**PaCCSC: Palliative Care Clinical Studies Collaborative**

PaCCSC is a national, multi-centre research network to support clinical studies in palliative care. Funding from the Australian Government Department of Health, through the National Palliative Care Program to Flinders University for the coordination of the development and implementation of the initiative, was announced in June 2006.
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PALLIATIVE CARE

Palliative care is an approach that improves the quality of life of patients and their families facing the problems associated with life-limiting illness, through the prevention and relief of suffering by means of early identification and impeccable assessment and treatment of pain and other problems: physical; psychosocial; and spiritual.

Palliative care:
- provides relief from pain and other distressing symptoms
- affirms life and regards dying as a normal process
- intends neither to hasten or postpone death
- integrates the psychological and spiritual aspects of patient care
- offers a support system to help patients to live as actively as possible until death
- offers a support system to help the family cope during the patient's illness and in their own bereavement
- uses a team approach to address the needs of patients and their families, including bereavement counselling, if indicated, and
- is applicable early in the course of illness, in conjunction with other therapies that are intended to prolong life, such as chemotherapy or radiation therapy, and includes those investigations needed to better understand and manage distressing clinical symptoms.

WHO definition
The Australian Palliative Care Clinical Studies Collaborative (PaCCSC) is the world’s first and still its largest national, multi-site phase III clinical trials group. This program, funded by the Australian Government through the Department of Health, is setting a benchmark in generating high quality evidence to directly influence clinical care in a population that, to date, has not been well studied.

The evidence for the medications used in palliative care either had not been studied or are difficult to extrapolate from other populations. This is because of the unique challenges of the frailty of this population and the real challenge of how to ensure that the net effect (both benefits and burdens) of any intervention are recognised.

PaCCSC works at the highest levels of generating quality evidence with processes and procedures in place to ensure that each site and each investigator continues to contribute high quality data that can directly inform clinical and funding decisions.

PaCCSC is only in existence because of the Australian Government’s commitment to improving palliative care nationally and improving the evidence base within current legislative and regulatory frameworks for prescribing in palliative care. This is no easy task and the reason why many other governments and academic groups have not taken on this role is because of its complexity.

PaCCSC relies on the dedication and enthusiasm of a large number of clinicians from right across Australia. Their drive and absolute dedication to improving the care of patients generates the energy and momentum to maintain PaCCSC and the work that it is doing.

Ultimately, this program is about improving the quality of care for the tens of thousands of patients with a life-limiting illness each year in this country. Without the participation of patients and, at times, their caregivers, PaCCSC would not be the success it is. I would like to thank each and every one of them and their families for taking time at a very crucial part of life to reach out and help others because of their willingness to contribute to this important process of improving the quality of care.

PaCCSC also has an extraordinary national coordinating team that continues to drive excellence in processes, engage new sites and deliver high quality data for both statistical and economic analyses. This places PaCCSC at the forefront of clinical trial research anywhere in the world and, again, I would like to thank them for their excellent work that continues on a day to day basis.

The care of people at the end of life can be improved. Already PaCCSC studies are influencing clinical care on a daily basis around the world. This work needs to continue in each of the symptom nodes (pain, breathlessness, nausea, bowel problems, anorexia, and delirium) in order to continue to deliver more refined care with an understanding of the balance of benefit and burden in this population.

I would ask that you support PaCCSC in any way you can given the magnitude of work that is still ahead of us, the importance of that work and the fact that this work is making a difference to clinical care already.

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**Professor David Currow**

Chief Investigator
SUMMARY

Background
A significant proportion of Australians will require palliative care as they near the end of life. The majority of this care is provided in the community which necessitates access at home to affordable and appropriate medicines.

In 2000, members of the Australian and New Zealand Society of Palliative Medicine (ANZSPM) were surveyed to compile a list of the medicines they considered essential in the practice of palliative care and the indications for which they were prescribed. A number of the medicines highlighted were already available on the nationally subsidised Pharmaceutical Benefits Scheme (PBS). However, many other medicines commonly used in palliative care were not listed on the PBS and were therefore not affordable for patients outside hospitals.

Many of the medications being prescribed in the palliative care setting are being used ‘off label’ for indications, routes of delivery and/or formulations not yet approved by the Therapeutics Goods Administration.

Palliative Care Medicines Working Group (PCMWG)

In response to the survey, the Commonwealth Department of Health established the Palliative Care Medicines Working Group (PCMWG) in 2002 to provide clinical and technical support, and advice to the Department on the following items including improving:

- access to palliative care medicines
- the quality use of palliative care medicines, and
- awareness of both the medicines available through the PBS, and the need for additional research to be done to support the registration of palliative care medicines on the Australian Register of Therapeutic Goods.

Recognising the complexity of the task, a broad range of stakeholders necessary to support the delivery of high quality effective palliative care across all settings were brought together. Initial work on medicines considered to be essential for good community-based palliative care was completed in 2003.

PCMWG membership included:
- Australian and New Zealand Society of Palliative Medicine
- Australian Pharmaceutical Advisory Council
- Cancer Australia
- Cancer Council Australia
- Clinical Oncological Society of Australia
- Commonwealth Department of Health – Pharmaceutical Benefits Branch
- Community Nursing
- Consumers Health Forum
- Drug and Therapeutics Information Services
- General Practice Advisory Group
- Joint Therapeutics Committee for Palliative Care Australia
- Medicare Australia
- Medicines Australia
- National Prescribing Service
- Palliative Care Australia
- Palliative Care Intergovernmental Forum
- Pharmaceutical Benefits Advisory Committee
- Pharmacy Guild of Australia, and
- Therapeutic Goods Administration
The Palliative Care Medications Scoping and Research Study systematically reviewed the available evidence and worked with individual sponsor pharmaceutical companies to support changes to the subsidies available for a list of priority medicines.

**Pharmaceutical Benefits for Palliative Care**

In February 2004, a dedicated palliative care section was established within the Schedule of Pharmaceutical Benefits. The medicines listed on the Pharmaceutical Benefits for Palliative Care allow a greater number of palliative care patients to access their medicines in the community affordably. This was the first section ever created in the PBS for a specific patient population.

There remained however, a number of medicines with continued use ‘off licence’, and where the evidence was insufficient for listing. In 2005, the Commonwealth requested advice from the PCMWG on the research infrastructure needed to support the development of the evidence base for medicines in palliative care.

**Definition of a palliative care patient for PBS purposes:** “A patient with an active, progressive, far-advanced disease for whom the prognosis is limited and the focus of care is on quality of life”.

**Initiation of PaCCSC**

In 2006, the Commonwealth provided significant support to build the infrastructure needed to help gather scientific evidence necessary for the medicine approval process, and to support a national clinical trials network. A competitive tender process was undertaken and the Palliative Care Clinical Studies Collaborative (PaCCSC) was born. PaCCSC randomised its first phase III trial patient in 2008 and at the time of printing had recruited over 1300 participants to nine phase III clinical trials. This is the world’s largest phase III study group in palliative care.

**PaCCSC initiating investigators**

Professor David Currow (Chief Investigator)
Ms Tania Shelby-James
Ms Debra Rowett
Doctor John Plummer
Professor Geoff Gourlay
Associate Professor Simon Eckermann
Associate Professor Amy Abernethy
In June 2006 the Australian Government provided seed funding to support the development of PaCCSC. PaCCSC is a collaborative network of researchers from around Australia who have joined forces to facilitate the generation of the scientific evidence to support an expanded evidence base for prescribing in palliative care.

The growth of PaCCSC

Recognising the increasing need to continually build networks beyond the palliative care arena, PaCCSC became a member-based organisation in early 2010. Three levels of membership are open to individuals: full clinical researcher, associate member and invited experts. There are various voting rights attached which provide members with a direct say in the direction of the Collaborative. Continuing to expand the Collaborative throughout a range of stakeholders and disciplines, as exemplified from the very beginning through the PCMWG, ensures a more relevant, inclusive and sustainable organisation in the long term.

The governance structure continues to evolve and in early 2013 a consumer representative was appointed at the highest level of the Collaborative on the Management Advisory Board. The Scientific Committee has also seen the introduction of an early career researcher position to aid the ongoing capacity building and professional development remit of PaCCSC.

As demonstrated throughout this report, PaCCSC conducts a variety of parallel studies across a growing network of recruiting sites that can directly inform clinical practice. The goal for all studies is to ensure effective and efficient recruitment of participants, advance clinical research theory in palliative care, and continue to build strong research capacity and knowledge throughout the discipline.

The initial studies were developed out of Palliative Care Medications Scoping and Research Study. Later studies have developed out of increasing clinical debate or concern about certain medicines currently in use. These debates continue and at the very heart of the research is the need to ensure the patient and caregivers perspective are always respected. All PaCCSC studies aim to do the best by the people relied upon for their participation.

The less visible work of PaCCSC

Publicly funded studies like those conducted by PaCCSC provide valuable, freely available information about the benefits, harms and costs of medicines used in palliative care. As opposed to being an add-on following a positive trial result, every protocol developed by PaCCSC includes a health economic analysis. Economic analyses undertaken alongside clinical trials have the potential to improve and enrich evidence-based decision making and provide substantial economic benefit to society, nationally and internationally by:

- improved quality of life for patients, families and informal carers
- better healthcare
- increased productivity
- reduced wastage on ineffective and costly medicines
- maximisation of benefits for patients from limited public funds, and
- reducing unnecessary toxicity from symptom control medications.
Gaining informed consent from individuals to participate in a clinical trial is Good Clinical Practice. However, in some populations, achieving this can be difficult and calls for special care. PaCCSC have adopted ethically valid consent approaches that are tailor to the population including: consent by the patient; a proxy; and pre-consent. Increased use of less traditional modes of informed consent enables greater participation in trials conducted in a palliative population, thereby improving the evidence base more rapidly in part by better reflecting the population served.

The first successfully completed randomised clinical trial undertaken by PaCCSC, the ketamine study, yielded both high placebo and nocebo response rates.

The placebo effect: when participants improve while receiving an inactive substance, and the nocebo effect: when participants experience adverse effects while receiving an inactive substance.

The existence of these effects is a major reason PaCCSC studies incorporate a control arm and double-blinding (where both clinician and patient are unaware of the treatment allocation) if no evidence-based standard of care exists. These effects help to further understand how and why patients respond positively or negatively to the care provided.

PaCCSC continues to drive the research capacity in palliative care. A number of recruiting sites have successfully undertaken their own research as a direct consequence of the skills and support obtained through PaCCSC, sometimes associated with obtaining funding grants. Other direct benefits also include stronger working links with other palliative care units, and mentoring of clinical researchers. For sites preparing for accreditation, participation in PaCCSC provides excellent evidence of quality processes and a ‘virtuous cycle’ of quality improvement in action. Surveyor comments have extended specifically to the results from research and the way in which research outcomes are informing clinical practice and service development.

People receiving palliative care and participating in a clinical study may withdraw or die after randomisation for reasons unrelated to the study intervention. Whilst this proportion of individuals is very low in other clinical disciplines, it is commonplace in palliative care and with the larger proportion of withdrawals, the larger the underestimate of benefit will be. This experience has led the Collaborative to develop the palliative-modified intention-to-treat analysis. This modified analytic approach addresses data after randomisation where there is a high rate of withdrawals due to death or deterioration.

The RAPID pharmacovigilance series, now into its fourth medication/indication dyad, is a proactive approach to meet the need for prospective, systematic collection of data on more widespread and longer term use of medicines regularly prescribed in palliative care. Involvement in the program now exceeds 90 sites in 18 countries and includes a ‘translation’ step whereby the participating clinicians, and colleagues at their local site, become more aware of both measures of effectiveness and harm for the medicines being studied. Whereas audit is retrospective data collection commonly focused on determining if guidelines have been followed, RAPID is providing good quality information on drug effects cheaply in the real time clinical context.

PaCCSC into the future

PaCCSC researchers continue to learn from each other and, through this, improve the study designs and methods employed. Researchers in this field must be able to demonstrate to the community the processes to balance the ability of people at the end of life to participate in research with the ethical processes to protect potential participants. Ultimately, the professional responsibility of the Collaborative is the generation and uptake of new, evidenced based, knowledge into practice and policy.
SITES

Phase III sites in Australia

Initiating site names
Braeside Hospital (also including Camden and Liverpool Hospitals), NSW
Curtin University (including Hollywood Private Hospital and St John of God Subiaco and Murdoch campuses), WA
Mater Health Services, QLD
Peter MacCallum Cancer Centre, VIC
Royal Prince Alfred Hospital, NSW
Southern Adelaide Palliative Services (including Repatriation General Hospital, Flinders Medical Centre, Blackwood Private and Flinders Private Hospitals), SA

Sites that subsequently joined the Collaborative
Alfred Health, VIC
Austin Health, VIC
Ballarat Health Service, VIC
Barwon Health (including Geelong Hospital and McKellar Centre), VIC
Calvary Mater Newcastle, NSW
Calvary Health Care, NSW
Greenwich Hospital, NSW
Nepean Hospital, NSW
Royal Melbourne Hospital, VIC
Sacred Heart Hospice, NSW
St Vincent’s Health Care Melbourne (including Fitzroy and Kew campuses), VIC
St Vincent’s Hospital Brisbane, QLD
The Prince Charles Hospital, QLD
Westmead Hospital, NSW

Sites that have also contributed to the Collaborative
Alfred Health, VIC
Ballarat Health Service, VIC
Camden Hospital, NSW listed under Braeside Hospital
Curtin University, WA
Flinders Medical Centre, SA listed under SAPS
Modbury Hospital, SA
Royal Prince Alfred Hospital, NSW

Sites that are in the process of joining the Collaborative
Cabrini Private Hospital, VIC
Liverpool Hospital, NSW
Lyell McEwin Hospital, SA
Sunshine Coast Hospital, QLD
Phase III and phase IV sites

**KEY**
- Phase III & IV sites
- Phase III sites
- Phase IV sites

**WA**
- Curtin University / Hollywood Hospice
- Sir Charles Gardiner Hospital

**SA**
- Southern Adelaide Palliative Services (SAPS)
- Lyell McEwin Hospital
- Modbury Hospital
- Royal Adelaide Hospital

**QLD**
- The Prince Charles Hospital
- Sunshine Coast Hospital
- St Vincent’s Hospital Brisbane
- Mater Health Services

**NSW**
- Braeside Hospital
- Calvary Mater Newcastle
- Sacred Heart Hospital
- Calvary Health Care
- Greenwich Hospital
- Liverpool Hospital
- Westmead Hospital
- Camden Hospital
- Nepean Hospital
- Royal Prince Alfred Hospital
- Royal North Shore Hospital

**VIC**
- Peter MacCallum Cancer Centre
- St Vincent’s Health Care Melbourne
- Alfred Health
- Austin Health
- Barwon Health
- Royal Melbourne Hospital
- Cabrini Private Hospital
- Ballarat Health Service

**TAS**
- Tasmanian Palliative Care Service
- Northern Tasmania Palliative Care Service
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*investigators for each study are listed in appendix 3
Symptom - pain

Title: A randomised, double-blind placebo controlled study of subcutaneous ketamine in the management of cancer pain. (ACTRN12607000501448)

This study aimed to explore a specific pain medication, ketamine. Severe pain related to cancer is usually treated with strong pain medications such as opioids, like morphine. Increasing doses of opioids do not always provide the pain relief needed without causing unpleasant side effects. Ketamine is a medication used in anaesthesia that has also been used to supplement the effects of opioids. The full effects (good and bad) of ketamine when used to control strong pain were not clear. Ketamine was identified by the initial scoping study as a medicine commonly used in the palliative care setting without appropriate evidence. More research was needed to support its continued use for the relief of pain caused by cancer.

The study was conducted between March 2008 and February 2011 and recruited 185 participants across 11 sites. The study demonstrated that there was no difference in pain levels between those patients who were allocated to placebo, and those who were allocated to ketamine. Some individuals did report an improvement in their own pain without the knowledge of which intervention they were receiving. The results found that you would need to treat 25 patients for each additional person to benefit over and above placebo.

In addition, patients who received ketamine did report a much higher level of side effects. Overall, one person in six receiving ketamine experienced these unpleasant side effects. Ketamine has limited use for pain relief and can cause unpleasant side effects for many.

Funding partner: Commonwealth Department of Health

Additional funding partner: NHMRC Palliative Care New Investigator Grants - awarded to Doctor Christine Sanderson for Calvary Healthcare to recruit to the study.
Symptom – gastrointestinal tract

Title: A randomised double blind placebo controlled trial of infusional subcutaneous octreotide in the management of malignant bowel obstruction in people with advanced cancer. (ACTRN12608000211369)

Bowel obstruction in the setting of advanced cancer is frequently encountered in palliative patients. Current management options include combinations of surgery where reasonable, nil by mouth, nasogastric decompression or continuous suction, pain relief, and medications to reduce secretions. None of these interventions have been the subject of an adequately powered study to determine the net clinical benefit, and more aggressive interventions such as surgery may not be appropriate for someone close to the end of life. Octreotide is a medication that has specific effects including the potential to inhibit the release of hormones controlling secretions in the gut. Other studies of octreotide for malignant bowel obstruction have suggested a benefit favouring the use of octreotide. A randomised controlled trial to examine the additional effect of octreotide over standard care was required.

The primary outcome was days free of vomiting. The study was conducted between August 2008 and May 2012 and recruited 106 participants across 12 sites.

The result of this study does not support the routine use of octreotide in addition to ranitidine and dexamethasone for the symptomatic treatment of inoperable malignant bowel obstruction. Octreotide was well tolerated, but the higher likelihood of hyoscine butylbromide administration for colicky pain suggests that there may be a symptomatic burden from octreotide in some patients.

Although there was no reduction in the number of days free of vomiting, secondary analyses suggest that a further study in vomiting refractory to standard supportive therapies is warranted.

**Funding partner:** Commonwealth Department of Health

*Graph 2: This graph shows the recruiting sites and then length of time they were open to recruiting. It also shows the contribution made by each site to overall study recruitment.*
Phase III clinical studies in progress

Symptom - delirium

Many patients who have advanced illness who enter hospital in a palliative care setting can experience delirium. The incidence of new episodes of delirium during admission has been reported as ranging between 20-45%.

Title: Randomised control trial of oral risperidone, oral haloperidol, or oral placebo with rescue subcutaneous midazolam in the management of delirium in palliative care inpatients. (ACTRN 12607000562471)

Delirium is prevalent in patients with advanced cancer and in the palliative care setting, and is associated with significant and distressing symptoms and a poor prognosis. Antipsychotic medications are considered as the first line treatment for delirium despite limited research evidence in any health care setting that they change the natural history of delirium. The few studies that exist explore post treatment efficacy in relation to total delirium score reduction, and do not guide management of target symptoms. There has been no systematic evaluation of the toxicity profile in relation to delirium management of antipsychotics in palliative care. Therefore a placebo controlled randomised control trial of antipsychotics to control targeted delirium symptoms was required, and also to consider broader implications on caregiver and patient distress.

Primary Objective: To compare the efficacy of oral risperidone solution and control (oral placebo solution with subcutaneous midazolam rescue). Secondary objectives: To compare oral haloperidol solution and control; and oral risperidone solution and oral haloperidol solution in control of targeted delirium symptoms at 72 hours from treatment commencement.

Recruitment commenced in August 2008 across 11 sites, and is now the largest controlled clinical study in delirium ever conducted. Recruitment is expected to complete in 2014.

Funding partner: Commonwealth Department of Health

Additional funding partners:
NHMRC Palliative Care New Investigator Grants - awarded to Associate Professor Meera Agar for a sub-study examining genetic markers for delirium.
NSW Cancer Council - awarded to Associate Professor Meera Agar and Doctor Christine Sanderson for Calvary Healthcare to recruit to the study.
Symptom - anorexia/appetite

Our patient wanted to enter the study in order to be able to enjoy the food at his upcoming wedding. He was very happy with the result, and had a wonderful wedding – and food! (Comment from a site research nurse.)

Title: Randomised, double blind, controlled trial of megestrol acetate, dexamethasone and placebo in the management of anorexia in people with cancer. (ACTRN 12608000405314)

Loss of appetite (anorexia) is a common and distressing problem in people with advanced cancer and other life-limiting illnesses. Dexamethasone is an inexpensive drug widely used in palliative care as an appetite stimulant. However, there is only low level evidence for its efficacy for this purpose in people with advanced cancer receiving palliative care, and varied treatment regimes in this population. Megestrol acetate is the other established treatment for this indication and there is Level 1 evidence for its efficacy in advanced cancer. There were similar rates of adverse events with the two agents, although the profiles of events were different. Despite the evidence, megestrol is not currently prescribed extensively as an appetite stimulant to Australian patients with advanced cancer, primarily due to its cost (only available on the PBS by authority for metastatic breast cancer). The current body of evidence does not provide sufficient evidence of net clinical benefit, relative efficacy, toxicity, or cost benefit of these two agents in people with advanced cancer receiving palliative care.

Objectives: The primary objective is to compare megestrol versus placebo and dexamethasone versus placebo for their ability to stimulate appetite in the palliative care setting. Secondary objectives are to compare relative consequences of therapy (efficacy, adverse events, quality of life and distress in participants and families, resource use and cost) and hence net clinical effect.

Recruitment commenced in January 2009 across 12 sites, and has reached 85% of the anticipated recruitment.

Funding partner: Commonwealth Department of Health
Symptom - breathlessness

Title: A randomised double-blind multi-site parallel arm controlled trial to assess relief of refractory breathlessness comparing fixed doses of morphine, oxycodone or placebo. (MOP) (ACTRN 12609000806368)

Breathlessness continues to be a major clinical problem for many people with advanced progressive illnesses such as chronic obstructive pulmonary disease, end-stage cardiac failure, and cancer, even when they are receiving the best treatment for their underlying disease. There are phase II/III data and one meta-analysis which support the use of morphine in this setting, but further good phase III data are needed in order to ensure that this is a well-tolerated and effective intervention suitable for a broad range of people with refractory breathlessness. It is also important to establish that the overall net benefit outweighs any toxicity encountered. It is not known whether the two opioids being studied are equally efficacious in treating dyspnoea. Further, a particular concern to many clinicians is the theoretical risk that opioids may cause respiratory depression. This study will specifically address this question through careful collection of non-invasive measures of respiratory function regularly throughout the study including end-tidal carbon dioxide at baseline and primary endpoint.

Study design: This is a phase III, multi-site, randomised double-blind parallel arm fixed dose controlled trial studying treatment approaches for the palliative relief of breathlessness in participants with refractory dyspnoea. Participants will be randomised to fixed dose identical-appearing sustained release morphine (20 mg every 24 hours), controlled release oxycodone (15mg every 24 hours), or placebo for one week. The intervention period will run for seven days; participants will receive study interventions at target doses and blinded therapy for constipation with each active arm together with identical appearing placebo for constipation for the placebo arm.

Objectives: Among participants with refractory breathlessness: To compare the efficacy for relieving the sensation of dyspnoea, level of function, safety and quality of life of two different opioids (sustained release morphine, controlled release oxycodone) with placebo, and the non-inferiority of either opioid; and to identify clinical and pharmacogenomic parameters that predict which individuals will achieve the greatest benefit from the interventions and establish any blinded participant preference.

Recruitment commenced in February 2010 across 11 sites, with recruitment currently at the midway point.

Funding partner: Commonwealth Department of Health
Title: A randomised double-blind multi-site parallel arm controlled trial to assess relief of refractory breathlessness comparing oral sertraline and placebo. (ACTRN 12610000464066)

This study complements other studies completed by the investigator team, and underway by PaCCSC. Although there are some interventions that may offer benefit (oxygen therapy, sustained release low dose morphine), there is still a need for a wider range of interventions to meet the needs of people with refractory breathlessness. Sertraline, an antidepressant of the selective serotonin reuptake inhibitor class, is primarily used to treat major depression as well as obsessive-compulsive, panic, and social anxiety disorders. Previous research has suggested that treatment of concomitant mood or anxiety symptoms can improve dyspnoea however studies are needed to further clarify its potential benefits for the treatment of breathlessness. The research team conducted a pilot study of sertraline using the proposed inclusion and exclusion criteria and the measures proposed in this study design. The pilot study demonstrated acceptability and feasibility of this study, however further phase III data were needed in order to ensure that this is a well-tolerated and effective intervention suitable for a broad range of people with refractory breathlessness. This study will evaluate critically a new but theoretically useful therapy whose role needs to be carefully defined. Although sertraline has been used in small uncontrolled studies, the evidence for a net clinical benefit is inadequate.

Aim: The primary aim is to test the efficacy of sertraline compared with placebo in relieving the sensation of intractable breathlessness. Secondary aims focus on the impact of the sertraline on improving quality of life, dyspnoea-related anxiety and depression, adverse effects, function and clinical predictors of benefit.

Recruitment commenced in January 2011 across seven sites.

Funding partner: Commonwealth Department of Health

I would like to thank you all for the opportunity of participating in the sertraline trial and the friendly, kind, and helpful nature of all the staff involved. I was more than happy to participate in the trial regardless of whether I personally got anything out of it, as I felt that if someone else can benefit from my participation, my job was done. I found I had a massive benefit from the trial. I found that for one reason or another it made me realise that I was obviously living in denial with my illness, for me to admit that it is overwhelming is to say the least. I have learnt that together with the helpful staff it was enough to get me out of my rut. Whether the double blinded trial medication worked or not, I feel in some respects is irrelevant however helpful it was. As it turns out, I felt that I was a burden to my family, particularly my dear wife. It has given me more independence and got me back on my feet, out in the garden and driving my new lovely car. (Comment from a sertraline study participant.)
**Symptom - nausea**

**Title:** A two-stage trial of antiemetic therapy in patients with cancer and nausea not related to anti-cancer therapy.

**Study 1 Title:** A randomised open label study of guideline-driven targeted antiemetic therapy versus single agent antiemetic therapy. (ACTRN 12610000482066)

Nausea in advanced cancer is a multifaceted problem. Recent systematic reviews have concluded that aetiology-based guidelines may be effective in reducing nausea, but no rigorously controlled studies have been undertaken to trial this approach. Moreover, evidence to support the implementation of guidelines in practice is limited and contradictory, and a number of barriers to the implementation of the guidelines have been identified. The primary aim of this study is to undertake a controlled trial to evaluate the efficacy of aetiology-based antiemetic guidelines in improving the management of nausea, by comparing outcomes with patients who are managed using single agent therapy (haloperidol) alone. Participants with resistant nausea following this approach will be invited to enter a second study, comparing an antiemetic as yet unlicensed for this indication levomepromazine (methotrimeprazine, Nozinan®) versus placebo with rescue antiemetics (best supportive care).

**Study design:** A randomised open label study of guideline driven targeted antiemetic therapy versus single agent antiemetic therapy.

**Objectives:** To determine whether guideline driven aetiology-based anti-emetic therapy (targeted therapy) is more effective than single agent therapy with haloperidol in patients with cancer and nausea not related to anticancer therapy.

This study is currently recruiting across nine sites and is expected to close within weeks.

**Funding partner:** NHMRC

**Study 2 Title:** A randomised controlled double blind study of levomepromazine or ondansetron versus placebo with rescue antiemetics (best supportive care) in patients with refractory nausea. (ACTRN 12610000481077)

Nausea in advanced cancer is a multifaceted problem. Recent systematic reviews have concluded that there is a paucity of evidence to support decisions about antiemetic therapy for patients with advanced cancer. A ‘mechanistic’ approach (where the decision to use a specific antiemetic drug depends on the aetiology of the nausea) has been shown to be effective in reducing nausea in uncontrolled studies. The empirical approach advocates the use of one drug irrespective of the cause of the nausea. This approach has also been shown to be effective. In some cases however, the nausea remains refractory to treatment despite multiple lines of treatment often in combination. A drug that may be potentially useful for treating refractory nausea in patients with advanced cancer is levomepromazine (methotrimeprazine, Nozinan®). This drug has not yet been rigorously evaluated in this setting and does not yet have a registered indication for use in palliative care. The primary aim of this study is to assess the efficacy of levomepromazine against placebo with rescue antiemetics (best supportive care (BSC)) in both arms in patients with nausea that has been demonstrated to be refractory to standard treatment as defined in study 1.

**Study design:** A randomised controlled double-blind trial evaluating the effectiveness of one agent unlicensed for this indication versus placebo with BSC rescue in all arms, in improving the management of refractory nausea in patients with advanced cancer.

**Objectives:** To assess the efficacy of parenteral levomepromazine versus placebo with BSC rescue in patients with cancer and nausea refractory to guideline driven targeted antiemetic therapy or single agent therapy with haloperidol.

**Funding partner:** NHMRC
Symptom – gastrointestinal tract

Title: A multi-site cluster randomised controlled trial comparing the severity of constipation symptoms experienced by palliative care patients receiving usual care compared to those diagnosed and managed according to the underlying pathophysiology. (Can Less Be Better) (ACTRN 12611000705987)

Constipation is a common, distressing and serious symptom, affecting between 50-90% of people referred to specialist palliative care services, with 40-70% of people failing to achieve adequate symptom control. The number of people with inadequate symptom relief adds to individual and societal burdens in terms of distress, independence, and increasing hospital and medical care. In palliative care, decisions regarding the prescription of laxatives are based predominantly on clinical experience and institutional approaches. Many of these do not consider the pathophysiological basis that underlies the symptom of constipation and results in numerous changes and additions to the medication regime. Another approach, adopted by gastroenterologists in the treatment of non-palliative care patients, undertakes to diagnose the underlying causes of functional constipation and then tailor treatment accordingly. Such an approach is being adopted to palliative care here.

Objectives:
1. To develop an approach to constipation that enables the underlying problems (slow transit of colonic contents, disordered defecation or an overlap of these problems), to be quantified in palliative care patients using well-tolerated and validated diagnostic methods, and
2. To compare whether constipation symptom severity of those patients randomly allocated to a mechanistic approach to the assessment and treatment of constipation have better patient outcomes than people palliated using standard current clinical care.

Funding partner: NHMRC
Symptom - breathlessness

Three hundred thousand Australians are breathless at rest or on minimal exertion, often for years, despite optimal treatment of the underlying causes. (Professor David Currow)

Title: Improving the treatment of breathlessness – a phase III randomised, controlled trial of sustained release morphine for the symptomatic treatment of chronic refractory breathlessness. (OPIOIDS+1 study)

Three hundred thousand Australians are breathless at rest or on minimal exertion, often for years, despite optimal treatment of the underlying causes. This includes more than 70,000 people who are chronically too breathless to leave their homes. The prevalence of chronic refractory breathlessness (breathlessness that isn’t easily controlled) will continue to increase as the population ages and the chronic progressive diseases which are experienced increase.

This new study will build on the strong research agenda of the investigators and will answer several practical questions about breathlessness including:

- whether increases in the dose of morphine beyond an initial response provides greater net benefit to patients
- what benefits to patients occur over time from this form of treatment, and
- whether the widespread co-prescribing of benzodiazepines (medications often prescribed by doctors to assist with breathlessness) with morphine are justified.

Internationally, no medication is registered for the symptomatic reduction of chronic refractory breathlessness despite recommendations from the American Thoracic Society and the American College of Physicians that regular, low dose morphine is the best evidence based option. As the medications used in this area are off patent there is no incentive for the pharmaceutical industry to sponsor trials of this nature and hence the awarding of the grant from the NHMRC is critically important to this area of medical science. Given the high prevalence of chronic refractory breathlessness, there is an urgent need for a variety of safe and effective treatment of chronic refractory breathlessness. There is uncertainty over ideal opioid dose titration, the co-prescribing a benzodiazepine and the underlying genetic and physiological factors involved in symptomatic benefit.

**Aim/objectives:** To enhance the evidence base for the pharmacological treatment of chronic refractory breathlessness.

**Study design:** A national, multi-site, enriched cohort study in which people for whom sustained release morphine provided initial symptomatic benefit will progress to a double-blind, double dummy, block randomised, placebo-controlled, parallel, three arm, phase III study. Recruitment will commence in 2014.

**Funding partner:** NHMRC
Phase IV clinical studies completed

Retrospective audit
Title: A retrospective case note audit of people referred to palliative care with the symptoms of interest (severe pain, acute confusional state, anorexia or bowel obstructions) or who have been prescribed index medicines of interest.

Multiple sites enable more successful completion of adequately powered phase III studies in palliative care. Audits of the frequency and distribution of the symptoms of interest can better inform research planning by determining realistic recruitment goals for each site. Six services participated in a standardised, retrospective, consecutive cohort audit of five symptoms of their inpatient populations to inform the design of double blind randomised controlled phase III studies. The audit covered all deaths in a three-month period for people who were referred to a specialist palliative care service who had at least one inpatient admission between referral and death. The audits were based around inclusion and exclusion criteria for the proposed studies.

Of the 468 people whose medical records were reviewed, potential study participant rates varied by symptom having accounted for general and specific inclusion and exclusion criteria. Of all inpatients, fewer than one third would be eligible to participate in at least one study. The audit directly informed an increase in the number of participating sites.

Funding partner: Commonwealth Department of Health

Prospective study
Title: A prospective observational study - understanding the burden of adverse drug reactions and their impact on symptoms at end of life.

The primary objective of this phase IV study was to develop pharmacovigilance and drug utilisation methodologies to support ongoing monitoring of drug use in palliative care to optimise benefits from medicines and minimise harms.

This work was designed as a prospective observational study using case note review on first referral to inpatient palliative care to identify potential adverse drug reactions on admission. Participants were asked about the symptoms they were experiencing at the time of admission and the impact of these symptoms on managing their affairs. Participants were asked to keep a medication and symptom diary on their return to community care and were followed at weekly intervals by the project officer. They were then followed until death or the end of the study in early 2010. A sub-study was also conducted with 30 patients who were invited to participate in a patient interview about their medicine use at the time of admission to inpatient palliative care. Recruitment for the prospective audit commenced in November 2009 and completed with a cohort of 150 patients from three phase IV sites.

Funding partner: Commonwealth Department of Health
**Phase IV clinical studies in progress**

**RAPID - pharmacovigilance studies**

RAPID is an international, multi-site, consecutive cohort, post-marketing study of the real world net clinical effects of medications used in hospice/palliative care. RAPID aims to have a large number of sites around the world in different care settings each entering data on a small number of patients in order to quickly improve the evidence base for clinical care. A new medication/indication will be studied approximately every three to six months. At any given time, a single indication will be studied even if a medication has more than one indication in hospice/palliative care practice.

It is called RAPID for several reasons:

- **Rapid** data collection (each site collects data on three (or more) consecutive patients commenced on the medication under study)
- **Rapid** collation and analysis of these data (web based technology is used)
- **Rapid** reporting those findings to clinicians (Journal of Palliative Medicine has agreed to publish these series of studies)
- **Rapid** influence on clinical practice through rapid dissemination of results.

This program is helping clinicians to understand the net clinical effects of the medications that are prescribed – the clinical benefits, the clinical harms and particularly help to identify those people who get benefit with no harm and those people who get harm with no benefit. The program is progressing well with the first three medication/indication dyads now complete and the fourth series making good progress. Data are collected at three time points: at commencement of the medication (baseline); at the time of expected immediate and short term benefit; and at the time of immediate and short term harm. The time to benefit and time to harm will vary with each medication under study and is defined by a committee drawn from participating sites around the world with a particular interest in that medication/indication.

The medication evaluations undertaken to date include:

- Metoclopramide / Nausea
- Haloperidol / Delirium
- Gabapentin and pregabalin / Neuropathic Pain
- Dexamethasone / Anorexia

**Funding partner:** Commonwealth Department of Health
Pilot studies

Clonazepam pilot study

Title: A single arm, open label study of low dose regular opioids with low dose regular benzodiazepine for the relief of refractory breathlessness.

Although there is emerging evidence that very low doses of morphine when given regularly can safely reduce breathlessness, there is still a need for a wider range of interventions to meet the needs of people with refractory breathlessness. Benzodiazepines are widely used around the world to treat breathlessness, however there have been no adequately powered studies that have explored net clinical benefit (symptom relief, side effects, maintenance of any benefit). Clonazepam is already in the Palliative Care Section of the Pharmaceutical Benefits Scheme, can be given once daily, has pharmacokinetic and pharmacodynamic profiles available, and can be administered by a range of routes. The data collected from the study confirmed that it is feasible to proceed to a phase III study using benzodiazepines as an adjunct to opioids in the symptomatic management of breathlessness given their current widespread use. This pilot data were submitted as part of the funding grant application for the Opioids+1 study and subsequently granted.

Funding partner: Foundation Daw Park

FAB Study: Fan, Activity and Breathlessness

Title: The hand held battery operated fan as a self-management strategy: assessing the fan’s capacity to increase physical activity in patients with breathlessness and reducing carer anxiety.

Breathlessness is a devastating symptom of advanced common diseases, related to use of emergency health services and worsening in intensity as death approaches. There is increasing interest in the use of various non-pharmacological interventions for the management of breathlessness, such as the use of a handheld battery operated fan. The fan offers a simple, cheap, easily obtained, portable and safe device for self-management of breathlessness, helpful for both patient and carer. A randomised crossover study has shown the effectiveness of the fan for giving relief in those breathless at rest. However, it is not known if this leads to improvement in other important patient outcomes such as activity, self-efficacy and reduction in hospital admissions. By the end of the pilot study the acceptability of the study design, including the practicalities of multi-site international collaboration and the recruitment rates will be assessed. The study will explore the variance of the primary outcome measure in this population in order to calculate the sample size required to adequately power a phase III randomised controlled study to determine whether a fan improves or maintains activity, reduces symptoms and caregiver burden, when compared with usual care.

Funding partner: Hull York Medical School Research Grant, UK.
Ketamine/codeine pilot study

Title: Mechanistic basis for the use of ketamine as an adjuvant to opioid analgesia – a pharmacokinetic drug-drug interaction?

Pain from damaged nerves is a common problem particularly in the aged and those with medical problems including diabetes, vascular disease and cancer.

A medication called ketamine which is used for anaesthetics is, at much lower doses, also used to help try and control severe chronic nerve pain. It appears that ketamine may increase the effective blood levels of opioids, such as codeine. This study will evaluate whether increased codeine levels are seen when both codeine and ketamine are administered in small doses to well volunteers.

Each participant will take a small regular dose of codeine for three days by mouth and receive a single dose of ketamine administered directly into the vein on the last day of the study. After an initial blood test to determine eligibility, 12 blood samples would be taken each of the last two days of the study to understand how the body breaks down codeine with and without the presence of ketamine in the body.

Funding partner: Foundation Daw Park

Medications management pilot study

Title: A pilot study to assess the feasibility of a prospective randomised controlled trial of a patient-centred medicines management approach to reduce the burden of iatrogenic symptoms in palliative care.

Many of the medicines used in palliative care have not been studied in people who require multiple medicines for a variety of medical conditions. There is limited evidence to help guide medicine choices to relieve symptoms and reduce the likelihood of adverse effects. The burden of advancing disease often results in a progressive increase in the number of medicines prescribed and greater complexity in medication regimens. This increases the likelihood that a patient might experience side effects, more discomfort or a significant adverse event. In other words, it can be difficult to distinguish symptoms associated with the disease processes from the side effects of medications.

Adverse effects from medicines have been widely studied but there has been limited research to understand the rates of adverse drug events and reactions in palliative care and how they affect the symptoms people experience. This research was conducted to inform a patient-centred approach to medicines management and inform the science of prescribing to minimise harm and enhance benefits for those with life-limiting illness.

Funding partner: Nil
Melatonin pilot study

Title: Randomised double blind placebo controlled phase II trial of oral melatonin for the prevention of delirium in hospital in people with advanced cancer.

Delirium is highly prevalent in advanced cancer with unique risk factors and precipitants. It is associated with substantive morbidity and mortality, patient/caregiver distress and significant costs to the healthcare system. There is support for circadian rhythm abnormalities in delirium causation, and based on this melatonin as a therapy is of interest - with two prior studies suggest a role for melatonin as a safe preventative agent in the elderly but with no data in palliative care populations. This clinical trial is evaluating whether oral melatonin is capable of preventing delirium in the advanced cancer population exposed to multiple clinical insults with a high propensity to precipitate delirium.

Funding partner: Cancer Institute NSW

Methylnaltrexone pilot study

Title: The role of peripheral opioid receptors in modulating breathlessness. An in vivo placebo controlled, cross over, double blind study of naloxone and methylnaltrexone on breathlessness during exercise in people with chronic obstructive pulmonary disease.

Recent work from the United States has demonstrated that a person’s own (endogenous) opioids help to modulate the feeling of dyspnoea in people with chronic obstructive pulmonary disease while exercising. In the USA study participants were administered naloxone and were found to be markedly more breathless with no change in work effort. This strongly supports a role for endogenous opioids in reducing the subjective sensation of dyspnoea. More recently, methylnaltrexone, an opioid antagonist, has become available. In routine clinical practice, the aim of combining methylnaltrexone with an opioid agonist such as morphine or oxycodone is to reduce the side effects of opioids (specifically constipation) while ensuring that analgesia continues. By adding a methylnaltrexone arm to the experiment conducted in the USA, important questions about the relationship between opioids and the control of dyspnoea by peripheral opioid receptors, especially in the large airways, can be answered.

Funding partner: Flinders University

Primary pulmonary hypertension study

Title: A prospective, randomised, placebo-controlled, double-blind, crossover study of the efficacy of sustained-release low dose morphine in the subjective sensation of dyspnoea due to maximally treated primary pulmonary hypertension in opioid naive participants.

Medications such as morphine can help to reduce the sensation of breathlessness for some people who have severe lung disease when the cause of their breathlessness has been maximally treated. Although morphine is frequently prescribed, there are limited data to quantify the benefit in people with a condition called primary pulmonary hypertension. The illness causes long term breathlessness that is difficult to improve. This pilot study reproduces a successful previous study completed in people with breathlessness with a wide range of causes, and focuses on people whose breathlessness is caused by primary pulmonary hypertension. This will help to inform the future care of a large number of people around the world and add to the increasing knowledge of management options.

Funding partner: Nil
Pyridostigmine pilot study
Title: Does pyridostigmine have benefit to improve the Bowel Function Index (BFI) scores of those palliative care patients who have baseline BFI scores > 30 despite regular laxatives when also taking medications that deliver an anticholinergic load: an open label pilot study of pyridostigmine.

Constipation may affect 50% of patients at the time of referral to specialist palliative care increasing to more than 90% of by the time of admission to specialist palliative care units. Opioids remain the most commonly cited contributing factor and the research to date remains predominantly focused in this area. However, there are likely to be numerous contributing factors. Given how commonly medications with anticholinergic adverse effects are prescribed in palliative care for symptom control, a cholinergic agent like pyridostigmine that reverses the peripheral effect of these medications on the colon potentially offers clinicians another targeted agent. There are no baseline data to report the safety of the use of pyridostigmine in this population. Establishing this is the first important step. This is an open label phase II study of regular pyridostigmine. People who report having poorly controlled bowel symptoms despite regular laxatives while concurrently taking other medications with an anticholinergic load will be approached. The primary aims of this pilot study are to examine if it is safe to conduct a phase III study of pyridostigmine.

Funding partner: Nil

Sertraline pilot study
Title: A double-blind randomised controlled pilot study of sertraline compared with placebo in people with refractory breathlessness.

Internationally, there is no registered medication for the treatment of refractory dyspnoea despite the burden that this symptom imposes daily on millions of people across the world. It is estimated that more than 2.1 million Australians have a diagnosis of chronic obstructive pulmonary disease (COPD) of whom 1.2 million have symptomatic disease. Estimates for the prevalence of COPD are that currently, 13% of the population has COPD, and 4.7% have severe COPD. There is significant burden on the health system from admissions as a result of COPD with rates of hospitalisation rising in tandem with increases in smoking prevalence in women post World War II.

Selective serotonin reuptake inhibitors (SSRIs) are a novel intervention for the relief of dyspnoea. It is not clear whether SSRIs improve dyspnoea and exercise tolerance by direct effects on respiration or by relieving anxiety symptoms. The aim of this pilot study was to test the efficacy of sertraline compared with placebo in relieving the sensation of breathlessness and improving quality of life. A blinded interim analysis was undertaken. These data supported a clinically significant change used in the power calculation for the phase III RCT.

Funding partner: NHMRC

Unexpected events pilot study
Title: Pilot survey of unexpected events in palliative care.

Many elderly patients take multiple medications for a variety of clinical conditions. While individual medications may relieve the symptoms and the condition for which they were prescribed, they may interact with other medications prescribed for the patient. In palliative care many patients are on multiple medications which they have been taking for many years. In some instances other medications are prescribed without reviewing existing prescriptions. When a patient sees more than one specialist due to multiple clinical problems, this situation may be compounded. Further problems arise due to the patient losing weight and becoming frail. As many of the prescribed medications have an ‘anticholinergic effect’, the combined medications may lead to the patient presenting with adverse effects. These adverse effects are quite frequently identified in palliative care. The aim of this pilot study was to identify if there are events that the patient may find troublesome that could be related to how medications are prescribed at the end of life.

Funding partner: Nil
Clinical vignette study
Title: Off-label prescribing in palliative care – a cross-sectional national survey of Australian palliative medicine doctors.

Regulatory bodies including the European Medicines Agency register medications (formulation, route of administration) for specific clinical indications. Once registered, prescription is at clinicians’ discretion. Off-label use is beyond the registered use. While off-label prescribing may, at times, be appropriate, efficacy and toxicity data are often lacking. The aim of this study was to document off-label use policies (including disclosure and consent) in Australian palliative care units and current practices by palliative care clinicians.

A national, cross-sectional survey was conducted online following an invitation letter. The survey asked clinicians their most frequent off-label medication/indication dyads and unit policies. Dyads were classified into unregistered, off-label and on-label, and for the latter, whether medications were nationally subsidised.

Funding partner: Nil

LifeSpace Assessment
Title: Palliative Care Life Space Assessment Validation Study (PC-LSA).

A Life-Space Assessment maps where a person goes, the frequency with which they go there, and their need for equipment or help from another person. The current Life-Space Assessment instrument asks patients to recall their activity levels over the past four weeks and then again at six months, which is not feasible given the limited life expectancy of palliative care populations. This validation study is being undertaken to determine whether this instrument is sensitive enough to be reliably used with community dwelling palliative care populations using a shorter follow up period (either 7, 14, or 21 days) compared to the usual 28 days.

The recruitment target for this study is 340 people. Since recruitment commenced in June 2013, 17 patients have been recruited with 14 patients having completed.

Funding partner: University of Notre Dame Research Incentive Scheme

Correlative studies

Consumer Impact
Title: The development of Consumer Impact Statements relating to patient and carer end of life experience: Exploring data collection methods.

Impact statements have been developed for use in a number of health related settings, most notably environmental health, but the use of impact statements in other areas of health is less common. However, there is a growing interest in promoting consumer input into health planning and decision making. There is currently no precedent for developing a statement that describes the impact of a symptom, condition or illness on patients’ and carers’ wellbeing. It is anticipated that consumer impact statements may be useful when applying to the Pharmaceutical Benefits Advisory Committee, by providing a consumer perspective on the need for medication to assist with a symptom, condition or disease. The primary objective of this project was to test and compare four methods of collecting data to determine which yielded the most useful information for impact statement development. Two symptoms common to people with life-limiting illnesses were examined to test these methods: anorexia (loss of appetite) and delirium (acute confusional state).

All forms of data collection methods were found to be appropriate. Self-administered surveys were more popular and provided clear concise answers. for the anorexia carer group. Although time consuming to analyse, focus groups provided excellent content as did interviews. The use of symptom diaries were less reliable but also provided good data.

Funding partner: Commonwealth Department of Health
Anticholinergic load pilot study

Title: Prospective study of predictors of the diagnosis of delirium: The association between serum anticholinergic levels and diagnosis or future development in palliative care patients with advanced cancer.

This study explored serum anticholinergic activity (SAA) on admission to an inpatient palliative care unit and its association with prevalent and incident delirium in palliative care patients with advanced cancer, after consideration of other demographic and aetiological factors. In the Australian palliative care inpatient setting, in those who were not imminently dying at admission, the rate of prevalent delirium was 15% and incident delirium 14%. Higher Memorial Delirium Assessment Scale scores during the admission were associated with the presence of cerebral metastases, benzodiazepine dose and severity of comorbid illness on admission. Performance status, SAA, clinical rated anticholinergic score, number of anticholinergic medications, opioids and corticosteroids at baseline showed no association with future development of delirium. SAA was 20%–50% higher in this cohort of advanced cancer than seen in other medical and surgical populations, and was associated with lower functional status, which may relate to an increase in endogenous anticholinergic substances associated with the dying process. The exploration of cholinergic mechanisms of delirium cannot be considered in isolation, and future pathophysiological studies will need to consider an array of approaches to piecemeal together a unifying understanding of delirium neuropathology. Correlation with proposed pathways mediating anorexia cachexia syndromes would also be important. Methods which can more accurately reflect central cholinergic dysfunction may be more indicative of the role of anticholinergic pathways, for example cerebrospinal fluid or neuro-imaging. These methods may also inform the degree of anticholinergic activity of opioids and benzodiazepines, in contrast to their effects on other neurotransmitter pathways.

Funding partner: Nil

TVT Study

Title: An international, multicentre, open randomised parallel group trial comparing a two-step approach for cancer pain relief with the standard three step approach of the WHO analgesic ladder in patients with cancer pain requiring step 2 analgesia.

This is an international, multicentre, open label randomised parallel group trial comparing a two-step approach for cancer pain relief with the standard three step approach of the WHO analgesic ladder in patients with cancer pain requiring step 2 analgesia (weak opioid). Starting a strong opioid (step 3) once non-opioid analgesia (step 1) was not effective means one change of medication for patients. This could result in less contact with health professionals, less confusion for patients (fewer medication changes), earlier access to strong opioids, avoidable costs for dispensed by unused medications, and overall improved pain control. The two step approach would only be advantageous however if it was more effective and had no more side-effects than the three step approach. The primary objective is to establish whether a two-step approach to cancer pain relief can achieve stable pain control more quickly but without increased side-effects compared to the standard three step approach of the WHO analgesic ladder.

Funding partner: Nil
PaCCSC Palliative Care Clinical Studies Collaborative

Other initiatives

ImPACCT
PaCCSC has close links with ImPaCCT (Improving Palliative Care through Clinical Trials) a New South Wales (NSW) collaborative clinical trials group in palliative care. ImPaCCT’s mission is to improve NSW palliative care services for people with advanced cancer and other life limiting illness through ethical, scientifically rigorous, collaborative research. ImPACCT studies underway or in development focus on:
- Improving service delivery and quality of care;
- Improving communication between health professionals and patients;
- Improving the assessment and management of common symptoms; (including development of a national guideline for cancer pain management in adults)
- Better understanding prescribing practices in palliative care.

_Funding partner:_ Cancer Institute NSW

Palliative Care Research Cooperative, USA
The Palliative Care Research Cooperative Group (PCRC) was established through multiple years of cross-institutional discussion and networking. In January 2010 the PCRC kick-off retreat was held in Denver, Colorado. It was here where the core principles were defined by 25 participants representing a broad range of disciplines in academic medicine, community-based hospice and palliative care, federal agencies, diverse research and clinical interests, private and public institutions. The Cooperative is funded by a grant from the National Institute of Health/National Institute for Nursing Research. The group is led by Amy Abernethy, MD, associate professor of medicine at Duke, and Jean Kutner, MD, professor of medicine at the University of Colorado. The PCRC promotes and conducts studies aimed at relieving suffering and improving quality of life for patients receiving palliative care services. PaCCSC is a member of the PCRC and the two organisations continue to maintain strong links with the aim of collaborating on international multi-site clinical studies in palliative care.

_Funding partner:_ National Institute of Health/National Institute of Nursing Research

Japan Research Group
Early in 2013 a team of Japanese researchers who were developing a multi-centre collaborative study group, focusing on medical interventions in Japan, visited PaCCSC to look at ways the two teams could learn from each other, and potentially, work towards some common phase III studies and complement the pharmacovigilance work PaCCSC is conducting. The group is led by Dr Tatsuya Morita, M.D., Palliative and Supportive Care Division, Seirei Mikatahara Hospital, Hamamatsu. Membership of the group includes representatives from palliative medicine; biostatistics; and information studies at The University of Tokyo/ JORTC, and palliative care physicians from Teine Kkeijinkai Hospital and Seirei Hamamatsu General Hospital. The group has considerable experience with oncology research as members of the Japan Collaborative Oncology study Group (JCOG) one of the biggest collaborative study groups in Japan and in the world, but has minimal experience in palliative care research.

Over the past 18 month period PaCCSC has continued to develop a cooperative relationship with the group. During their time in Australia they visited PaCCSC central coordinating office and a number of phase III recruiting sites. The group will make a second visit to Australia in March 2014 to continue the knowledge exchange with the aim of pursuing future funding opportunities, to assist in furthering the interaction between the two teams of researchers, and the further development and implementation of clinical studies research in palliative care across the two countries. PaCCSC have shared various resources; skills; procedures; contract information; evaluation processes; governance and committee structures including the role of the Data and Safety Monitoring Committee and safety reporting; education and recruitment materials; and study related information to assist the Japanese group with local establishment.

_Funding partner:_ Nil
GOVERNANCE AND SUPPORTING ITEMS

Our major funding partners

Commonwealth Government
The PaCCSC contract was awarded to Flinders University after an open tendering process. PaCCSC has continued to be supported by successive Commonwealth Governments. Initial funding was provided to:
- establish PaCCSC to support multi-site clinical drug trials and finalise the governance structure
- support the development of protocols, procedures and forms
- consult with the PCMWG and pharmaceutical companies to identify the drugs that will be progressed in the first wave of clinical trials
- identify participating sites for the first wave of trials
- develop appropriate methodology with the assistance of the Trials Management Committee for the first wave of trials, and
- develop on-line data, communication and audit structures using CareSearch.

2007-2011. Six Commonwealth funded studies were complemented by a further three NHMRC funded studies.

Subsequent funding was made available for the period 2007-June 2011 in which the two phase III studies open to recruitment increased to six studies, along with the addition of three NHMRC funded studies. The requirements of this agreement were:
- undertake four phase III clinical medication studies and develop a further phase III clinical medication study protocol
- conduct drug utilisation research including the quality use of medicines
- increase investigator capacity to undertake multi-site clinical medication studies
- actively seek new partners
- organise and manage publicity, promotional and marketing activities
- disseminate the results of the clinical medication studies , and
- develop strategies to ensure the sustainability into the future.

2011-2014. Two studies have completed and seven studies are open to recruitment.

At the expiration of the second contract, PaCCSC had successfully closed its first phase III trial and had a further eight phase III trials open to recruitment. The requirements of the current agreement are to:
- complete the first wave of clinical medication studies
- staff a central coordinating office, and
- disseminate the study findings.

National Health and Medical Research Council
The NHMRC invites all researchers in Australia to apply for funding through schemes ranging from scholarships to research programs. NHMRC funding supports research across the full spectrum of health and medical research, from basic science through to clinical, public health and health services research. PaCCSC, through a number of its site investigators and members has been successful in being awarded competitive funding for three clinical medication studies. A further clinical medication study has recently been awarded to the Collaborative building on the underpinning work conducted to date. These studies have been awarded Project Grants which support integrated teams of the highest quality researchers to pursue broadly based, collaborative research addressing complex problems.
The governance structure of PaCCSC was developed after consultation with the palliative care community and includes the following:

- Department of Health
- Flinders University
- PaCCSC Chief Investigator
- Site Investigators
- Central Coordinating Office
- PaCCSC Investigators
- Management Advisory Board
- Scientific Committee
- Data and Safety Monitoring Committee
- Members
- Trials Management Committee
- Publications Sub-committee
- Pilot Study Sub-committee
- Trial Data Analysis Sub-committees
- Symptom Node Sub-committees
- Trial Sub-committees

Chart 1: PaCCSC governance structure.
Management Advisory Board

The Management Advisory Board (MAB) has responsibility for clinical and scientific governance of PaCCSC.

Report from the Chair

My involvement with PaCCSC began in January 2006 when I was invited to attend the Infrastructure Development Workshop that produced recommendations to the Commonwealth Department of Health to provide funding to establish the Collaborative. The workshop was the culmination of substantial preliminary work by Professor David Currow and his group at Flinders University. There was a strong argument for the creation of an entity such as PaCCSC because the evidence base for appropriate pharmacotherapy that would support funding under the Pharmaceutical Benefits Scheme for this patient population at that time was sparse. A logical remedy was to develop a rigorous clinical research base to provide such evidence. A multi-centre national collaborative approach was considered to be the most appropriate model for several reasons, not the least of which was to facilitate recruitment of sufficient numbers of patients to support adequately powered clinical trials. The workshop endorsed, amongst other things, the management structure, which included determining the terms of reference for the MAB, the Scientific Committee (SC), the Trial Management Committee (TMC) and the independent Data and Safety Monitoring Committee (DSMC).

The MAB is responsible for the overall governance of PaCCSC, including clinical and scientific governance. The SC, TMC and the DSMC report to the MAB. The committee and reporting structures ensure that all projects are carried out to the highest international standards for clinical trials, underpinned by formal standard operating procedures, which are regularly reviewed. From the inception of the Collaborative until 2014, membership of the MAB has included individuals representing important stakeholders and this has served the Collaborative very well. However, the MAB considers that additional people with fundraising skills will be required in the future to join the MAB to ensure the viability of the Collaborative.

Generous Commonwealth Government funding first became available in 2006, with subsequent funding made available the following year for four years and again in 2011 which is due to terminate soon. PaCCSC has recently been successful in attracting research funding from competitive bodies such as the NHMRC for some of its projects, but substantially more funds will be needed to maintain the impetus that has been generated so far.

The Collaborative is achieving impressive outcomes that were mere aspirations in 2006. There are now participating centres in all mainland states and over 1300 patients have been randomised into nine phase III studies, two of which are completed. There are several pilot studies in progress, and one phase IV study which continues to attract sites both nationally and internationally. Several international collaborations are active and the number is growing. There is an impressive body of publications that deal with various aspects of the Collaborative. The model adopted by the Collaborative is attracting international attention, with other countries now starting to emulate what we do in Australia.

It is a privilege to be associated with PaCCSC whose efforts are likely to provide significant benefit to many people at the end of life in Australia and internationally.

Emeritus Professor Felix Bochner, AM, Chair

Membership (external to PaCCSC):

- Australian and New Zealand Society of Palliative Medicine
- Australian Government Department of Health
- Australasian Society of Clinical and Experimental Pharmacologists and Toxicologists
- Ex officio members - TGA and PBAC
- Medicines Australia
- National Prescribing Service
- PaCCSC Consumer Representative(s)
- Palliative Care Intergovernmental Forum or any successor body
- Therapeutic Guidelines/Australian Medicines Handbook
Scientific Committee

The Scientific Committee has responsibility for the overall review of clinical study proposals and associated ethics applications, publication, dissemination and implementation of study outcomes.

Report from the Chair

Palliative and supportive care is a clinical discipline which has evolved from the need to provide high quality and consistent care to individuals in the latter stages of life-limiting illnesses. To achieve outcomes which are highly valued by the community, the clinicians working in this challenging domain need, wherever possible, to provide the best available care underpinned by high quality evidence. The work of PaCCSC has grown out of the particular need to provide the evidence to underpin the support of the financial cost of pharmaceuticals used in palliative care through the Australian Government’s Pharmaceutical Benefits Scheme. As the work of PaCCSC has evolved, studies now being considered also include non-pharmaceutical approaches to therapy. Underpinning the concept of the studies undertaken by PaCCSC is that they will be well-designed and of high scientific quality.

To oversee the rigour and quality of the PaCCSC studies particularly in the design phase, PaCCSC had the foresight at the commencement of its operations to establish a Scientific Committee charged with ‘the overall review of clinical study proposals and associated ethics applications, publications, dissemination and implementation of study outcomes’. This Committee has now overseen the design of all of the studies initiated by PaCCSC. Its composition has been such as to ensure that the review of all studies has been conducted with a high degree of independence and rigour. The work of the Scientific Committee has set such a standard for PaCCSC studies that when they have gone forward from PaCCSC for consideration by Human Research Ethics Committees any issues raised have never been about the design or scientific basis of the studies. As studies conducted by PaCCSC have been successfully completed, the work of PaCCSC has expanded to include overseeing the organisation’s publication and dissemination strategies through its Publications Sub-committee. The high quality scientific review of all PaCCSC protocols has meant that once studies are completed and papers are written for publication, these papers are being readily considered by high impact journals because it is obvious to reviewers that they are considering studies which have been intrinsically worthwhile, have been well designed, have been rigorously carried out and then appropriately analysed and presented. In addition, the successful completion of a number of studies by PaCCSC has placed the organisation in the position that it has now been able to compete successfully for the highest level of competitive peer-reviewed funding available in Australia through the NHMRC.

The PaCCSC model of building a national clinical research network underpinned by strong policies, central administration and coordination, and the design and conduct of studies of high scientific quality has meant that this model has rapidly gained international attention and is now being reproduced in other countries. The Scientific Committee has been very pleased to have contributed to PaCCSC well-deserved success.

Emeritus Professor Lindon Wing, OAM, Chair

Membership:
Chair, who also holds a position on the MAB (independent)
Chair, Trials Management Committee
ANZSPM Representative
Biostatistician
Clinical Pharmacist
Clinical Pharmacologist
Health Economist
PaCCSC Chief Investigator
PaCCSC Site Investigator
PaCCSC Site Investigator (early career)
PaCCSC National Manager (observer)
PaCCSC National Project Officer (observer)
Publications Sub-Committee
The Publications Sub-Committee is a sub-committee of the Scientific Committee and ensures the inclusion of all PaCCSC members in the promotion of PaCCSC studies through publication in peer reviewed journals and presentation of materials at scientific gatherings, and to safeguard the process.

Membership:
Chair, who also holds a position on the Scientific Committee (independent)
Chair, Scientific Committee
PaCCSC Chief Investigator
PaCCSC Site Investigators x 2
PaCCSC National Manager (observer)

Data and Safety Monitoring Committee
PaCCSC has actively chosen to seek the services of an independent Data and Safety Monitoring Committee who is responsible for safety evaluation and determination and reporting of adverse events for all studies conducted by the Collaborative. The Mater Research Institute contracts to provides this service.
Trials Management Committee

The Trial Management Committee (TMC) has responsibility for the development, review and oversight issues specific to each of the studies including applications for external funding for individual studies, recruitment, outcomes and study milestones. There are various subcommittees of the TMC that are convened when required.

Report from the current and past Chairs

The Trial Management Committee (TMC) is the “engine room” of the collaborative providing oversight of protocol development, recruitment and key performance indicators (KPI), data safety and adverse events, data quality and monitoring and to ensure studies are conducted in a manner aligned with the principles of Good Clinical Practice (GCP).

The inaugural TMC was critical, and comprised of key clinicians engaged in clinical trials across the country, who contributed to development of research questions meaningful to clinical practice and then operationalising these into clinical trial protocols. The TMC also conducted a feasibility audit, to determine feasibility issues relating to the conduct of these trials within the sites of the Collaborative.

Early in development, it was critical for the TMC to meet face to face, to develop collaboration and to work through key operational issues to allow PaCCSC to build the considerable momentum needed to have the initial clinical trials up and running in a timely manner. Since then the committee has contributed to protocol development and operationalising further clinical trials, covering the symptoms of constipation, nausea, and dyspnoea, and three pilot studies in dyspnoea, delirium and constipation.

More broadly, the TMC is a forum for investigators to bring issues for discussion and problem solving in a supportive environment, to maintain enthusiasm and momentum within busy clinical sites for the ‘business’ of clinical trials, and to capacity build and provide mentorship for new investigators. It has been the vehicle for substantive learning and capacity building across the collaborative. The TMC and its members are critical links between PaCCSC and the clinical palliative care community. The impact of conducting clinical trials along side clinical care include building a culture of enquiry and generating the next research questions, ensuring prescribing policies align with an evidence base, and considering the translation of the outcomes of trials into practice. It has also allowed the palliative care community to better engage and broaden our conversation with our colleagues outside the field, for example respiratory physicians, gastroenterologists and geriatricians, who have been willing contributors to the science underpinning the protocols.

The TMC has developed better engagement with Human Research Ethics and Governance, to articulate better the issues and considerations of conducting trials in palliative care. There has also been an ability to listen to the voice of our participants about why these trials are significant for them, but also the issues that are difficult for them.

The TMC remains a dynamic and collaborative group, critical to the success of the collaborative, bringing both strong corporate knowledge of PaCCSC and skills in clinical trials, but also new enthusiastic members strengthening our engagement with the clinical community across the country.

Professor Janet Hardy – Inaugural Chair
Associate Professor Meera Agar – Current Chair

Membership:
PaCCSC Chief Investigator
PaCCSC Site Investigators (all sites)
Chair of each of the Symptom Node Sub-committees
Lead investigator of each study
PaCCSC National Manager (observer)
PaCCSC National Project Officer (observer)
**Membership**

PaCCSC actively encourages membership to extend the underlying knowledge of the Collaborative; broaden the scope of the trials being conducted and prioritise subsequent studies which, among other funding streams, continue to seek competitive category one funding.

**There are three levels of membership available:**

1. Full Clinical Researcher Membership - is open to active clinical researchers who can demonstrate: success in competing for research funds in a context relevant to palliative care; completing studies against those research funds; and publishing the results in peer reviewed journals.

2. Associate Membership - is open to anyone with an interest in palliative care clinical studies.

3. Invited Experts (biostatisticians, health economists, trial methodology experts, clinical pharmacologists, ethicists etc) who are recognised as individuals with extensive knowledge based on research, experience, or occupation in a particular area of study. Experts may be called upon for advice.

**Graph 3: PaCCSC Membership distribution.**
Building capacity

PaCCSC plays a significant role in building the research capacity of the health workforce to understand the need for, and benefits gained, from conducting clinical research in palliative care. There has been considerable effort made to raise the awareness, educate and train those individuals choosing to work in this field to ensure they become the future leaders of research and research conduct in Australia.

Training and workshops

Good clinical practice (GCP) training

PaCCSC has convened a number of training opportunities for participating site staff to undertake GCP training. Whether via full day workshops or providing licences for self-paced on-line learning, training has covered areas such as what is GCP; the current regulatory environment; provided guidance to research staff in the conduct of their role and responsibilities at their site; and explored issues relating to informed consent, documentation and safety reporting. More advanced training is now being provided as evidence of the increase in the level of underpinning knowledge obtained by staff.

Pre-study commencement workshops

A two day workshop was held prior to the opening of each study. One session included the lead and principal investigators along with study staff to discuss and clarify the study protocol. The remaining three sessions focussed on data collection, recruitment strategies, data management and ongoing GCP training, such as regulations, roles and responsibilities, adverse events, Standard Operating Procedures, and consenting procedures.

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Concept development workshop

PaCCSC and Australian and Asia Pacific Clinical Oncology Research Development Group (ACORD) teamed up to provide early career clinical researchers’ in palliative care and oncology a one day Concept Development Workshop in Canberra on 2nd September 2013. The workshop was titled ‘Getting started in clinical research: Writing a concept outline to get things moving’, and was attended by over 20 delegates.

Critical appraisal workshops

A series of one-day critical appraisal workshops designed to help attendees read clinical papers with confidence were sponsored by PaCCSC and expertly facilitated by internationally renowned medical education and critical appraisal training providers Dr Narinda Gosall from Superego Cafe.

Workshops were held:
- the day prior to the 2012 ANZSPM Conference in Queenstown, New Zealand (11 attendees)
- as a pre-conference offering to the 2013 PCA Conference in Canberra, Australia (52 attendees)
- as a post-conference offering to the 2013 PCNA Conference in Melbourne, Australia (30 attendees)

PaCCSC also sponsored two Palliative Care Advanced Trainees to attend a two day critical appraisal workshop in Sydney in October 2012 once again facilitated by Superego Cafe.

Publications

As a Collaborative, PaCCSC have auspiced over 50 peer reviewed journal articles, letters and opinion pieces and the list continues to grow. A full list of published items is located in appendix 2.

Presentations

Presenting work at national and international scientific meetings is critical to sharing the work conducted by PaCCSC and its members.
Promotional events and tools

Exhibitions
Having achieved a number of successes since the commencement of the Collaborative PaCCSC undertook to exhibit at a national level at the Palliative Care Australia Conference in 2013. Both central coordinating office staff and site staff pooled resources to promote the Collaborative to conference attendees.

Picture 1: PaCCSC exhibition at PCA 2013

Annual research forum
As a member-based organisation, PaCCSC welcomes those who are active researchers as well as those who have an interest in building evidence and the quality of the care we offer. The annual scientific meeting of PaCCSC members in March each year - the PaCCSC Annual Research Forum - includes a day looking at current research that is being done in a very open and honest forum. Three questions are asked by each member presenting a current study, a proposed study or a recently completed study.

1. What is working well?
2. What is not working well?
3. What would you do differently next time?

Picture 2: Professor Geoffrey Mitchell, The University of Queensland presenting at the Annual Research Forum

The Forum goes from strength to strength each year. It was excellent to see the exponential learnings across the clinical trials teams and the innovative research being undertaken. The most striking feature of the Forum was the spirit of collaboration, lots of new faces and willingness to share ideas.

(Associate Professor Meera Agar)
PaCCSC have had a website since commencement, however in 2013 a significant redevelopment project was embarked upon. The redevelopment included making the site ‘user friendly’ for our sites to enter data by creating a gateway directly from the website to the research data management system; more consistent and recognisable to all users by using the PaCCSC style guide and branding; and to increase the amount of information available to both members and the general public. Statistics provided by CareSearch show that not only is the website being used as the primary portal for research data entry and study resources by our staff, but it is also attracting significant views in the public domain of study information, and news and events items.

**Graph 3: Visitation to the PaCCSC Website for the 11 month period March 2013 - February 2014**

**Newsletters**

Since 2006, PaCCSC has produced 22 newsletters and distributed these via email to the now 109 members. Issued quarterly, the newsletter has grown from a basic three page summary of site reports, investigator queries and KPI’s to a much larger and more varied document. The newsletter contains all the essential information for the conduct of the suite of PaCCSC studies. This includes: study and site progress reports, KPI’s and analysis. Room is available for a range of information: features from sites, awards to staff, new study information, grant and funding announcements, publications and more. The newsletter is both a place for serious communication and for lighter moments and is an entertaining record of the Collaborative’s progress over time.
Monitoring

As with many other areas of operations, monitoring has evolved over the life of the Collaborative. The evolution of the differing processes has been a combination of pragmatism, experience and refinement of the important elements of quality such as primary outcome, safety, and compliance with regulations. The process has included the use of site staff, support monitors and changes in the breadth and depth of the specific elements being examined.

Site staff have assisted in monitoring of other sites and subsequent to this experience future monitoring of the individual’s own site demonstrated that eight out of 11 sites achieved a reduction in the average number of errors found. Not only do site staff improve their own performance through involvement in monitoring, but PaCCSC operations are streamlined, and staff capacity and skills are improved.

Monitoring has ensured that both study quality and data quality are rigorous and can be relied upon. The dynamic monitoring program is continually expanding the suite of monitoring strategies with work now being undertaken to include: study specific monitoring plans, centralised monitoring procedures and using a risk based approach to increase efficiency.
Important milestones

THE HON MARK BUTLER MP
Minister for Mental Health and Ageing
Minister for Social Inclusion
Minister Assisting the Prime Minister on Mental Health Reform

MEDIA RELEASE

10 December 2012

1,000th Sign-Up for Palliative Care Clinical Trials

Australians with life-limiting illnesses are helping others in a similar situation around the country and worldwide by taking part in trials of palliative medicines.

Speaking at Melbourne’s Palliative Care Nurses Australia Conference, Minister for Ageing Mark Butler said the Australian Government-funded clinical trials had recruited their 1,000th participant.

“These world-leading studies, by the Palliative Care Clinical Studies Collaborative, led by Flinders University in South Australia, will answer many questions on the most effective use of medicines,” Mr Butler said.

“Unlike most other areas of medicine, palliative care services around the world are extremely varied.”

“The Australian Government has provided almost $14 million to the collaborative since 2007, a very significant investment in global terms in palliative care clinical studies.”

“This project has shown that such trials are not only possible but essential.”

“People with life-limiting illnesses deserve exactly the same quality of health care as everyone else.”

Mr Butler said that patients who have volunteered to take part in the clinical trials have shown they want to help improve the quality of palliative care for others.

“These trials help decide whether particular medications are beneficial in palliative care, giving us important guidance for the future as well as peace of mind for patients, families and carers.”

The evidence from the completed studies is already being put into practice worldwide, while the randomised trial model is being replicated around the world.

Further studies are underway in Australia and overseas.

The collaborative was established by the Australian Government and now includes 12 centres around the country working with palliative care professionals.

For more in

SENATOR THE HON BRETT MASON
Parliamentary Secretary to the Minister for Health and Ageing

MEDIA RELEASE

FM9/07

$15.4 million for new palliative care initiatives

The Australian Government today announced more than $15 million in funding for four new palliative care initiatives.

Senator for Health and Ageing, Senator Brett Mason, said the Division of General Practice in regional and rural areas to develop access to palliative care would be targeted.

The successful implementation of the previous phase of this project, which specialised models of palliative care, and continues to acknowledge the need for practitioners in the delivery of palliative care in rural and regional areas.

Senator Mason also launched a program of clinical trials of palliative care drugs.

A total of $9.46 million for clinical trials for six drugs—Ketorolac, Nitazoxamide and Respiratol—in the Palliative Care Clinical Initiative, he said.

The aim is to determine which drugs are most appropriate for use in palliative care, information for the future care of palliative care patients and peace of mind for themselves and their families.

Further evidence of the Government’s commitment to supporting in palliative care patients and their families, said Senator Mason.

Carolyn Martin 0423 826 768

Launch of the Palliative Care Clinical Studies Collaborative (PaCCSC)

The Palliative Care Clinical Studies Collaborative (PaCCSC) would like to invite you to the Official Launch of PaCCSC by the Parliamentary Secretary to the Minister for Health and Ageing, Senator the Hon. Brett Mason.

Wednesday, 29 August 2007, 2:00pm

Level 5, Suites 1 & 2
Melbourne Exhibition Centre
3 Clarendon Street, Southbank
RSVP by Friday, 17 August 2007
Dorothy S Ellwood
Phone: (03) 9637 2001
Email: dorothy.s.ellwood@health.gov.au

PaCCSC Palliative Care Clinical Studies Collaborative

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Speakers

Senator the Hon. Brett Mason
Parliamentary Secretary to the Minister for Health and Ageing

Dr Norman Bean
Producer and President of the ABC’s Health Report

Professor David Gurrar
Department of Paediatrics
and Supportive Services
Flinders University

Flinders University receives funding for PaCCSC from the Australian Government Department of Health and Ageing under the National Palliative Care Program.
## APPENDICES

1: Standard operating procedures

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2: Publications listing


36. Hardy et al, Published reply to KA Jackson et al and W Leppert, Clin Oncol; 31(10):1375-6.


52. Ritchie CS, Currow DC, Abernethy AP, Kutner JS. Multisite studies offer a solution to recruitment challenges in palliative care studies. Palliat Med. 03/2013; 16(9):225.


### 3: Investigator listing

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<td>A/Prof Amy Abernethy, MD, Program Director, PCORC, Duke University, USA</td>
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<td>Prof Samar Aoun, Associate Dean of Research, School of Nursing and Midwifery, Curtin University, WA</td>
<td>A/Prof Judy Bauer, School of Human Movement Studies, University of Queensland, QLD</td>
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<tr>
<td>Prof Janet Hardy, Head of Pharmacy Practise, Faculty of Pharmacy and Pharmaceutical Sciences, University of Melbourne, VIC</td>
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<td>Dr Mark Hill, Senior Lecturer in Cell Development, Proliferation and Death, University of NSW, NSW</td>
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<td>Dr Roger Hunt, Palliative Care Physician, Queen Elizabeth Hospital, SA</td>
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<td>Dr Aminah Jatoi, Prof of Oncology, Mayo Clinic, Rochester, Minnesota, USA</td>
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<td>Dr Rohit Joshi, Department of Medical Oncology, Discipline of Medicine, University of Adelaide, SA</td>
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<td>Ms Bernadette Kenny, Clinical Trials Manager, Southern Adelaide Palliative Services, SA</td>
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<td>Prof Christine McDonald, Director of Palliative Care, Barwon Health, VIC</td>
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<td>Dr Don Mahler, Section of Pulmonary and Critical Care Medicine, Dartmouth-Hitchcock Medical Center, Lebanon, USA</td>
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<td>A/Prof Peter Lawlor, Palliative Care Medicine, University of Ottawa, Canada</td>
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<td>A/Prof Brian Le, Physician - Palliative Medicine/Medical Oncology, Melbourne Health, VIC</td>
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<td>Prof John Miners, Pharmacology and Therapeutics, School of Medicine, Flinders University, SA</td>
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<td>Prof Geoffrey Mitchell, Head MBBS Program, Faculty of Medicine and Biomedical Sciences, University of Queensland, QLD</td>
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<td>Dr Jane Nikles, Research Project Manager, Discipline of General Practice University of Queensland, QLD</td>
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<td>Dr Lawrie Palmer, Director of Palliative Care, Modbury Hospital, SA</td>
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<td>Dr Selvin Pather, Staff Specialist, Royal Prince Alfred Hospital, NSW</td>
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<td>Prof Jane Phillips, Prof of Palliative Nursing, University of Notre Dame, NSW</td>
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<td>A/Prof Jennifer Phillip, Co-Deputy Director, Centre for Palliative Care, VIC</td>
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<td>Dr John Plummer, Senior Hospital Scientist, Flinders Medical Centre, SA</td>
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<td>Dr Stephen Quinn, Senior Statistician, Flinders University, SA</td>
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<td>Ms Debra Rowett, Director, Drugs and Therapeutics Information Service, SA</td>
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<td>Dr Dimitar Sajkov, Senior Consultant, Respiratory and Sleep Medicine, Flinders Medical Centre, SA</td>
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<td>Dr Christine Sanderson, Director of Palliative Care, Calvary Health Care Sydney, NSW</td>
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<td>Ms Tania Shelly-James, Senior Research Fellow, Flinders University, SA</td>
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<td>Dr Helen Skerrman, Senior Research Fellow, Faculty of Health, Queensland University of Technology, QLD</td>
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<td>Prof Andrew Somogyi, Prof in Clinical and Experimental Pharmacology, University of Adelaide, SA</td>
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<td>A/Prof Odette Spruyt, Director Pain and Palliative Care, Peter MacCallum Cancer Centre, VIC</td>
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<td>Dr James Stephenson, Palliative Medicine Consultant, Palliative Care Unit, The Prince Charles Hospital, QLD</td>
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<td>Ms Kate Swetenham, Director, Southern Adelaide Palliative Services, SA</td>
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<td>Prof Nicholas Talley, Pro-Vice Chancellor, Faculty of Health, University of Newcastle, NSW</td>
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<td>Prof Martin Taftersall, Professor of Medicine, Central Clinical School, University of Sydney, NSW</td>
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<td>A/Prof Jennifer Tieman, Director, CareSearch, Flinders University, SA</td>
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<td>Dr Tim To, Medical Consultant, Southern Adelaide Palliative Services, SA</td>
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<td>Dr Hope Uronis, Medical Instructor, Department of Medicine, Duke University, USA</td>
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<td>Dr Louise Welch, Palliative Care Physician, Sunshine Coast Palliative Care Service, Nambour Hospital, QLD</td>
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<td>A/Prof Marie Williams, Associate Head, School of Health Sciences, University of South Australia, SA</td>
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<td>Susan D Whicker, Alta Mira Consulting, SA</td>
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<td>Dr David Woods, Senior Lecturer in Palliative Care, Department of Health and Human Services, TAS</td>
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<td>Prof Patsy Yates, Head, School of Nursing, Queensland University of Technology, QLD</td>
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APPLICATION FOR FREE MEMBERSHIP

PaCCSC actively encourages membership to extend the underlying knowledge of the Collaborative, to broaden the scope of the trials being conducted, and to prioritise subsequent studies which, among other funding streams, continues to seek competitive category one funding.

This application for membership must be signed and dated by the applicant, be signed by two nominees (who are either current members or site staff of PaCCSC), and be accompanied by a brief CV.

Applications will be considered and the level of membership advised by email. Please see membership details on the reverse for more information.

I hereby apply for membership of PaCCSC and in doing so agree to promote the activities of the Collaborative.

Applicant Details

Title:  Full Name:  Applicant Specialty (or discipline):  

Business Address:  

Phone:  Fax:  Mobile:  

Email:  

Date:  Signature:  

Nominators

Nominee 1

Title:  Full Name:  Signature:  Date:  

Nominee 2

Title:  Full Name:  Signature:  Date:  

Return Form and CV to:

PaCCSC – Flinders University  p (08) 8275 1926
C/- Daw House Hospice  f (08) 8374 0350
700 Goodwood Road  e paccsc@flinders.edu.au
Daw Park SA 5041
PaCCSC Membership Details

The Palliative Care Clinical Studies Collaborative (PaCCSC) is a national initiative to improve the evidence base for the community availability for medications used in palliative care that do not have sufficient data for either registration or subsidy applications with the Therapeutic Goods Administration.

Rigorous, adequately powered studies with integrated pharmacoeconomic analyses are the basis of the studies that are undertaken by the Collaborative. Other studies (Phase II and Phase IV studies, population base surveys etc.) are undertaken with a view to taking forward the study design ultimately for an adequately powered phase III study to provide evidence to inform practice and policy.

Benefits of membership of PaCCSC include building capacity in the palliative care community for clinical research, improving the care that is offered by services participating in active, rigorous clinical research and better interaction with peers and colleagues in other disciplines so that those patients not referred to palliative care benefit from access to a wider range of symptom control medications than currently available.

Principles underlying the Collaborative are:

- An inclusive Collaborative that extends its reach to many clinical researchers in palliative care both nationally and internationally.
- Open for individual not institutional membership.
- The aims and focus of PaCCSC clinical studies will primarily be pharmacological interventions.
- Capacity building for health professionals and individuals from other disciplines (e.g. biostatistics and health economics) who want to develop skills in clinical study design, execution, analysis and dissemination and with an interest in palliative care.
- Targeting areas where the evidence base is poor, and where improvement of the evidence base is likely to lead to significant improvement in patient care.
- The standard of studies conducted will be sufficient to inform registration with the Therapeutic Goods Administration and subsequent subsidy applications with the Pharmaceutical Benefits Advisory Committee.
- Studies will be conducted independent of the pharmaceutical industry although close cooperation with this industry is sought and encouraged where appropriate. (Independence is defined as the data at all times being held by the Collaborative for collection, analysis and publication independent of industry control).

To achieve these principles PaCCSC actively encourages membership to extend the underlying knowledge of the Collaborative, to broaden the scope of the trials being conducted, and to prioritise subsequent studies which, among other funding streams, continues to seek competitive category one funding.

Levels of Membership

There are three levels of membership available:

1. Full Clinical Researcher Membership – active clinical researchers who can demonstrate:
   - success in competing for research funds in a context relevant to palliative care, and
   - completing studies against those research funds, and
   - publishing the results in peer reviewed journals.

   The process requires evidence of this (e.g. provision of a CV) together with a nominee and seconder who are already full members.

2. Associate Membership - is open to anyone with an interest in palliative care clinical studies. A nominee who is a full or associate member and seconder who is already a full member is required to put forward the nomination.

3. Invited experts (biostatisticians, health economists, trial methodology experts, clinical pharmacologists, ethicists etc) who are recognised as individuals with extensive knowledge based on research, experience, or occupation in a particular area of study. Experts may be called upon for advice on their respective subject. A nominee who is a full or associate member and seconder who is already a full member is required to put forward the nomination.

Benefits of Membership

Attendance at the annual scientific meeting (PaCCSC Annual Research Forum) which is conducted early each calendar year for all members and invited experts. All members (full and associate) can submit a two page précis of a new study to be considered at the meeting.

Other benefits of membership include:

- Voting rights as provided below.
- Receipt of a quarterly newsletter.
- The ability to actively contribute to building the evidence base to support quality practice in palliative care.
- The ability to collaborate actively with the largest palliative care clinical trials group nationally.

Voting rights for full and associate members

Full and associate members:

- Are eligible to vote on new study proposals put forward by members at the annual scientific meeting.
- Will be called to vote for two full members of PaCCSC to the Management Advisory Board (MAB) where their membership will be for a two year term (for a maximum of three consecutive terms).
- Will be called to vote for the position of Chair of the Trials Management Committee.
- Are able to join trial subcommittees. Trial subcommittees are aligned under symptom nodes and include pain, delirium, anorexia, bowel obstruction, nausea, dyspnoea and constipation.
FEEDBACK SURVEY

Feedback questions for the PaCCSC Research Report
Please help us to provide the information that you are interested to read in our Research Report. The comments and information you provide will be used to produce our next report.

About You
Which category best describes your current relationship with PaCCSC? (please tick)
- [ ] Current Member
- [ ] Palliative Care Health Professional
- [ ] Researcher
- [ ] Other

Content
- [ ] Easy to read
- [ ] Interesting
- [ ] Difficult to read
- [ ] Not of interest

What features did you like the most?

Report Layout
- [ ] Easy to follow
- [ ] Too busy
- [ ] Just right
- [ ] Too long
- [ ] Too short

Report Format
Please rank (1 = Best, 4 = Worst) the following format options according to your preference:
- [ ] Format report (like this)
- [ ] Magazine style
- [ ] Brochure style
- [ ] Newspaper style

This report has made me more aware of:
- [ ] PaCCSC Governance
- [ ] PaCCSC Research
- [ ] PaCCSC Operations
- [ ] PaCCSC Publications
- [ ] People involved with PaCCSC

I would like to see more of:

I would like to see less of:

Return Form and CV to:
PaCCSC – Flinders University
C/- Daw House Hospice
700 Goodwood Road
Daw Park SA 5041

p (08) 8275 1926
f (08) 8374 0350
e paccsc@flinders.edu.au
6: Acknowledgements

Patients and their family/caregivers that have participated in the studies knowing that they may not gain any benefit by participating but who were prepared to volunteer their time and energy in the knowledge that they were helping others in the future.

Committee members, past and present, who give of their time and expertise, and the PaCCSC consumer representative.

Human Research Ethics Committees who have developed a good understanding of the difficulties with palliative care research and have been prepared to work through the issues in order for recruitment to proceed.

Study staff at each site, the investigators, site coordinator, research nurses, and other clinicians who actively assist with the implementation of the study at that site.

Staff, past and present, at the PaCCSC central coordinating office.

Flinders University.

Contact us

Palliative Care Clinical Studies Collaborative (PaCCSC)
Flinders University, School of Health Sciences
Palliative and Supportive Services
C/- Daw House Hospice
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Flinders University receives funding for PaCCSC from the Australian Government Department of Health through the National Palliative Care Program.