal cavity

2. evaluation of patients' preferences for receiving chemotherapy via the intraperitoneal route instead of the standard intravenous infusion.

Keeping up the quality of cancer trials

The AGITG and ANZGOG audit program began in May 2006, made possible by infrastructure funding from the Cancer Institute (p. 6). Trials are audited internally at the CTC and externally at the clinical sites. This program is on target and progressing well. Site staff have appreciated a review of their trial conduct and compliance with regulatory requirements and almost all audits have had a satisfactory outcome.

The goal of the audit program, continuous improvement, is being achieved through:

- identification of site difficulties and reporting of such to the CTC, alerting trial staff to gaps in knowledge as well as management or process difficulties at trial sites
- on-site incidental training and recommendations during audit
- inclusion of a site's preventive actions in the responses to audit findings, with reporting of such
- workshops on preparation for audit at meetings of the trial collaborative groups.

Karen Pinto
AGITG–ANZGOG auditor

ANZGOG TRIALS

Trial	Participants	Interventions	Main outcome measures	Status
CURRENT TRIALS				
TRIPOD: Phase II trial of intraperitoneal chemotherapy	Women with ovarian and related cancers	• paclitaxel + cisplatin injected into the abdominal cavity	• feasibility • safety • quality of life	Recruitment target: 35–100 **Recruitment: 5**
ICON 7: Randomised, two-arm, multicentre GCIG trial of adding bevacizumab to standard chemotherapy in patients with epithelial ovarian cancer	Women with epithelial ovarian cancer who have not received systemic anti-tumour therapy	• bevacizumab + standard carboplatin and paclitaxel • standard carboplatin and paclitaxel	• progression-free survival	Recruitment target: 90 **Recruitment: 5**
SCOTROC 4: Multicentre randomised trial of carboplatin flat dosing vs intrapatient dose escalation in first-line chemotherapy	Women with ovarian, fallopian tube or peritoneal carcinoma who are unsuitable for platinum–taxane therapy	• 6 cycles carboplatin, fixed dose • 6 cycles carboplatin, with changes to dose depending on neutrophil count	• progression-free survival	Recruitment target: 150 **Recruitment: 41**
HOSTT: Phase II study to evaluate maintaining haemoglobin levels above 120 g/L vs over 100 g/L (ANZGOG 0401)	Women with untreated cancer of the cervix receiving cisplatin and radiation therapy	• red cell transfusion	• feasibility of treatment • safety • quality of life	Recruitment: 6 patients of 100 for the pilot stage of the trial.
TRIALS IN FOLLOW-UP				
Tarceva: Phase III study of erlotinib versus observation (EORTC 55041)	Women with high-risk stage I or stages II–IV ovarian cancer which has not progressed after platinum chemotherapy	• maintenance erlotinib • standard care (observation alone)	• progression-free survival	Closed **Recruitment: 42**
Calypso: Caelyx in platinum-sensitive ovarian cancer patients	Women whose disease has progressed after treatment	• pegylated liposomal doxorubicin + carboplatin • paclitaxel + carboplatin	• progression-free survival	Closed **Recruitment: 71**
GOG 182: Phase III randomised trial of paclitaxel + carboplatin versus triplet or sequential doublet combinations in patients with epithelial ovarian or primary peritoneal carcinoma (GOG 182)	Women with advanced (stage III or IV) primary ovarian or peritoneal cancer	• gemcitabine or topotecan with carboplatin (doublet therapy) • carboplatin + paclitaxel (triplet therapy)	• survival • progression-free survival	Closed **Recruitment: 183**
Prospective study of risk-reducing salpingo-oophorectomy and longitudinal CA-125 screening among women at increased genetic risk of ovarian cancer (GOG 199)	Women aged >30 at risk of ovarian cancer	• choice of preventive surgery • screening	• incidence of ovarian cancer • prevalence of clinically occult ovarian cancer • predictive value of ROCA algorithm • quality of life	Closed **Recruitment: 83**
Phase II trial of weekly docetaxel for patients with relapsed ovarian cancer (ANZGOG 0201)	Women whose disease progressed after treatment	• docetaxel	• toxicity • time to progression • survival	Closed **Recruitment: 37**

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Xanthi Coskinas
Oncology associate program manager

PATIENT PREFERENCES STUDIES

Patient preferences studies are an important way of identifying the degree of benefit patients expect to accept therapy for their cancer (p. 41). These studies have not been done for lung cancer patients. The ALTG and the CTC are starting to examine these issues.

Australasian Lung Cancer Trials Group

The Australasian Lung Cancer Trials Group (ALTG) was formed in 2004 to support investigator-initiated lung cancer trials. The ALTG comprises about 100 members from various backgrounds and is working with the CTC as its central coordinating centre.

The CTC and representatives of committees of the ALTG form an operational executive, which is responsible for leading the group in developing and managing new trial concepts, sought from the ALTG membership and industry. The operational executive then assists clinical investigators to develop these ideas from concepts to working protocols. The collaboration has five studies in various stages of development.

International collaborations have been established with the National Cancer Institute of Canada Clinical Trials Group and the Dutch Association of Physicians for Pulmonary Diseases and Tuberculosis group.

TRIALS

MATES: Thalidomide treatment may improve survival and quality of life in people with mesothelioma that has stabilised or improved after permetrexed chemotherapy. The Maintenance Thalidomide in Mesothelioma Quality of Life and Prognostic Marker Study (MATES), a Dutch trial, is investigating thalidomide as a maintenance treatment. The recruitment target in Australia is 100 patients of the total of 216 worldwide. The Australian group has added two substudies examining quality of life and predictive biomarkers.

NITRO: Protocol development activities, including feasibility assessment, have started for an ALTG trial examining whether adding nitroglycerin patches to chemotherapy will improve survival and quality of life. This trial, Nitroglycerin Patches for Non-Small-Cell Lung Cancer (NITRO), will be the ALTG's first home-grown trial.

Cooperative Trials Group for Neuro-Oncology (COGNO)

The newly formed Cooperative Trials Group for Neuro-Oncology (COGNO) is coordinated from the CTC. COGNO plans to take part in and initiate trials to evaluate new therapies and interventions to prevent and mitigate disease. Michelle Cummins is the oncology associate program manager for COGNO trials, with support from Kathleen Scott.

OBJECTIVES OF COGNO

- To encourage members of the medical and scientific community, through participation, to assist in the conduct, evaluation, promotion and development of clinical trials in brain tumours
- To promote the use of clinical trials evaluating current therapies and new treatments for brain tumours and to improve the impact of new clinical trials on future clinical practice
- To promote the incorporation of translational studies into new clinical trials in brain tumours.
- To freely publish the results of research and clinical trials and to make available for general use, on the same terms to all interested bodies, licences for Australian and New Zealand patents issued in the course of research and clinical trials

The Australian New Zealand Breast Cancer Trials Group

The CTC is randomisation and statistical centre for the Australian New Zealand Breast Cancer Trials Group (ANZ BCTG).

The group's breast cancer trials are coordinated at the operations office at the University of Newcastle. The CTC registers and randomises the trials and also undertakes statistical and other analyses of trial data.

Australian and New Zealand Germ Cell Trials Group

The Australian and New Zealand Germ Cell Trials Group (ANZGCTG), an established network of over 100 clinicians and researchers, is the only national organisation dedicated to high-quality clinical research for people affected by germ cell cancers. The coordinating centre for the group is at the CTC.

Amy Boland
ANZGCTG trial coordinator

In 2006, the group secured funds for infrastructure from the federal government's Strengthening Cancer Care Initiative, which is now managed by Cancer Australia. This funding has been instrumental in the group's recent expansion, including a concept development meeting in July 2006. Promising new research proposals were discussed, including a phase II study of a seven-day aprepitant schedule to prevent nausea and vomiting in patients receiving chemotherapy for metastatic germ cell tumours.

The Chemo & Cognition study opened in 2007 at four Australian sites, with funding support from the Cancer Council. The objective of this longitudinal observational study is investigation of cognitive impairment in men with testicular cancer. The study has been designed to minimise the methodological problems of previous studies.

ANZGCTG TRIALS

Trial	Participants	Interventions	Main outcome measures	Status
Accelerated BEP: feasibility study of accelerated BEP as first-line chemotherapy for advanced germ cell tumours An intergroup collaboration between ANZGCTG and ANZGOG	Patients with intermediate and poor-risk advanced germ cell tumours (and selected good-risk tumours).	Bleomycin, etoposide, cisplatin, pegfilgastrim	• feasibility • safety • efficacy • lung function • neurotoxicity	Recruitment target: 25 **Open to recruitment**
Chemo & cognition: cognitive function and treatment for testicular cancer	Patients being treated and followed up for testicular cancer	Non-interventional study	• cognitive function	Recruitment target: 154 **Open to recruitment**

5

A BETTER FUTURE FOR NEWBORNS

INIS: preventing the damaging effects of neonatal infection

Newborn infants, particularly those born prematurely, have an immature immune system and so are at risk of infection. Infection can cause inflammation in major organs, resulting in death or permanent disability. Each year, of over 2500 babies in Australia and New Zealand who develop serious infection, about 250 die and another 375 survive with lifelong disability.

The International Neonatal Immunotherapy Study (INIS) is a major international, double-blind, placebo-controlled randomised trial of polyclonal immunoglobulin (IVIG) added to antibiotic therapy for newborn infants with serious infection.

In the INIS trial, infants with low birthweight and suspected serious infection have received infusions of IVIG (Intragam P) or saline. The main outcome being measured is survival without major disability at 2 years, corrected for gestational age.

The trial has 24 centres in Australia and New Zealand actively participating. INIS finished recruitment in May 2007. The Australian and New Zealand cohort of 1398 babies was 40% of the global recruitment total of 3493 babies. As recruitment has finished, the focus of trial operation is on gathering follow-up data to assess the children's development status. Of the babies in the trial, 895 have reached the two-year mark (92% of these have already been followed up) and 1202 have reached one year.

Lucille Sebastian, *INIS manager*

FUNDING FOR INIS

United Kingdom Medical Research Council,
Sydney University Sesqui grant,
Telstra Foundation,
Ian Potter travel grant,
National Health and Medical Research Council,
Financial Markets Foundation for Children,
New Zealand Health Research Council.

BOOST II: Oxygen therapy for premature babies

Each year, over 600 infants born at less than 28 weeks gestation are discharged from hospitals in Australia. Although they have a fairly normal life expectancy, they are at risk of disease and disability, such as chronic lung disease, poor growth, visual deficits, cerebral palsy, sensory disabilities and cognitive impairment.

Oxygen is has long been a common therapy. But uncertainty about the best level of oxygenation for extremely preterm infants has existed for over 50 years. Levels of oxygen in a lower range may increase rates of heart abnormalities and lung disease, and impair brain development; levels in a higher range may increase blindness and lung disease, and impair brain development.

The CTC's BOOST II trial (Benefits of Oxygen Saturation Targeting) is one of several large trials around the world aiming to ascertain which of two currently used ranges of oxygen saturation is better for very premature babies. Infants are randomised to one of two target oxygen saturations, and receive oxygen therapy for several weeks, until 36 weeks corrected gestation, when they can breathe air.

The trial is in the recruitment phase. Recruitment has been steady and is expected to reach its target by 2009.

Participants:
Neonates born before 28 weeks gestation

Intervention:
- supplementary oxygen to 85–89% saturation
- supplementary oxygen to 91–95% saturation

Outcome measures:
- death or survival with major disability at 2 years
- retinopathy of prematurity
- chronic lung disease

Recruitment target: 1200
Recruitment: 397
Funding: NHMRC

META-ANALYSIS OF NEONATAL TRIALS

The first prospective meta-analysis in neonatology is the international Neonatal Oxygenation Prospective Meta-analysis (NeOProM) (p. 30).

BOOST II is one of five trials evaluating the best level of oxygenation for extremely preterm infants. The group expects to have final data from about 5200 infants by 2013.

Alpana Ghadge
BOOST II manager

6

REDUCING CARDIOVASCULAR DISEASE MORTALITY

The international FIELD trial: aiming to reduce complications of diabetes

The CTCs FIELD (Fenofibrate Intervention and Event Lowering in Diabetes) trial, with 9795 patients in Australia, New Zealand and Finland, aimed to prevent cardiovascular events in patients with diabetes by using fenofibrate to modify blood lipids.

Since publication of the main findings in *The Lancet* in 2005, the FIELD team has been working on research and further publications investigating different subsets of the FIELD cohort — as was planned in the trial protocol. FIELD also continues with long-term follow-up of all surviving patients.

In 2007, the FIELD investigators reported, in a *Lancet* paper, that treatment with fenofibrate reduces the need for laser therapy for diabetic eye disease (see research highlights, p. 10).

A substudy of patients from the FIELD Helsinki cohort showed that fenofibrate changes the distribution of cholesterol particles in the blood. It did not affect the level of high-density lipoprotein (HDL) cholesterol; however, it reduced the proportion of larger particles (HDL3) and increased the proportion of small, dense HDL particles. Fenofibrate also reduced the level of very low-density lipoprotein (VLDL) cholesterol particles all of which should favourably affect the risk of cardiovascular events.

A meeting between the management committee members and Australian principal investigators in December 2007, sponsored by Solvay and hosted by the CTC, brought forth new ideas and avenues for further research.

FIELD staff: Anthony Keech (FIELD study chair), Dana Tse, Mark Donoghoe, Diana Zannino, Merryn Voysey, Rachel O'Connell

The LIPID team: Helen Pater (project manager), Wendy Hague (manager of LIPID in the 1990s and now director of the CTC's clinical trials program), Adrienne Kirby and Liz Barnes (LIPID statisticians)

LIPID cholesterol lowering trial: 15 years on

The Long-Term Intervention with Pravastatin in Ischaemic Disease (LIPID) trial was the CTC's first large, long-term multicentre trial. After the end of the trial in 1997, about 85% of patients continued on lipid-lowering therapy.

Patients are still being followed up by letter and telephone, and other data come from searches of registers of morbidity, mortality and cancer. Now, after over 15 years of follow-up of these patients, the information is being used to assess the long-term safety and cost-effectiveness of pravastatin treatment.

The size and longevity of the LIPID study data set provide a rich source for research on the effects of lipid-lowering treatment and the relationships between patients' characteristics, their risks and their subsequent cardiovascular events. During 2006, the results of an assessment of the long-term safety of pravastatin treatment, especially with regard to the incidence of new cancers, were presented. Also, a study describing the cost-effectiveness of pravastatin use by elderly patients was published.

GENOMIC STUDIES

The LIPID trial continues to provide new data for study. Blood samples collected over the first six years of the trial are now being analysed in relation to biomarkers and risk factors for cardiovascular disease (p. 42). As these are biological as well as clinical investigations, they are being conducted in collaboration with new partners from various parts of Australia and the rest of the world — currently Germany, Sweden and the United States.

PRAVASTATIN AND COENZYME Q10

The mechanism of action of pravastatin and its relation with coenzyme Q10 was explored in a prospectively planned study of blood plasma samples from patients who subsequently died from cardiovascular disease or had a myocardial infarction or stroke. This substudy was published in 2006.

6

PREDICT SUBSTUDY

PREDICT is a substudy of the ASPIRE trial, its purpose a simple clinical prediction model for a patient's risk of recurrent VTE. The model uses a combination of patient characteristics with an estimate of residual thrombosis from the earlier episode measured by compression ultrasound and D-dimer (a test for detecting fragments of blood clot in the blood). Patients found to be at low risk of VTE may then be able to avoid warfarin treatment and its side-effect — bleeding.

As part of ASPIRE, PREDICT is much more efficient and cost-effective than it would be as a stand-alone study.

PREDICT is supported by a grant from the Australasian Society of Thrombosis and Haemostasis and the National Heart Foundation.

Sarah Chinchen, trial monitor, and Rebecca Mister, manager of ASPIRE

Using aspirin to prevent recurrent venous thrombosis: the ASPIRE trial and the INSPIRE meta-analysis

The aim of ASPIRE is to determine whether aspirin is better than placebo in preventing recurrent venous thromboembolism (VTE) in patients who have been treated for an earlier VTE with warfarin for at least 6 months. The trial is to recruit 2000 patients from Australia, New Zealand, Singapore, India and European countries.

The first patient was enrolled in 2003, and the main phase of the study began in January 2005. To date, 39 centres in Australia, New Zealand and Singapore are taking part. Because of changes in the clinical management of venous thrombosis in Australia, recruitment has been less than planned. This has been managed by a modification to the calculations in the study design — facilitated by good compliance by current patients — and expansion of the trial to new international sites for an increase in recruitment.

Participants
People who have had a first episode of unprovoked proximal deep-vein thrombosis or pulmonary embolism and completed anticoagulant treatment.

Study drug: low-dose acetylsalicylic acid (aspirin)

Main outcome measures
- venous thromboembolism or fatal pulmonary embolism
- vascular events (cardiovascular death, symptomatic venous thromboembolism, myocardial infarction or stroke)
- net clinical benefit (death, major vascular event or major bleeding)

Recruitment target: 2000
Recruitment: 478 from Australia, New Zealand and Singapore

Funding: NHMRC, Bayer, Australasian Society of Thrombosis and Haemostasis, New Zealand Health Research Council

National coordinating centres have been set up in the United Kingdom and India. Preparation Agreements, ethical and regulatory submissions and feasibility surveys commenced in 2007 in preparation for recruiting 350 patients per year at, ultimately, 20 sites in the UK (coordinated at Queen Mary University in London) and 10 sites in India (coordinated at St John's Medical College and Research Institute in Bangalore).

European patients have been included through collaboration with the Italian investigators of the WARFASA study, who have recruited over 300 patients from 38 sites, bringing the total recruitment to almost 800 patients. The ASPIRE and WARFASA investigators have agreed to combine their data in a prospective meta-analysis, INSPIRE.

VIGOUR collaboration

VIGOUR (the Virtual Coordinating Center for Global Collaborative Cardiovascular Research) is an international alliance of investigators from academic institutions undertaking clinical trials on treatments of patients having acute cardiovascular events, such as myocardial infarction and stroke.

As part of the VIGOUR collaboration, the CTC is able to take part in large trials which are beyond the capacity of Australian investigators alone. Professor John Simes is a VIGOUR leader.

The CTC is the global statistical centre for VIGOUR's international HERO-2 trial.Statistical analyses for the HERO-2 trial.

Rachel O'Connell
Biostatistician for HERO-2 studies

MEMBERS OF VIGOUR

- NHMRC Clinical Trials Centre, University of Sydney, Australia
- Duke Clinical Research Institute, Duke University, North Carolina, USA
- Cleveland Clinic Foundation, Cleveland, Ohio, USA
- Duke Clinical Research Institute of Pharmacy, Duke University, North Carolina, USA
- Green Lane Coordinating Centre, Green Lane, Auckland, New Zealand
- Flinders Coordinating Centre, Adelaide, South Australia
- Flinders Clinical Trial Pharmacy, Adelaide, South Australia
- Leuven Coordinating Centre, University Hospital, Gasthuisberg, Leuven, Belgium
- Canadian Coordinating Centre, University of Alberta, Alberta, Canada
- Latin American Coordinating Centre, Rosaria, Argentina

STATISTICAL ANALYSES FOR THE HERO-2 TRIAL

The HERO-2 trial (Hirulog and Early Reperfusion or Occlusion) compared two antithrombosis treatments for acute myocardial infarction in 17 073 patients in 46 countries. The large data set continues to be the source of new findings from the analyses at the CTC.

A study published in 2007 examined the survival of patients who suffered a reinfarction after admission to hospital for a first infarction. Patients who had a reinfarction had 2.4 times the mortality rate of patients who did not. The detailed statistical analysis showed that various factors were related to higher mortality, including lack of reperfusion therapy for the second infarction. Treatment by drug therapy or percutaneous coronary intervention was shown to have been under utilised, particularly in non-Western countries.

7

COMBINING TRIALS FOR OPTIMAL EVIDENCE

USING THE POWER OF MULTIPLE TRIALS IN META-ANALYSIS

Combining the results of individual trials in a meta-analysis is a well-established method of clarifying the effects of a treatment. But reanalysis of the raw data from individual patients in all the trials is better: it maximises the use of the data, improving its quality, and increasing the range and power of the analyses. Such projects require cooperation and collaboration among trial groups as well as the resources to extract and analyse the data and to coordinate the group.

Even more powerful is prospective meta-analysis, in which the hypotheses and analyses for the combined data are planned before any trial results are available. The investigators agree to pool their future data. Ideally, these decisions are made early, during the conception and design stage of the trials. Prospective meta-analysis is considered the 'gold standard' systematic review method. It provides the same strengths as a single large-scale randomised trial, but can be easier to put into practice.

The CTC is a member of several international meta-analysis groups and is a leader in prospective meta-analysis methodology. During the past two years, preparatory work for several new studies — especially in neonatal and perinatal medicine — has been undertaken by the CTC and its international collaborations.

Perinatal meta-analyses

APPROPRIATE LEVELS OF OXYGEN SATURATION FOR EXTREMELY PRETERM INFANTS

The Neonatal Oxygenation Prospective Meta-analysis (NeOProM) Collaboration has been formed to undertake a prospective meta-analysis of data from about 5200 patients in five trials to answer the important clinical question of the best level of oxygenation for extremely preterm infants. This will be the first prospective meta-analysis in neonatology.

A collaborative group was formed in 2003 and the first participating trial, the CTC's BOOST II, (p. 25), started enrolling patients in 2005. The protocol for the meta-analysis currently being finalised. Results should be available in 2013.

ANTIPLATELETS FOR PREVENTION OF PRE-ECLAMPSIA AND ITS CONSEQUENCES

There has been good evidence from clinical trials and meta-analysis that antiplatelet agents (principally low-dose aspirin) prevent pre-eclampsia, a leading cause of morbidity and mortality in pregnant women and their babies. Uncertainty remains about whether some women benefit more than others, what dose of aspirin is best and when in pregnancy treatment should start. Rather than undertaking new trials, the best way to answer these questions is to utilise existing data from each trial.

In the first individual-patient-data review in the perinatal field, data from 38 000 women were collected from 38 eligible trials by the PARIS (Perinatal Antiplatelet Review of International Studies) Collaboration. The study showed that therapy with antiplatelet agents is safe, and reduces (by about 10%) the relative risk of pre-eclampsia, preterm birth, and serious adverse outcomes of pregnancy. No subgroups were identified as benefiting more or less from the treatment. Especially for populations with a high risk of pre-eclampsia, the more widespread use of antiplatelet agents would be worthwhile.

The results were published in *The Lancet* in 2007. Analysis of the dataset at the CTC is continuing.

BENEFITS AND RISKS OF ELECTIVE HIGH-FREQUENCY VENTILATION VERSUS CONVENTIONAL VENTILATION IN PRETERM INFANTS WITH RESPIRATORY DISTRESS SYNDROME

After 18 trials enrolling more than 3500 infants with respiratory distress, the effect of high-frequency ventilation is still uncertain. An analysis of data from these trials by the international Prevention of Ventilation-Induced Lung Injury Collaborative Group (PreVILIG) will take into account the risk profiles of the infants and identify the characteristics of the infants most likely to benefit from the treatment.

INHALED NITRIC OXIDE FOR PRETERM INFANTS

Premature infants requiring assisted ventilation are at risk of injury to their lungs and brains. Inhaled nitric oxide may help, but the results of trials so far have been contradictory. Some studies have shown a reduction in lung injury, one has shown a reduction in brain injury, and several others have shown no effect. The different patient characteristics and different trial characteristics may explain this difference. Collection and reanalysis of data from about 2500 individual patients in the nine trials will commence in 2008, in a collaboration with neonatologists in the US and Canada.

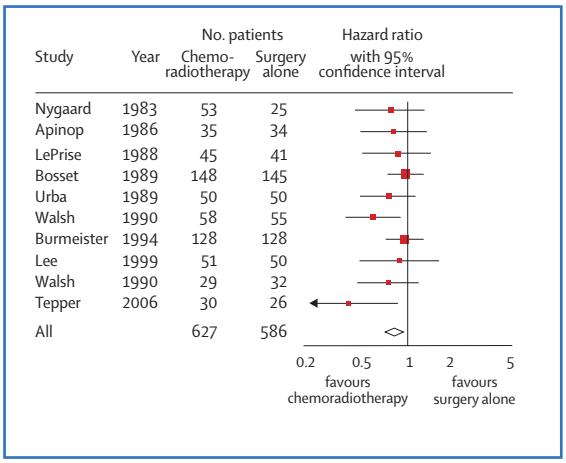
Dr Lisa Askie is a world leader in individual-patient-data meta-analysis in perinatology. She is the project coordinator of the PARIS Collaboration, project coordinator and co-chair of the NeOProM Steering Group, and a member of the MAPPiNO and PreVILIG steering groups.

Definitive evidence from meta-analyses of data from cancer trials

Meta-analyses of data from published cancer trials have provided new evidence to guide treatment.

OESOPHAGEAL CANCER

Patients with oesophageal cancer are usually treated with surgery, but outcomes can be poor. Chemotherapy or chemoradiotherapy may be given before surgery but whether this is beneficial has not been clear because trials have been small and have not had adequate statistical power.



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Despite eight previous published meta-analyses, this research addressed survival benefits in a new way by incorporating all the information available from the studies and by examining clinical subgroups. Analysis of results from 17 trials showed a clear benefit of chemoradiotherapy, but a less certain benefit in adenocarcinoma than in squamous cell carcinoma.

These results were published in *The Lancet Oncology* in 2007.

BREAST CANCER

A review of randomised trials examined the benefits of postmastectomy radiation therapy. The method involved incorporating the quality of the individual trials in the meta-analysis to obtain estimates of benefit which reflect clinical practice more closely (Research highlights, p. 12).

John Simes
Co-chair of the international PCAT Collaboration

Cardiovascular disease

PRIMARY CORONARY ANGIOPLASTY VERSUS THROMBOLYSIS: THE PCAT COLLABORATION

For patients who have arrived at a hospital shortly after a myocardial infarction caused by a blocked coronary artery, the most effective treatment is mechanical opening of the artery by an operation involving a balloon or stent. However, it takes time to arrange for the procedure and prepare the patient, in addition to any delay in the patient reaching hospital. Restoring the blood flow with drugs is less likely to be successful, but can be done more quickly.

In an international study, the investigators pooled and reanalysed data from 6763 patients in 22 trials comparing primary percutaneous coronary intervention with fibrinolytic drug therapy, taking into account the delays between the onset of symptoms and treatment. The outcome measured was mortality after 30 days.

Mortality was lower in those who had the mechanical procedure even if the treatment was delayed. However, its advantage was greater for patients who were slow to present to hospital, and lesser with a longer delay between reaching hospital and having the procedure. Although the study showed that percutaneous coronary intervention results in lower mortality, in the real world, where timely intervention may not be available, drug therapy is still a viable treatment strategy.

The results underlined the importance of early hospital treatment for all patients who have had a myocardial infarction. The study was also an example of using published data and precise analysis techniques to arrive at new authoritative evidence.

LONG-TERM CHOLESTEROL LOWERING WITH STATINS

The Cholesterol Treatment Trialists' Collaboration (CTTC) was first formed in 1990, before the results of various large international trials showed that cholesterol-lowering therapy with statins reduced the risk of death from coronary heart disease. The purpose of the collaboration is prospective meta-analysis of data from 14 constituent clinical trials involving over 90 000 patients. The protocol for its studies was published in 1995, and the first analysis of results appeared in 2005.

In 2007, the collaboration presented the results of the subgroup analyses of data from 18 686 patients with diabetes in these trials. Statin therapy reduced the risk of vascular events consistently in all the studied subgroups of patients with diabetes, even in patients with type 1 diabetes and those who had not previously had any cardiovascular disease.

IMPROVING THE ANALYSIS AND CONDUCT OF CLINICAL TRIALS

Biostatistics is fundamental to clinical trials research

BIOSTATISTICS

METHODOLOGICAL RESEARCH PROJECTS

CLINICAL TRIALS

As new concepts are proposed by trial groups, biostatisticians at the CTC develop trial designs most likely to answer the questions presented. The collaborative trial groups include national experts trialling new therapies in gastrointestinal cancer (colorectal, stomach and oesophagus), breast cancer, gynaecological cancer (cervix, ovarian), neonatal disorders, diabetes, cardiovascular disease and thrombosis. The statistical designs include single-arm and randomised phase II designs and randomised phase III designs.

Biostatisticians monitor ongoing trials (including triggers for interim analyses, such as the activity of the investigational regimen and the rate of severe toxicity), develop statistical analysis plans and prepare and interpret statistical reports for independent data safety and monitoring committees. They also contribute to and oversee the science for presentations at national and international conferences. Presentations include reports on the effect of sentinel-lymph-node biopsy on lymphodoema rates in breast cancer (SNAC, p. 13), toxicity and benefits of chemotherapy treatments in colorectal (p. 11) and biliary tract cancers (p. 18), and fenofibrate in patients with diabetes mellitus (p.26).

RANDOMISATION

Methods of randomisation are continually evolving. The biostatistics group designs randomisation schemes, such as permuted blocks, minimisation and dynamic balancing, provides unblinding services for double-blind studies and monitors the balance of allocations between treatments. Randomisation schemes are implemented via the internet or via telephone calls in an interactive voice response system (IVRS). For some studies, there is also an element of randomisation 'shadowing', in which allocations provided electronically are validated manually.

EDUCATION

The CTC is intimately involved in the Biostatistical Collaboration of Australia (p.9). Additionally, CTC biostatisticians coordinate the unit 'Controlled trials' offered in the Master of Clinical Epidemiology and Master of Public Health programs at the University of Sydney. A two-day course in clinical trials methods and interpretation, for potential clinical and research investigators and triallists, is regularly run by the CTC. Ongoing units in the Basic Sciences in Oncology course teach critical appraisal to medical specialist trainees. Senior CTC biostatisticians supervise students doing projects as part of the Master of Biostatics degree or other higher degrees (MSc or PhD).

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Adrienne Kirby,
senior biostatistician

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Some methodological research projects

RISK FACTOR DEVELOPMENT AND VALIDATION

The data from the international studies HERO-2, with 17 073 patients (p. 29), and FIELD, with 9795 patients (p. 26), has been used to compare different methods of updating risk models for their suitability and applicability in countries with vastly different cultures and health care systems. This work has been led by Rachel O'Connell and Malcolm Hudson in a team that includes PhD students.

Related methodological projects include the evaluation of biomarkers as predictors of outcome. This includes evaluating the strength of biomarkers as potential surrogates in relation to outcomes, as well as the interaction between potential surrogates and treatment

SAMPLE SIZE FOR TRIALS WITH ALTERNATIVE OUTCOMES

Calculating the number of patients needed for a clinical trial and the power of a proposed analysis is part of the work of biostatisticians. When more than one outcome is of prime importance, the computations become complex. CTC biostatisticians have developed solutions which can accommodate different adjusted critical significance levels (α) for multiple outcomes while maintaining a fixed overall level of significance. An advantage of this new method is that the power of detecting a difference of a given size is maintained.

In trials with two or three alternative outcomes which are not highly correlated with each other (< 0.8), a simple Bonferroni adjustment is conservative and is closer to the exact solution than other ad hoc approximations currently in use.

These new looks at old problems were presented at the *International Clinical Trials Symposium*.

ANALYSIS OF TIME SERIES DATA

Automated logging devices can collect real-time data from patients, which leads to a large number of data points over time for each patient. Other more traditional methods, such as daily diaries, also give rise to time series of measurements. Analysis of multivariate non-stationary time series poses a real challenge to statisticians. An account of some of the issues involved has been published in the *Australian and New Zealand Journal of Statistics* in an article illustrating the concepts with associations between daily changing pollen counts and eye and nasal symptoms, together with the effect of having asthma.

Short time series of measurements within subjects often arise in the context of clinical trials. Linear mixed-effects models can be used to quantify treatment effects in such situations. This approach was used to investigate changes in bone mineral density in patients treated with placebo or zoledronic acid to prevent bone loss after liver transplantation, recently published in the *Annals of Internal Medicine*.

MIXED LINEAR MODELS: ROBUST ALTERNATIVES TO THE *F* TEST

Mixed linear models are popular and used to analyse data in many fields. The models are usually fitted by maximum-likelihood techniques that rely on the data distribution being normal. The estimates of the parameters and the related tests are very sensitive to the assumption of normality. This sensitivity can lead to incorrect conclusions. In this study, published in *Biometrics*, biostatisticians developed two robust methods to overcome this problem by computing an alternative to the *F* test. The first method is a likelihood-based approach and the second is an extension of the Wald statistic. Both have been tested by simulation and both are suitable for balanced study designs.

AN EVIDENCE BASE FOR DECISION MAKING AND POLICY

Assessment of new technologies, diagnostic tests and procedures

The CTC has a contract to review new and existing health technologies, diagnostic tests and procedures for the Australian Government's Medical Services Advisory Committee (MSAC).

The government's intention is that evidence of safety, effectiveness and cost-effectiveness, obtained through systematic reviews and health-economic analyses, should underpin public funding of medical procedures. Each report is based on a systematic review of the scientific literature and other information sources, including clinical expertise. The reports are published on the MSAC's website.

BREAST MAGNETIC RESONANCE IMAGING

Breast magnetic resonance imaging (MRI) can be used in screening for and diagnosis of breast cancer.

The addition of breast MRI to mammography improves the detection of breast cancer — but also the rate of false detections of cancer — in young women at high risk due to genetic predisposition or family history. It is still not known whether the earlier detection of breast cancer in this patient group improves their outcomes. Interim public funding for breast MRI was recommended for the diagnosis of breast cancer in women at high risk, when it is used as part of an organised surveillance program.

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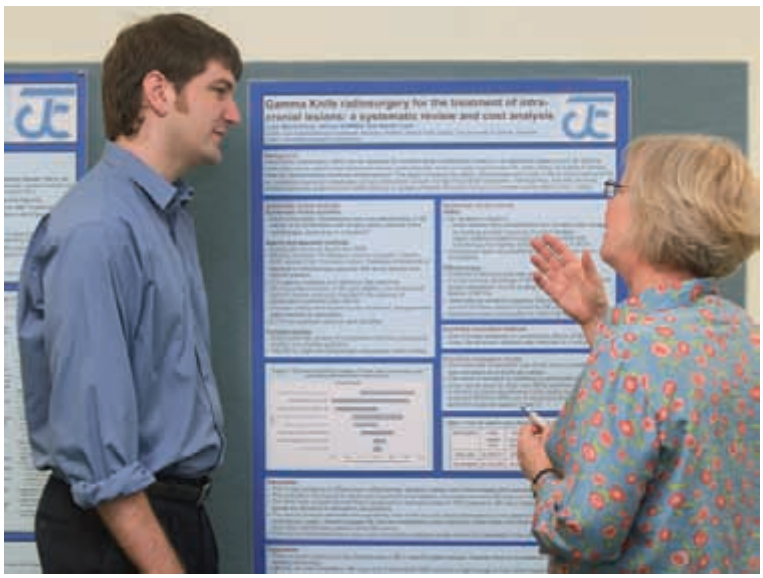

The Gamma Knife review was presented as a poster at the International Clinical Trials Symposium

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Sally Lord

Suzanne Dyer

EVIDENCE-BASED DECISIONS ABOUT USING NEW TESTS

The clinical value of a new test depends on whether it improves patient outcomes. Cases of disease detected by new tests are rarely evaluated by clinical trials, so decisions about their use often rely on studies of test accuracy. But is this enough?

In their publication, 'When is measuring sensitivity and specificity sufficient to evaluate a diagnostic test, and when do we need randomised trials?' Sally Lord and her co-authors explain the assumptions required if evidence about test accuracy is to be used to plan treatment. They describe a useful framework for deciding when this evidence will suffice.

NATIONALLY FUNDED CENTRES

The CTC, through its contract with MSAC, provided the Australian Government with reviews of evidence for nationally funded centres, which provide Australians with equitable access to rare, costly medical technologies or procedures.

Peritonectomy

Peritonectomy is treatment for peritoneal tumours (pseudomyxoma peritonei and peritoneal mesothelioma). The surgical procedure is performed in combination with intraperitoneal chemotherapy and is often followed by further local and systemic chemotherapy. The review identified only poor-quality studies which did not compare peritonectomy with alternative procedures. It was considered that conducting the procedure in a single centre may have safety advantages. It was recommended that one centre should undertake research and evaluation to determine the effectiveness of this service in the longer term.

Selective dorsal rhizotomy

Selective dorsal rhizotomy is an operation on the spinal nerve rootlets to treat spasticity in the lower limbs in children with cerebral palsy. It involves extensive preoperative investigations, including gait analysis, and a postoperative rehabilitation program.

The review found that rhizotomy plus physiotherapy improves spasticity and general motor function, compared with physiotherapy alone. Establishing one nationally funded centre was recommended, along with development of national protocols and collection of long-term follow-up data to allow for monitoring of adverse events.

Pulmonary thromboendarterectomy

Pulmonary thromboendarterectomy (PTE) is an operation for removing blood clots that obstruct blood flow to the lungs. PTE is a high-risk procedure involving heart–lung bypass. This review showed that the procedure could improve function and blood flow and concluded that it may substantially benefit patients. Establishing a nationally funded centre was recommended.

Paediatric liver transplantation

Paediatric liver transplantation is the only treatment available for children with acute liver failure or end-stage liver disease. The review found that survival results from three existing Australian centres compared well against international data. It was found that demand for transplantation could be met by a single centre, but two centres would be appropriate to ensure equity of access. Development of paediatric liver transplantation management guidelines, improved data collection, and surgical workforce succession planning were also recommended.

Systematic reviews and the Cochrane Collaboration

Systematic reviews follow rigorous methods to search for all clinical trials on a particular topic and then to combine that information into summaries of the best available evidence.

The Cochrane Collaboration is the largest organisation in the world engaged in the production and maintenance of systematic reviews of health care interventions. The Cochrane Library publishes the reviews of over 50 specialist groups, one of which is the Cochrane Breast Cancer Group, based at the CTC. This group coordinates almost 200 authors who prepare accurate and up-to-date reviews on all aspects of breast cancer (box).

The group edits the reviews, maintains a specialised register of over 8000 references to trials in breast cancer, advises on methodological and clinical content and facilitates peer review.

The Cochrane Breast Cancer Group is supported by the Commonwealth Department of Health and Ageing.

RECENT REVIEWS COORDINATED AND EDITED AT THE CTC:

- Compared aromatase inhibitors and other endocrine therapy, finding that in women with advanced breast cancer, survival was better with aromatase inhibitors.
- Assessed the effectiveness and safety of Chinese medicinal herbs in alleviating side-effects of chemotherapy. The herbs may offer some benefit to breast cancer patients in terms of bone marrow improvement and quality of life.

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Sharon Parker and Nicole Holcroft

Cochrane systematic reviews are available at:
www3.interscience.wiley.com/cgi-bin/rwhome/106568753/home

SCOPE OF THE REVIEWS OF THE COCHRANE BREAST CANCER GROUP

Prevention
- physical activity
- breast feeding
- dietary prevention
- endocrine prevention
- prophylactic surgery

Early detection
- screening methods (mammography, breast self-examination, clinical breast examination, genetic screening)
- participation in screening

Diagnosis
- pathology
- investigations

Management
- chemotherapy (ductal carcinoma in situ (DCIS), locally advanced and advanced disease)
- complementary and alternative therapies (herbal medicine, homeopathy, traditional Chinese medicine), diet and physical therapies (acupuncture, chiropractic, manual therapy, massage)
- endocrine therapy (DCIS, locally advanced and advanced disease)
- immunotherapy (DCIS, locally advanced and advanced disease)
- psychosocial interventions
- radiotherapy (DCIS, locally advanced and advanced disease)
- supportive care
- surgery (curative and plastic surgery)
- prevention and management of treatment-related adverse events and side-effects related to surgery, chemotherapy, radiotherapy

Familial breast cancer

Rehabilitation and other

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TRANSFERRING EVIDENCE INTO PRACTICE

Members of the Cochrane Breast Cancer Group undertook a systematic review, Trastuzumab for HER2 positive breast cancer, for the National Breast and Ovarian Cancer Centre.

This review was used for the NBOCC's clinical practice guidelines: Recommendations for use of trastuzumab (Herceptin) for the treatment of HER2-positive breast cancer.

- Assessed the effect of exercise during treatment for breast cancer. Improvements in fatigue were ambiguous and any improvement in other treatment-related side-effects lacked evidence.
- Assessed the effectiveness of chemotherapy before, rather than after, surgery for breast cancer. Preoperative chemotherapy did not make a difference to survival time, but it had some advantages, such as reducing the size of the tumour to be removed.
- Assessed the value of mammography screening. The review showed that screening reduces breast cancer mortality but also results in diagnosis and treatment of some conditions that may not have progressed to cancer. Women need to be informed of the possible consequences of screening.
- Investigated the sequencing of chemotherapy and radiotherapy in early breast cancer. Different sequences appeared not to have a major effect on survival or recurrence if radiation therapy commenced within 7 months of surgery.
- Compared surgery (with or without adjuvant tamoxifen) with tamoxifen alone for women aged over 70 years, finding that surgery controls breast cancer better than tamoxifen, but does not extend survival. Tamoxifen alone should be offered only to women with hormone-responsive tumours who are unfit for surgery.
- Reviewed genetic risk-assessment services and also reviewed of the effectiveness of different methods to communicate a primary diagnosis of breast cancer to women. Both found that adequate evidence to answer the review questions was not available.

In addition to its editorial and coordinating function, the CTC group has recently completed its own reviews to answer questions about breast cancer treatment.

- From studies totalling 21 191 women with early breast cancer, it was found that adjuvant chemotherapy that included a taxane reduced the risk of death and the number of cancer recurrences, compared with non-taxane regimens.
- A review asked the question: Is there is any benefit to increasing the intensity of a treatment regimen for metastatic breast cancer, particularly given the potential harm caused by more dose-intensive treatment? This review investigated the value of adding more chemotherapy drugs to a regimen, with the finding that this did improve the response of the tumour. There was insufficient evidence to determine the effect on overall survival.

Nicholas Wilcken and Davina Ghersi, co-coordinating editors of the Cochrane Breast Cancer Group

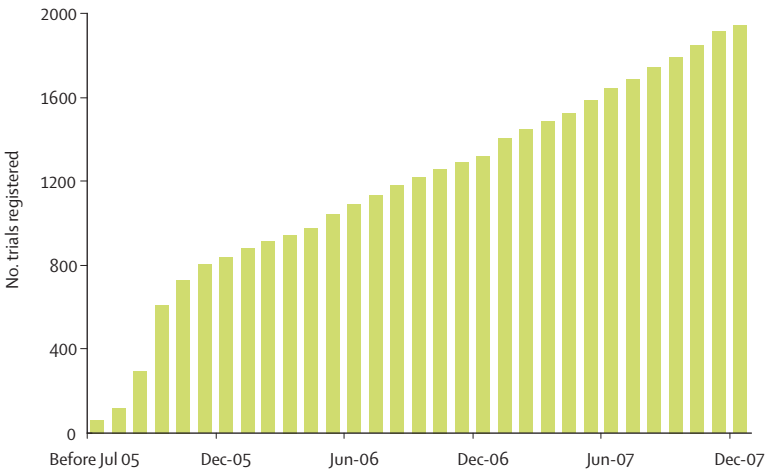
The Australian New Zealand Clinical Trials Registry

Some of the staff of the ANZCTR: Fergus Tai, Lisa Askie, Nicole Holcroft and Thuyen Vu, with Jenny Chow, executive officer for Systematic Reviews and Health Care Assessment

The Australian New Zealand Clinical Trials Registry (ANZCTR) is an on-line, prospective register of clinical trials. It captures trials being conducted in Australia, New Zealand and the neighbouring region, with representation as well from far-flung countries in Europe, Asia and North and South America. All data required by the registry and submitted by the sponsor are publicly available. Registration of trials is expected to lead to more efficiency and less duplication of research and less bias in the publication of clinical evidence.

The ANZCTR is a primary register of the World Health Organization and is recognised by the International Committee of Medical Journal Editors. It is part of a worldwide system in which anyone looking for trials related to a certain condition can access a one-stop search portal, which provides a short list of potential trials and their details within seconds. It is also a source of information for patients and doctors wanting to participate in current trials.

Since the Australian registry was first established in 2005, the number of trials registered has grown to nearly 2000: 82% of registered trials have an Australian sponsor, 11% are from New Zealand and 7% are from other countries. About 27% have a commercial sponsor.



DEFINITION OF RESEARCH TO BE REGISTERED AS A TRIAL

Any research study that prospectively assigns human participants or groups of humans to one or more health-related interventions to evaluate the effects on health outcomes.

— International Committee of Medical Journal Editors and World Health Organization

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ANZCTR website, where researchers can register trials and others can freely obtain information about current trials.

Registering a trial is voluntary, so currently not all Australian trials appear. Encouraging participation has been one focus of the efforts of the ANZCTR. One incentive is that timely registration is a condition of publishing research results in major medical journals. Linking registration with ethics approval is another potential incentive: the recently released Australian *National statement on ethical conduct in human research* has a clause stating that clinical trials should be registered before participants are enrolled.

Establishing the ANZCTR has been a major milestone for trials registration in Australia. Now, using the benefits of wide consultation, the registry is focusing on the scope of the required data, long-term sustainability, international linkages and easier accessibility (particularly via a project to facilitate access by cancer patients).

The ANZCTR has a high-level external advisory committee with wide representation, including representatives of government, research groups, consumers, the pharmaceutical industry, and medical journals. It is being funded, for its first five years, by the National Health and Medical Research Council.

END-OF-LIFE COMMUNICATION: A FOUNDATION FOR CLINICAL GUIDELINES

One of the most important aspects of medical care at the end of life is communication.

Health professionals need guidelines on how to discuss dying, life expectancy and future symptoms with patients and their families. However, this is an example of a research question which does not lend itself to the method of a randomised controlled trial. A systematic review by the CTC, in collaboration with the Medical Psychology Unit at the University of Sydney, has now provided the evidence to underpin specific guidelines and communication skills training for health professions about these sensitive and difficult topics.

The review found:

- Doctors tend to underestimate patients' needs for information. Patients are more satisfied with the overall care given if they are told about their situation.
- Patients and those caring for them in English-speaking and non-English-speaking cultures can differ, although individual differences are paramount.
- Doctors and patients have different perceptions of the patients' comprehension.
- For doctors to avoid giving information can make patients feel worse. Patients are better off if information balances honesty with empathy and hope.
- People caring for dying patients need to be included in communications so that they can adjust and prepare. Consistency in the facts, joint and separate opportunities for discussion, confidentiality and protecting patient rights are all relevant.

Australian guidelines based on this review were published as a supplement to the *Medical Journal of Australia* in 2007.

APPLYING TRIAL RESEARCH TO INDIVIDUAL PATIENTS

Vlatka Duric
Clinical psychologist

Patients' preferences about treatment

Cancer treatments, such as chemotherapy treatments, have benefits and harms. Although clinical trials can show the average benefit and the average harm of a cancer treatment in a cohort of patients, how the treatment affects an individual is not apparent from clinical trial evidence.

Patients and clinicians making decisions about treatments need to ask: how much benefit will make the side-effects and inconvenience of treatment worthwhile?

Vlatka Duric, Martin Stockler and their colleagues have been doing a series of studies in which patients and clinicians are asked, to trade off a treatment's benefits against its harms. Participants are asked to identify the smallest improvement in survival time or survival rate they judge necessary to make that therapy worthwhile.

In the first studies of the series, women who had had breast cancer indicated that small improvements in survival were enough to make chemotherapy, radiotherapy and endocrine therapy worthwhile. Most participants indicated that small benefits were sufficient to make the treatment worthwhile..

In the most recently completed study, the reasons for women's judgments about chemotherapy were explored. This study, published in 2007, was the first to evaluate psychosocial motivations of preferences for adjuvant chemotherapy in early breast cancer. Preferences were highly variable and individual. They were associated with minimising regret, parenting concerns, doubts about the information provided and feeling that they had no choice, but they were not associated with scores for anxiety, optimism, or perceived quality and quantity of social support.

The study showed the importance for clinicians of asking about circumstances, attitudes, and preferences when sharing decision making about undertaking treatment.

WHAT MAKES CHEMOTHERAPY FOR COLON CANCER WORTHWHILE?

Patients' preferences for adjuvant chemotherapy for early colon cancer and their quality of life during treatment are currently being explored in the next study of the series. This also has a methodological component: the standard structured interview and a new self-administered questionnaire are being compared as methods for eliciting this information from patients. Results will be available in 2008.

"As soon as there is any benefit, regardless of how small it is, I would go for it."

— A woman who had completed chemotherapy for breast cancer

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RISK ASSESSMENT WITH LIPID RISK-FACTOR SCORES

–3 points
- revascularisation after qualifying event (myocardial infarction or unstable angina)

–1 point
- pravastatin treatment

1 point
- HDL cholesterol <1.0 mmol/L
- increase in white cell count 1 x 109/L
- low creatinine clearance

2 points
- male sex
- obesity
- prior myocardial infarction
- angina
- revascularisation before qualifying event

3 points
- age 55–64 years
- history of stroke
- breathlessness
- current smoking

4 points
- diabetes mellitus
- atrial fibrillation

7 points
- age 65–69 years
- multiple myocardial infarction

9 points
- aged 70 years or over

Predicting risk for individual patients

Models of risk can be used for various purposes: estimating prognostic scores for individual patients, identifying patients at low risk who may not require treatment, identifying patients at high risk who may benefit more from treatment, showing the benefit versus the harm of a treatment, and shedding light on how it works in the body.

The large numbers of patients in many clinical trials make them an excellent source of high-quality data for risk-stratification models. Characteristics of patients in the study cohort and their relation to various outcomes can be analysed to show the typical risk factors for a particular outcome. For example, cardiovascular risk models predict how factors like age, smoking and cholesterol levels, separately or together, influence the risk of a myocardial infarction or stroke. The predictive ability of a model can be assessed in two ways: by its ability to correctly rank patients for risk and by the fit of the predicted probabilities with the observed rates.

INDIVIDUAL PATHOPHYSIOLOGY IN CARDIOVASCULAR DISEASE

LIPID trial

In the past, CTC biostatisticians developed such a risk model from the data in the LIPID trial (p. 27). Current LIPID studies have a more seasoned approach and are examining the interplay between clinical factors, novel markers of the pathophysiological processes associated with atherothrombosis, and genetic factors.

These studies are testing whether, in patients with existing coronary heart disease, new events, such as myocardial infarction and stroke, are linked to combinations of blood cholesterol levels, inflammation, oxidation and thrombosis. Individual differences in these factors and the effects of lipid-lowering treatment on each are taken into account.

The analyses of the LIPID study have great significance for a leading worldwide health problem. Risk stratification of patients may lead to identifying individuals most likely to benefit from taking statin drugs, a major expense in Australian health care. Data from the LIPID study are also contributing to risk-factor models of the international Cholesterol Treatment Trialists' Collaboration, which has a database of over 90 000 patients.

HERO-2 trial

Several biostatistical studies are making use of the data from over 17 000 patients in the international HERO-2 trial (p. 29). One such study is comparing the performance of model-updating methods for application in different geographical regions. Simple recalibration (re-estimation of the intercept and slope of the linear predictor within regions) and model revision (re-estimation of all regression coefficients within regions), with and without shrinkage, are compared with the global additive model (developed from the HERO-2 data) with a built-in region effect. The relative performance of these methods in the different geographical regions, which vary in sample size, is of primary interest.

Another compares the performance of risk models that vary in terms of required inputs, precision of measurement of risk factors and ease of calculation. Results of these studies will add to the information available for individual clinical decision making in acute coronary heart disease.

STAFF AND STAFF ACTIVITIES

CTC EXECUTIVE

John Simes, BSc(Med)(hons), MB BS(hons), MD, SM, FRACP, director and senior principal research fellow

Anthony Keech, MB BS, MSc, FRACP, deputy director and principal research fellow

Wendy Hague, MB BS, MBA, PhD, director, Clinical Trials Program, and senior research fellow

CLINICAL DATA MANAGEMENT

Lee Marshall, head

Senior clinical data coordinators

Karen Bracken, BEc, MPH

Sarah Mulray, BA, MPH

Dania Nour, BSc(hons), MSc

Susan Wonders, BDS (to Sep 2006)

Clinical data coordinators

Larry O'Leary, BSc

Mark Maclean, BA, DCR(T), CM

Sarah McIntosh

Emma Vlahos, BCom, BSc

SITE MANAGEMENT

Kathleen Scott, BSc(hons), PhD, head

Rebecca Mister, BSc, MSc, acting head (Sep 2006 to Oct 2007)

CANCER TRIALS

Martin Stockler, MB BS(hons), MSc, FRACP, cancer trials co-director and associate professor

Corona Gainford, MB BCh, BAO(hons), MSc, MRCP (UK), clinical research fellow

Peter Grimison, BSc(Med) MB BS(hons), FRACP, clinical research fellow

Managers

Burcu Vachan, BSocSc(hons), MPH, oncology program manager

Danielle Miller, BSc(hons), MPH, oncology program manager (Aug 2006–Aug 2007)

Xanthi Coskinas, BSc, GradDipHIM, associate program manager, SNAC trials, and ALTG (from Aug 2007)

Reena Gill BSc, MPH, associate program manager, AGITG

Julie Martyn, PhD, associate program manager, ANZGOG

Alison Pearce, BAppSc, associate program manager, ALTG (to Jul 2007)

Kate Wilson, BA, MPH, associate program manager, AGITG

Study coordinators and data managers

Kass Adams, BAppSc(hons)

Christine Aiken, BSocSc, MHlthSc

Amasy Alkhateeb, BSc(hons)

Amy Boland, BPsych(hons), GradCertHealthInfoMan

Radhika Butala, MIPH, BHMS

Kerrie Carlton BAppSc, MSc

Candace Carter, BSc

Xanthi Coskinas, BSc, GradDipHIM (to Jul 2007)

Michelle Cummins, BSc, PhD

Megan Evans, BAppSc (from Jul)

Alyson France, BSc/ BTeach, GradDipAppSc

Kim Gillies BA(hons)

Merryn Hall, BSc

Jam Lee, RN, BN, GradCertOncol, MBA

Alan Lucas, BAppSc

Anne McCall, BSc(hons), MSc

Sian Munro, BSc PhD

Helen Mueller, BSc, MSc

Hannah Paterson, DipAppSc, BA

Julia Shoulder, BSc(hons)

Justine Simard-Lebrun, BA

Raymond Tangunan, BAppSc

Eric Tsobanis, BScN(hons), MBA

Victoria Tunney, BSc(hons)

Lakshmi Waniganayake, BDS, MPH

Vicky Wegener

Nicole Wong, RN, BN, BSc(hons)

Clinical trial assistants

Agnes Aubonnet, DDS, PhD

Christina Halteh, BSc(hons)

Felicity Howard, BAppSc, GradCertHSM

Rebecca James, BA–BSc, GradDipEd

Julie Poulter

Ashna Sharma, BAppSc

ASPIRE TRIAL

Rebecca Mister, BSc, MSc, project manager

Ann Ratcliffe, RGN, DipPaed, study monitor (to Nov 2006)

Sarah Chinchen, BSc(hons), data manager–study monitor (from Nov 2006)

NEONATAL TRIALS

William Tarnow-Mordi, MRCP(UK), FRCPCH, coordinator of neonatal trials

INIS trial

Priya Duggal-Beri, BBiotech(hons), PhD, project manager (to Sep 2006)

Lucille Sebastian, BSc(hons), PhD, project manager (from Dec 2006)

Jezreel Blanco, BMedSc(hons), clinical trial assistant

BOOST II trial

Alpana Ghadge, BSc, MSc, PhD, GradCert TradeMarksLawPract, project manager

Mediha Survery, BAppSc, clinical trial assistant

FIELD TRIAL

Li Ping Li, BMed, GradCertDM, safety and outcomes manager and substudy coordinator

San Yip Chan, administrative assistant

Kew Flood, clinical trial assistant

Sonia Gillies, clinical trial assistant

Sandra Healey, BA(hons), GradDipFA, RN, substudy coordinator

Frank Liang, BMed, MInfSc, data manager

Wendy Liao, BMed, ECG reader

Diane Schipp, BEd, clinical coder, serious adverse events

Dana Tse, BMedSc(hons), PhD, research assistant–medical writer

Jun Zhang, BMed, MHIM, data manager, pathology coordinator

LIPID FOLLOW-UP STUDY

Helen Pater, BAppSc, project manager

STARTUP TRIAL

Anthony Keech, MB BS, MSc, FRACP, chief investigator

David Burgess, BMed, MPH, FRACP, co-investigator and project manager

SYSTEMATIC REVIEWS AND HEALTH CARE ASSESSMENT

Davina Ghersi, AssocDip, BAppSc, MPH, PhD, director, and senior research fellow

Lisa Askie, BN, MPH, PhD, acting director, and research fellow

Jenny Chow, AssocDip, executive officer

Medical Services Advisory Committee review group

Sally Lord, MB BS, DipPaed, MS, FRACGP, manager, epidemiologist and research fellow

Suzanne Dyer, BSc(hons), GradCertPH, PhD, project manager

Alison Griffiths, BA(hons), research associate

Luke Marinovich, BA(hons), MPH, project manager

Fergus Tai, BAppSc, research assistant

Wei Lei, BMed, MM, project officer

Silke Walleser, BSc(hons) MPH, project officer

Cochrane Breast Cancer review group

Sharon Parker, RN, BHSc, MPH, group coordinator

Davina Ghersi, AssocDip, BAppSc, MPH, PhD, coordinating editor

Nicole Holcroft, BSc(hons), trial search coordinator

Fergus Tai, BAppSc, assistant trial search coordinator

Australian New Zealand Clinical Trials Registry

Davina Ghersi, AssocDip, BAppSc, MPH, PhD, director, and senior research fellow

Lisa Askie, BN, MPH, PhD, acting director, and research fellow

Nicole Holcroft, BSc(hons), project officer

Emma Smith, BSc(hons), MSc, PhD, senior project officer

Fergus Tai, BAppSc, research assistant

Suchaya Thongyoo, BAppSc, research assistant

Thuyen Vu, BSc, project officer

Systematic review projects

Sally Lord, MB BS, DipPaed, MS, FRACGP, manager, epidemiologist and research fellow

Henry Ko, BEng(Med)(hons), GradIEAust, project officer

Charlene Thornton, BN, GradDipMid, MSc, project officer

Wei Lei, BMed, MM, project officer

BIOSTATISTICS AND CONSULTING

Val Gebski, BA, MStat, associate professor and principal research fellow

Malcolm Hudson, BSc(hons), PhD, visiting professor and principal research fellow

Kew Flood, administrative assistant

Senior biostatisticians

Karen Byth, BSc(hons), MSc, PhD, DIC, CStat RSS, senior lecturer

Patrick FitzGerald, BAppSc, GradDipMath, MAppSc, PhD, senior lecturer

Peta Forder, BSc(hons), MPH, MBiostat, lecturer

Stephane Heritier, MMath, MBA, PhD, senior lecturer

Adrienne Kirby, BSc(hons), MSc, senior lecturer

Biostatisticians

Elizabeth Barnes, BAppSc, MStat

Christopher Brown, BSc

Samuel Copt, MEc, PhD

Alistair Merrifield, MSc, PhD

Rachel O'Connell, BMath, MMedStat

Christopher Pardy, BSc(hons)

Avinesh Pillai, BSc, MSc(hons)

Tatiana Sourjina, MD, MPH, MStat

Elizabeth Williamson, PhD

Merryn Voysey, GradDipMathStat

Diana Zannino, BSc(hons), MSc

Biostatistics Collaboration of Australia (BCA)

Erica Jobling, executive officer, Biostatistics Collaboration of Australia

Sarah Goodman-Jones, administrative assistant

FLEXETRIALS DATA SYSTEM

Emma Vlahos, BCom, BSc, business analyst

PUBLICATIONS

Rhana Pike, BA, GradCert, MA, ELS, senior publications officer

INFORMATION SYSTEMS

Vinod Malhotra, manager

Infrastructure

Dinh Tran, BMath, MCompSc, infrastructure manager

Liem Tran, BMath, GradDipCompSc, computer systems officer

Asanka Perera, BSc, computer systems officer

Database administration

Anh Tai Nguyen, BMath, database manager

Software engineers

Seshu Atluri, BE

Anne Foy, BSc

Jianpeng Gu, MCompSc

Ashaar Riaz, BSc, MCompSc

James Robson, BSc

Ravinder Singh, BTech

Bei Zhong, MCompSc

BUSINESS ADMINISTRATION

Kim Russell-Cooper, BA(hons), MBA, general manager

Cynthia Carr, BEd, HRD, human resources and administration manager

Margaret Edwards, personal assistant to the director

Suzanne Everett, BSW, human resources and administration coordinator

Agnes Ho, MPracAcc, finance officer

Anne Madden, BA, executive officer

Faith Papuni, personal assistant to the deputy director

Doris Rattos, administrative assistant

Ayanthi Salgado LLB, MA, DipIntAff, operations manager, ANZGOG

Bebe Sim, MAcc, CPA, finance manager

QUALITY ASSURANCE

Phillipa Smith, BPharm(hons), MSc, adviser

Karen Pinto, DipTeach, BA, PostgradDip Psychol, AGITG and ANZGOG trial audit coordinator

PREFERENCES STUDIES

Vlatka Duric, BSc(hons), MPsych, PhD, clinical psychologist

THIRD INTERNATIONAL CLINICAL TRIALS SYMPOSIUM

Jenny Chow, AssocDip, project manager

RESEARCH STUDENTS

Peter Grimison, BSc(Med), MB BS(hons), FRACP, PhD student

Michaella Smith, BSc, MB BS(hons), MMSc, PhD student

ACADEMIC STAFF

John Simes, BSc(Med)(hons), MB BS(hons), MD, SM, FRACP, senior principal research fellow and professor

Anthony Keech, MB BS, MSc, FRACP, principal research fellow and professor

Lisa Askie, BN, MPH, PhD, research fellow

Karen Byth, BSc(hons), MSc, PhD, DIC, CStat RSS, senior lecturer

Vlatka Duric, BSc(hons), MPsych, PhD, associate lecturer

Peta Forder, BSc(hons), MPH, MBiostat, lecturer

Corona Gainford, MB BCh, BAO(hons), MSc, MRCP (UK), clinical research fellow

Patrick FitzGerald, BAppSc, GradDipMath, MAppSc, PhD, senior lecturer

Val Gebski, BA, MStat, principal research fellow and associate professor

Davina Ghersi, AssocDip, BAppSc, MPH, PhD, senior research fellow

Wendy Hague, MB BS, MBA, PhD, senior research fellow

Stephane Heritier, MMath, MBA, PhD, senior lecturer

Adrienne Kirby, BSc(hons), MSc, senior lecturer

Sally Lord, MB BS, DipPaed, MS, FRACGP, research fellow

Martin Stockler, MB BS(hons), MSc, FRACP, associate professor

Honorary associates of the CTC

Dr Sally Baron-Hay, ANZGOG

Dr David Bernshaw, ANZGOG

Dr Alison Brand, ANZGOG

Dr Timothy Brighton, ASPIRE

Dr Michael Brown, ALTG

Dr Ian Campbell, SNAC 2

Associate Professor Philip Clarke, Health economics

Dr Andrew Davidson, NITRO trial ALTG

Dr John Eikelboom, ASPIRE

Dr Michael Friedlander, ANZGOG

Professor Alexander Gallus, PREDICT (ASPIRE)

Professor P Grantley Gill, SNAC

Dr David Goldstein, AGITG

Dr Geraldine Goss, ANZGOG

Dr Michelle Grogan, ANZGOG

Dr Alison Hayes, Health economics

Dr Trevor Leong, AGITG

Ms Karen Livingstone, ANZGOG

Dr Ian Marschner, HERO 2

Dr Nicole McCarthy, ANZGOG

Dr Sue-Anne McLachlan, ALTG

Dr Michael Michael, AGITG

Dr Linda Mileshkin, ANZGOG

Dr Christopher Milross, ANZGOG

Prof Andreas Obermair, Oncology

Dr Robert Padbury, AGITG

Dr Timothy J Price, AGITG

Prof Michael Quinn, ANZGOG

Dr Kushwin Rajamani, FIELD

Dr Danny Rischin, ANZGOG

Dr Mark Rosenthal, COGNO

Dr Ben Solomon, ALTG

Dr Christopher Steer, EORTC

Professor William Tarnow-Mordi, BOOST II, INIS

Dr Niall Tebbutt, AGITG

Dr Ru-dee Ting, FIELD

Associate Professor Guy Toner, ANZGCTG

Dr Paul Vasey, ANZGOG

Dr Michelle Vaughan, ANZGOG

Dr Neil Wetzig, SNAC

Professor John Zalcberg, AGITG

STAFF ACTIVITIES

SUPERVISION OF RESEARCH DEGREES

John Simes

Davina Ghersi: PhD

Peter Grimison: PhD

Kirsten Howard: PhD

Rachel O'Connell: PhD

Michaella Smith: PhD

Anthony Keech

David Burgess: PhD

Gemma Ritchie: PhD

Val Gebski

Goran Hu: PhD

Bee Choo Tai: PhD

Martin Stockler

Haryana Dhillon: PhD

Peter Grimison: PhD

Phillipa Marx: MSc

Michaella Smith: PhD

Yu Yang Soon: MB BS(hons)

DEGR EES COMPLETED IN 2006–2007

Karen Bracken: MPH

Davina Ghersi: PhD: 'Issues in the design: conduct and reporting of clinical trials that impact on the quality of decision making'

Peter Grimison: MPH

Luke Marinovich: MPH

DEGREES IN PROGRESS

Amy Boland: GradCertHealthInfoMan

Christopher Brown: MBiostat

David Burgess: PhD, 'Treatment of coronary artery disease and its complications'

Xanthi Coskinas: MClinEpi

Kim Gillies: MHlthSc

Peter Grimison: PhD: 'Integrating quality-of-life data and traditional outcome measures to improve decision making about cancer treatments'

Rebecca James: MScMed

Rachel O'Connell: PhD, 'Risk factor modelling'

Christopher Pardy: MStat

Michaella Smith: PhD, 'Assessing quality of life and arm symptoms following axillary surgery for breast cancer'

REPRESENTATION ON EXTERNAL COMMITTEES

John Simes

ANZ Breast Cancer Trials Group scientific advisory committee

Aspirin to Prevent Recurrent Venous Thrombo-embolism (ASPIRE) trial management committee (chair)

Australasian Gastro-Intestinal Trials Group (AGITG) scientific advisory committee, operations executive committee, MAX trial management committee, Quasar 2 trial management committee, Da Vinci trial management committee

Australian New Zealand Clinical Trials Registry policy advisory committee

Cancer Institute NSW board

Cholesterol Treatment Trialists Collaboration (joint coordinator)

Cochrane Breast Cancer Group co-editor

Cochrane Collaboration prospective meta-analysis methods working group (coordinator)

Benefits of Oxygen Saturation Targeting (BOOST II) trial management committee

Current Controlled Trials advisory group

Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) management committee, executive, audit subcommittee (chair), and cost-effectiveness subcommittee

Intensive Blood Pressure Reduction for Acute Cerebral Haemorrhage Trial (INTERACT) safety and data monitoring committee (chair)

International Breast Cancer Intervention Study (IBIS-II) international steering committee

International Trials of Aspirin to Prevent Recurrent Venous Thrombo-embolism (INSPIRE) steering committee (chair)

Long-term Intervention with Pravastatin in Ischaemic Disease (LIPID) management committee, executive, samples subcommittee (chairman)

Mitomycin C, Avastin and Xeloda in Metastatic Colorectal Cancer (MAX) trial management committee

National Health and Medical Research Council large-scale clinical trials committee (chair), project grants committee

NHMRC Clinical Trials Centre management review committee and scientific advisory committee

Percutaneous Coronary Angioplasty versus Thrombolysis (PCAT) collaborative group (co-coordinator)

Sentinel Biopsy versus Axillary Clearance (SNAC) trial management committee

Trials editorial board

Virtual Coordinating Centre for International Collaborative Cardiovascular Research (VIGOUR) statistical group (chair) and a VIGOUR leader

World Health Organization clinical trial registries technical advisory group

Zoloft Effects on Depressive Symptoms and Time in Advanced Cancer (ZEST) trial management committee

Tony Keech

Asian-Pacific Society of Atherosclerosis and Vascular Disease Prevention executive committee (APSAVD) (founding member and treasurer)

Asia-Pacific Study on CHD Risk Factor Intervention (ASPAC) management committee (principal investigator and study chairman)

BLISS study safety and data monitoring committee (chairman)

Cardiac Society of Australia and New Zealand clinical trials working group scientific committee (chairman)

Cholesterol Treatment Trialists' Collaboration (joint coordinator and convenor)

Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) management committee (principal investigator and study chairman), ophthalmology substudy committee, scientific substudies committee, cost-effectiveness substudies committee

Heart Protection Study (HPS) steering committee, executive committee (co-principal investigator)

International Journal of Cardiology clinical trials editor

ISIS Trials Group steering committee

Long-term Intervention with Pravastatin in Ischaemic Disease (LIPID) study management committee, executive, and quality assurance subcommittee

NHMRC Clinical Trials Centre management review committee and scientific advisory committee

National Health and Medical Research Council training awards committee

NSW Department of Health shared assessment committee

PLoS Medicine editorial board

Prospective Pravastatin Pooling (PPP) project international steering committee

Royal Prince Alfred Hospital clinical trials (ethics) subcommittee

University of Sydney College of Health Sciences board of postgraduate studies

University of Sydney Faculty of Medicine budget advisory committee and faculty awards committee, Department of Public Health research committee

Virtual Coordinating Centre for International Collaborative Cardiovascular Research (VIGOUR)

Lisa Askie

Benefits of Oxygen Saturation Targeting (BOOST) II trial management committee

Cochrane Collaboration handbook advisory group

International Clinical Trials Registry Platform, World Health Organization, registers working group

Meta-Analysis of Preterm Patients on Inhaled Nitric Oxide (MAPPiNO) Collaboration steering group

Neonatal Oxygen Prospective Meta-analysis (NeOProM) collaboration steering committee (chair)

Perinatal Antiplatelet Review of International Studies (PARIS) collaboration steering committee, writing committee (chair)

PLoS ONE academic editor

Prevention of Ventilation Induced Lung Injury Collaborative Group (Previlig) steering committee

Royal Prince Alfred Hospital clinical trials (ethics) subcommittee

Xanthi Coskinas

Sentinel Node Biopsy versus Axillary Clearance (SNAC) and SNAC 2 trial management committees

Peta Forder

Australasian Lung Cancer Trials Group scientific advisory committee, operational executive committee

Cancer Institute NSW Partnership operational executive committee

Laparoscopic Approach to Carcinoma of the Endometrium (LACE) management committee

Corona Gainford

Australasian Gastro-Intestinal Trials Group (AGITG) trials operations committee

Australia New Zealand Gynaecological Oncology Group (ANZGOG) trials operations committee

Cancer Institute NSW executive committee

Cancer Institute NSW audit subcommittee

Patrick FitzGerald

Australasian Lung Cancer Trials Group scientific advisory committee

Australian Pharmaceutical Biostatistics Group management committee

Cooperative Trials Group for Neuro-Oncology (COGNO) scientific advisory committee

Australasian Gastro-Intestinal Trials Group scientific advisory committee

Val Gebski

Australian New Zealand Breast Cancer Trials Group scientific committee and ANZ 9311 management committee

Australasian Gastro-Intestinal Trials Group (AGITG) scientific advisory committee, MAX trial management committee, Da Vinci trial management committee

Australasian Kidney Trials Network advisory board

Biostatistics Collaboration of Australia steering committee and teaching committee

Joint Radiation Oncology Centre research committee

Medical Journal of Australia, statistical consultant

NMRC Singapore Indomethacin study for closure of PDA safety data and monitoring committee

NSW Health Eastern Sydney Area ethics committee clinical trials subcommittee

Sentinel Node Biopsy versus Axillary Clearance (SNAC) trial management committee

Davina Ghersi

Cochrane Collaboration handbook advisory group; methodology review group advisory board; prospective meta-analysis methods group co-convener; breast cancer group joint coordinating editor

World Health Organization International Clinical Trials Registry Platform coordinator

Cancer Trials NSW clinical trials committee

NSW Health Pilot Shared Scientific Assessment Scheme reference group

University of Sydney course advisory committee, Master of Health Science and Graduate Certificate in Health Science (Clinical Data Management)

Reena Gill

Australasian Gastro-Intestinal Trials Group (AGITG) scientific advisory committee, operations executive committee, Quasar 2 trial management committee, Da Vinci trial management committee

Peter Grimison

Medical Oncology Group of Australia awards committee

Wendy Hague

Aspirin to Prevent Recurrent Venous Thromboembolism (ASPIRE) management committee

Benefits of Oxygen Saturation Targeting (BOOST II) management committee

International Neonatal Immunotherapy Study (INIS) Australian and New Zealand management committee

Long-Term Intervention with Pravastatin in Ischaemic Disease (LIPID) management committee

Adrienne Kirby

Biostatistics Collaboration of Australia teaching committee

Long-Term Intervention with Pravastatin in Ischaemic Disease (LIPID) management committee

Sally Lord

3rd Annual Meeting of Health Technology Assessment International (HTAi) scientific advisory committee

Danielle Miller

Australasian Gastro-Intestinal Trials Group (AGITG) scientific advisory committee, operations executive committee, biological subcommittee

Australian New Zealand Breast Cancer Trials Group

Rebecca Mister

Aspirin to Prevent Recurrent Venous Thromboembolism (ASPIRE) management committee

Julie Martyn

Australia New Zealand Gynaecological Oncology Group research advisory committee, study coordinators committee

Gynaecological Cancer Intergroup harmonization working group

Sharon Parker

Cochrane Collaboration colloquium policy advisory group

Clinical Practice Guidelines For Communicating Prognosis and End-of-Life Issues with Adults in the Advanced Stages of a Life-Limiting Illness, and their Caregivers Australian and New Zealand expert advisory group

Rhana Pike

Australasian Medical Writers Association executive committee

Ayanthi Salgado

Australia New Zealand Gynaecological Oncology Group study coordinators committee, consumer and community committee and fundraising committee

Clinical Oncological Society of Australia Executive Officers Network clinical trial research agreement committee

Kathleen Scott

NSW Cancer Institute partnership operations executive committee

Co-operative Trials Group for Neuro-oncology (COGNO) operations executive and scientific advisory committees

Martin Stockler

ACP Journal Club associate editor

Australian New Zealand Breast Cancer Trials Group scientific advisory committee

Australian New Zealand Germ Cell Trials Group scientific advisory committee

Australia New Zealand Gynaecological Oncology Group scientific advisory committee

Australasian Leukaemia and Lymphoma Group safety and data monitoring committee

Australasian Lung Cancer Trials Group scientific advisory committee

Australia Asia-Pacific Clinical Oncology research development workshop steering committee

Cancer Council Australia oncology education committee

Cancer Council Victoria grant review panel

Cancer Trials NSW trial selection committee (chair)

Evidence Based Medicine associate editor

National Breast Cancer Centre hormone therapy working group (chair)

National Breast Cancer Centre information advisory group (chair)

National Breast Cancer Foundation research expert advisory committee

National Cancer Institute quality of life intergroup committee

NHMRC oncology grant review panel, palliative care research grant review panel, palliative care research working group

Burcu Vachan

Australasian Gastro-Intestinal Trials Group scientific advisory committee, operations executive, biological subcommittee, annual scientific meeting planning committee

Australian and New Zealand Germ Cell Trials Group operations executive and executive

Australia New Zealand Gynaecological Oncology Group operations executive and research advisory committee

Australasian Lung Cancer Trials Group operations executive and scientific advisory committee

Australian New Zealand Breast Cancer Trials Group

Cancer Institute NSW infrastructure grant subcommittee

Cancer Institute NSW partnership grant operational executive committee

Kate Wilson

Australasian Gastro-Intestinal Trials Group (AGITG) scientific advisory committee, operations executive committee, MAX trial management committee, Quasar 2 trial management committee, Da Vinci trial management committee, study coordinators subcommittee (chair), annual scientific meeting planning committee

Academic teaching

John Simes

Decision analysis,
Master of Public Health and Master of Medicine, University of Sydney

Anthony Keech

Controlled clinical trials, Master of Public Health and Master of Medicine, University of Sydney

University of Sydney Medical Program

Cardiology training,
Royal Prince Alfred Hospital

Clinical tutor, Royal Prince Alfred Hospital

Lisa Askie

Advanced clinical data management,
Master of Health Information Management, University of Sydney

Advanced systematic reviews,
Master of Clinical Epidemiology, University of Sydney (co-coordinator)

Controlled clinical trials,
Master of Public Health,
University of Sydney

Evidence-based medicine in the clinical years, University of Sydney Medical Program

Elizabeth Barnes

Basic sciences in oncology, NSW Cancer Council

Principles of statistical inference, Biostatistics Collaboration of Australia

Christopher Brown

Controlled clinical trials, Master of Public Health and Master of Medicine, University of Sydney

Basic sciences in oncology, NSW Cancer Council

Peta Forder

Advanced clinical trials, Biostatistics Collaboration of Australia

Basic sciences in oncology, NSW Cancer Council

Controlled clinical trials, Master of Public Health and Master of Medicine, University of Sydney

Principles of statistical inference, Biostatistics Collaboration of Australia

Corona Gainford

University of Sydney Medical Program

Patrick FitzGerald

Advanced clinical trials, Biostatistics Collaboration of Australia

Controlled clinical trials, Master of Public Health and Master of Medicine, University of Sydney

Principles of statistical inference, Biostatistics Collaboration of Australia

Val Gebski

Advanced clinical trials, Biostatistics Collaboration of Australia (coordinator)

Basic sciences in oncology, NSW Cancer Council

Controlled clinical trials, Master of Public Health and Master of Medicine, University of Sydney

Radiation oncology training, RACR trainees, Westmead Hospital, NSW Cancer Council

Peter Grimison

University of Sydney Medical Program

Stephane Heritier

Advanced clinical trials, Biostatistics Collaboration of Australia

Adrienne Kirby

Basic sciences in oncology, NSW Cancer Council

Controlled clinical trials, Master of Public Health and Master of Medicine, University of Sydney

Principles of statistical inference, Biostatistics Collaboration of Australia (coordinator)

Sally Lord

Advanced evaluation of diagnostic tests, Master of Public Health and Master of Medicine, University of Sydney

Basic sciences in oncology, NSW Cancer Council

Controlled clinical trials, Master of Public Health and Master of Medicine, University of Sydney

Decision analysis, Master of Public Health and Master of Medicine, University of Sydney

Evidence-based medicine, University of Sydney Medical Program

Luke Marinovich

Evidence-based health care, Master of Applied Science (Health Information Management), University of Sydney

Rebecca Mister

Advanced clinical data management, Master of Health Information Management, University of Sydney

Christopher Pardy

Basic sciences in oncology, NSW Cancer Council

Principles of statistical inference, Biostatistics Collaboration of Australia

Martin Stockler

Australia & Asia-Pacific Clinical Oncology Research Development (ACORD) workshop faculty

Clinical epidemiology for physician trainees, Royal Prince Alfred Hospital

Critical appraisal of literature for physicians, Westmead Hospital

Evidence-based medicine in the clinical years, University of Sydney Medical Program (chair and coordinator)

Explaining adjuvant therapy, Cancer Institute NSW

Making sense of cancer trials, Cancer Council NSW

Medical oncology clinical training, Royal Prince Alfred Hospital

Oncology and palliative care, University of Sydney Medical Program (block chair)

Patient-based measures, Master of Medicine, University of Sydney (course coordinator)

Quality of life in oncology, Cancer Institute NSW

Supportive care research methods, Sydney Institute of Palliative Medicine

Burcu Vachan

Basic sciences in oncology, NSW Cancer Council

Evidence-based medicine, University of Sydney Medical Program

PUBLICATIONS

Journal articles

Ahern V, Boyages J, **Gebski V,** Moon D, Wilcken N. Selective mastectomy in the management of locally advanced breast cancer. International *Journal of Radiation Oncology, Biology, Physics* 2007; 68(4):1010-1017.

Ahern V, Koh ES, **Gebski V,** Sathiyaseelan Y. Paediatric medulloblastoma: patterns of care and radiotherapy quality assurance in Australia. *Australasian Radiology* 2007; 51(5): 458–464.

Askie L, **Ghersi D**, **Simes J**. Prospective registration of clinical trials. *Australian Journal of Physiotherapy* 2006; 52(4): 237–239.

Askie LM, Duley L, Henderson-Smart DJ, Stewart LA; on behalf of the PARIS Collaborative Group. Antiplatelet agents for prevention of pre-eclampsia: a meta-analysis of individual patient data. *Lancet* 2007; 369: 1791–1798.

Atlantis E, **Barnes EH**, Singh MA. Efficacy of exercise for treating overweight in children and adolescents: a systematic review. International Journal of Obesity 2006; 30(7): 1027–1040.

Atlantis E, Chow CM, **Kirby A**, Fiatarone Singh MA. Worksite intervention effects on physical health: a randomized controlled trial. *Health Promotion International* 2006; 21(3): 191–200.

Atlantis E, Chow CM, **Kirby A**, Fiatarone Singh MA. Worksite intervention effects on sleep quality: a randomized controlled trial. Journal of Occupational Health Psychology 2006; 11(4): 291–304.

Baigent C, **Keech A,** Kearney P, Collins R, Simes J; on behalf of the Cholesterol Treatment Trialists' Collaboration. Efficacy and safety of cholesterol-lowering treatment—authors' reply [letter]. *Lancet* 2006; 367(9509): 470–471.

Beslija S, Bonneterre J, Burstein H, Cocquyt V, Gnant M, Goodwin P, Heinemann V, Jassem J, Kostler WJ, Krainer M, Menard S, Petit T, Petruzelka L, Possinger K, Schmid P, Stadtmauer E, **Stockler M**, Van Belle S, Vogel C, **Wilcken N**, Wiltschke C, Zielinski CC, Zwierzina H. Second consensus on medical treatment of metastatic breast cancer. *Annals of Oncology* 2007; 18(2): 215–225.

Beslija S, Bonneterre J, Burstein H, Cocquyt V, Gnant M, Goodwin P, Heinemann V, Jassem J, Köstler WJ, Krainer M, Menard S, Petit T, Petruzelka L, Possinger K, Schmid P, Stadtmauer E, **Stockler M,** Van Belle S, Vogel C, Wilcken N, Wiltschke C, Zielinski CC, Zwierzina H. Second consensus on medical treatment of metastatic breast cancer. *Annals of Oncology* 2007; 18: 215–225.

Brand AH, Bull CA, **Cakir B**. Vaginal stenosis in patients treated with radiotherapy for carcinoma of the cervix. *International Journal of Gynecological Cancer* 2006; 16: 288–293.

Burgess DC, Burgess MA, Leask J. The MMR vaccination and autism controversy in the United Kingdom 1997–2005: inevitable community outrage or a failure of risk communication? Vaccine 2006; 24: 3921–3928.

Burgess DC, Kilborn MJ, **Keech AC**. Interventions for prevention of postoperative atrial fibrillation and its complications after cardiac surgery: a meta-analysis. *European Heart Journal*. 2006; 27: 2846–2857.

Bushnell CD, Griffin J, Newby LK, Goldstein LB, Mahaffey KW, Graffagnino CA, Harrington RA, White HD, **Simes RJ**, Califf RM, Topol EJ, Easton JD. Statin use and sex-specific stroke outcomes in patients with vascular disease. *Stroke* 2006; 37(6): 1427–1431.

Butow PN, Solomon M, Young JM, Whelan T, Salkeld G, **Wilson K**, Harrison JD, Hruby G, Mansour O, Kennedy N, Tattersall MH. Consumer impact of an interactive decision aid for rectal cancer patients offered adjuvant therapy. *Colorectal Disease* 2006; 8(8): 676–682.

Byth K, Cox DR, **Forder P**. Assessing the relationship between symptoms of allergic rhinoconjunctivitis and pollen counts. *Australian and New Zealand Journal of Statistics* 2006; 48(4): 417–428.

Cebon J, **Hargreaves C**, **Stockler M**, **Nowak A**, **Dhillon H**, **Dickman B**, **Gebski V**; Australasian Gastro-Intestinal Trials Group (AGITG) AG0001H Investigators. Somatostatin receptor expression, tumour response, and quality of life in patients with advanced hepatocellular carcinoma treated with long-acting octreotide. *British Journal of Cancer* 2006; 95(7): 853–861.

Chan QW, Upshur R, Singh JA, **Ghersi D**, Chapuis F, Altman D. Waiving confidentiality for the greater good. *BMJ* 2006; 332: 1086–1089.

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ABSTRACTS BY COLLABORATIVE GROUPS

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Askie LM. Australian Clinical Trials Registry: present and future. *International Clinical Trials Symposium;* 24–26 Sep 2007; Sydney.

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Askie L. Aspirin and pre-eclampsia — the PARIS Collaboration. *Society of Obstetric Medicine of Australia and New Zealand, Annual Scientific Meeting;* 10–12 Nov 2006; Sydney.

Askie L. How do nurses get into research? *Paediatric Society of New Zealand 59th Annual Scientific Meeting;* 26–28 Nov 2007; Christchurch.

Askie L. Neonatal oxygen therapy: too much of a good thing? *Perinatal Society of Australia and New Zealand 11th Annual Congress.* 1–4 Apr 2007; Melbourne.

Askie L. Oxygen in neonatal treatment — implications for large scale randomised trials in medicine. *Paediatric Society of New Zealand 59th Annual Scientific Meeting;* 26–28 Nov 2007; Christchurch.

Askie L. Promoting perinatal randomised trials: BOOST, bubbles for babies and more. *Celebration Symposium for Professor David Henderson-Smart;* 22 Nov 2007; Sydney.

Askie L. Publication of results from clinical research. *Australasian Health and Research Data Managers Association, Australasian Clinical Research Conference;* 23–25 Aug 2006; Brisbane.

Askie L. Australian Clinical Trials Registry. *Trans Tasman Radiation Oncology Group (TROG) seminar 'Success in clinical trials: key people and processes';* 24 May 2007; Sydney.

Askie L. Update on the Australian Clinical Trials Registry. *International Committee of Medical Journal Editors meeting;* 13–15 Apr 2007; Sydney.

Askie L. Antiplatelets to prevent pre-eclampsia: the PARIS Collaboration. *Westmead International Update Symposium;* 18 May 2007; Sydney.

Byth K. Shared primary outcomes. *International Clinical Trials Symposium;* 24–26 Sep 2007; Sydney.

Copt S, Heritier S. Robust MM-estimation and inference in mixed linear models. *27th Annual Meeting of the International Society for Clinical Biostatistics;* 27–31 Aug 2006; Geneva.

Gebski V. Invited participant. CONSORT III meeting to develop and extend the CONSORT statement. Jan 2007.

Hochman J, Simes RJ (co-chairs). Antithrombotic therapy in acute coronary syndromes. State of the art 2007. 56th Annual Scientific Sessions, American College of Cardiology; 24–27 Mar 2007; New Orleans.

Keech A. Changing endpoints during follow up: when and how? *International Clinical Trials Symposium;* 24–26 Sep 2007; Sydney.

Keech A. Effects of long-term fenofibrate therapy on cardiovascular events among 9795 people with type 2 diabetes mellitus. *38th Annual Scientific Meeting of the Japan Atherosclerosis Society Meeting;* 13–14 Jul 2006; Tokyo.

Keech A. Effects of long-term fenofibrate therapy on cardiovascular events among 9795 people with type 2 diabetes mellitus: the FIELD study, a randomized controlled trial. *5th Congress of Asia-Pacific Society of Atherosclerosis and Vascular Diseases;* 10–17 Apr 2006; Jeju Is, Korea.

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Keech A. Silent myocardial ischemia: a deafening silence. Solvay Symposium. *European Society of Cardiology;* 1–5 Sep 2007; Vienna.

Keech A. Update on fibrates. *American Heart Association Scientific Sessions 2006;* 12 Nov 2006; Chicago.

Keech AC, Best J. Highlights from the FIELD trial: a landmark trial. *Annual Scientific Sessions of the American Diabetes Association;* 9–13 Jun 2006; Washington.

Keech AC, Simes RJ. Clinical trial design and management: the role of PPAR-alpha agonists in prevention of CVD. *Satellite symposium, XIV International Symposium on Atherosclerosis;* 20 Jun 2006; Rome (speaker and session chair). *Atherosclerosis Supplements* 2006; 7 (3): 174.

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Keech AC. Metabolic syndrome and diabetes. *NHLBI National Cholesterol Education Program;* Jul 2006; New York.

Keech AC. New efficacy and safety data in the FIELD study: *Fenofibrate Update Conference;* 28–29 Jul 2006; Chicago.

Keech AC. Prevention of macrovascular and microvascular events in diabetes mellitus with fenofibrate. Implications for fenofibrate. Mar 2007; Tokyo.

Keech AC. Role of PPAR-alpha agonists in diabetic disease. *Meeting of the Metabolic Syndrome Institute;* 14–18 Jul 2006; New York.

Keech AC. To manage diabetes: management in the early stages. *Solvay Scientific Meeting;* Jul 2006: China.

Lord SJ. Assessing diagnostic tests without the benefit of randomised controlled trials. Diagnostic Test Panel Session. *Health Technology Assessment International;* 3 Jul 2006; Adelaide.

Sebastian L. Building systems and solutions for the support of perinatal clinical research coordinators. *International Clinical Trials Symposium;* 24–26 Sep 2007; Sydney.

Simes J. Risk stratification for cholesterol treatment. Cholesterol Treatment Trialists Collaboration meeting. Satellite of *American Heart Association Scientific Sessions 2006;* 12 Nov 2006; Chicago.

Simes J. The importance of trials and future funding models. *International Clinical Trials Symposium;* 24–26 Sep 2007; Sydney.

Simes J. Where should we get the evidence? Cardiovascular disease on a global scale: what should be studies and how? *World Congress of Cardiology;* 2–6 Sep 2006; Barcelona.

Simes RJ. Costs and benefits of cancer care and clinical trials research. *Research Driven Cancer Care Meeting;* Feb 2007; Auckland.

Simes RJ. In celebration of a record of achievement by Professor Marvin Zelen. May 2007; Boston.

Simes RJ. Prevention of macrovascular and microvascular events in diabetes mellitus patients: implications from the FIELD study in clinical practice. *Malaysian Endocrine and Metabolic Symposium;* Mar 2007; Kuala Lumpur.

Stockler M [co-chair]. Patient and survivor care poster discussion session. *43rd Annual Meeting of the American Society of Clinical Oncology;* 1–5 Jun 2007; Chicago

Stockler M. Capecitabine in advanced breast cancer. Roche Investigators' Meeting; June 2007; Chicago.

Stockler M. What have we learnt from measuring quality of life in oncology? *Annual Scientific Meeting of the Clinical Oncological Society of Australia;* 29 Nov–1 Dec 2006; Melbourne.