



RESEARCH REPORT 2004-2005

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The NHMRC Clinical Trials Centre is a leading Australian clinical trial and research centre.

It is committed to excellence in its contribution to evidence-based health care with the mission to improve outcomes in Australia and internationally through the use of clinical trials research.



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The National Health and Medical Research Council Clinical Trials Centre has the purpose of improving outcomes in health through clinical trials research. It was established by the National Health and Medical Research Council in 1988 as a research centre at the University of Sydney.

The CTC provides the knowledge and infrastructure to ensure the quality, timely completion and reporting of clinical trials. It has vast expertise in the design, conduct and analysis of randomised controlled trials, particularly in cancer and cardiovascular disease. Over 100 staff have specialised skills, taking in clinical trials design, biostatistics, database design, randomisation and drug distribution, outcome assessment, quality assurance, and regulatory and ethical issues. In the past 16 years, the CTC has participated in more than 50 investigator-initiated, collaborative-group clinical trials and coordinated some of the largest randomised trials initiated by Australian investigators (LIPID and FIELD studies, each with over 9000 patients). Over 40 000 patients have been randomised to these trials. All clinical trials undertaken through the CTC are conducted strictly according to guidelines for clinical trials research and conduct, and are audited by sponsors, the CTC itself and regulatory authorities.

The CTC has a history of working collaboratively with cooperative groups, clinical trial networks and other organisations, and has played a central role in establishing some of these groups. These activities have been recognised in increased grant funding to enable further collaboration and to increase the number of investigator-initiated trials in Australia.

In its research, the CTC has prospered: it has developed strategies for patient recruitment, trial and data management, study coordination, information systems and randomisation in an environment of academic excellence. In addition to trials management, the CTC is a leader in biostatistical methodology and analysis and in systematic review of health evidence. The integrated expertise of the CTC staff is turned to good use in frequent educational activities in Australia and elsewhere.

This report covers the CTC's achievements for the biennium, 2004–2005.

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FROM THE DIRECTORS

The past two years has seen the CTC follow a research direction which has three major strands:

- initiating major clinical trials in high-priority disease areas commonly affecting the Australian population
- advances in methods for understanding clinical trials and for using evidence from trials
- combining results from trials to improve the quality of the evidence and integrating that evidence with information about risks and preferences of individual patients.

Ultimately, we aim to generate better research evidence and narrow the gap between research evidence and practice.

Focusing on high-priority questions and trials that benefit most from the CTC's strengths is a major research theme. New trials have a long gestation; we review existing evidence, acquire funding, build collaborations, achieve agreement among the collaborators about the research question, and conduct pilot studies, all before a major trial is launched.

The CTC has a policy of conducting trials of most value to the health of the Australian population. Thromboses, or blood clots, sometimes occur after major surgery or during pregnancy, but sometimes they occur for no apparent reason. The ASPIRE trial, which is using aspirin treatment to prevent unprovoked recurrence of deep-vein thrombosis or pulmonary embolism, was set up in 2003 and is now in recruitment. If effective, this simple and inexpensive treatment could prevent recurrent thrombosis in thousands of patients each year, potentially leading to substantial healthcare savings. It is also part of an international prospective meta-analysis, which will challenge and strengthen its findings. We have started new trials to improve the health of newborn babies: first INIS, a trial of preventing the serious long-term effects of infection, and now BOOST II, which is attempting to find the optimum level of oxygen treatment for premature babies.

One of the CTC's recent successes has been the SNAC trial, which arose initially from the concerns of women with breast cancer about the complications of breast surgery. That the research question was relevant to patients was confirmed by SNAC's rapid recruitment of over 1000 women. We are now establishing SNAC 2, which will recruit more women and extend the amount and type of information we will acquire from the trial. Like the first trial, this is a collaboration with the Royal Australasian College of Surgeons.

The CTC has recently received funding for major enabling activities. Recent grants to the CTC and its collaborative groups in cancer is enabling the CTC to move ahead with applying its generic systems and expertise to many different trials, our

own and others'. Cancer trial initiatives in association with the Australasian Gastro-Intestinal Trials Group and the new Australia New Zealand Gynaecological Oncology Group are under way.

Late in 2005 the main results of the FIELD study were presented and simultaneously published in *The Lancet*. FIELD, the largest completed trial worldwide in diabetes, with almost 10,000 patients, was designed to test whether fenofibrate can prevent heart attack, death from coronary heart disease and other major vascular events. The results of FIELD were mixed; fenofibrate did not significantly reduce the risk of a major coronary event (the primary trial outcome measured), but the trial result showed that fenofibrate reduced the number of cardiovascular events overall, including nonfatal heart attack and hospitalisation for angina. The drug also benefited patients in reducing the need for procedures such as coronary artery bypass grafting, amputations and laser treatments for eyes. FIELD was a major undertaking of the CTC. Initial discussions about the feasibility of such a trial began over 10 years ago, when it was known that fenofibrate and similar drugs were particularly suited to improving the blood lipids of people with diabetes and that fenofibrate reduced plaque in arteries. This large trial resolved much of the uncertainty about its clinical effects. The trial results are also guiding clinicians on the use of fenofibrate for patients with type 2 diabetes and reassuring them as to its overall safety, alone and in combination with other drugs.

The power of studying a large number of patients was shown by the results of the Cholesterol Treatment Trialists' Collaboration, also published late in 2005. The collaboration first designed this prospective meta-analysis in 1994. The first cycle of the study was an analysis of data from 14 trials, comprising 90 056 patients, of statin drugs to lower cholesterol and reduce the risk of cardiovascular disease. The results provided definitive evidence that substantial reductions in LDL cholesterol with statin treatment benefit patients with a high risk of any type of occlusive vascular event. Most trials are tied to studying a single main outcome (a specific kind of event, such as death or stroke) because cost limits the sample size. Meta-analysis combines data from multiple trials and patients, but the analysis may lead to conflicting conclusions. The results of the CTC prospective meta-analysis therefore represent an advance in knowledge brought about by an advance in methods. The CTC is co-coordinator of the collaboration (with the Clinical Trial Service Unit and Epidemiological Studies Unit in the UK).

In 2005 the Australian Clinical Trials Registry was established at the CTC with funding from the National Health and Medical Research Council. We have been aware for many years of the advantages of public registration of trials in progress. The registry is the realisation of an ideal that has been 20 years in



the making, after it was shown in the 1980s that published research may present a biased picture. A significant proportion of trials research is never published, leading to wasted effort by researchers and patients and bias in the published evidence. As well, knowledge of ongoing trials prevents unnecessary duplication of research. The new register has a complete and comprehensive catalogue of all clinical trials in Australia. It will lead to the conduct of more relevant and timely and hence more ethical clinical research and aims to offer a reliable and unbiased source of information for systematic reviews, prospective meta-analyses and evidence-based guidelines. The register is an essential part of our strategy for improving health outcomes through better use of clinical trials research.

Achievements in statistics have included methods for selecting sample sizes in designs when the effects of two different treatments influence each other, new ways with dynamic randomisation methodology, and how to assess surrogate outcomes when some data are unavailable.

Integrating trial evidence with other information about patients can improve clinical decision making. Researchers at the CTC have been focusing on studies of patients' preferences about cancer treatment. We have used established results of trials of various treatments for breast cancer to look in the other direction and ask women themselves to what degree the treatments were worthwhile. These studies have suggested that surprisingly small benefits may be sufficient to justify treatments.

Another approach to applying trial evidence to real patients has been work on prognostic models. Risk-factor models are being constructed as decision aids for identifying patients at high risk; in those who are at high risk, the absolute benefit of treatment is often greater. Development of risk models and other clinical and methodological advances are possible because of the accumulated data sets and long-standing research expertise of the CTC and its collaborators.

One of the CTC's objectives is to pass on the expertise gained through our experience in collaborative trials research. Academic staff members of the CTC teach and administer graduate training courses at the University of Sydney and other universities. Senior staff supervise higher degree students working on projects that are crucial to the CTC's research aspirations. In addition, several CTC research staff have been recently awarded doctoral degrees. Their projects are an integral part of the CTC's research program.

The considerable achievements of the CTC in the past two years have been a result of dedicated cooperative effort from staff members of the CTC and their research colleagues. The research program owes its strength to the support of government and industry funding bodies, national and international clinical investigator groups and other sponsors.

John Simes
Director

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 professor in the departments of Medicine and Public Health and Community Medicine at the University of Sydney, and is a specialist medical oncologist at Royal Prince Alfred Hospital.



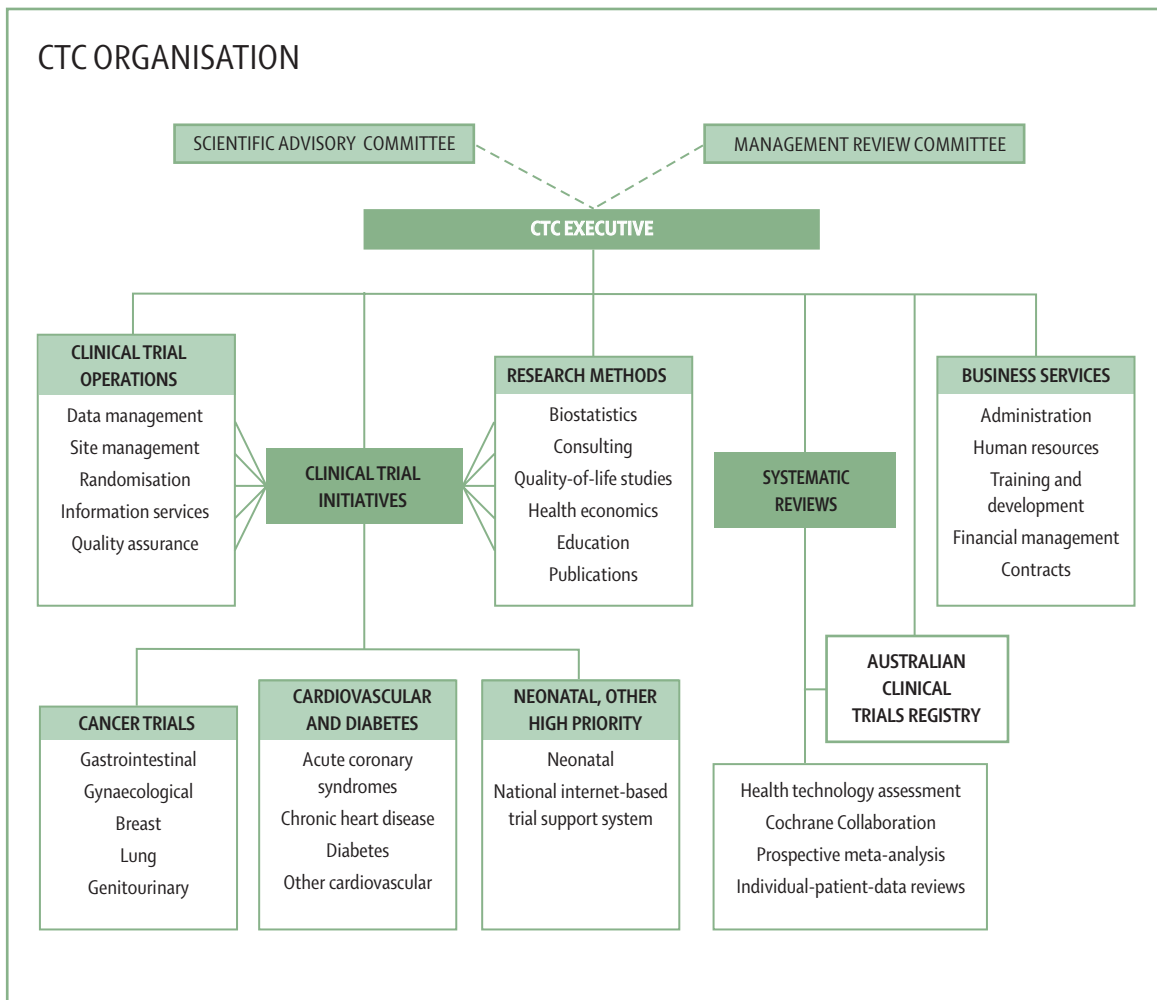
Anthony Keech
Deputy director

Anthony Keech, cardiologist and epidemiologist, co-directs the CTC research program. He is professor in the Department of Medicine at the University of Sydney and a leading international figure in lipid and cardiovascular clinical trials. Professor Keech is chairman of the FIELD

study on heart disease and diabetes, the largest trial of patients with diabetes and the largest trial ever conducted in Australia, which was completed in 2005. He is also a practising consultant cardiologist at Royal Prince Alfred Hospital.



CTC ORGANISATION



CTC EXECUTIVE

At right (left to right): Wendy Hague, director of the clinical trials program, John Simes, director, and Anthony Keech, deputy director.



At left: Dorothea Sophia, who retired in 2005, was business manager of the CTC with responsibility for the CTC's business services.



FUNDING IN 2004-2005

Granting body	Project	2004	2005
National Health and Medical Research Council	Program grant	1 315 000	1 353 799
National Health and Medical Research Council	Research fellowships	291 000	317 641
National Health and Medical Research Council	Clinical trials	894 575	1 360 979
National Health and Medical Research Council	Australian Clinical Trials Registry	—	120 000
University of Sydney	Infrastructure and institute grants	804 235	805 586
University of Sydney Cancer Research Fund	Patients' preferences study	47 500	—
Department of Health and Ageing	Reviews of medical technologies and procedures	406 204	712 862
Department of Health and Ageing	Biostatistics Collaboration of Australia	146 095	69 020
Department of Health and Ageing	Cochrane reviews	60 000	55 000
Department of Education, Science and Training	Clinical Trials and Data Information Network	470 000	—
NSW Department of Health	ASPIRE study	50 000	62 500
NSW Cancer Council	Cancer trials	65 425	137 132
NSW Cancer Council	Cochrane systematic reviews	—	6 053
NSW Cancer Institute	Infrastructure support for cancer trials (partnership grant)	—	641 694
National Breast Cancer Council	Cochrane systematic reviews	—	5 404
National Breast Cancer Foundation	SNAC study	49 727	141 600
Cure Cancer Australia	Breast cancer systematic review	—	34 622
Cancer Council Australia	SCOTROC study	—	30 000
SA Cancer Council	ZEST study	—	24 400
Waikato Breast Cancer Trust	SNAC study	29 174	18 155
National Heart Foundation	LIPID study	—	140 000
Australasian Society of Thrombosis & Haemostasis	ASPIRE study	57 455	—
National Institute for Clinical Excellence and National Health Service (UK)	Cochrane reviews	—	35 631
UK Medical Research Council	INIS study	107 205	75 782
University of Glasgow	SCOTROC study	—	61 380
Cardiac Society of Australia and New Zealand	Scholarship	—	29 406
Australasian Gastro-Intestinal Trials Group	Cancer trials	531 256	297 617
Australian New Zealand Breast Cancer Trials Group	Breast cancer trials	138 314	128 313
Gynecologic Oncology Group (US)	Gynaecology trials	262 354	247 507
Merck and University of Oxford	VICTOR study	214 106	—
Aventis Pharma	Cancer trials (GOG 0201)	87 345	15 921
Aventis Pharma	ATTAX study	95 796	148 277
Alphapharm	ATTAX 2 study	—	47 537
Bayer	ASPIRE study	100 000	100 000
Bristol-Myers Squibb	C017 study	746 843	933 541
Fournier Pharma	FIELD study	7 596 760	7 662 416
Pfizer	DaVinci study	130 874	104 934
Roche (through AGITG)	MAX study	—	302 745
Schering Plough	CALYPSO study	—	50 000
Various	Donations, consultancies, workshops, student fees	322 723	251 282
TOTAL FUNDING		15 019 965	16 528 735

BUILDING CAPACITY FOR CLINICAL TRIALS RESEARCH

THE CLINICAL TRIALS PROGRAM

Flexetrial: the internet-based clinical trials data and information network
Grant to develop internet-based systems
Oncology program initiatives

COLLABORATIONS

Research collaborations
Biostatistics Collaboration of Australia

THE CLINICAL TRIALS PROGRAM

The CTC has participated in more than 50 investigator-initiated, cooperative-group clinical trials, and coordinated some of the largest randomised trials initiated by Australian investigators (LIPID and FIELD studies, each with over 9000 patients). Over 40 000 patients have been randomised to these trials. All clinical trials undertaken through the CTC are conducted strictly according to guidelines for clinical trials research and conduct, and are audited by regulatory authorities, sponsors and the CTC itself.

This history has been a basis for expansion and consolidation of the clinical trials program over the past few years. The continuing enhancement of the strategic directions of the program has three main ingredients.

- First, the CTC instituted a matrix structure for the operation of clinical trials. The functions of project management, data management and site management, which are common to all trials, became discrete parts of the management structure. The three groups work to identify ways to increase efficiency and effectiveness and assist project managers and their teams to meet their objectives, which includes training staff in these functions.
- Second, the CTC continues to develop the generic, internet-based trial management system, Flexetrial; managers of CTC trials and other investigator-initiated trials can slot into this ready-made system of trials management.
- Third, the CTC has maintained and strengthened ties with Australia-wide groups of investigators. Their potential to increase the number and relevance of their trials has recently been boosted by new grants for trials infrastructure.

Therefore the CTC finishes 2005 with a solid basis for the prospect of new and better trials in 2006.



The CTC: a national asset

After steering many trials and helping others in theirs, the CTC has a critical mass of expertise in all aspects of trials design, conduct and analysis. Staff include clinical data managers, data systems specialists, clinicians, biostatisticians and other highly qualified and experienced professionals. It is well placed to apply this experience in sustaining new and better trials research.

Australian clinical trials programs are well established in the areas of cancer, vascular disease, diabetes and HIV. However, trials in many other areas are lacking, as is shown by the requests of groups approaching the CTC for help, the lack of high-level evidence for some new treatments and for the true value of new technologies, and the controversies in defining optimal health care.

It is difficult for an individual clinical researcher to launch a major clinical trial, and the cost to create and maintain a database to regulatory standards is high. The CTC has foreseen this need, and has resolved to help narrow the gaps in trials research by developing support systems for investigators. Grants received in 2005 are clearing the way toward making this possible.

Flexetrial: the internet-based clinical trials data and information network

Assisted by a Systemic Infrastructure Initiative grant from the Department of Education, Science and Training covering the years 2002 to 2004, the CTC has been developing Flexetrial, a generic internet-based clinical trials data and information network that meets national and international standards and which is currently being implemented in several national and international investigator-initiated trials.

Partners in this CTC-led project are the University of Queensland, Monash University, the University of Sydney and Phase Forward.

Flexetrial has been shaped with the specific needs of public health clinical trials research in mind. The aim is to enable academic research institutions, among others, to conduct large multicentre national and international clinical trials in Australia more efficaciously, economically and efficiently than has been possible so far. A particular focus of the CTC's strategy in recent years has been to build and strengthen the infrastructure for clinical trials in areas of national interest.

New grants: a national internet-based trial support system

The CTC was fortunate in gaining an NHMRC Enabling Grant in 2005 to generate and mobilise clinical trials expertise and internet-based trials systems over the next five years. Grants from the Enabling Grants Scheme are intended to support excellent facilities or activities (to be available to Australian researchers) where there is a clearly demonstrated national need for them to underpin aspects of the national health and medical research effort.



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.



The grant will allow the CTC to continue and expand on the work already done in developing Flexetrials.

The next step is to bring about its use in the Australian research community so that it can fulfil its purpose as a national resource for public-good, investigator-initiated trials in new areas of need. The system will be available to interested investigators to help them launch new high-quality clinical trials.

Priority will be given to trials:

- evaluating surgery
- evaluating new health technologies
- assessing management strategies (such as multidisciplinary care, hospital in the home)
- in alternative and complementary medicine
- in supportive and palliative care, ambulance services and nursing care.

Funds from the new grant will complement the funding from government and industry for specific trials and projects.

The CTC already has strong links with Monash University, the University of Queensland and the George Institute for International Health. The CTC's trials system will facilitate or foster collaborations with other major clinical trial centres in Australia wishing to undertake related activities.

Oncology program initiatives

The CTC houses the secretariats of the Australasian Gastro-Intestinal Trials Group (AGITG) and the Australian and New Zealand Gynaecological Oncology Group (ANZGOG). Both are multidisciplinary clinical trials groups dedicated to improving the outcomes of patients through randomised phase III trials and novel phase II studies. They consist of clinical investigators working directly with patients in hospitals around Australia and elsewhere. These investigators know the needs of patients. They conceive new trials and conduct them, recruit patients to trials, hold scientific meetings and participate in various educational activities.

The CTC plays a key role in the design, conduct and analysis of clinical trials undertaken by these groups.

Grant for the CTC's work with cancer collaborative groups

In 2005, the CTC was successful in obtaining a grant from the Cancer Institute NSW to support the work of these groups over the next three years. It will be used to appoint expert dedicated oncology clinical trials staff to help conduct the next generation of trials, expand the clinical trials program and run an effective quality-assurance program.

This program will also assist hospitals throughout New South Wales, including those in regional and rural areas, to participate in and conduct high-quality clinical trials run through these two groups. It will give cancer patients more opportunity to participate in clinical trials that answer important clinical questions about prevention, treatment and supportive care.

Support through this grant will enable the groups to, first, increase and strengthen their existing networks, second, initiate clinical trials to address important public health questions faster and, third, report the results sooner.

Grant for a clinical trials partnership in trial operations, biostatistics and audit

The CTC has successfully conducted or been an active participant in 38 cancer trials and has provided strategies or systems for patient recruitment, trial and data management, study coordination, information systems and randomisation in an environment of academic rigour and excellence. In addition, the CTC is a leader in biostatistical methodology and analysis.

With this background, the CTC has been recognised as a major partner in a new cooperative clinical trials program involving other New South Wales centres and groups: three years of funding from the Cancer Institute NSW was obtained in 2005. The research program of this partnership will support investigator-initiated cancer clinical trials undertaken or coordinated in NSW and led or supported by the NSW Cancer Trials Group (CTG).

The CTC will contribute to clinical trials operations facilities (including the internet-based clinical trials database system); leadership, advice and support in biostatistics; and a quality-assurance program, including auditing.



BUILDING POTENTIAL THROUGH COLLABORATION WITH OTHERS

Part of the CTC's contribution to the national capacity in medical research is through its strong links with collaborative groups of widely dispersed investigators.

The focus in the past has been on evaluating strategies for treating and preventing the major causes of illness and premature death in Australia: cardiovascular disease, cancer and diabetes. Australasian collaborations of cardiologists and physicians are part of international efforts for treatment of acute myocardial infarction (the large trials of the international VIGOUR group, including the recent HERO-2 trial) and preventing coronary heart disease events (LIPID trial; see page 31). The recently completed FIELD trial (see page 26) evaluated prevention of cardiovascular events in diabetes. Many of the groups examining treatments for various cancers and taking part in international oncology studies have been set up and managed by the CTC.

More recently, new associations have been looking at less common, but very important, causes of death and disability: the ASPIRE group for deep-vein thrombosis (see page 16), and the neonatal groups for preventing disability in babies (see page 29).

The CTC also works closely with people in Australian universities in projects such as the internet-based trials infrastructure project and the Biostatistics Collaboration of Australia.

Much of the CTC's research involves contracts with industry and government, because of the nature of the work (such as drug trials) and the scale of funding required. Partnerships that lead to better health outcomes are a long-standing part of the CTC's tradition.



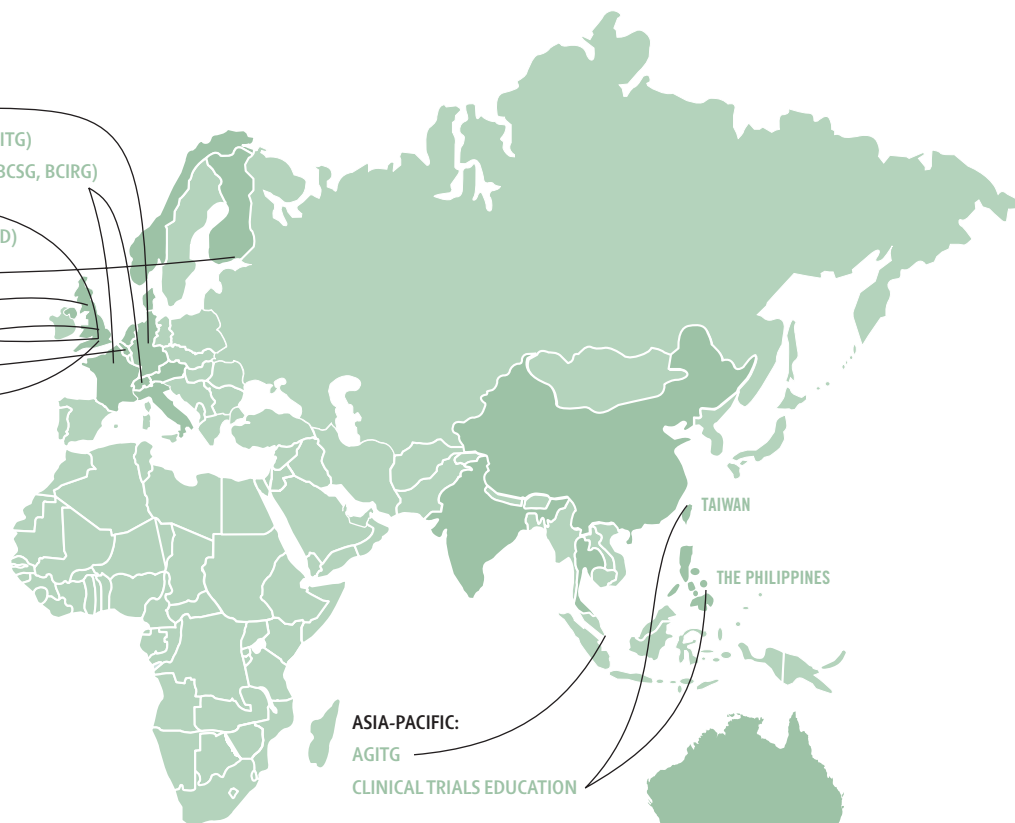
Institution	Nature of institution	Activity
ANZ Breast Cancer Trials Group (ANZ BCTG)	Collaborative group for breast cancer trials: Australia, New Zealand International collaborations: International Breast Cancer Study Group (IBCSG), Breast International Group (BIG), International Breast Cancer Intervention Study (IBIS)	Statistical centre for group, including randomisation
ANZ Germ Cell Tumour Study Group (ANZ GCTG)	Collaborative group for testicular cancer trials: Australia, New Zealand	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 Society of Thrombosis and Haemostasis	Professional group undertaking thrombosis trials: Australia, New Zealand	Coordinating centre
ANZ Gynaecological Oncology Group	Collaborative group undertaking gynaecological cancer trials: Australia, New Zealand International collaborations: Gynecological Cancer Intergroup (GCIG), International Gynaecological Cancer Intergroup (IGCI), Gynecologic Oncology Group (GOG)	Coordinating centre
Australian Clinical Trials Registry	National register of Australian clinical trials	Coordinating centre



COLLABORATIONS

EUROPE:

- GASTROINTESTINAL TRIALS
(EORTC, ESPAC, MRC, OCTC, WITH AGITG)
- BREAST CANCER TRIALS (ANZ BCTG, IBCSG, BCIRG)
- CHOLESTEROL TREATMENT TRIALISTS' COLLABORATION (OXFORD)
- FIELD TRIAL
- INIS TRIAL (NPEU)
- SCOTROC TRIAL
- VIGOUR GROUP
- COCHRANE COLLABORATION



ASIA-PACIFIC:

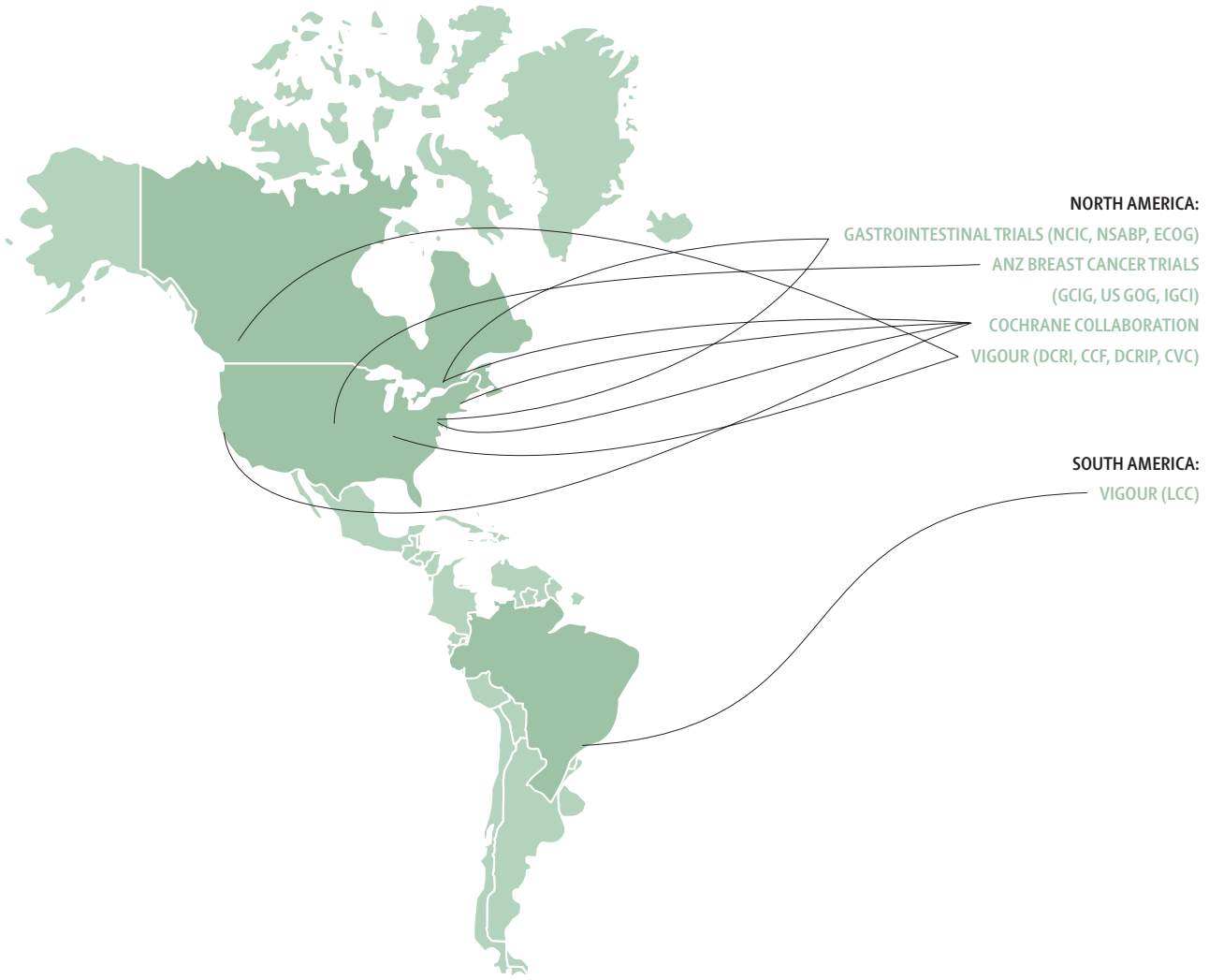
- AGITG
- CLINICAL TRIALS EDUCATION

AUSTRALIA AND NEW ZEALAND:

- AGITG, ANZ BCTG, ANZ GERM CELL TRIALS GROUP, ANZ GOG, ASPIRE, ACTR, BIOSTATISTICS COLLABORATION OF AUSTRALIA BOOST, CHOLESTEROL TREATMENT TRIALISTS' COLLABORATION, COCHRANE COLLABORATION, FIELD TRIAL, INIS TRIAL, LIPID TRIAL, MSAC, SCOTROC, SNAC, AND VIGOUR GROUP: FMC, GLCC



Institution	Nature of institution	Activity
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
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
Department of Health and Ageing	Government, Australia	Provide assessments of new technologies and other research services BCA: biostatistics education
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
LIPID Study Group	Collaborative group for LIPID cholesterol-lowering trial: Australia, New Zealand	Coordinating centre



Institution	Nature of institution	Activity
National Cancer Institute of Canada Clinical Trials Group (NCIC CTG)	Trials research group	Collaboration on cancer trials and meta-analysis
National Heart Foundation	Nongovernment organisation , Australia	Coordinate the LIPID trial for the NHF
National Perinatal Epidemiology Unit (NPEU), University of Oxford	Research institution: UK	Co-collaborator on the INIS neonatal trial
NSW Cooperative Oncology Group	Collaborative group: NSW	Coordinate centre for the group
Oxford Clinical Trials Consortium (OCTC)	Trials research group: UK	Cancer trials
Prospective Pravastatin Pooling project	Collaborative group: Australia, New Zealand, United States, Scotland	Coordinate 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)



Erica Jobling
Executive officer, Biostatistics
Collaboration of Australia

Biostatistics Collaboration of Australia: meeting a national need for qualified biostatisticians

A postgraduate education program in biostatistics, delivered by distance means, is conducted by the Biostatistics Collaboration of Australia (BCA), a virtual training institution conducted from offices at the CTC. The collaboration comprises the University of Sydney, the Australian National University, Macquarie University, Monash University, the University of Melbourne, Newcastle University and the University of Queensland.

The BCA's program fills the gap between programs in public health and epidemiology and general statistics courses. By combining the best talents from around the country, this collaboration has developed a focused curriculum with a mission to provide Australia with well-trained professional biostatisticians. The courses deliver a sound mathematically based grounding in statistical methods with a strong emphasis on application to all areas of health and medical research.

The BCA was established in 2001 in response to a shortage of biostatistical expertise in Australia. It is an unincorporated consortium of leading biostatisticians from universities, government and industry. Representatives from these bodies comprise the steering committee, which administers the program.

In 2004, 142 students were enrolled in the program, with an increase to 172 in 2005. The group recently developed an additional elective unit, 'Advanced clinical trials and meta-analysis', which educates students to an advanced level in the statistical principles, issues and methods of the design and analysis of randomised controlled trials.



As part of the BCA's quality-assurance guarantees, the BCA was independently reviewed in August 2004. The review found that:

The BCA has been successfully established as an outstanding multi-institutional system for developing, strengthening and sustaining Australia's workforce of career biostatisticians. Through intensive coordination of expertise in seven universities and the use of distance education, the BCA is able to offer an educational program in biostatistics that is unique throughout Australia, and indeed the world, in terms of its depth and scope.

The NSW Department of Health employs trainees in a biostatistics officer training program. Students complete the Master of Biostatistics as part of this. Since 2001, six students have graduated with masters degrees from the University of Sydney.



BIostatistics COLLABORATION OF AUSTRALIA STEERING COMMITTEE

- Ms Caro Badcock, Covance Pty Ltd
- Professor John Carlin, University of Melbourne
- Dr Keith Dear, Australian National University
- Professor Annette Dobson, University of Queensland
- Ms Kate Brown, Department of Health and Ageing
- Associate Professor Andrew Forbes, Monash University
- Associate Professor Val Gebski, University of Sydney
- Associate Professor Gillian Heller, Macquarie University
- Associate Professor Ian Marschner, Pfizer Pty Ltd
- Dr Philip McCloud, Roche Products Pty Ltd
- Ms Helen Moore, NSW Department of Health
- Dr David Sibbritt, University of Newcastle
- Associate Professor Judy Simpson, University of Sydney

CTC statisticians contribute to the Biostatistics Collaboration of Australia by developing, coordinating and teaching various subjects, including: 'Principles of statistical inference' – Adrienne Kirby, coordinator (left), 'Advanced clinical trials and meta-analysis' – Stephane Heritier, coordinator (centre), and 'Design of experiments and randomised controlled trials' – Val Gebski, coordinator, with University of Newcastle (right).

NEW TRIALS

CO 17

MAX

ASPIRE

BOOST II

STARTUP

CO 17: a new treatment for colorectal cancer that has progressed after chemotherapy

Cetuximab is a monoclonal antibody, which targets the epidermal growth factor receptor (EGFR), a protein on the surface of many cancer cells and some normal cells. When cetuximab binds to EGFR, the natural growth factors are barred from the receptor and therefore are unable to stimulate the cells. This leads to inhibition of cell growth and induction of cell death. Monoclonal antibodies are an important class of anticancer drug because they are very specific.

The CO 17 study is designed to determine the effectiveness of cetuximab (Erbix) on survival and quality of life in people with advanced colorectal cancer whose cancer has progressed after chemotherapy. It is sponsored by the AGITG in conjunction with the National Cancer Institute of Canada Clinical Trials Group (NCIC CTG). It is an investigator-initiated phase III study using cetuximab and best supportive care versus best supportive care alone for heavily treated metastatic colorectal cancer.

The CTC has coordinated all clinical aspects of the trial in Australia, New Zealand and Singapore.

Recruitment opened to the CO 17 trial in Australia in November 2003, with a target of 100 patients over two years. At the close of recruitment in August 2005, Australia had recruited 252 patients (from the international target of 500) to the trial. The trial received a positive report following an audit by Bristol-Myers Squibb US in 2005. Now in the follow-up stage, CO 17 remains one of the CTC's most successful trials in terms of recruitment and coordination. The results will be presented at an international meeting early in 2007.

ETHICS APPROVAL FOR ALL TRIALS

Each clinical trial is reviewed and approved by a central scientific committee (NSW Shared Scientific Assessment Committee), the University of Sydney Ethics Committee, and the ethics committees of each participating institution.

Participants:

Patients with heavily treated metastatic colorectal cancer who have a positive test for epidermal growth factor receptor (EGFR)

Study drug: cetuximab (Erbix)

Primary outcome measure: survival

Recruitment: 252

Recruitment target: 500 (100 from Australia and New Zealand)

Funding: Bristol-Myers Squibb

Cooperative group: NCIC, AGITG

PATIENTS WITH TREATED
EGFR-POSITIVE COLORECTAL CANCER

Cetuximab + best
supportive care

Best supportive care

TIME TO PROGRESSION, SURVIVAL, QUALITY OF LIFE



MAX: combination treatment compared with a single drug for colorectal cancer

The MAX study is a new trial designed to determine the optimal low-toxicity regimen for a broad range of patients with advanced colorectal cancer. The study aims to improve the duration of survival without compromising quality of life.

The MAX study, which is sponsored by the AGITG and supported by Roche Products Pty Ltd, is an investigator-initiated phase II–III study using monotherapy compared with combination treatment for previously untreated metastatic colorectal cancer. Capecitabine (Xeloda) and mitomycin C are standard chemotherapy treatments, and bevacizumab (Avastin) is a recombinant humanised anti-VEGF monoclonal antibody, which inhibits the growth of tumour blood vessels.

The CTC is coordinating all aspects of the trial, and the CTC's internally developed internet-based data system will be used for collection of data from participating institutions in Australia, New Zealand and the United Kingdom, ensuring that processes for conduct of the trial are the best available. Recruitment began in June 2005.



MAX team

Sian Munro, Kate Wilson (trial coordinator) and Michelle Cummins
(not pictured: Alyson France)

Participants:
Patients with previously untreated metastatic colorectal cancer

Study drug: capecitabine, bevacizumab and mitomycin C

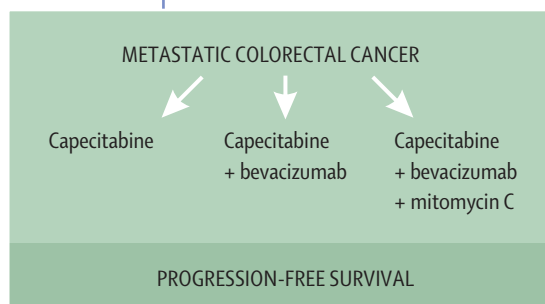
Primary outcome measure: progression-free survival

Recruitment target: 333

Recruitment: 104 from 26 Australian sites

Funding: Roche Products Pty Ltd

Cooperative group: AGITG





Rebecca Mister
ASPIRE study manager

ASPIRE and the WARFASA study are joining in the prospectively designed meta-analysis, INSPIRE (see page 44).

TRIAL MONITORING

Arising from the policy of having common trials systems that apply to all CTC trials, generic procedures for trial monitoring have been developed. Monitoring activities expanded during 2004–2005, with the strengthening of generic CTC monitoring plans, on-site monitoring procedures and the training of staff as dedicated site monitors.

Staff of the AGITG CO 17 and MAX trials and the ANZGOG Calypso trial have recently been trained in site monitoring.

Monitoring processes will continue to be adapted to internet-based data-capture case-report forms which are also used in the ASPIRE and BOOST II trials. This allows CTC staff to view data on line before visiting sites.

Aspirin may prevent recurring deep-vein thrombosis: ASPIRE study

Patients who have had deep-vein thrombosis or pulmonary embolism are at risk of recurrence after stopping warfarin treatment. Long-term warfarin prevents recurrence, but may cause significant bleeding. Preventing recurrence with low-dose aspirin is being investigated in the ASPIRE (Aspirin to prevent recurrent venous thromboembolism) study. Low-dose aspirin is a simple, inexpensive, and widely practicable treatment which could potentially help thousands of patients.

ASPIRE is a multicentre, randomised double-blind placebo-controlled trial examining the efficacy and safety of low-dose aspirin after initial anticoagulation therapy to prevent recurrent venous thromboembolism.

After a pilot study which began in 2003, recruitment of sites and patients began in 2004. The target is 1500 participants in Australia and New Zealand and 3000 internationally.

ASPIRE is the first trial to use the CTC's internet-based trials management system, Flextrials.

Participants:

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

Study drug: acetylsalicylic acid (aspirin)

Main outcome measures:

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

Recruitment target: 3000

Recruitment: 241

Funding: NHMRC, Bayer, Australasian Society of Thrombosis and Haemostasis (ASTH)

Cooperative group: ASTH

DEEP-VEIN THROMBOSIS OR PULMONARY EMBOLISM
TREATED WITH HEPARIN AND WARAFIN

Aspirin

Placebo

THROMBOSIS OR EMBOLISM

BOOST II (Benefits of oxygen saturation targeting): finding the right level of oxygen for newborn babies

Each year in Australia, about 850 children born before 28 weeks of gestation are admitted to neonatal intensive care units and about 75% are discharged home alive. These very premature infants have a higher than normal risk of chronic lung disease, poor growth, respiratory illness, visual deficits, cerebral palsy, sensorineural disability and cognitive impairment. They account for most of the costs of neonatal intensive care.

The most common therapy is oxygen. It has been associated with better survival and less disability. However, premature infants are highly sensitive to the harmful effects of oxygen. Levels of oxygen in a lower range may increase heart abnormalities and lung disease and impair brain development; levels in a higher range may increase blindness and lung disease, and impair brain development.

Currently, the best level of oxygenation is not known. A wide spectrum of opinion and practice exists. BOOST II is one of several large trials around the world which will ascertain which of two currently used ranges of oxygen saturation is better in terms of net benefit. Infants will be randomised to a target oxygen saturation of 85–89% or to a target of 91–95%. These levels are lower than those of the first BOOST trial (91–94% and 95–98%) in which the higher saturation showed no benefit.

The trial is currently about to begin randomisation. It will enrol 1200 very premature babies from the major hospitals in Australia and will contribute to a worldwide prospective meta-analysis of data from about 5000 babies.

This trial will answer important questions about the benefits and risks of higher compared with lower oxygen levels, and will improve the care of thousands of Australian children and millions more worldwide.

Blinding of clinical staff in BOOST II

BOOST II has a novel blinding method successfully used in the first BOOST trial.

The oximeters, which display oxygen saturation in the infant's blood, will be calibrated to display a value 3% higher than the actual saturation in infants in the low-oxygen group, or 3% lower than the actual saturation in infants in the high-oxygen group.

The high-oxygen group will have an actual target range of 91–95% and the low-oxygen group an actual target range of 85–89%. Staff will aim for an oxygen saturation of 88–92% for all and remain unaware of the real saturation range.



Pulse oximeter

The pulse oximeter is a machine about the same size as a DVD player, kept on a shelf near the baby. These pictures show a pulse oximeter and its display. In this case, the baby's oxygen saturation reading is 99% and heart rate is 81.



Alpana Ghadge

BOOST II study manager

Participants:

Neonates born before 28 weeks gestation

Study drug: Supplementary oxygen to 85–89% saturation or 91–95% saturation from the day of birth until the baby breathes air

Primary outcome measure:

Death or survival with major disability at two years

Main secondary outcome measures:

- retinopathy of prematurity
- chronic lung disease

Recruitment target: 1200

Funding: NHMRC in Australia (Health Research Council in New Zealand)

Cooperative group:

BOOST II Investigators





David Burgess
Coinvestigator and coordinator
of the STARTUP study

Preparing for a trial with a meta-analysis

A review of existing trials can be a starting point for a new trial. Going through this process ensures that the new trial is not a duplicate and does not look for answers that have already been found. A preliminary meta-analysis of the available evidence supports the reasons for undertaking the trial and helps the investigators to refine the hypotheses.

It is unscientific and unethical to embark on new research without first analysing systematically what can be learned from existing research
— *Iain Chalmers*

STARTUP has been aided by the STARTUP investigators' meta-analysis of trials concerned with ways of preventing postoperative atrial fibrillation. The meta-analysis showed that the interventions were effective in preventing monitor-recorded atrial fibrillation and that a multicentre trial of the most effective strategies was warranted to ascertain the net clinical benefit. These results were presented in 2005 and will be published in 2006.

Searching for the best way to control heart rhythm after heart surgery

Atrial fibrillation, a fast irregular rhythm of the heart, is the most common cause of delay in discharge from hospital after cardiac surgery and the most common reason for readmission to hospital. The occurrence of postoperative atrial fibrillation has been linked to stroke, delirium and neurocognitive decline. There is no consensus on a preventive strategy. Surgical techniques are continually improving and beta-blockers are now routinely being used after surgery to reduce atrial fibrillation. Despite this, postoperative atrial fibrillation is still increasing.

STARTUP (Stop atrial fibrillation after revascularisation using prevention) was commenced as a pilot study to test two of the most promising treatments to prevent atrial fibrillation: biatrial overdrive pacing for 96 hours after the operation, and amiodarone, an antiarrhythmic drug, before and after the operation. Biatrial pacing uses temporary wires placed during the surgery at the heart's right atrium and left atrium. The pacemaker is set at ten beats per minute above the person's intrinsic heart rate ("overdrive pacing") to suppress atrial ectopic beats.

The preliminary results of the pilot study confirm the high incidence of atrial fibrillation after surgery: 43% of patients had atrial fibrillation, highlighting the need for a definitive prevention strategy.

David Burgess was awarded a scholarship from the Cardiac Society of Australia and New Zealand for his research on STARTUP in 2005. The principal investigator is Professor Anthony Keech.

Participants:

People aged over 55 years at risk of atrial fibrillation after cardiac surgery

Design: two-by-two factorial

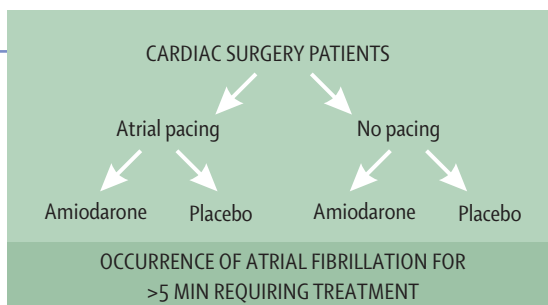
Interventions:

- biatrial overdrive pacing
- amiodarone, 10 mg/kg per day for five days before and five days after operation

Primary outcome measures: atrial arrhythmia for more than five minutes requiring treatment

Recruitment: 70

Funding: NHMRC Program Grant to seed new research



IMPROVING SURVIVAL AND QUALITY OF LIFE IN CANCER

BREAST CANCER

GASTROINTESTINAL CANCER

GYNAECOLOGICAL CANCER

Established cancer trials continue the CTC's tradition

The CTC has a strong record of working with cancer cooperative groups, clinical trial networks and other organisations (including the pharmaceutical industry), locally and internationally, in the conduct of investigator-initiated clinical trials contributing to the welfare of patients and public health.

The oncology program has played a key role in establishing and operating some of these: for example, the AGITG (see page 21) and the ANZGOG (see page 24). The groups have international links with overseas and international collaborative groups, including the National Surgical Adjuvant Breast and Bowel Project (NSABP), the National Cancer Institute of Canada Clinical Trials Group (NCIC CTG), the European Organisation for Research and Treatment of Cancer (EORTC), the Oxford Clinical Trials Office (OCTO), the Gynaecologic Cancer Intergroup (GCIG), the Gynecologic Oncology Group (GOG) and the Medical Research Council (MRC) (see page 10). These alliances have resulted in researchers from sites in Australia and New Zealand successfully recruiting patients to international trials, including: C07, ESPAC-3, advanced GIST, CO 17 gastrointestinal cancer trials, and Calypso and GOG 199 gynaecology trials. The CTC is responsible for site activation, recruitment, monitoring, audit and other trial activities.

The CTC is the randomisation and statistical centre for the Australian New Zealand Breast Cancer Trials Group (ANZ BCTG), which works with the International Breast Cancer Study Group (IBCSG). The CTC has also been involved in quality-of-life and cost-effectiveness studies for this group.

With the rapid development of new therapies and a greater emphasis on biological mechanisms of action, collaboration on such trials is now a critical component of success in answering important questions. A benefit of such enterprises is faster access of patients to novel therapies. As well, Australian clinicians, researchers and patients can contribute to the continued development of new and improved treatments in a global environment.

Oncology program executive

Wendy Hague, Burcu Cakir, Martin Stockler,
John Simes (not pictured: Kathleen Scott,
Corona Gainford and Val Gebiski)





Xanthi Coskinas
SNAC study coordinator

A popular trial to reduce the side-effects of breast cancer surgery

The SNAC (Sentinel node biopsy versus axillary clearance) trial, which started recruiting patients in 2001, is the first large trial of surgical treatment of breast cancer in Australasia. Its aim is to ascertain whether the outcomes after biopsy of a sentinel lymph node are as good as the outcomes after axillary node clearance, the standard procedure.

The trial arose from a realisation that lymphoedema (pain and swelling in the arm), a common complication of breast lymph node surgery, was a major concern of women with breast cancer. Removal of sentinel nodes is much less invasive and may be much less damaging than removal of many lymph nodes.

The trial is expected to provide important information on the effects of axillary surgery and the quality of life of women having breast cancer surgery.

Recruitment was completed in May 2005, over a year earlier than projected, with 1088 patients enrolled. The success of recruitment was attributed to the interest of women and clinicians in the new procedure, the support of cancer organisations, the workshops and newsletters provided by the management team, and the fact that the Royal Australasian College of Surgeons (RACS) facilitated the collaboration of the centres. Patients were recruited from a broad range of small and large, and public and private, centres. Before hospitals could take part in the trial, their surgeons took part in workshops where they developed their skills in discussing trials with patients and obtaining consent. Each centre was first accredited by a management committee review of 20 consecutive cases of the sentinel node biopsy procedure, including operative and nuclear medicine techniques.

The trial's measured outcomes include both objective and self-reported quality-of-life measures. Patients are followed up at one, six and twelve months, and then annually.

SNAC 2

SNAC 2 is an extension of the SNAC 1 trial, and is expected to begin recruitment early in 2006. The expected number of participants is 1012. Its aim is to determine the safety and effectiveness of sentinel-node-based management of the axilla for women with primary breast cancer. SNAC 2 has extended the eligibility criteria of SNAC 1 to include women with multiple primary tumours in the same breast and women with tumours larger than 3 cm. The primary endpoint for this trial is the risk of recurrence of the tumour, particularly local axillary recurrence. Also, the diagnostic accuracy of sentinel node biopsy is a particular focus of the trial.

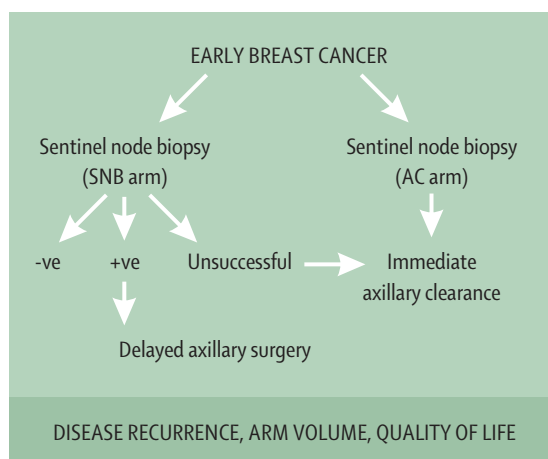
Participants (SNAC 1):
Women with a single primary breast tumour <3 cm in diameter in whom disease staging was indicated

Main outcome measures:
Early axillary morbidity, lymphoedema, axillary tumour recurrence, survival, disease-free survival, use of adjuvant therapies, number of surgical episodes, days in hospital

Recruitment: 1088

Funding: Medical Benefits Fund, Commonwealth Department of Health and Ageing, National Breast Cancer Foundation, National Health and Medical Research Council

Cooperative group:
Royal Australasian College of Surgeons (RACS)



Trials of the Australasian Gastro-Intestinal Trials Group

The CTC is the coordinating centre for the Australasian Gastro-Intestinal Trials Group (AGITG), which has a network of clinical investigators across Australia and New Zealand.

Since it began in 1991, the AGITG has participated in or conducted 24 gastrointestinal cancer trials and recruited more than 1250 patients to investigator-initiated trials, trials that in most cases would not, and often could not, be conducted by industry. The CTC's participation in the different trials ranges from provision of single services, such as randomisation or statistical analysis, to complete management of the trials.

The CTC coordinated an AGITG trial investigating whether it is better to start chemotherapy on diagnosis of colon cancer, when patients still feel well, or to wait until they have symptoms. The results, published in the *British Journal of Cancer*, showed that delayed treatment did not affect the patients' survival, and allowed them better quality of life in the meantime. The study was analysed and reported as part of a meta-analysis (see page 42).

The CTC provided data management and statistical services to the AGITG and the Trans-Tasman Radiological Oncology Group (TROG) for the trial on whether adding chemoradiotherapy to surgery helped people with cancer of the oesophagus. The trial was completed, and results were published in 2005 in *Lancet Oncology*. The chemotherapy was safe and reduced the growth of the tumours, but did not necessarily improve survival.

Another completed trial, a pilot study of the use of octreotide in advanced hepatocellular carcinoma, has also been completed and will be published soon.



Danielle Miller
Associate program manager for the AGITG trials

Some AGITG trials

Trial	Participants	Interventions	Main outcome measures	Status
Da Vinci: Phase III trial of irinotecan versus irinotecan + De Gramont schedule 5-fluorouracil and folinic acid in patients with previously treated metastatic colorectal cancer (AG0103CR)	People with previously treated metastatic colorectal carcinoma	<ul style="list-style-type: none"> irinotecan + 5-fluorouracil + leucovorin irinotecan 	<ul style="list-style-type: none"> objective tumour response toxicity safety progression-free survival quality of life overall survival 	The trial was planned as a 2-way trial also looking at the role of celecoxib in reducing side effects, but these arms have been suspended. Recruitment target: 300 Recruitment: 9
ATTAX: Phase II study evaluating a weekly schedule of docetaxel with cisplatin and 5-fluorouracil or capecitabine (AG0603G)	Patients with advanced oesophageal or gastric cancer	<ul style="list-style-type: none"> docetaxel, cisplatin, 5-fluorouracil docetaxel, capecitabine 	<ul style="list-style-type: none"> tumour response 	Recruitment target: 100 Recruitment: 75
ATTAX2: Phase II study of cetuximab plus docetaxel in docetaxel-refractory patients with EGFR-positive cancer (AG0603G EXT)	Patients with advanced oesophageal or gastric cancer	<ul style="list-style-type: none"> cetuximab + docetaxel 	<ul style="list-style-type: none"> tumour response 	Recruitment target: 35 Recruitment: 8
GOFURTO: Phase II study of fixed dose rate gemcitabine–oxaliplatin integrated with concomitant 5-fluorouracil and radiotherapy to treat localised pancreatic cancer (AG0503P)	Patients with localised pancreatic cancer	<ul style="list-style-type: none"> radiotherapy, gemcitabine and oxaliplatin 	<ul style="list-style-type: none"> tumour response safety 	Recruitment target: 45 Recruitment: 10



Some AGITG trials (continued)

Trial	Participants	Interventions	Main outcome measures	Status
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 (AG0501CR)	Patients with previously untreated metastatic colorectal cancer	<ul style="list-style-type: none"> • capecitabine • capecitabine + bevacizumab • capecitabine + bevacizumab + mitomycin 	<ul style="list-style-type: none"> • toxicity • response • progression-free survival 	<i>Recruitment target:</i> 333 <i>Recruitment:</i> 104
ABC: Phase II trial of gemcitabine in fixed dose rate infusion compared with cisplatin in patients with biliary tract carcinoma (AG0403BT)	Patients with inoperable biliary tract carcinomas	<ul style="list-style-type: none"> • gemcitabine • cisplatin 	<ul style="list-style-type: none"> • tumour response • safety 	<i>Recruitment target:</i> 45 <i>Recruitment:</i> 25
ESPAC-3: European study of adjuvant chemotherapies in resectable pancreatic cancer	Patients with histologically proven cancer of the pancreas who have undergone surgery	<ul style="list-style-type: none"> • surgery + 5-fluorouracil + leucovorin • gemcitabine • surgery 	<ul style="list-style-type: none"> • survival • progression-free survival 	<i>Recruitment target:</i> 150 <i>Recruitment:</i> 74
C06: Oral uracil and ftorafur + leucovorin compared with 5-fluorouracil + leucovorin for patients with stages II and III carcinoma of the colon	Patients with stage II or stage III adenocarcinoma and no metastatic disease and a life expectancy of at least ten years (excluding diagnosis of cancer)	<ul style="list-style-type: none"> • 5-fluorouracil + leucovorin • UFT (tegafur and uracil) + leucovorin 	<ul style="list-style-type: none"> • disease-free survival • survival • quality of life • prognostic significance of genetic and biologic markers 	Closed <i>Recruitment:</i> 11
C07: 5-fluorouracil + leucovorin compared with 5-fluorouracil + oxaliplatin for the treatment of patients with stages II and III carcinoma of the colon	Patients with resected stage II or stage III colon carcinoma	<ul style="list-style-type: none"> • 5-fluorouracil + leucovorin • 5-fluorouracil + oxaliplatin 	<ul style="list-style-type: none"> • disease-free survival • survival 	Closed <i>Recruitment:</i> 134
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	Patients with pretreated metastatic colorectal cancer with positive EGFR	<ul style="list-style-type: none"> • cetuximab + supportive care • supportive care 	<ul style="list-style-type: none"> • survival • time to progression • response • quality of life 	<i>Recruitment target:</i> 100 <i>Recruitment:</i> 252
EORTC 62005: Phase III study of two different doses of imatinib mesylate in patients with CD117-expressing metastatic or unresectable gastrointestinal stromal tumour	Patients with metastatic gastrointestinal stromal tumour	<ul style="list-style-type: none"> • imatinib 2X daily • imatinib 1X daily 	<ul style="list-style-type: none"> • progression-free survival • survival • tumour response 	Closed <i>Recruitment:</i> 116
EORTC 40983: Phase III reoperative and postoperative chemotherapy with oxaliplatin + 5-fluorouracil + leucovorin versus surgery alone in resectable liver metastases from colorectal origin: phase III study	Colon cancer with liver metastases	<ul style="list-style-type: none"> • 5-fluorouracil + leucovorin + oxaliplatin • surgery 	<ul style="list-style-type: none"> • progression-free survival • survival 	Closed <i>Recruitment:</i> 35
EORTC 62024: Gastrointestinal stromal tumors (GIST) expressing KIT receptor: adjuvant imatinib mesylate (Glivec) versus no further therapy after surgery	Patients with resected gastrointestinal stromal tumour	<ul style="list-style-type: none"> • imatinib 	<ul style="list-style-type: none"> • overall survival • relapse-free survival • relapse-free interval 	<i>Recruitment target:</i> 8 <i>Recruitment:</i> 6

Trials of the Australian New Zealand Breast Cancer Trials Group

The Australian New Zealand Breast Cancer Trials Group (ANZ BCTG) has an agreement with the CTC to provide an ANZ BCTG randomisation and statistical centre which undertakes clinical trials registration, randomisation and statistical services. Quality-of-life and economics substudies are also under the remit of activities conducted at the CTC in collaboration with the ANZ BCTG operations office in Newcastle led by Professor John Forbes.

This service was formally reviewed in 2005 by invited international clinical trialists: Eleanor McFadden, expert data manager experienced in international multisite clinical trials and Mark Buyse, a biostatistician well known to cancer trials. The review revealed the high level of commitment and collaboration between the two centres, resulting in an excellent level of service to the sites in Australia and New Zealand recruiting patients to breast cancer trials.

Some ANZ BCTG trials

Trial	Participants	Interventions	Main outcome measures	Status
ANZ O2P2 (IBIS II): International multicentre trial of anastrozole vs placebo in postmenopausal women	1. Postmenopausal women at risk of breast cancer 2. Postmenopausal women with hormone-sensitive ductal carcinoma in situ	<ul style="list-style-type: none"> tamoxifen anastrozole 	<ul style="list-style-type: none"> breast cancer 	Opened July 2005 <i>Recruitment:</i> 1000 (international) 18 (Australia and New Zealand) <i>International target:</i> 10 000
IBCSG 22: Low dose cytotoxics as anti-angiogenesis treatment following adjuvant induction chemotherapy	Women with oestrogen-receptor-negative and progesterone-receptor-negative early breast cancer	<ul style="list-style-type: none"> 12 months of low-dose oral chemotherapy 	<ul style="list-style-type: none"> breast cancer recurrence 	Opened March 2002. <i>Recruitment:</i> 307 (international), 10 (Australia and New Zealand) <i>International target:</i> 900
ATLAS: Adjuvant tamoxifen: longer against shorter	Patients with previous breast cancer	<ul style="list-style-type: none"> tamoxifen 	<ul style="list-style-type: none"> mortality nonfatal events 	Closed in 2005. <i>Recruitment:</i> 784 (Australia and New Zealand)
ANZ 0001: Phase II trial to evaluate oral capecitabine vs cyclophosphamide, methotrexate and 5-fluorouracil (CMF) for advanced breast cancer	Patients with advanced breast cancer and no previous chemotherapy	<ul style="list-style-type: none"> intermittent capecitabine continuous capecitabine standard CMF 	<ul style="list-style-type: none"> time to progression tumour response quality of life 	<i>Closed in 2005</i> <i>Recruitment:</i> 324
ANZ 0201 (TIBER): Phase II trial of ZD1839 (Iressa) in patients with hormone-insensitive or hormone-resistant inoperable breast cancer	Advanced hormone-resistant or receptor-negative breast cancer, or progression after two hormone therapies	<ul style="list-style-type: none"> ZD1839 (Iressa) daily until disease progression 	<ul style="list-style-type: none"> clinical benefit 	Closed to recruitment in September 2004 after interim assessment showed a low rate of clinical benefit.



Julie Martyn
Associate program manager
for ANZGOG trials

Trials of the Australia New Zealand Gynaecological Oncology Group

The Australia New Zealand Gynaecological Oncology Group (ANZGOG) works to improve outcomes for women with gynaecological cancer via a coordinated approach to clinical trials research. The group is a member of the international Gynecologic Cancer Intergroup (GCIg) and the United States Gynecologic Oncology Group (GOG), and is also linked with the Australian Ovarian Cancer Study, a large translational and epidemiological study funded by the US National Cancer Institute (NCI).

In late 2005 the CTC started the Australian and New Zealand participation in two international trials of ovarian cancer. The chief investigator of both trials is Associate Professor Paul Vasey.

Calypso (Caelyx in platinum-sensitive ovarian patients), a trial of the Gynecologic Cancer Intergroup, is comparing liposomal doxorubicin (Caelyx) + carboplatin and paclitaxel + carboplatin as a second-line treatment for patients with epithelial ovarian cancer in late relapse. Funding is provided by the lead international group in France (Gineco).

SCOTROC4 is one of a series of trials of the Scottish Gynaecological Cancer Trials Group (SGCTG). This trial will examine whether a dose-escalation strategy for carboplatin chemotherapy is better than a fixed dose for women with ovarian, or related, cancers. The CTC will receive funds from a successful multistate Cancer Council grant to support recruitment at sites through per-patient payments, as well as central funding from the Scottish group.

Kathleen Scott, oncology program co-manager, is responsible for ANZGOG trials.

Refining chemotherapy regimes for ovarian cancer

The standard care for ovarian cancer is surgery followed by chemotherapy with a combination of a platinum and taxane (such as carboplatin and paclitaxel). More than half the patients with advanced ovarian cancer develop recurrent disease within a few months. The need for effective but minimally toxic chemotherapy treatments has led researchers to seek new agents and new combinations of drugs and to refine the dosing regimens.

Current trials are comparing:

- different dosages of the same drug (SCOTROC4)
- new combinations (GOG 182)
- new forms of drugs (Calypso, in which the new drug is doxorubicin in polyethylene glycol (PEG)-coated liposomes giving it a longer half-life and better penetration of the tumour).

ANZGOG trials

Trial	Participants	Interventions	Main outcome measures	Status
SCOTROC4: Multicentre randomised trial of carboplatin flat dosing vs inpatient dose escalation in first-line chemotherapy of ovarian, fallopian tube and primary peritoneal cancers	Women with ovarian, fallopian tube or peritoneal carcinoma for whom platinum-taxane therapy is unsuitable	<ul style="list-style-type: none"> • 6 cycles carboplatin, fixed dose • 6 cycles carboplatin with changes to dose depending on neutrophil count 	<ul style="list-style-type: none"> • disease progression 	<i>Recruitment target:</i> 1300 (international), 150 (Australia and New Zealand) Open to recruitment
CALYPSO: Caelyx in platinum-sensitive ovarian patients	Women whose disease has progressed after treatment	<ul style="list-style-type: none"> • pegylated liposomal doxorubicin + carboplatin • paclitaxel + carboplatin 	<ul style="list-style-type: none"> • disease-free survival 	<i>Recruitment target:</i> 864 (international), 125 (Australia and New Zealand) Open to recruitment
ANZGOG 0201: Phase II trial of weekly docetaxel for patients with relapsed ovarian cancer	Women whose disease has progressed after treatment	<ul style="list-style-type: none"> • docetaxel (Taxotere) 	<ul style="list-style-type: none"> • toxicity • time to progression • overall survival 	Closed. Final publication in preparation
GOG 182: Phase III randomised trial of paclitaxel + carboplatin versus triplet or sequential doublet combinations in patients with epithelial ovarian or primary peritoneal carcinoma	Women with advanced stage (stage III or IV) primary ovarian or peritoneal cancer	<ul style="list-style-type: none"> • gemcitabine or topotecan with carboplatin (doublet therapy) or carboplatin + paclitaxel (triplet therapy). 	<ul style="list-style-type: none"> • survival • toxicity • disease-free survival 	<i>Recruitment:</i> 3882 (international), 183 (Australia and New Zealand) In follow-up
GOG 199: Prospective study of risk-reducing salpingo-oophorectomy and longitudinal CA-125 screening among women at increased genetic risk of ovarian cancer	Women aged >30 at risk of ovarian cancer.	<ul style="list-style-type: none"> • choice of preventive surgery • screening 	<ul style="list-style-type: none"> • survival • quality of life 	<i>Recruitment:</i> 2400 (international), 100 (Australia and New Zealand) Open to recruitment
HOSTT (ANZGOG 0401): Phase II study to evaluate the impact of maintaining haemoglobin levels above 120 g/L vs over 100 g/L	Women with previously untreated cancer of the cervix receiving concurrent cisplatin and radiation therapy	<ul style="list-style-type: none"> • Red cell transfusion 	<ul style="list-style-type: none"> • different haemoglobin levels • progression-free survival 	<i>Recruitment:</i> 100 in pilot study 400 in stage 2 (Australia, New Zealand and Taiwan) Open to recruitment in 2006

PREVENTING HEART DISEASE

FIELD TRIAL

Preventing cardiovascular disease in diabetes

The FIELD study, Australia's largest clinical trial, was completed in 2005, and the main results were published in *The Lancet*. FIELD—Fenofibrate Intervention and Event Lowering in Diabetes—aimed to find out whether treatment with fenofibrate, a potent modifier of blood lipid levels, would reduce the risk of fatal coronary heart disease in people with type 2 diabetes. The trial recruited 9795 patients and followed them up over an average of five years.

Fenofibrate raises blood levels of high-density lipoprotein cholesterol (HDL, the protective cholesterol form) and reduces low-density lipoprotein cholesterol (LDL) and triglycerides. Whether this physiological benefit is translated into better health and survival for diabetes sufferers was the general question of the trial. Specifically, it asked whether fenofibrate treatment would lower the risk of fatal coronary heart disease or myocardial infarction.

Fenofibrate did not reduce deaths from heart disease. It did, however, reduce myocardial infarction by about a quarter. Patients in the fenofibrate group were less likely to have revascularisation (bypass grafting or procedures to remove arterial blockages) of coronary and other arteries. Fenofibrate benefited patients in reducing the need for procedures to repair blood vessels, such as laser treatments for eyes. The total number of cardiovascular disease events was statistically significantly lower (by 11%) in the fenofibrate-allocated patients; those without any history of cardiovascular disease and younger patients were more likely to benefit from fenofibrate.

CTC staff who worked for FIELD, with representatives of Fournier Pharma, at the final investigators' meeting in November 2005.



Many patients in the trial started taking statin lipid-lowering drugs over the five years of follow-up, presumably in response to their cholesterol levels. This was anticipated in the trial design, although the actual rates of statin use were higher than expected, particularly in the group of patients with prior cardiovascular disease. By the close of the trial, 32% in the placebo group and 16% in the fenofibrate group were taking statins. The difference between the groups in statin use may have masked an extra 5–7% effect of fenofibrate, and thus at least partly explained why the observed effect of fenofibrate was less than expected.

Analysis of data on the safety of the study drug showed that patients allocated fenofibrate did not discontinue their medication more often than those allocated placebo. Fenofibrate was not related to any specific cause of death or to any specific harm, such as cancers.

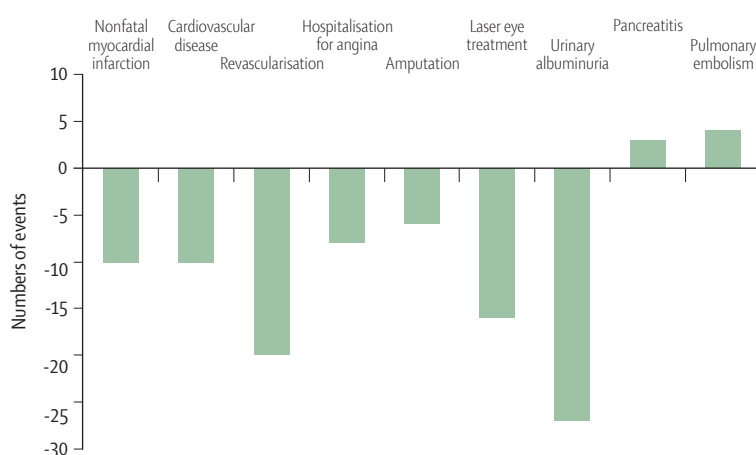
In 2005, FIELD was audited to assess the scientific quality and accuracy of selected areas and data fields relevant to the main trial conclusions. Twenty-seven randomly selected sites were visited for site auditing. The examination of trial-related activities and documents aimed to verify that the data were recorded, analysed and accurately reported according to the protocol, the sponsor’s standard operating procedures, Good Clinical Practice guidelines and applicable regulatory requirements. The auditors checked medical records for whether patients met the inclusion criteria for the trial, whether their medical history was properly documented and whether there were any undocumented events. The auditors’ review of the central management of the trial examined all aspects of data collection and recording, with additional probing of the accuracy of cancer reporting. There was a very low rate of errors in both site and internal audits, leading to a high level of confidence in the integrity of data and results. Under-reporting of events from the hospitals was rare and not related to randomised treatment.

People

FIELD has been internationally managed by a team at the CTC, headed by the study chairman, Professor Anthony Keech, and the international Management Committee, which has representatives from the three participating countries—Australia, New Zealand and Finland—and the sponsor, the French pharmaceutical company, Fournier Pharma.

The coordinator of the trial at the CTC is Dr Sarah Blakesmith; Karen Pinto is monitoring coordinator. The FIELD New Zealand project office is led by Dr Caroline Lintott from Christchurch, and Anne Salo coordinates the activity across Finland from Helsinki.

Significant absolute benefits and harms per 1000 persons treated over 5 years in the FIELD study (all $P < 0.05$)



Methodological features of the FIELD trial

Patients were only considered if the patients’ treating doctors were uncertain about the value of lipid-lowering for the patient and felt that there was no definite indication for such treatment. No patient was on lipid-lowering therapy at study entry. In this way, the trial was based on uncertainty about treatment, or equipoise.

When the trial was being planned, the statins were showing promise as effective drugs to reduce the risk of cardiovascular disease. Therefore, adjusting the effects of fenofibrate for statin use was planned in the protocol. Prespecifying this analysis was prescient, as many patients did go on to take statins.

Blinded interim statistical reviews were planned in the study protocol. FIELD patients turned out to be healthier than anticipated in the original study design. When the study was first reviewed, the number of participants with prior myocardial infarction was less than expected, so the sample size was increased. On the second review, it became apparent that there would be too few primary events for the study’s power to be maintained, and therefore the primary outcome was changed from coronary death to coronary events. Thus, the protocol allowed for diverse contingencies.

The study had a 16-week run-in phase before randomisation. For the first four weeks, patients followed diet recommendations. This was followed by a six-week placebo period, then a six-week period on the study drug. This allowed patients time to consider long-term participation and the doctors and researchers to evaluate the short-term effects of fenofibrate treatment.



SUBSTUDIES ADD VALUE TO CLINICAL TRIALS

VIGOUR COLLABORATION

INIS SUBSTUDY

LIPID SUBSTUDY

FIELD SUBSTUDY

QUALITY-OF-LIFE SUBSTUDY

With an established team of specialist researchers in clinical trials, the CTC is well placed to add value to its main trial findings by conducting substudies or secondary analyses that extend the value of trial data.

Substudies are usually optimally valid when they are designed during the design phase of the main trial. The CTC research teams are aware of this, and so the feasibility of various additional studies is always taken into consideration when new trials are being developed. As well as the planned secondary analyses, other substudies may be done as a follow-up to a trial, because the main results are often a spur to further exploration of the data.

Types of trial substudy include:

- quality-of-life assessments
- exploration of treatment mechanisms
- genetic, biochemical and anatomical investigations
- extended follow-up beyond the main trial
- analyses of data from selected patient groups, such as people in an age group
- methodological research work
- health-economic analyses

VIGOUR COLLABORATION

The CTC is currently participating in substudies of the recently completed HERO-2 trial (on page 52), one of the large international cardiovascular trials of the VIGOUR collaboration (Virtual Coordinating Center for Global Collaborative Cardiovascular Research), which comprises investigators from academic institutions in over 40 countries undertaking clinical trials of treatment for acute cardiovascular events.

In VIGOUR:

- organisations are self-sufficient, yet working collaboratively
- any investigator or any group can take the lead in a clinical trial
- each organisation maintains sufficient relevant expertise
- groups have compatible systems and accountability to each other for quality production
- common site data and site descriptors are used across the whole collaboration
- all groups use standard operating procedures for data management, monitoring, audit and biostatistics.

Advantages to the CTC are: access to the latest treatments; making a contribution to important scientific questions; international resources to tackle questions beyond the capacity of Australian investigators alone; and opportunities to consider subsidiary research questions and to initiate new questions. The CTC is responsible for regional data management and statistical analysis for HERO-2. Professor John Simes is a VIGOUR leader.



INIS: preventing the damaging effects of neonatal infection

Serious infection in a newborn often places the baby at risk of death or permanent disability. The International Neonatal Immunotherapy Study (INIS) is a major international, double-blind, placebo-controlled randomised trial testing the effects of immunoglobulin for newborn babies with serious infection.

Newborn infants, particularly those born early, are deficient in immunoglobulin (IgG) and so are at risk of infection. Each year over 2500 babies in Australia and New Zealand develop serious infection: about 250 die and another 375 survive with lifelong disability. Polyclonal intravenous immunoglobulin (IVIg) may help to reduce death and brain inflammation resulting from infection.

The trial now has 24 centres actively participating. Of the babies in the trial, 168 have reached the two-year mark (95% of these have already been followed up) and 496 have reached one year.

Substudies at the CTC

The CTC is the coordinating centre for Australia and New Zealand and is making particular contributions to the trial by conducting substudy research.

1. Two substudies on methods to improve recruitment and consent in randomised controlled trials in neonatology are in progress (see box opposite).
2. The economic implications of the trial will be assessed by an economic evaluation. The costs considered include the study drug (IVIg), hospitalisations, specialist care and long-term care of children with a disability, and a sensitivity analysis which uses a range of variation to allow for different suppositions. For both treatment and control groups, the life years gained and the quality-adjusted life years gained per child after the age of two will be calculated and the difference between the randomised groups evaluated.

William Tarnow-Mordi is principal investigator of INIS.

He is Professor of Neonatal Medicine at the University of Sydney, and based at Westmead Hospital. He works at the CTC on development of neonatal clinical trials one day a week.



Lorraine O'Regan and
Priya Duggal-Beri (trial coordinator)
INIS trial



Using INIS to improve recruitment in neonatal trials: two substudies

After the first years of the INIS trial, recruitment began to drop below target, leading to a need for strategies to increase the numbers. The use of educational newsletters and DVD videos in obtaining consent in large randomised trials has not been tested in other large trials. The coordinating group at the CTC is testing these two interventions for their value in improving recruitment.

These INIS substudies randomly allocated sites to either arm or to both arms to receive:

- a personalised letter to each staff member with the regular monthly newsletter and educational supplement describing a new topic each month (duration: six months)
- a DVD video showing typical case scenarios of appropriate methods of obtaining consent from parents, with an actor playing the parent, and a supplementary booklet.

The effect on recruitment will be measured by any changes in recruitment rates, the perceptions of local research staff and the types of babies enrolled.

If the study shows that these materials are effective, tools like these may be used in other clinical studies and may help in aspects of medical practice, such as communicating with staff and parents and seeking consent for procedures and treatments.

If the trial shows a 3% reduction in permanent disability, it is projected that the cost savings to Australian health services will be more than the cost of the INIS trial itself.

3. The INIS study is validating the questionnaires used in Australia and New Zealand, with the aim of seeing how well the responses from parents and paediatricians correlate. In a further validation, 900 of the 1500 babies to be recruited in Australia and New Zealand will be assessed with the Bayley Infant Scales of Development II. The Bayley assessment is expensive and labour-intensive, and validation against parent and paediatrician questionnaires will provide paediatric researchers with information about whether there is a need for this assessment in large pragmatic trials (like INIS). So far, 158 babies of a planned 900 have had a Bayley assessment.

Eligibility criteria:

- a proven or suspected serious infection, and
- a birth weight under 1500 grams, or receiving artificial respiratory support by endotracheal tube, or having evidence of infection in a normally sterile site, and
- antibiotics already prescribed

Study drug:

Intragam P or saline (placebo) over four to six hours and repeated after 48 hours

Main outcome measures:

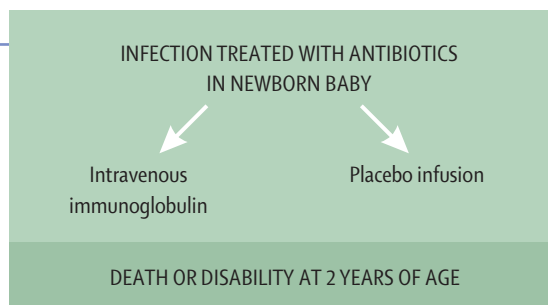
- survival without major disability at two years, corrected for gestational age
- death, infection, chronic lung disease before hospital discharge, major cerebral abnormality before hospital discharge, death or disability after two years, length of hospital stay, and number of hospital admissions

Recruitment target: 5000 internationally, 1500 in Australia and New Zealand

Recruitment to 2005: 2150 internationally, 1010 in Australia and New Zealand

Funding:

UK Medical Research Council, Sydney University Sesqui grant, Telstra Foundation, Ian Potter travel grant, NHMRC, Financial Markets Foundation for Children, NZ Health Research Council.



LIPID trial: pravastatin treatment for up to 11 years

The Long-Term Intervention with Pravastatin in Ischaemic Disease (LIPID) trial was the CTC's first large, long-term multicentre trial. It showed that lipid lowering with pravastatin prevented recurrent coronary heart disease events in 9014 patients. Patients continued to be followed up after the trial finished in 1997, and data are still being collected over seven years later. Since the end of the trial, about 85% of patients have continued on lipid-lowering therapy, the most common being the original pravastatin.

After 1999, funding for clinic visits ceased and patients have since been followed up by letter and telephone, in addition to searches of directories, disease registers and electoral rolls. The aim of the extended follow-up is to examine the long-term safety and cost-effectiveness of pravastatin treatment and to assess the effects of treatment on the risk of outcomes such as total mortality, coronary heart disease mortality, acute myocardial infarction, stroke, cancer and other major cardiovascular events.

In 2005, the results of 11 years of follow-up were presented at the Annual Scientific Sessions of the American Heart Association. Data were missing for only 185 of the original cohort of 9014. People who were originally allocated to pravastatin over the initial six years of the trial, compared with those allocated to placebo, continued to benefit from the initial pravastatin treatment. As well, there was no evidence of harm (such as cancer) from long-term treatment.

Lipid-lowering treatment for people with low cholesterol

About a third of the patients in the LIPID trial had low levels of both high-density lipoprotein cholesterol (good cholesterol) and low-density lipoprotein cholesterol (bad cholesterol), a subgroup for whom a fibrate or nicotinic acid is often recommended. In the light of these recommendations, the LIPID investigators decided to undertake a subgroup analysis of the benefits of pravastatin for these patients. Treatment reduced their risk of coronary events, death and, in particular, stroke. These results were published in the *European Heart Journal* in 2005.

Cost-effectiveness in the older patient group

Prevention and treatment of cardiovascular disease are responsible for the highest proportion of total health expenditure, by disease group, in Australia, attributable to hospital treatment, medication and nursing home care. Hospital costs are higher in the elderly, owing to the complexity of their disease and a higher incidence of other conditions. Such treatment burden is projected to increase further as the population ages.

A LIPID substudy showed in 2001 that pravastatin treatment was just as effective for patients aged 65 years and over as for younger patients. For each 1000 patients aged 65 to 74 years at the start of the LIPID study, six years of pravastatin therapy prevented 43 deaths, 33 myocardial infarctions, 32 hospitalisations for unstable angina, 13 strokes, or 133 major cardiovascular events.

Costly treatment with cholesterol-lowering drugs has often been withheld from elderly patients because it used to be thought that cholesterol levels were less of a risk factor in this population. The LIPID investigators recently carried out an economic analysis of the use of pravastatin in the younger compared with the older subgroup, which is to be published in 2006.



Helen Pater
LIPID trial manager



Nutrition

Diet was an important consideration in the LIPID study. Participants received dietary advice before the trial began and at intervals during the trial. A sample of 1077 people took part in a survey of their eating habits when the trial began, and most of these also took part in follow-up surveys as the trial progressed.

In a substudy published in the *American Journal of Clinical Nutrition* in 2005, the higher coronary heart disease mortality over the period of the trial in patients from New Zealand was reported to be related to the amounts and types of dietary fats reported in the initial survey.

Genetic and biochemical studies

Blood samples collected over the first six years of the study are now being analysed in relation to various risk factors and biomarkers for cardiovascular disease to investigate the importance of new potential prognostic markers of cardiovascular disease.

A case-control substudy found that brain natriuretic peptide (BNP) levels predicted the risk of recurrent cardiovascular events independently of other factors such as the LIPID risk score (see page 51), treatment with pravastatin and levels of other biomarkers. In another case-control study, the biomarker TIMP-1 (tissue inhibitor of metalloproteinases), was found to be associated with higher cardiovascular risk; this was interpreted as a possible protective mechanism against metalloproteinases. Leptin, a hormone produced by fat cells, may be a link between obesity and cardiovascular disease. Leptin levels in blood samples from men in the LIPID study were investigated in another substudy, which showed that leptin levels predict recurrence of cardiovascular disease. These studies were presented at international meetings in 2005.

The mechanism of action of pravastatin, and its relationship with coenzyme Q10, was explored in a prospectively planned study of blood plasma samples from patients who subsequently died from a cardiovascular cause or had a myocardial infarction or stroke, compared with control patients. This substudy will be published early in 2006.



Claudia Anderson
Coordinator of the FIELD
ophthalmology substudy

New information from substudies of the FIELD trial — a study of 9795 patients with diabetes

The FIELD trial investigated the use of fenofibrate lipid-lowering treatment to prevent heart disease among patients with diabetes (see page 26).

Carotid artery measurement substudy

A substudy from the trial was published in 2005. A sample of about 400 patients from FIELD had carotid ultrasound to measure the thickness of the intima-media layer of the carotid artery wall. Intima-media thickness is a well-described early indicator of cardiovascular disease and is known to be higher in people with diabetes.

People with a longer duration of diabetes had a thicker intima-media layer. The main finding of interest in this substudy was that the thickness was related to the level of albumin in the urine, even for levels in the normal range.

Ongoing substudies

Now that the main results of the FIELD trial have been published, the data are being analysed for other substudies that were planned before the trial began: on clinical aspects, such as vision changes (1200 patients) and quality of life (1500 patients), and laboratory-measured aspects, such as the relationship between fenofibrate lipid-lowering treatment and the distribution of lipid particle sizes in the blood (2000 patients).

Quality-of-life substudies add value to trials

A guiding principle at the CTC is that direct measures of benefit, harm and cost are incorporated into trials during their design, so that data collection is optimal. An important aspect of our research program is to improve the methods of assessment of quality and cost data and to integrate measures of quality of life, utility, preference and resource use.

Quality-of-life assessment includes utility-based measures for heart disease patients (UBQ-H) and cancer patients (UBQ-C), developed at the CTC. Quality-of-life, utility and survival are combined by using quality-adjusted survival analysis, also developed at the CTC. Recent studies on quality of life in cancer have been done by Vlatka Duric, Anna Nowak, John Simes, Martin Stockler and others.



Martin Stockler
Co-director of cancer trials

Quality of life in the phase II study of octreotide in advanced hepatocellular carcinoma

This 63-patient study has been completed and a manuscript submitted for publication by the study investigators. The analysis has concentrated on describing the baseline quality of life of these patients and validation of both the previously reported FACT-Hep and a novel tool, the Patient Disease and Treatment Assessment Form, which was developed at the CTC.

Assessing quality of life in routine clinical practice

This study assessed the use of the Patient Disease and Treatment Assessment Form by outpatients with cancer. Patients completed the forms while waiting to see the oncologist. The items cover physical and emotional symptoms of cancer and wellbeing. The aim is to use the form in practice to provide information to clinicians and to improve care.

Analysis and validation of baseline quality-of-life data from the ANZ 0001 trial

ANZ 0001 is an ongoing multicentre study of capecitabine versus cyclophosphamide-methotrexate-5-fluorouracil (CMF) chemotherapy as first-line chemotherapy for advanced breast cancer. Quality of life and treatment acceptability are key outcome measures. The study uses the Chemotherapy Acceptability Questionnaire, a new instrument developed by the CTC, as well as other validated tools. A substudy describing quality of life in the first 150 women randomised to the trial and information on the validity of the questionnaires was presented at the annual meeting of the American Society of Clinical Oncology in 2004.

Quality of life in cervix cancer

This multinational collaborative project of the European Organisation for Research and Treatment of Cancer (EORTC) to develop a quality-of-life module for cervix cancer trials involves the Australia New Zealand Gynaecological Oncology Group (ANZGOG) and the CTC, and is being led in Australia by Vlatka Duric.

IMPROVING THE CONDUCT OF CLINICAL TRIALS

BIostatISTICS PROJECTS

TRIALS ON TRIAL

AUDIT AND QUALITY ASSURANCE

An important purpose of the CTC is to work toward improving the efficiency and utility of clinical trials, throughout Australia and elsewhere. One way of doing this is by methodological research, particularly in biostatistics. Clinical trials raise questions for methodological research, and then the results of methodological research can be applied to the design, conduct and analysis of a wide range of clinical trials. The research therefore bears upon practical and real-life clinical problems.

Better biostatistical methods are continually being sought and tested. Knowledge gained from these methodological projects is spread beyond the CTC through major educational projects, such as the program of the Biostatistical Collaboration of Australia, publications, and the CTC's many alliances and partnerships.

Trials are conducted rigorously in accordance with the appropriate regulatory requirements. The CTC has established an organisational structure with assigned responsibilities and authorities to manage and assess the quality of systems and services. Trial operations are continually assessed, audited and improved.

Biostatistics projects

A new modification to dynamic-balancing randomisation

Random allocation of participants to treatment groups is fundamental to clinical trial design. In simple randomisation, participants are allocated from random number sequences. Better balance of the characteristics of participants across the treatment groups can be achieved by more sophisticated methods of random allocation. Randomisation methods that balance treatment allocation according to known prognostic factors are well established and are used in practice. However, they continue to be improved.

Some of the CTC's biostatisticians:

*Avinesh Pillai, Rachel O'Connell,
Peta Forder, Adrienne Kirby,
Stephane Heritier, Tatiana Sourjina
and Chris Brown*



Biostatisticians from the CTC have recently completed and published a modification of a method previously developed at the CTC, dynamic-balancing randomisation. Participants are allocated to treatment groups after a check of previous allocations according to a hierarchy of strata; that is, imbalances across treatment groups in important characteristics (defined before the trial) can be corrected first. The method was compared with other randomisation methods by simulation in two trials.





Val Gebski
Head of Biostatistics

A new approach to interim analyses

Current research projects are focusing on statistically valid and efficient ways to use preliminary outcome data from patients when final data are not yet available. In some trials the outcomes of patients are reported by sites but it takes time for these outcomes to be properly confirmed by the adjudication of a central committee. This research will allow more efficient, and earlier, identification of treatment differences. The statistical method uses the strength of association between the preliminary and final outcome status to obtain a valid result from preliminary data.

Competing risks

The multiple outcomes of patients in clinical trials complicate the statistical analysis of the results. In a cancer clinical trial, for example, an investigator may wish to estimate the efficacy of treatments by comparing patients' survival in the two arms of the trial. However, the patients may also die from other causes. Estimating patients' survival requires statistical models that measure the risks of different events; when the risks of different events are affected by each other (competing risks), the models must account for this. Biostatisticians are analysing these risks in simulation studies in order to arrive at the best models of survival in these situations.

Surrogate outcomes

A surrogate outcome is an intermediate measure that is related to the main outcome of a trial. A research interest of the CTC is the degree to which a surrogate is associated with the main outcome, and how well this can be measured. Often, because of costs or other factors, the potential surrogate outcome will only be measured in a substudy of the main trial. In this situation, the substudy patients provide information about the links between the true and surrogate outcomes and the treatment, and such correlations can be used to allow available data for patients not in the substudy to be included in the analysis. This leads to more precise estimates of the treatment effect. This was the subject of an article recently published in *Statistics in Medicine*.

■ IMPROVING PATIENT COMPLIANCE IN LONG-TERM TRIALS

A large clinical trial can be an opportunity for research projects exploring ways of improving the conduct of future trials.

Wendy Hague completed a PhD in 2004 on strategies for improving patient compliance with treatments in long-term trials. The topic issued from earlier work on recruitment strategies in the LIPID trial. The objective was to determine whether site management practices and staff characteristics, in addition to patient attitudes and behaviours, were associated with subsequent discontinuation of study medication.

The information obtained was used in the design of a prospective substudy for the CTC's large trial, FIELD. A questionnaire was developed, which was completed by patients when they were recruited into FIELD; the analysis, which will be conducted after the close of the FIELD study, will show, in a prospective study, the characteristics associated with patients changing their medication.



Two designs for comparing treatments in clinical trials

Two-way factorial trial design

	Placebo	Drug 1
Placebo	Group 1	Group 2
Drug 2	Group 3	Group 4

Groups 2 and 4 are the intervention group for drug 1, and groups 3 and 4 are the intervention group for drug 2.

Three-arm trial design

Placebo	Group 1
Drug 1	Group 2
Drug 2	Group 3

This design has no Group 4, that is, no patients taking both drugs.

Graphical methods for assessing factorial designs

A two-way factorial design can be a way of answering two questions in a single clinical trial. The power of the trial to study each of two treatments can be similar to that of a simple two-arm trial with the same sample size. However, if the treatments interact (reinforce or antagonise each other), the assessment of power becomes more complicated.

Biostatisticians at the CTC have developed a method for examining the loss of power due to the presence of an interaction in such a trial. The power of a two-way factorial design over a range of interaction values can be compared with that of a three-arm study to show which will be more economical in terms of sample size. The study was published in *Clinical Trials*.

Analysing variability in meta-analysis

Evidence from randomised trials is the gold standard for comparisons of medical interventions, but there is often other evidence from observational and other studies that could contribute information to such comparisons. However, these studies can be confounded by other factors, leading to bias. Meta-analytic approaches that combine evidence across a range of studies, both randomised and observational, make it possible to test for the presence of specific effects and therefore make use of these nonrandomised studies.

The heterogeneity of treatment effects associated with different classes of design was assessed in a methodological study that provided models for analysing reported summary statistics and for calculating weightings of evidence contributed by the different classes of study in meta-analysis. Variation in results among case-control, prospective, and other study types was examined and compared with the effects found in two large clinical trials. The result from the final model corresponded to the pooled effect and reduced the uncertainty of the risk estimate from the findings of the trials alone.

Longitudinal nonparametric methods

Recent research on nonparametric methods is improving the validity of quality-of-life and other analyses in which the distributions of data are not normal, such as repeated measures of ordinal outcomes and multistate responses. The CTC's biostatisticians are improving the methods of analysis of these data sets. The methods are being applied to the design of new trials to improve efficiency and find the right sample size, therefore minimising costs.

Relative efficiency of parametric and bootstrap estimates of costs

Large randomised trials commonly provide quality-of-life and cost data in addition to data for answering the trial's main question. These data are collected for important substudies to establish the benefits and costs associated with a new treatment. However, the data are not normally distributed, and established methods of analysis are not ideal. In a recent study, the biostatisticians have been using a new method of analysis by transforming the data and using parametric methods. The method appears to be more accurate and efficient than previous approaches, and is likely to be useful in cost-effectiveness analyses in future trials.

Trials on trial: a CTC initiative for better conduct and reporting of clinical trials

A recent series of articles in the *Medical Journal of Australia*, designed to improve the conduct and reporting of clinical trials in Australia and internationally, has been a way in which the CTC has met its commitment to better trials through educational activity.

Much of the rapidly increasing trials research over the past half century (see graph) has been poorly or inadequately reported. The international standard dealing with this is the CONSORT (Consolidated Standards of Reporting Trials) statement, which is in the form of a checklist of essentials for running a trial and writing the paper for a scientific journal. The statement was revised and extended between 1996 and 2001. The MJA series clarifies and illustrates the 22 descriptors in the CONSORT list.

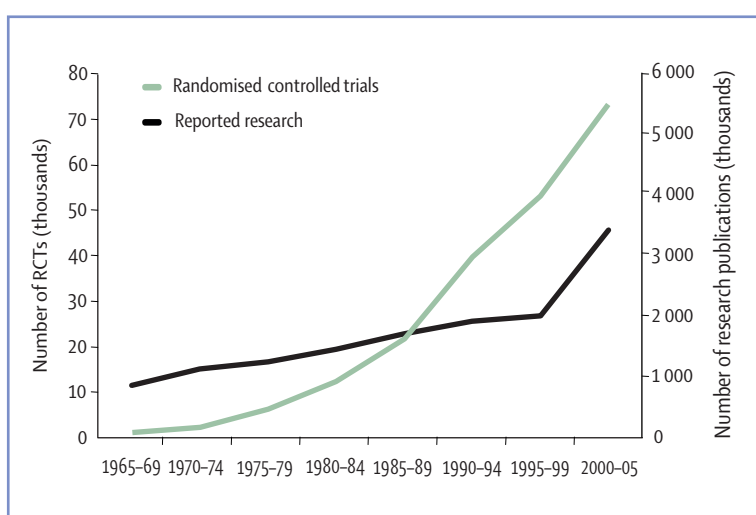
The articles were originally written in order to demystify the the technical language of evidence-based medicine for clinicians. However, the series has been useful for a wide range of readers—including anyone wanting to know from reading a journal article whether all the information has been properly reported and the results are valid.

The first article described the elements of a good study, and subsequent articles have dealt with issues such as the design of a trial, including acceptable randomisation and blinding methods, how to choose an intervention and its outcome measures, and calculating sample size; the conduct of a study, including recruitment and data collection; reporting results, including adverse events and how to consider subgroups; and how to interpret the evidence, taking into account possible bias or imprecision.

The articles also emphasise biostatistical analysis of trials data, reflecting the expertise of the CTC in this area. Authors of the articles in this series have been various clinical trials practitioners, from the CTC and elsewhere, whose expert knowledge has been integrated into the theme crafted by Tony Keech and Val Gebski, the co-authors on all.

Reports of randomised controlled trials compared with total publications

(Source: PubMed)



Quality assurance and audit

Generating reliable clinical data is essential for every clinical study, and the CTC's quality assurance program has been developed to ensure this. Combining effective operating procedures with education and training for all staff has been a successful approach to achieving data integrity, compliance with regulatory requirements and optimal outcomes for the CTC's clinical projects.

As a minimum, all staff involved with a clinical study have participated in a comprehensive course in Good Clinical Practice (GCP) principles in the Australian regulatory context. A set of CTC policies, standard operating procedures and work instructions form the backbone of the quality assurance program. This program is regularly reviewed. For example, in the past two years, the document-control system for standard operating procedures and archiving were upgraded and a quality-assurance web site was developed to increase access of staff to regulations, CTC policies, standard operating procedures, work instructions and templates for use in project work.

Four external audits have been conducted during the past two years. A trial of a new treatment for colorectal cancer, NCIC CO 17, was externally audited by the pharmaceutical company, Bristol-Myers Squibb in the USA, and the C06 and C07 colorectal carcinoma trials were audited by the international lead coordinating cooperative group, the US National Surgical Breast and Bowel Project (NSABP). In addition, procedures for randomisation and statistical analysis, which the CTC undertakes for the Australian New Zealand Breast Cancer Trials Group (ANZ BCTG), were reviewed by two expert consultants in biostatistics and data management. The observations were favourable and future trials with these groups are forthcoming.

PROMOTING HIGH STANDARDS THROUGH EDUCATION AND TRAINING

All new clinical staff at the CTC are trained in Good Clinical Practice and specific standard operating procedures. During 2005, the knowledge and skills for preparing and conducting an audit were presented at workshops for the Cancer Council, the Australasian Gastro-Intestinal Trials Group and the Australasian Health and Research Data Managers' Association.



Laurie Snaithe
Head, quality assurance and audit

COMBINING TRIAL EVIDENCE

COCHRANE COLLABORATION

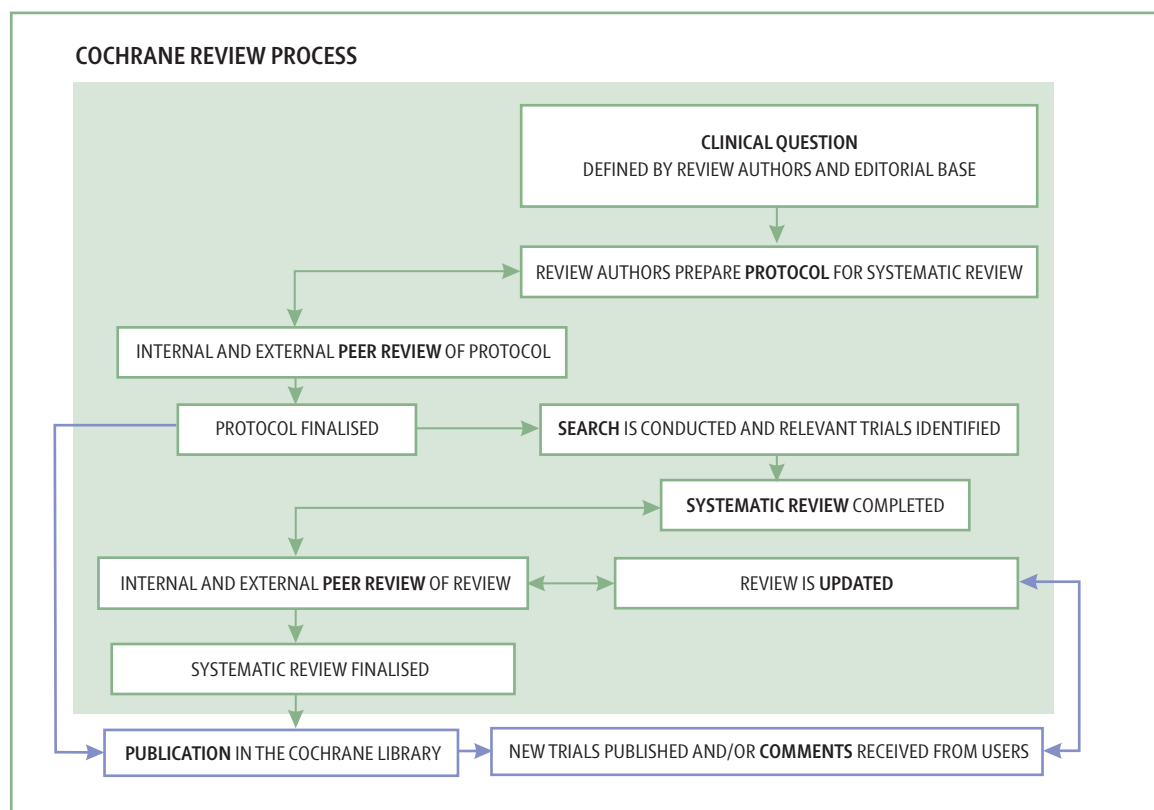
PROSPECTIVE META-ANALYSIS

Combining the evidence from multiple clinical trials in a systematic review is a powerful tool for answering important clinical questions when a single definitive large-scale trial has not been conducted. Systematic reviews combine the results of all relevant high-quality studies that ask the same clinical question. An important role of the CTC is extracting the best evidence from the available trials.

Even more powerful is combining trials before they have started, so that the question in the review uses prospective data. The CTC is a leader in prospective meta-analysis projects and in methods for their conduct and analysis. Several of the CTC's trials have been a part of international prospective meta-analysis collaborations.

Systematic reviews by the Cochrane Collaboration

The Cochrane Collaboration is the largest organisation in the world engaged in the production and maintenance of systematic reviews of health care interventions. The reviews are available through the Cochrane Library collection (which is free to Australians) via the internet.



SUPPORT AND INFORMATION PACK EVALUATED

The CTC staff working for the Cochrane Breast Cancer Group evaluated the new Support and Information Pack, developed by the Cancer Council NSW for patients with a new diagnosis of cancer.

The evaluation aimed to determine the perceived usefulness of the pack to patients, their carers and families and health professionals, and also to make recommendations to improve further evaluation of the information pack.

Not all the CTC's Cochrane reviews are in breast cancer ...

Tamoxifen for hepatocellular carcinoma

Tamoxifen, which acts on oestrogen receptors, is a commonly used treatment for preventing recurrence of breast cancer. Cells of hepatocellular carcinoma (liver cancer) also have oestrogen receptors, an observation which led to trials of tamoxifen for patients with this disease. They have had conflicting results. A systematic review of ten trials showed that tamoxifen had no significant effect on survival or tumour size and did not improve quality of life. The results of this review, prepared for the Cochrane Library, were also published in *Cancer*.

The Cochrane Breast Cancer Group is a review group of the Cochrane Collaboration. Its activities are coordinated by a team of editors based at the CTC. The group compiles evidence relating to the management of women with breast cancer. Through the coordination of systematic reviews, staff at the CTC are also actively engaged in developing protocols for new reviews and training new authors.

The Cochrane Breast Cancer Group continues to receive support and funding from the Commonwealth Department of Health and Ageing via a program to support Australian-based Cochrane Collaboration activities.

Recent reviews by CTC members of the Cochrane Breast Cancer Group

Single-agent therapy compared with combination chemotherapy for metastatic breast cancer

One way to investigate the effect of more-intensive compared with less-intensive chemotherapy is to compare regimens containing a single drug with regimens containing more than one drug (possibly more active but more toxic). Data from trials focusing on such questions were investigated in this systematic review.

It was found that adding chemotherapy agents to the same single-agent cytotoxic generally resulted in a more intense chemotherapy regimen, with both better tumour response and worse toxicity. These more intense therapies were usually associated with better progression-free and overall survival, especially when the single agents were the more traditional drugs. The findings are not necessarily applicable to some of the more modern single agents, such as the taxanes and capecitabine.

Antitumour-antibiotic-containing regimens for metastatic breast cancer

Several large randomised trials have supported the use of the antitumour antibiotics over standard CMF (cyclophosphamide, 5-fluorouracil, methotrexate) regimens, but the evidence for survival benefit has not been conclusive.

This review found that chemotherapy that included antitumour antibiotics was more likely to result in tumour response but did not improve survival of women with advanced breast cancer when compared with chemotherapy that did not contain these types of drugs. Doxorubicin and related drugs might decrease the cancer's progression but also increase adverse effects, including heart failure.

Taxane-containing regimens for metastatic breast cancer

Taxanes are among the most active chemotherapy agents for advanced breast cancer. In a systematic review, taxane-containing chemotherapy regimens were compared with regimens not containing a taxane for women with metastatic breast cancer.

Taxanes were reported to be more effective than some, but not all, regimens with which they were compared, and of the two major taxanes, docetaxel may be more active than paclitaxel.

Platinum-containing regimens for metastatic breast cancer

This review looked at trials of treatment that included platinum, alone or in combination with other chemotherapy drugs, for advanced breast cancer.

The findings of significant excess toxicity, apparent lack of benefits for overall progression or survival, and the availability of less toxic and efficacious agents, spoke against the use of platinum in routine clinical practice, at least as a first option.





Systematic reviews group:

Davina Ghersi, Sally Lord, Nicole Holcroft, Lisa Askie, Jenny Chow, Silke Walleser, Sharon Parker, Suzanne Dyer

Drugs used in chemotherapy for breast cancer

Taxanes

The first taxane, paclitaxel, was obtained from the Pacific yew tree, *Taxus brevifolia*. Taxanes can now be derived from other species of yew. Taxanes block the normal disintegration of intracellular spindles, preventing the separation of chromosomes, and therefore stopping cell division and multiplication.

Antibiotics

Doxorubicin and mitomycin are derived from the fungus, *Streptomyces peucetius*. Antitumour antibiotics act by binding to DNA, preventing transcription and therefore nucleic acid synthesis and also by inhibiting enzyme activity and causing DNA to break.

Alkylating agents

Cyclophosphamide, one of the early anticancer drugs, is the most common alkylating agent used for breast cancer. It is metabolised in the cell to form an active agent, which attacks DNA, preventing it from uncoiling, and so stops cell function. More recent alkylating agents are the platinum, cisplatin and carboplatin, whose mechanisms of action are not so clearly defined.

Vinca alkaloids

Vinblastine and vincristine are alkaloids found in the Madagascar periwinkle, *Catharanthus roseus*. They act by binding to tubulin, preventing the cell from forming spindles and dividing.

Antimetabolites

Antimetabolites, first used in 1948, mimic natural intracellular compounds and block biochemical pathways. The antimetabolite, 5-fluorouracil, prevents DNA synthesis.

WORKSHOPS AND FORUMS

In November 2004, the Cochrane Breast Cancer Group conducted a workshop, "How to read and do a Cochrane systematic review", attended by people representing a range of disciplines, including clinicians and consumers.

In May 2005, the group conducted a protocol-development workshop.

In October 2005, the group, in conjunction with the Breast Cancer Action Group, conducted a forum, "Decision making in breast cancer: making the best of the evidence", in Melbourne in association with the annual Cochrane Colloquium.

The audience included women with breast cancer and associated clinical professionals. Among the topics presented by the seven internationally and nationally known speakers were results from the latest trials of breast cancer treatment and interpretation of the evidence they provide.

GRANT FOR SYSTEMATIC REVIEW OF INTERVENTIONS FOR LOCALLY ADVANCED BREAST CANCER

In 2005, the CTC received a grant from the Cure Cancer Australia Foundation for a systematic review of interventions for locally advanced breast cancer.

The systematic review process will lead to identifying current trials which are yet to answer questions about treatment and areas where properly designed trials should be undertaken. The review is likely to find current gaps in evidence-based information and to contribute to improved clinical practice guidelines.

The objective is better outcomes for women who have multimodal treatments for breast cancer, such as several chemotherapy drugs or chemotherapy with radiotherapy.

The principal investigators are Nicholas Wilcken and Davina Gherzi.

Prospective meta-analysis of data from clinical trials

In a meta-analysis, the results of more than one independent clinical trial are integrated. In a prospective meta-analysis, the hypotheses and analyses for the combined data are planned before the constituent trials have finished. The investigators agree to pool their future data. Ideally, these decisions are made during the conception and design stage of the trials so that the criteria for defining endpoints and so on can be similar where possible.

Prospective meta-analysis is a powerful and scientifically rigorous approach to combining trial evidence, with the strengths of a single large trial. The trials, treatments, subgroups, outcomes and analysis plans are all prespecified before the results of the constituent trials are known.

The CTC is a member of several collaborations and is a leader in prospective meta-analysis methodology.

Cholesterol lowering with pravastatin: the Prospective Pravastatin Pooling project

The investigators from the LIPID, CARE, and WOSCOPS trials formed the PPP in 1992 to combine data from the three large trials of lipid-lowering with pravastatin. The objective was to use the pooled data to study the efficacy of pravastatin in reducing less common events, such as stroke, and in subgroups whose numbers were too small in the individual trials. The protocol was published in 1995. John Simes and Tony Keech are members of the international steering committee.

Since the end of the last of these trials, LIPID, in 1998, several meta-analyses have been completed. The group recently published studies of the effects of pravastatin for patients with chronic kidney disease. It was shown that the drug was beneficial for these patients (especially those at higher risk) as well as reducing cardiovascular risk, and may also modestly reduce the rate of kidney function loss.

Prospective meta-analysis in colorectal cancer

In patients with advanced cancer of the colon but with no symptoms, chemotherapy may be given immediately on diagnosis or may be withheld until symptoms develop. Chemotherapy (with its side-effects) for a patient who initially feels well needs to be justified by evidence that it has a benefit. The timing of chemotherapy has been the subject of debate. Inconclusive results from clinical trials and a range of opinions among medical oncologists who treat colorectal cancer led to two trials of immediate chemotherapy compared with deferred therapy, in Australia and in Canada.

The investigators from both trials designed a meta-analysis of the combined results before the trials began. This was wise planning because the numbers of patients eventually recruited were too low in the individual trials, but the meta-analysis went ahead. Results were published recently in the *British Journal of Cancer*.

Efficacy and safety of long-term cholesterol lowering: Cholesterol Treatment Trialists' Collaboration (CTTC)

In 1990, the investigators from several cholesterol-lowering trials came together and decided to pool the data from trials of lipid-modifying treatments in future analyses. It had been well known that lower cholesterol levels are associated with lower risk of coronary heart disease.

Several large trials of statin cholesterol-lowering drugs in the 1990s showed that lowering cholesterol (particularly LDL cholesterol) was beneficial in reducing the risk of coronary events in general for a wide range of people. However, the individual trials were not large enough to show the effects of statins on the risk of death from coronary heart disease or on other specific outcomes (such as stroke), particularly in subgroups of participants.

The main analyses were to be of the effects on death from any cause, death from coronary heart disease, and death from other causes. Secondary analyses were effects on stroke, cancer and vascular procedures. Events in subgroups (such as people with diabetes or hypertension, men and women) were also to be analysed.



Tatiana Sourjina, statistician for the CTTC



CTTC TRIALS			
Study	Date of results	Number of participants	Target population
4S	1994	4 444	Prior heart disease
WOSCOPS	1995	6 595	Men with high cholesterol, no heart disease
CARE	1996	4 159	Prior heart disease
Post-CABG	1997	1 351	Prior coronary artery bypass grafting
AFCAPS/ TexCAPS	1998	6 605	No heart disease
LIPID	1998	9 014	Prior heart disease
GISSI-P	2000	4 271	Prior heart disease
LIPS	2002	1 677	Prior heart disease
HPS	2002	20 536	High risk of heart disease
PROSPER	2002	5 804	Elderly
ALLHAT	2002	10 355	Hypertensive
ASCOT	2003	10 305	Hypertensive + 3 risk factors
ALERT	2003	2 102	Renal transplant
CARDS	2004	2 838	Diabetes + 1 risk factor

The first of these analyses was reported in *The Lancet* in 2005. Data from 90 056 participants were analysed. The study confirmed the benefit of using statins to prevent coronary heart disease events and showed that the effects were related to the reduction in LDL cholesterol achieved.

Tony Keech is joint coordinator of the collaboration and was on the writing committee of this important publication, with Christine Pollicino, Adrienne Kirby, Tatiana Sourjina, and John Simes.

Primary coronary angioplasty vs thrombolysis (PCAT) collaboration

The PCAT collaboration undertakes meta-analysis of clinical trials investigating the relative benefits of treatments to restore coronary blood flow after myocardial infarction. In a recent meta-analysis the group reanalysed individual-patient data from 25 trials to determine the role of delays in starting treatment in comparisons of blood-modifying drug treatments (fibrinolysis) and vessel-opening procedures (percutaneous coronary angioplasty, which involves extra delay). Time to treatment was an important determinant of the outcome, but primary percutaneous coronary angioplasty was associated with lower mortality at 30 days, regardless of delays.

John Simes is co-coordinator of the collaboration.

Combining new trials of deep-vein thrombosis: the international ASPIRE–WARFASA collaboration

The investigators of ASPIRE (Aspirin to prevent recurrent venous thromboembolism) (see page 16) are collaborating with the investigators of the WARFASA study (initiated in Italy) in the prospectively designed meta-analysis, INSPIRE. The two trials have similar study designs and the two management committees have harmonised the protocols to allow a prospective meta-analysis to be done.

In INSPIRE, the combined analysis uses individual patient data from both trials. With a planned combined enrolment of 3000 patients, the meta-analysis will have more than 90% power to detect a 30% risk reduction in recurrent thrombosis with aspirin compared with placebo. Patients will be followed up for an average of three years.



BRINGING AN EVIDENCE BASE TO DECISION MAKING AND POLICY

AUSTRALIAN CLINICAL TRIALS REGISTRY

ASSESSMENT OF NEW TECHNOLOGIES, TESTS AND PROCEDURES

HEALTH ECONOMICS

Finally, an Australian register of clinical trials

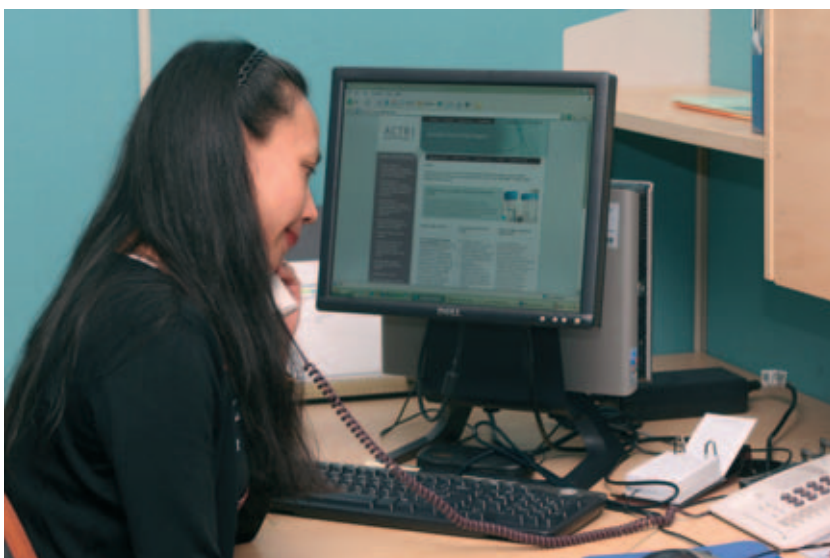
The Australian Clinical Trials Registry (ACTR) was established at the CTC in 2005, with funding of \$1.5 million over five years from the National Health and Medical Research Council (NHMRC). The registry is an on-line, comprehensive, prospective, national register of all clinical trials being conducted in Australia.

The need for a national clinical trials register had been recognised for many years, but this was brought to a head by the announcement from the International Committee of Medical Journal Editors (ICMJE) in September 2004 that articles reporting trials would be published only if the trial had been publicly registered before the first patient was enrolled. Their deadline for registration of new trials was 1 July 2005 and for ongoing trials was 13 September 2005. Therefore the ACTR was established within a few months during 2005. The ACTR team is working with the NHMRC and the Therapeutic Goods Administration to further refine and develop the registry.

The register includes trials from the full spectrum of therapeutic areas—pharmaceuticals, surgical procedures, preventive measures, lifestyle, devices, treatment and rehabilitation strategies and complementary therapies. It covers all clinical trials involving Australian researchers or Australian participants. The registry will prove to patients and health practitioners that the treatment options they choose are based on the most up-to-date and comprehensive information available.

The Australian Clinical Trials Registry has been reviewed by the International Committee of Medical Journal Editors who have declared that the registry meets their requirements. As part of a program to coordinate registration of trials worldwide, the World Health Organization has recently set up the WHO International Clinical Trials Registry Platform (ICTRP), which is linking the national registries, including the Australian registry.

WWW.ACTR.ORG.AU



The executive group for the ACTR is Lisa Askie, Davina Ghersi and John Simes. Davina Ghersi is also a member of the scientific advisory group of the WHO International Clinical Trials Registry Platform and chair of the ICTRP Member Registers Working Group.

Emma Smith
ACTR project officer





Lisa Askie
ACTR manager



Davina Gheri
Director, systematic reviews and health care assessment

BENEFITS OF THE AUSTRALIAN CLINICAL TRIALS REGISTRY

Patients and health professionals have access to a searchable, accessible, and comprehensive register. Patients and health professionals have greater assurance that all clinical trials results are reported, including those with adverse findings.

The registry will increase the efficacy of the current clinical trial effort through:

- greater efficiency because gaps in research can be identified and duplication of research effort will be less
- the potential for recruiting more trial participants (especially for rare or life-threatening conditions), because potential patients and their doctors will be aware of the trials available
- more incentive for publishing trial results, even when the results are unfavourable
- providing a reliable and unbiased source of information for systematic reviews, prospective meta-analyses and evidence-based guidelines.

The Australian Clinical Trials Registry has an advisory board with wide representation, including:

Australian chief medical officer	Professor John Horvath
National manager of the Therapeutic Goods Administration	Dr David Graham
Nominee of the Therapeutic Goods Administration	Dr John Rankin
Chief executive officer of the NHMRC	Mr William Lawrence
Nominee of the University of Sydney, independent of ACTR	Professor Don Nutbeam
Chief investigator of the ACTR project (ex officio)	Professor John Simes
Member or nominee of the NHMRC Research Committee	Professor Terry Nolan
Member or nominee of Australian Health Ethics Committee	Dr Garry Pearce
Industry representative	Ms Deborah Monk
Representative of the clinical research community	Professor Caroline Crowther
Editor of an ICMJE-affiliated medical journal	Dr Martin Van Der Weyden
Health consumer advocate	Dr John Stubbs
Chief Executive of the New Zealand Health Research Council	Dr Bruce Scoggins

MINIMAL REGISTRATION

DATA SET: *this is the worldwide standard for the fields in a clinical trials database, specified by the World Health Organization in November 2005*

1. Unique trial number
2. Trial registration date
3. Secondary IDs
4. Funding sources
5. Primary sponsor
6. Secondary sponsors
7. Contact for public queries
8. Contact for scientific queries
9. Public title of the study
10. Scientific title of the study
11. Countries of recruitment
12. Health condition or problem studied
13. Interventions
14. Key inclusion and exclusion criteria
15. Study type
16. Date of first enrolment
17. Target sample size
18. Recruitment status
19. Primary outcome
20. Key secondary outcomes



Assessment of new technologies, diagnostic tests and procedures

The CTC has a contract with the Australian Government's Medical Services Advisory Committee (MSAC) to review new and existing health technologies, diagnostic tests and procedures for which funding is sought under the Medicare Benefits Schedule. Assessments for MSAC are based on a systematic review of the scientific literature and other information sources, including clinical expertise. During 2004–2005, the CTC and clinical specialists completed several reviews of the evidence for funding new procedures.

Drug-eluting stents

Coronary artery stenosis is commonly treated by a stent, a small metal mesh expandable tube, which is inserted and expanded to scaffold the vessel to improve blood flow. A drug-eluting stent is coated with a drug that is gradually released to inhibit cell growth which may block the artery. A drug-eluting stent is much more costly than a bare-metal stent and has not been shown to reduce rates of death or myocardial infarction.

The review compared drug-eluting stents with bare-metal stents and found that on the strength of current evidence, drug-eluting stents reduced the rate of repeat procedures for up to one year and were as safe as bare-metal stents. There was insufficient evidence to show a difference in the rates of myocardial infarction, coronary artery bypass grafting or mortality. The technology is cost-effective if a cost of \$3700–\$6200 is considered acceptable to avoid a target lesion revascularisation, but there is still uncertainty when the assumptions are varied to account for patients receiving more than one stent, the varied risks of the patients and the differences between trial conditions and routine Australian clinical practice.

Positron emission tomography for lung cancer

Positron emission tomography (PET) uses short-lived radiopharmaceuticals to detect and assess perfusion and metabolic activity in various organ systems.

The review team and the MSAC advisory panel developed two specific questions in relation to non-small-cell lung cancer:

- What is the preoperative value of PET (using a radiolabelled analogue of glucose) plus usual staging in patients with potentially curable non-small-cell lung cancer?
- What is the additional value of PET in patients with a solitary pulmonary nodule where the results of conventional imaging or tests have been inconclusive or unavailable?

The review found that PET improved diagnostic accuracy when added to conventional staging of non-small-cell lung cancer. Also, for single nodules of more than 1 cm, PET is a potentially useful clinical aid when biopsy or conventional imaging are inadequate. Public funding for these indications was recommended.

Positron emission tomography (PET) for epilepsy

In about a quarter of epilepsy patients seizures cannot be adequately controlled by medical treatment, and some are considered for surgery. Positron emission tomography (PET) is sometimes used in addition to computed tomography (CT) and magnetic resonance imaging (MRI) to acquire information about the focus of the seizure before surgery.



Sally Lord
Manager, health care assessment

New guidelines for assessing diagnostic tests

Assessments of diagnostic tests have been informed by a rapidly evolving body of research on the methods for conducting systematic reviews of diagnostic tests.

In 2005 the CTC assisted MSAC in preparing a document, *Guidelines for the assessment of diagnostic technologies*, to guide review groups at the CTC and elsewhere. This document provides:

- guidelines: MSAC's recommended methods for identifying, appraising and summarising evidence about the safety, effectiveness and cost-effectiveness of a diagnostic test
- assessment framework: MSAC's approach for integrating and interpreting this evidence to draw conclusions about the net clinical benefit of the test.

A diagnostic test is defined as any technology or procedure that is used to confirm, exclude or classify disease.



This review of PET imaging found that the technology is safe; provides additional localising information in some patients, of whom a proportion will have good post-surgical outcomes as a consequence; and is likely to be cost-effective in the long term.

SIR-Spheres for the treatment of nonresectable liver tumours

SIR-Spheres are yttrium-90 microspheres that are implanted into malignant liver tumours to deliver high doses of ionising radiation. They are used to treat liver metastases from colorectal cancer and hepatocellular carcinoma in combination with chemotherapy. The review compared the safety and effectiveness of SIR-Spheres, alone or in addition to chemotherapy, with the alternative treatments.

Colorectal cancer is the most common cancer and the third most common cause of cancer death reported to Australian cancer registries, and hepatocellular carcinoma is the most common primary liver cancer. Optimising their treatments would have wide-ranging benefits.

Although one trial reported improved survival with SIR-Spheres, further evidence is needed to determine the effectiveness of SIR-Spheres in combination with current systemic chemotherapy regimes.

Magnetic resonance cholangiopancreatography

Disorders of the pancreas and bile duct are typically manifested by pain or jaundice due to duct obstruction. Delayed treatment due to false-negative results and unnecessary procedures due to false-positive results are associated with serious risks to the patient. Common causes of obstruction include stones and stricture of the common bile duct.

Magnetic resonance cholangiopancreatography (MRCP) is a specialised MRI technique that produces images of the bile ducts, pancreas and surrounding tissues. It was compared with computed tomography (CT) imaging and endoscopic retrograde cholangiopancreatography (ERCP, requiring patients to swallow an endoscope) in patients needing more than a conventional clinical assessment and ultrasound imaging.

The review found that MRCP was generally safer than ERCP and had better outcomes for some patients, depending on the surgical and other treatment they went on to have. It is likely to be as effective as CT scanning for detecting bile duct stones.

Brachytherapy to treat prostate cancer

Brachytherapy is the implantation of radioactive sources in or near tumours. For prostate cancer (the most common cancer in men), radioisotopes are inserted directly into the prostate gland. The radioactive sources destroy tumour cells of the prostate gland without significantly irradiating adjacent normal tissue.

Brachytherapy has been proposed as a more efficient treatment (shorter treatment, time in hospital and recovery time) for localised prostate cancer, with the additional advantages of limiting the side-effects to adjacent tissues that occur with conventional external-beam radiotherapy and the surgical risks associated with radical prostatectomy. However, the procedure may have short- and long-term complications.

The study compared iodine radioisotope brachytherapy and radical prostatectomy, external beam radiation therapy and active surveillance for treating early localised prostate cancer. The outcomes assessed included survival; tumour progression; urinary, rectal and sexual function; quality of life, and costs.

The evidence available did not show a difference between the treatments in survival or disease progression; however the safety profiles of the treatments were found to differ. There was not enough evidence to ascertain the cost-effectiveness of strategies.

Current practices and future directions in the diagnosis, prevention and treatment of lymphoedema

Lymphoedema is the abnormal swelling of body tissues, most often in the limbs, caused by a failure of the lymphatic system, most often after cancer surgery. Affected limbs become swollen and may be painful, normal function is compromised and recurrent infection can occur.

There are currently no Australian standards for the treatment of lymphoedema. A review of lymphoedema in Australia showed a lack of high-quality evidence to support many of the treatments in use, professional education, training and resources.

Advances in treating cancer to reduce the risk of lymphoedema are being trialled in Australia and include the use of sentinel lymph node biopsy in the axillary staging of breast cancer (see page 20).

Endometrial ablation techniques for chronic refractory menorrhagia

Endometrial ablation is a procedure that aims to destroy the endometrial lining of the uterus, causing a reduction in or elimination of menstrual bleeding.

The review considered the safety, effectiveness and cost-effectiveness of newer techniques of endometrial ablation available in Australia compared with earlier techniques in women with chronic refractory menorrhagia. The available evidence showed that second-generation endometrial ablation procedures appear to be at least as safe and as effective as first-generation endometrial ablation procedures.



Urovysion assay for detecting recurrence of bladder cancer

Bladder cancer is common in Australia, particularly among men. The standard method for detecting recurrence of bladder cancer is cystoscopy, in which a flexible scope is inserted through the urethra of an anaesthetised patient. Urovysion fluorescence in situ hybridisation (FISH) assay is a new technique that detects chromosomal aberrations related to bladder cancer by treating and examining cells from a urine sample. The reviewers asked: what is the value of the Urovysion assay in conjunction with cystoscopy versus cystoscopy alone to diagnose recurrence of transitional cell carcinoma? The review showed that, for most patients, the Urovysion test does not greatly increase the probability of detecting recurrence. For patients with a high risk of recurrence, the test may reduce the number of cystoscopies. A cost-effectiveness model showed that including Urovysion in the clinical pathway increased the expected cost for patients, with no expected improvement in clinical outcomes.

Financial costs and quality of life are important to clinical decision making and health policy

How medical treatment affects patient-oriented outcomes (such as survival, quality of life and preferences) and society-oriented outcomes (such as cost-effectiveness and cost-utility) are critical for decision making in clinical practice and health policy.

A focus of the CTC's research program is continual improvement of the methods of assessing quality of life (see page 33) and calculating cost-effectiveness and cost-utility.

Better measurement of the costs and benefits of hospital care

Measures of hospital efficiency such as cost per case-mix-adjusted admission have been adopted for funding hospitals and for benchmarking and relative performance measurement. Current hospital funding mechanisms based on case-mix ignore differences in quality or outcomes of care. Therefore, economic incentives are created to reduce quality to minimise the cost per admission.

Such performance measures, which ignore the value of quality, encourage practices of quality-skimping, cost-shifting and 'quicker, sicker' care. Also, patients may need further care after they have been discharged from hospital. The costs of this care may not be counted in measures of hospital efficiency. A better incentive is funding that depends on the quality of care, with an economic trade-off between the cost and the value of care.

A series of studies at the CTC has identified measures of efficiency that include economic incentives for the quality of services in hospital and over time; that is, they measure relative provider performance consistent with an underlying objective of maximising net benefit. Included is a framework that includes data linkage and risk-factor adjustment to overcome incentives for cost-shifting and cream-skimming.



Simon Eckermann
Health economist





Simon Eckermann and Alison Griffiths
Health economists

Cost-effectiveness of pravastatin therapy in older people with coronary heart disease

The LIPID investigators recently carried out an economic analysis of the use of pravastatin in the younger compared with the older subgroup, to be published in 2006 (see page 31).

HEALTH ECONOMICS VISITING FELLOW

Professor Andy Willan visited the CTC for four weeks in 2005. Professor Willan is a biostatistician and clinical trial methodologist who is a senior scientist at the Hospital for Sick Children, professor in the department of Public Health Sciences at the University of Toronto and professor emeritus in the Department of Clinical Epidemiology and Biostatistics at McMaster University.

He and Simon Eckermann presented a program of seminars demonstrating methods for net benefit analysis, expected value of information and optimal trial design.

Uncertainty in cost-effectiveness, predictive conditioning and extrapolation beyond the life of a trial

Decision making based on incremental cost-effectiveness ratios has been aided by recent developments in estimating the range of the cost-effectiveness ratio distribution from randomised trials using bootstrapping, a statistical method of repeated random sampling. However, the method can introduce structural uncertainty into estimation of precision.

A methodological study at the CTC has identified a new way of increasing the precision of the incremental cost-effectiveness ratio by combining within-trial and beyond-trial uncertainty. This informs decision makers of the relative uncertainties related to within-study and beyond-study effects.

Systematic reviews of new technology: economic analyses

When systematic reviews of new technologies are undertaken for the Australian government (page 47), if the evidence shows that a technology, test or procedure has better health outcomes than current practice, a cost-effectiveness analysis is also done. Such a comparison of the costs of the new and standard procedures is undertaken to assist decisions about the allocation of funding. Economic evaluations use a broad health-care-system perspective to identify which option might maximise the health benefits or minimise their cost. These studies include sensitivity analyses of incremental effects, costs and cost-effectiveness.

The CTC's health economists work alongside the CTC's systematic reviews team on the health economic component of MSAC reviews. In 2005 these and similar reviews included brachytherapy for prostate cancer and Urovision, an assay for detecting recurrence of transitional cell carcinoma of the bladder.

APPLYING TRIAL RESEARCH TO INDIVIDUAL PATIENTS

RISK MODELS

PATIENT PREFERENCES

Models to predict risk for individual patients

The results of a clinical trial may show that treatment reduces the risk of an event across a broad range of patients. However, patients are different in many ways, including their initial risk. For example, a treatment may benefit older patients more because their risk is intrinsically higher.

Large multicentre trials can amass data from thousands of patients over many years. Analysis of the clinical course of these patients allows us to accurately estimate risks in groups of patients with various common characteristics and then to determine how different factors predict risk. Thus, pragmatic risk factor tools can be created to assess risk and guide decisions about treatment for individual patients.

A model of long-term cardiovascular risk from the LIPID trial

LIPID was the CTC's first large cardiovascular prevention trial. The LIPID cohort, now followed up for over 11 years, has been used to develop a prognostic model for coronary mortality among patients who have been admitted to hospital for a coronary heart disease event (see page 31).

Important independent risk factors for CHD death, in a Cox regression analysis, were older age, prior myocardial infarction, cardiac symptoms of angina or dyspnoea, male sex, diabetes mellitus, smoking, high white cell count, low HDL cholesterol, hypertension, prior stroke and atrial fibrillation. Coronary revascularisation after (but not before) an acute CHD event and pravastatin treatment both reduced the risk of CHD death.

A risk score based on these factors enabled patients to be classified into three risk categories, with 4.7%, 11.5% and 32.8% risk of death from coronary heart disease over ten years. Those in the higher-risk group could expect more benefit from pravastatin treatment.

The LIPID risk model for CHD death provides a simple but effective means of identifying patients at very high or low risk of CHD death, which should be a practical guide for stratifying patients for more conservative or intensive treatment strategies and for choosing patients for participation in future clinical trials.

These results were presented at the annual scientific meeting of the American Heart Association in Dallas in November 2005.

Adrienne Kirby, Chris Brown and Val Gebski, biostatisticians



HERO-2 PROGNOSTIC INDEX

Rachel O'Connell, a CTC statistician, has been using the data set from the HERO-2 trial for research on risk models in her PhD project.

She has been developing the HERO-2 prognostic index (HPI). The HPI applies well internationally and is likely to be useful in many clinical settings.

Using international data for a model of risk after acute myocardial infarction

The HERO-2 trial (Hirulog early reperfusion occlusion) was a large international trial in 47 countries of two antithrombosis treatments for acute myocardial infarction. HERO-2 recruited 17 073 patients, who received bivalirudin or unfractionated heparin by random allocation.

Baseline patient data from this trial were used to develop a prognostic index (HERO-2 prognostic index, HPI) of the risk of death within 30 days after myocardial infarction. Factors contributing to risk included age, blood pressure, heart rate and the location of the myocardial infarction. Because of the global distribution of patients, this study provided a rare opportunity for comparing the new prognostic index with earlier indices developed in Western populations by allowing internal calibration to populations from other regions.

The prognostic index performed well in internal validation and predicted risk in an external data set of Western patients, but is still to be tested in non-Western data sets.

HERO-2 has also been an opportunity to explore and validate the statistical methods for building a prognostic model. The first of these statistical studies will be ready for publication in 2006.

Eliciting preferences from cancer patients to improve decision making

Anticancer treatments improve survival rates, delay progression of the disease and improve cancer-related symptoms, but they also have side-effects and are inconvenient.

The average benefits conferred by adjuvant chemotherapy for groups of women with early breast cancer are well-established and beyond reasonable doubt, but the actual benefit for any particular woman cannot be known. Many women judge small benefits sufficient to make the side-effects and inconvenience worthwhile.

The important question for patients and clinicians is: for individual patients, how much benefit is needed to make the additional side-effects and inconvenience worthwhile?

Vlatka Duric and Martin Stockler of the CTC and their colleagues are examining this question in a series of studies in which people who have experienced the treatment are asked to weigh the benefits and harms of anticancer treatments, particularly chemotherapy. Participants identify the smallest improvement in survival time or survival rate they judge necessary to make that therapy worthwhile.

Comparing patients' and their partners' preferences for adjuvant chemotherapy in early breast cancer

Clinicians often include the life partners of patients with breast cancer in making decisions about treatments. In this study, both patients and their partners were interviewed. Cancer patients' and partners' judgments of the value of adjuvant chemotherapy differed considerably and included considerations other than length and quality of life.



Patients' preferences, quality of life and adjuvant radiation therapy for women with early breast cancer

Radiation therapy reduces the risk of local recurrence but has little effect on survival in women with small breast cancers. Preferences for adjuvant radiation were elicited from 95 women who had had it after surgery. Most women judged small benefits sufficient to make the radiation therapy worthwhile.

Results were presented at the annual scientific meetings of the Clinical Oncological Society of Australia and the Royal Australian and New Zealand College of Radiologists in 2005.

Adjuvant endocrine therapy in early breast cancer: what makes it worthwhile?

Endocrine (hormone) therapy for breast cancer may cause menopausal symptoms, infertility and osteoporosis. The side-effects of endocrine therapy may be less intense than those of chemotherapy, but they could be more important than clinicians realise.

In a collaboration with UK researchers, a sample of women with early breast cancer taking part in a trial of endocrine therapy were interviewed. The results of this study were published recently in the *British Journal of Cancer*. The findings were unexpected: women having endocrine therapy needed bigger benefits to make treatment worthwhile than women having chemotherapy. This suggests that shorter treatments, such as chemotherapy, may be easier to cope with, even if the side-effects are more severe.

Vlatka Duric and Martin Stockler

Patients' preferences for adjuvant chemotherapy in early colon cancer: what makes it worthwhile?

This project will determine the preferences of patients who have had adjuvant chemotherapy for early colon cancer. Preferences are elicited by a questionnaire and a face-to-face interview. In a related study, clinical researchers and medical oncologists were surveyed by questionnaire on the same topic.



PATIENT PREFERENCES STUDIES

Vlatka Duric completed a PhD in psychological medicine from the University of Sydney at the CTC.

Her subject was patient preferences—to determine how individuals trade off the benefits, harms and uncertainties of chemotherapy treatment adjuvant to surgery for early breast cancer.

Preferences were highly variable, but many judged marginal benefits sufficient to make chemotherapy worthwhile. Patients and their life partners had different preferences, but not systematic differences in their preferences. Psychosocial factors explained only some of the variation.

STAFF AND STAFF ACTIVITIES

Directors

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 research fellow

Dorothea Sophia, BEd, GCM, business director

Clinical data management

Susan Wonders, BDS, head (2004)

Lee Marshall, head (2005)

Larry O'Leary, BSc, clinical data coordinator

Claire Monro, BA, data systems developer

Karen Lee, BEc, clinical data coordinator

Emma Vlahos, BCom, BSc, business analyst

Randomisation

Andrew O'Callaghan, BSc (hons), head

Site management

Kathleen Scott, BSc (hons), PhD, head (2004)

Cancer trials

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

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

Managers

Burcu Cakir, BSocSci (hons), MPH, oncology program manager

Julie Martyn, PhD, associate program manager, ANZGOG

Danielle Miller, BSc (hons), associate program manager, AGITG

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Sonia Yip, BSc (hons), PhD, associate program manager (2004)

Study coordinators

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Tara McFarquhar, BSc

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Alison Pearce, BAppSci

Katherine Sen, BSc

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Kate Wilson, BA, MPH

Data manager-study monitors

Christine Aiken, BSocSci

Michelle Cummins, BSc, PhD

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Alan Lucas, BAppSci, randomisation and safety officer

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Justine Simard-Lebrun, BA

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Michelle Hall

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Julie Poulter

Julia Shoulder, BSc (hons)

ASPIRE trial

Sarah Mulray, BA, MPH, project manager (2004)

Rebecca Mister, BSc, MSc, project manager (2005)

Ann Ratcliffe, RGN, DipPaed, study monitor

Daria Jones, BSc (hons), clinical trial assistant

Sarah Chinchin, BSc (hons), clinical trial assistant

Neonatal trials

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

INIS trial

Anne Cust, BSc, BA, MPH (hons), project manager (2004)

Priya Duggal-Beri, BBiotech (hons), PhD, project manager (2005)

Rebecca Barsenbach, BSc, clinical trial assistant (2005)

Megan Hay, BMedSci (hons), clinical trial assistant (2004)

Lorraine O'Regan, BSc (hons), clinical trial assistant (2005)

BOOST II trial

Alpana Ghadge, BSc, MSc, PhD, GradCert TradeMarks Law Pract, project manager

Lorraine O'Regan, BSc (hons), clinical trial assistant

FIELD trial

Elizabeth Keirnan, BScAgr, BA, MMgt, PhD, project manager (2004)

Sarah Blakesmith, BSc (hons), PhD, clinical trial coordinator (2005)

Karen Pinto, DipTeach, BA, PostgradDip Psychol, clinical trial associate, monitoring coordinator

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Colin Sutton, BSc, MSc, quality control and data systems manager

Ben Taylor, administrative assistant

Russell Taylor, BSc, data manager

Sharon Walder, BAppSci, clinical trial associate

Jun Zhang, BMed, MHIM, data manager

LIPID follow-up study

Helen Pater, BAppSci, project manager

Kirsty Mehalski, BSc, MSc, DipDiet, research dietitian

STARTUP trial

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

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



Systematic reviews and health care assessment

Davina Gherzi, AssocDip, BAppSci, MPH, director, systematic reviews and health care assessment and Australian Clinical Trials Registry, and senior research fellow

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Sue Carrick, RN, MHLthSci, program manager, Cochrane reviews

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Nicole Holcroft, BSc (hons), project officer

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Fergus Tai, research assistant

Opal Thongyoo, research assistant

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Australian Clinical Trials Registry

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Emma Smith, BSc, MSc, PhD, project officer

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

Erica Jobling, executive officer, Biostatistics Collaboration of Australia

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Sharon Parker and Nicole Holcroft

Systematic reviews and health care assessment

Flexetrial data system

Sue Stewart, MSc, GradCertFinAcc, BAppSc, project logistics manager (2004)

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Rebecca Murray, BIS, business analyst (2004)

Publications

Rhana Pike, BA, MA, ELS, publications officer

Information systems

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Jon Barnett, BE (hons), ME, manager

Infrastructure

Dinh Tran, BMath (Comp), MCompSci, infrastructure manager

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Asanka Perera, BSc, computer systems officer

Database administration

Anh Tai Nguyen, BMath (Comp), database manager

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Anne Foy, BSc (Comp)

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Mustapha Kara-ali, BE, MBIomedEng

Jaime Marquez, BS(Eng)

Ashaar Riaz, BSc (ElectEng), MCompSci

James Robson, BSc (hons)

Ravinder Singh, BTech(CompSci)

Rosi Wang, Bmed, BSc, MHLthSci

Bei Zhong, MCompSci

Business administration

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Margaret Edwards, personal assistant to the director

Suzanne Everett, BSW, human resources and administration coordinator

Maki Joseph, DipEd, finance officer

Faith Papuni, personal assistant to the deputy director

Doris Rattos, administrative assistant

Bebe Sim, MAcc, CPA, finance manager

Quality assurance

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Phillipa Smith, BPharm (hons), MSc, adviser

Quality-of-life studies

Vlatka Duric, BSc (hons), MPsychol, PhD, clinical psychologist and associate lecturer

Cost-effectiveness evaluation

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Alison Griffiths, BA (hons), research associate

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Anna Nowak, MB BS, PhD, FRACP, postdoctoral research fellow

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



Supervision of research degrees

John Simes

Davina Gherzi, PhD
Wendy Hague, PhD
Kirsten Howard, PhD

Anthony Keech

David Burgess, PhD
Gemma Ritchie, PhD

Lisa Askie

Marion Kibuka, MHLthSc

Val Gebbski

Goran Hu, PhD
Mark Jones, PhD
Bee Choo Tai, PhD

Davina Gherzi

Daria Jones, MPH (hons)

Malcolm Hudson

Stephen Brown, PhD
Piea Peng Lee, PhD
Catherine Rytmeister, PhD
David Warton, PhD

Martin Stockler

Vlatka Duric, PhD
Paul Glare, MMed
Mark Haran, MMed
Nick Pavlakis, MMed
Alison Salkeld, BMedSc

Degrees completed in 2004–2005

David Burgess: MPH

Vlatka Duric: PhD, 'Patient preferences in early breast cancer: who decides what makes it worthwhile and how?'

Simon Eckermann: PhD, 'Examining hospital performance: the right methods and finding the right level'

Peta Forder: MBIostat

Wendy Hague: PhD, 'Identification of determinants of patient compliance in placebo-controlled clinical trials and appropriate strategies to improve study compliance'

Elizabeth Keirnan: PhD, 'Psychiatry and postmodernism'

Kirsty Mehalski: PhD, 'Muscle fat metabolism in exercise by 1H NMR spectroscopy'

Claire Monro: GradDipCompSc

Dinh Tran, MCompSc

Kate Wilson, MPH

Degrees in progress

Kass Adams: MPH

Christine Aiken: MHLthSc

Chris Brown: MBIostat

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

Xanthi Coskinas: MCLinEpi

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

Mary Ellen Harrod: PhD, 'Physiological and behavioural correlates of behavioural activation and inhibition'

Daria Jones: MPH (hons)

Lisa Higgins, MBIostat

Sally Lord: MEpi

Luke Marinovich: MPH

Andrew O'Callaghan, MSc

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

Alison Pearce: MPH

Sharon Walder, MPH

Vicky Wegener, BAppSc

Representation on external committees

John Simes

ANZ Breast Cancer Trials Group scientific advisory committee

Aspirin to prevent recurrent venous thromboembolism (ASPIRE) (study chair)

Australasian Gastro-Intestinal Trials Group (AGITG) scientific advisory committee

Australian and New Zealand Germ Cell Trials Group

Australian and New Zealand Gynaecological Oncology Group

Cancer Institute NSW board

Cholesterol Treatment Trialists Collaboration (joint coordinator)

Cochrane Breast Cancer Group editorial board

Current Controlled Trials advisory group

Department of Health and Aged Care Medicare services advisory committee (MSAC)

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

Hirlog Early Reperfusion Occlusion (HERO-2) international steering committee and executive

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

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

NHMRC clinical trials and large-scale grants committee

NHMRC Clinical Trials Centre management review committee and scientific advisory committee

NHMRC project grants committee

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

Prospective Pravastatin Pooling (PPP) project international steering committee

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

Tony Keech

ASEANZ cardiovascular and lipid forum advisory board

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)

Department of Health and Ageing medical services advisory committee supporting committee

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

International Journal of Cardiology, associate editor

ISIS Trials Group steering committee

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

National Heart Foundation (NSW) Heart Week hospital campaign committee, public campaign committee

National Heart Foundation (NSW) working party on guidelines for cardiac rehabilitation
NHMRC Clinical Trials Centre management review committee and scientific advisory committee

NHMRC training awards committee

NSW Department of Health shared assessment committee

Prospective Pravastatin Pooling (PPP) project international steering committee

Royal Prince Alfred Hospital clinical trials (Ethics) subcommittee

UK Heart Protection Study steering committee

University of Sydney board of postgraduate studies, College of Health Sciences

University of Sydney Faculty of Medicine budget advisory committee and faculty awards committee



Virtual Coordinating Centre for International Collaborative Cardiovascular Research (VIGOUR)

Vlatka Duric

Cancer Council NSW, trial selection committee
European Organisation for Research and Treatment of Cancer quality of life group—gynaecology

Val Gebski

ANZ Breast Cancer Trials Group scientific committee
ANZ Breast Cancer Trials Group trial ANZ 9311 management committee
Australasian Gastro-Intestinal Trials Group (AGITG) IG9801 management committee
Australasian Gastro-Intestinal Trials Group (AGITG) scientific committee
Joint Radiation Oncology Centre research committee
Medical Journal of Australia, statistical editor
NMRC Singapore Indomethacin study for closure of PDA safety data and monitoring committee
NMRC Singapore trial SHN01 safety data and monitoring committee
NSW Health Eastern Sydney Area ethics committee clinical trials subcommittee
Sentinel node biopsy vs axillary clearance (SNAC) trial management committee

Davina Gheri

Cochrane Collaboration international steering group; executive; handbook advisory group; advisory board, Methodology Review Group; co-convenor, Prospective Meta-Analysis Methods Group; joint coordinating editor, Breast Cancer Group, Central Register of Controlled Trials advisory group
International Clinical Trials Registry Platform, World Health Organization, scientific advisory group, and chair, WHO Registers Working Group
NSW Cancer Council Cancer Trials NSW trial selection committee
NSW Health Pilot Shared Scientific Assessment Scheme reference group
Prospective meta-analysis of weight management in childhood and adolescent obesity management committee
University of Sydney course advisory committee, MHLthSc and Graduate Certificate in Health Science (Clinical Data Management)

Wendy Hague

Aspirin to Prevent Recurrent Venous Thromboembolism (ASPIRE) trial 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) executive, management committee, finance subcommittee, audit subcommittee

Sally Lord

HTAi 2006 (3rd Annual Meeting of Health Technology Assessment International) scientific committee

Anna Nowak

Cancer Council NSW, trial selection committee
Cancer Council NSW, centre selection committee

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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 working party

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Australian and New Zealand Gynaecological Oncology Group research advisory committee and audit committee

Laurie Snaith

Australian and New Zealand Gynaecological Oncology Group audit committee
Clinical Oncological Society of Australia quality assurance committee
Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) audit subcommittee

Martin Stockler

Cancer Trials NSW trial selection committee (chair)
ANZ Breast Cancer Trials Group protocol 0001 management committee (study chair)
Clinical Oncological Society of Australia enabling grant steering committee
Cochrane Breast Cancer Group
Good Prognosis Germ Cell Trial management committee
ISource National Breast Cancer Centre medical oncology advisory group
National Breast Cancer Centre hormone therapy working group (chair)
National Breast Cancer Centre information advisory group (chair)
NSW Cancer Control Network governing committee
NSW Cooperative Oncology Group (chair)
Pilot phase II study of sandostatin LAR in patients with advanced hepatocellular carcinoma management committee
Trans-Tasman Radiation Oncology Group (TROG) and the Australasian Gastro-Intestinal Trials Group (AGITG) protocol IG9401 management committee
University of Sydney evidence-based medicine resource group

Academic teaching

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Decision analysis, Master of Public Health and Master of Medicine, University of Sydney
University of Sydney medical program
Medical oncology clinical training, Royal Prince Alfred Hospital

Anthony Keech

Controlled clinical trials, Master of Public Health and Master of Medicine, University of Sydney
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Cardiology training, Royal Prince Alfred Hospital
Clinical tutor, Royal Prince Alfred Hospital

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Evidence-based health care, Master of Science, University of Oxford

Sue Carrick

Sociology and politics of health care, Faculty of Nursing, University of Sydney

Burcu Cakir

Evidence-based medicine, Graduate Medical Program, University of Sydney
Basic sciences in oncology series, Cancer Institute NSW

Vlatka Duric

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Cancer Trials NSW, orientation training for oncology data managers and study nurses

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Rhana Pike

Science and technical editing (convenor),
postgraduate program in editing and
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Martin Stockler

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

Medical oncology clinical training, Royal Prince
Alfred Hospital

Quality of life in oncology, Cancer Council NSW
Making sense of cancer trials, Cancer Council
NSW

Oncology and palliative care, University of
Sydney medical program (block chair)

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

Clinical epidemiology for physician trainees,
Royal Prince Alfred Hospital

Critical appraisal of literature for physicians,
Westmead Hospital

Supportive care research methods, American
Society of Clinical Oncology, 2004

Supportive care research methods, Sydney
Institute of Palliative Medicine

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

PUBLICATIONS

Journal articles

Ackland SP, Jones M, Tu D, Simes J, Yuen J,
Sargeant A-M, Dhillon H, Goldberg RM,
Abdi E, Shepherd L, Moore MJ. A meta-analysis
of two randomised trials of early chemotherapy
in asymptomatic metastatic colorectal cancer.
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Simes RJ, Van de Werf F, White HD, Califf RM.
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B, Donaldson L, Briffa K. Cost-effectiveness of
rehabilitation after an acute coronary event: a
randomised controlled trial. *Medical Journal of
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Burmeister BH, Smithers BM, Gebski V,
Fitzgerald L, Simes RJ, Devitt P, Ackland S,
Gotley DC, Joseph D, Millar J, North J,
Walpole ET, Denham JW, for the Trans-
Tasman Radiation Oncology Group (TROG)
and the Australasian Gastro-Intestinal
Trials Group (AGITG) Surgery alone versus
chemoradiotherapy followed by surgery for
resectable cancer of the oesophagus: a
randomised controlled phase III trial. *Lancet
Oncology* 2005; 6(9): 659–668.

Byles JE, Tavener M, O'Connell RL, Nair BR,
Higginbotham NH, Jackson CL, McKernon
ME, Francis L, Heller RF, Newbury JW, Marley
JE, Goodger BG. Randomised controlled trial
of health assessments for older Australian
veterans and war widows. *Medical Journal of
Australia* 2004; 181(4): 186–190.

Byth K, Cox DR. On the relation between initial
value and slope. *Biostatistics* 2005; 6(3):
395–403.

Byth K, Gebski V. Factorial designs: a graphical
aid for choosing study designs accounting for
interaction. *Clinical Trials* 2004; 1: 315–325.

Carrick S, Ghersi D, Simes J, Wilcken N.
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breast cancer. *Cochrane Database of Systematic
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Carrick S, Parker S, Wilcken N, Ghersi D, Marzo
M, Simes J. Single agent versus combination
chemotherapy for metastatic breast cancer.
Cochrane Database of Systematic Reviews 2005;
(2): CD003374.

Chin YS, Jayamohan J, Clouston P, Gebski V,
Cakir B. Driving and patients with brain
tumours: a postal survey of neurosurgeons,
neurologists and radiation oncologists. *Journal
of Clinical Neuroscience* 2004; 11(5): 471–474.

Cholesterol Treatment Trialists' (CTT)
Collaborators. Efficacy and safety of
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- Duric V, Stockler MR, Butow P, Sharpe L, Beith J, Sullivan A, Boyle F, Dhillon H, Coates AS, Simes RJ.** Predictors of the benefits women consider necessary to make adjuvant chemotherapy worthwhile for early breast cancer. *40th Annual Meeting of the American Society of Clinical Oncology*; 5–8 Jun 2004; New Orleans.
- Duric V, Stockler MR, Butow P, Sharpe L, Heritier S, Beith J, Boyle F, Wilcken N, Coates A, Simes RJ.** Comparing patients' and their partners' preferences for adjuvant chemotherapy in early breast cancer. *American Society of Clinical Oncology Annual Meeting*; 13–17 May 2005; Orlando.
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- Forder P, Byth K.** Assessing the relationship between allergic rhinoconjunctivitis symptoms and pollen exposure. *20th International Workshop on Statistical Modelling*. 10–15 Jul 2005; Sydney.
- Gebski V, Heritier S, Simes J, Pillai A, Luke V, Keech A.** Computer modelling of adaptive randomisation schemes in large randomised controlled trials. *20th International Workshop on Statistical Modelling*. 10–15 Jul 2005; Sydney.
- Gherzi D, Wilcken N, Simes RJ.** Taxane-containing regimens for metastatic breast cancer: a systematic review. *Leura V International Breast Cancer Conference*; 10–14 Nov 2004; Sydney
- Griffiths KA, Lundman P, Skilton MR, **Pillai A, Grieve S, Celermajer DS, Keech AC.** New carotid plaque formation is very common in type 2 diabetic adults. *Cardiac Society of Australia and New Zealand Annual Scientific Meeting*; 7–11 Aug 2004. *Heart Lung and Circulation* 2004; 13S2: S130.
- Hargreaves C, Peiris S.** Statistical process control charts applied to hospital infection data. *55th Session of the International Statistical Institute*; 5–12 Apr 2005; Sydney.
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- Hudson M, Kirby A.** Relative efficiency of parametric and bootstrap estimates of cost. *55th Session of the International Statistical Institute*; 5–12 Apr 2005; Sydney.
- Keech AC, Best JD, Scott RD, Barter PJ, Simes RJ, Forder P, Taskinen M-R,** for the FIELD study investigators. Significant lipid changes in a large-scale trial of fenofibrate to prevent cardiovascular disease in type 2 diabetes. *Annual Scientific Session of the American College of Cardiology*; 7–10 Mar 2004; New Orleans. *Journal of the American College of Cardiology* 2004; 43 (5, supplement 2): 462A.
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- Lefkovits J, Eccleston D Warren R, Clark D, Chan R, Ajani I, **Keech A, Horrigan M.** Neither clopidogrel pre-treatment nor heparin-coated stents reduces peri-procedural troponin I elevation. *Cardiac Society of Australia and New Zealand Annual Scientific Meeting*; 7–11 Aug 2004. *Heart Lung and Circulation* 2004; 13S2: S46.
- Li Z, **Hudson M, Lord S, Gebski V.** Decision models for valuing effectiveness of new diagnostic technologies—with application to PET diagnostic testing. *55th Session of the International Statistical Institute*; 5–12 Apr 2005; Sydney.
- Lord S, Gherzi D, Marinovich L.** Synthesizing evidence about emerging diagnostic technologies for practice and policy—mind the gap! *12th Cochrane Colloquium*; 2–6 Oct 2004; Ottawa.
- Lord S, Irwig L, Gherzi D, Marinovich L, Simes RJ.** Assessment framework for ranking evidence about the clinical value of diagnostic tests. *1st Annual Meeting of Health Technology Assessment International*; 30 May–2 Jun 2004; Krakow, Poland.
- Marinovich L, Gherzi D, Lord S.** Data maturity and systematic reviews of new health technologies. *12th Cochrane Colloquium*; 2–6 Oct 2004; Ottawa.
- (Thomas C. Chalmers Award for originality of thought, high-quality science, relevance for the advancement of the science of systematic reviews, and clarity of presentation)
- Marinovich L, Lord S, Gherzi D.** Test results, treatment decision and patient outcomes: linking the evidence to assess new diagnostic tests. *2nd Annual Meeting of Health Technology Assessment International*; 20–22 Jun 2005; Rome
- Marks P, Dhillon H, Stockler M, Nowak A.** Oncology Clinical Research Workforce Survey 2004: professional certification—do we need it? *Clinical Oncological Society of Australia Annual Scientific Meeting*; 24–26 Nov 2004; Canberra.
- Medd J, **Stockler MR, Chan L, Eisinger D, Maher P, Mitterdorfer A, Lalak A.** Patients' perceptions of urodynamic studies and prostate biopsies and their willingness to participate in trials to make the tests less unpleasant. *Urological Society of Australasia*; 10–13 Nov 2004; Newcastle.
- Mehalski K, Barnes E, Colquhoun D, Baghurst K, Simes J, Nestel P, Brand-Miller J.** Characteristics of a high-glycaemic index diet in patients with existing CVD. *Nutrition Society of Australia Annual Scientific Meeting*; 30 Nov 2005; Melbourne.
- Mieog S, **Gherzi D.** Is timing important in systematic reviews of interventions for breast cancer? *13th Cochrane Colloquium*; 22–26 Oct 2005; Melbourne.
- Nestel P, **Pollicino C, Mehalski K, Baghurst K, Colquhoun D, Simes J, Tonkin A,** for the LIPID study investigators. Dietary contribution to cardiovascular risk factors in subjects with cardiovascular disease in Australia and New Zealand. *15th International Symposium on Drugs Affecting Lipid Metabolism*; 24–27 Oct 2004; Venice.
- Nestel PJ, Blankenberg S, **Simes RJ, Kirby A, Tonkin A.** Tissue inhibitor of metalloproteinase (TIMP-1) is a predictor of recurrent cardiovascular events in the LIPID Study. *European Society of Cardiology Congress*; 3–7 Sep 2005; Stockholm.
- Nowak AK, Byth K, Gebski V, Fong AK, Coate AS, Harvey V, Stockler M.** What troubles women starting chemotherapy for advanced breast cancer in a randomized trial? *40th Annual Meeting of the American Society of Clinical Oncology*; 5–8 Jun 2004; New Orleans.

- Nowak AK, Hargreaves C, Gill PG, Wetzig N, Ung O, Campbell I, Kollia J, Young L, Macphee A, GebSKI V, Stockler MR.** Health-related quality of life before and 1 month after axillary surgery in a randomized trial of sentinel node biopsy versus axillary clearance: the SNAC trial. *27th Annual San Antonio Breast Cancer Symposium*; 8–11 Dec 2004; San Antonio.
- Parker S, Carrick S, Ghersi D, Young L.** Addressing the information needs of the lay reader. How much is enough? *12th Cochrane Colloquium*; 2–6 Oct 2004; Ottawa.
- Shakespeare TP, Zhang XJ, GebSKI V, Tang J, Lim K, Lu J, Jiang G.** Results of the PRIMER 2 randomized study comparing *P* values plus 95% confidence intervals (*P*+*CI*) vs. *P* values plus confidence levels (*P*+*CL*) vs. *p* values plus 95% confidence intervals plus confidence levels (*P*+*CL*+*CL*) for optimizing oncologists' interpretation of published clinical research. *8th Biennial ESTRO Meeting. Radiotherapy and Oncology* 2004; 73: S359 (abstract 841).
- Shimpi RA, Griffin J, Granger CB, Califf RM, Van de Werf FJ, Simes RJ, Muir AJ.** Predictors of gastrointestinal bleeding in patients receiving thrombolytic therapies for acute ST-elevation myocardial infarction. *Annual Meeting of the American Gastroenterological Association*; 15–20 May 2004; New Orleans. *Gastroenterology* 2004; 126 (Suppl. 2): A607.
- Simes J, Kirby A, Colquhoun D, Hunt D, Keech A, Pater H, Hague W, White H, Shaw J, Tonkin J;** for the LIPID study investigators. Long-term safety and effectiveness of cholesterol lowering with pravastatin treatment over 11 years: the LIPID trial extension. *American Heart Association Annual Scientific Sessions*; 13–16 Nov 2005; Dallas.
- Söderberg S, Colquhoun D, Keech A, Pollicino C, Barnes E, Simes J, Tonkin A.** Leptin but not adiponectin is a predictor of recurrent cardiovascular events in the LIPID Study. *European Society of Cardiology Congress*; 3–7 Sep 2005; Stockholm.
- Steinbeck K, Baur, Morris A, Ghersi D.** Prospective collaborative meta-analysis of trials of weight management interventions in childhood overweight and obesity. *14th European Congress of Obesity*; 1–4 Jun 2005; Athens.
- Steinbeck K, Morris A, Buar L, Ghersi D,** on behalf of the ACAORN management SIG. Prospective collaborative meta-analysis of trials of weight management interventions in childhood overweight and obesity. *13th Cochrane Colloquium*; 22–26 Oct 2005; Melbourne.
- Stockler MR, Duric V, Beith J, Boyle F, Friedlander M, Sullivan A, Wilcken N, Dhillon H, Coates AS, Simes RJ.** Patients' preferences for adjuvant chemotherapy in early breast cancer: what makes it worthwhile? *Clinical Oncological Society of Australia Annual Scientific Meeting*; 24–26 Nov 2004; Canberra.
- Sullivan L, Pendlebury S, Kirby A, Rodger A, Joseph D, Campbell I, Stockler M.** Health-related quality of life during and after post-operative radiotherapy for T1N0 breast cancer. How does it really feel? *Annual Scientific Meeting of the Royal Australian and New Zealand College of Radiologists*; 6–9 Oct 2005; Sydney.
- Sullivan L, Pendlebury S, Kirby A, Rodger A, Joseph D, Campbell I, Stockler M.** Health-related quality of life during and after post-operative radiotherapy for T1N0 breast cancer. How does it really feel? *Clinical Oncological Society of Australia Annual Scientific Meeting*; 16–18 Nov 2005; Brisbane.
- Sun X, Ma T, Zhang X, Tong L, Parker S, Wang L, Li Y.** Methods to involve medical students from developing countries in Cochrane systematic reviews: preliminary experiences from China. *12th Cochrane Colloquium*; 2–6 Oct 2004; Ottawa.
- Thewes B, Meiser B, Duric V, Stockler M, Friedlander M.** What survival benefits do pre-menopausal early breast cancer patients consider necessary to make endocrine therapy worthwhile? *Psycho-oncology* 2004; 13 (8): S40–S41.
- West MJ, Blankenberg S, Simes RJ, Pollicino C, Kirby A, Nestel P, White H, Tonkin A,** for the LIPID investigators. Brain natriuretic peptide predicts cardiovascular outcome in stable CHD patients: the Long-term Intervention with Pravastatin in Ischaemic Disease (LIPID) study. *Annual Scientific Meeting of the Cardiac Society of Australia and New Zealand*; 5–8 Aug 2005; Perth.
- West MJ, Blankenberg S, Simes RJ, Pollicino C, Kirby A, Tonkin A.** Brain natriuretic peptide: a predictor of cardiovascular outcome in the LIPID study. *European Society of Cardiology Congress*; 3–7 Sep 2005; Stockholm.
- Wilson V, Byth K.** Detecting glaucoma using visually evoked potentials. *55th Session of the International Statistical Institute*; 5–12 Apr 2005; Sydney.
- Woollett A, Richards A, Provis A, May J, Tepes S, Dhillon H,** for the COSA Data Managers Group. Standard operating procedures: a survey identifying needs and priorities. *Clinical Oncological Society of Australia Annual Scientific Meeting*; 24–26 Nov 2004; Canberra.
- of 800 mg after progression on 400 mg—an international, intergroup study of the EORTC, ISG and AGITG.** *40th Annual Meeting of the American Society of Clinical Oncology*; 5–8 Jun 2004; New Orleans. [AGITG]

Selected invited presentations

- Askie L.** Update on the Australian Clinical Trials Registry. *Association of Regulatory and Clinical Scientists*; 2005; Sydney.
- Ghersi D.** Evidence-based medicine and the graduate medical program at the University of Sydney. *Evidence-based Healthcare and the Cochrane Collaboration*; 27 Feb 04; Milan, Italy.
- Ghersi D.** Evidence-based medicine and clinical trials. *International Symposium for Evidence-based Medicine*; 13 Sep 2005; Seoul.
- Henderson IC, Wilcken N, Ghersi D, Davis N, Parker S, Carrick S.** How to read and do a Cochrane systematic review. *Leura V International Breast Cancer Conference*; 10–14 Nov 2004; Sydney.
- Heritier S.** Dynamic balancing randomisation: a tree-based method of randomisation and its properties. *Sydney Summer Statistics Workshop*; 27 Feb 2004; University of Sydney, Sydney.
- Stockler M.** The design and analysis of controlled trials in the management of pain, depression and fatigue. Educational Session, American Society of Clinical Oncology ASCO New Orleans, June 2004 [chair and speaker].
- Stockler M, Goldstein D, Wilcken NC, Glare P, Dhillon H, Nowak A, Turner J, Koczwara B, Healey T, Jefford M, Simes RJ.** A double-blind, placebo-controlled trial of Zolof's effects on symptoms and survival time in advanced cancer: the ZEST trial. *Pfizer Oncology Weekend Workshop*; Mar 2004; Sydney.
- Stockler M.** Turning good ideas into successful clinical trials with concept outlines. *Sydney Institute of Palliative Medicine Symposium*; Mar 2004; Sydney.
- Stockler M.** Turning good ideas into successful clinical trials with concept outlines. *Australia Asia-Pacific Clinical Oncology Research Development Workshop (ACORD)*. Aug 2004; Palm Cove.
- Stockler M.** Academic independence versus industry support. *Australia Asia-Pacific Clinical Oncology Research Development Workshop (ACORD)*. Aug 2004; Palm Cove.

Presentations by collaborative groups

- Hiukka A, Leinonen E, Hilden H, Nakano T, Taskinen M-R.** Determinants of remnant-like particle cholesterol in type 2 diabetes. *75th European Atherosclerosis Society Congress*; 23–26 Apr 2005; Prague. [FIELD]
- Zalberg JR, Verweij J, Casali PG, Le Cesne A, Reichardt P, Blay JY, Issels RD, Van Glabbeke M, Evrard V, Judson IR.** Outcome of patients with advanced gastro-intestinal stromal tumors (GIST) crossing over to a daily imatinib dose

