IMPACCT: Improving palliative, aged and chronic care through clinical research and translation

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Director IMPACCT
Research Collaboration: Lessons from Palliative Care
Overview

- To provide an overview of the:
- Development the Palliative Care Clinical Studies Collaborative (PaCCSC);
- Achievements of this research collaborative
- Considerations for establishing research collaborations
Collaboration

A means of producing something joined and new, from the interactions of people, or organisations, their knowledge or resources.

• Successful collaborations are facilitated by relationships – the personal bonds or connections.
• Relationships give collaborations strength, allowing it to form and function effectively.
• The quality of these relationships is determined by: trust, reciprocity and mutual benefit.
What is PaCCSC?

The Australian Palliative Care Clinical Studies Collaborative (PaCCSC) is the world’s first and largest national, multi-site phase III clinical trials group that aims to:

- Set the benchmark for generating high quality evidence to underpin and optimise quality palliative care clinical practise
- Build health workforce capacity to conduct high quality clinical research in patients nearing the end of life
- Translate the research results into clinical practice
Challenging common myths

- Patients at the end of life do not want to participate in researchs
- Funders are not interested in end-of-life research
- Research Ethics Committees won’t allow research for hospice / palliative care patients
- It is not ethical to do research on people at the end of life
- It is not ethical to use placebos in hospice / palliative care research
Context

• Many medications and other interventions that are commonly used at the end of life to assist with managing or alleviating patients’ symptoms have little or no evidence to support their use.

• Pharmaceutical companies are generally not attracted to this area of clinical research because there are few, if any, commercial gains given that these medications are mostly off-patent.
Why does PACCSC exist?

- **Strategic Direction – 1**
  Maintain a network of national and international members who collaborate to conduct high quality clinical research in the end of life setting.

- **Strategic Direction – 2**
  Conduct high quality clinical research to build the evidence base to support the quality use of medicines and positively influence healthcare practice in people nearing the end of life. This work may impact on and/or promote access to registered (AUST-R) medicines for use in palliative care.

- **Strategic Direction - 3**
  Build national capacity in the palliative care sector to support/facilitate high quality clinical research and its translation into clinical practice.
Evolution of PaCCSC

• 2000 - National Palliative Care Strategy
• 2000 - ANZSPM survey - essential palliative care medicines
• 2002 - Palliative Care Medicines Working Group
• 2004 - PBS itemised section for palliative care medicines
• 2006 - PaCCSC funded to develop the evidence base for palliative care
• 2008 – March opened first Phase III clinical trial
• 2011 – Feb closed first Phase III clinical trial
• 2017 – March celebrated its 10th Birthday in March
• 2017 – July Moved to UTS
Completed Phase III Studies

- Ketamine (complex cancer pain)
- Octreotide (bowel obstruction)
- Risperidone / haloperidol (delirium)
- Megestrol / dexamethasone (anorexia)
- Morphine/oxycodone (breathlessness)
- Nausea 1, Nausea 2 and Nausea 3 (nausea)
- Can Less Be Better (constipation)
- Sertraline (breathlessness)
A decade of achievements

PaCCSC annual grants and publications
2006 - 2015

Publications annually

Category 1 Grants
Category 2 Grants
Publications
Achievements to date

• PaCCSC Members have secured:
  • 4 Category 1 NHMRC Grants to conduct clinical studies across PaCCSC sites/network, plus new investigator NHMRC grants and numerous Category 2 grants
  • Published over 100+ peer reviewed-publications
  • Presented at over 100+ national and international scientific meetings
  • Currently have two NHMRC Grants (BEAMS and Nausea) in progress
  • Currently have three member project grants under review with the NHMRC to conduct 3 Phase III clinical studies, valued at $2.6M
Changing Practice

- Ketamine study paper published Sept 2012
- Broad dissemination program undertaken
- Follow up survey of ANZSPM members conducted Sept 2013 – 123 members responded out of a possible 392, of which 92% had heard of the study
- Practice change paper published in 2014

Where is PaCCSC?

- PaCCSC is a member based organisation – our members come from across Australia and from the international health professional community
- PaCCSC has participating hospitals and health services in Australia where the benefits from conducting research and from the results achieved can be applied directly to patients
- The PaCCSC central coordinating office is located at the University of Technology Sydney, NSW
<table>
<thead>
<tr>
<th>PaCCSC Australian Sites</th>
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<tr>
<td>St Vincent’s Hospital/Centre for Palliative Care, Victoria</td>
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<td>The Royal Melbourne Hospital, Victoria</td>
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<td>The Austin Hospital, Victoria</td>
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<td>Barwon Health, Geelong, Victoria</td>
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<td>Mater Health Services, Queensland</td>
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<td>The Prince Charles Hospital, Queensland</td>
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<td>St Vincent’s Private Hospital, Queensland</td>
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<td>Nambour Hospital, Queensland</td>
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<td>Southern Adelaide Palliative Services, South Australia</td>
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<td>Lyell McEwin Hospital, South Australia</td>
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<td>Braeside Hospital, New South Wales</td>
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<td>Calvary Mater Newcastle, New South Wales</td>
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<td>Sacred Heart Hospice, New South Wales</td>
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<td>Calvary Health Care, Kogarah, New South Wales</td>
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<td>Greenwich Hospital, New South Wales</td>
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<td>John Hunter Hospital, New South Wales</td>
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<td>Liverpool Hospital, New South Wales</td>
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<td>Concord Hospital, New South Wales</td>
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<td>Ballarat Health Service, Victoria</td>
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<td>Hollywood Hospital/Curtin University, Western Australia</td>
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<td>St John of God Hospitals, Western Australia</td>
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<td>The Alfred Hospital, Victoria</td>
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PaCCSC Sites
Suite of Studies: Phase I-IV
Phase III trials driven by symptom burden

The PaCCSC suite of Phase III clinical studies focuses on a number of symptom nodes commonly experienced by the palliative population. These include:

- Pain
- Nausea
- Gastrointestinal (bowel obstruction, constipation)
- Breathlessness
- Cognitive Disorders
- Appetite/anorexia
# Symptom nodes studies matrix

<table>
<thead>
<tr>
<th>Symptom Node ↓</th>
<th>Hypothesis generating idea (Pharmacovigilance &amp; other)</th>
<th>Phase I/II; pilot; feasibility</th>
<th>Phase III (initiation or open to recruitment)</th>
<th>Dissemination &amp; knowledge transfer (post close to recruitment)</th>
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<tr>
<td>Cognitive disorders</td>
<td>Midazolam for agitation</td>
<td>Palliative sedation</td>
<td>Melatonin for delirium</td>
<td>Risperidone / haloperidol for delirium dissemination</td>
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<td>Nausea</td>
<td>Haloperidol Cyclizine</td>
<td>New nausea</td>
<td>Nausea 3</td>
<td>Nausea 1 &amp; 2 analysis</td>
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<tr>
<td>Pain</td>
<td>Amitriptyline; Targin</td>
<td>CADET; Lignocaine</td>
<td>PAX-1</td>
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<tr>
<td>Gastro intestinal</td>
<td>Macrogol (Movicol) for constipation Ascitic Taps</td>
<td>Pyridostigmine for constipation; PERT 1 &amp; PERT 2</td>
<td>Ranitidine/ dexamethasone for bowel obstruction PERT 3 (follow on)</td>
<td>Octreotide practice change survey</td>
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<td>Breathlessness</td>
<td>Benzodiazepines</td>
<td>OPRA</td>
<td>BEAMS; PEARL Trial</td>
<td>MOP dissemination; Sertraline analysis</td>
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<td>Anorexia / appetite</td>
<td>Mirtazapine; Fn14 Cancer Induced Cachexia</td>
<td>Cannabis</td>
<td>Cannabis (follow on)</td>
<td>Megestrol analysis</td>
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<tr>
<td>Collateral Studies</td>
<td>Missing data Hypodermoclysis</td>
<td>Renal Supportive Care</td>
<td></td>
<td>Blood Transfusions</td>
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Current PaCCSC Phase III Studies

1. **BEAMS** - A pragmatic, phase III, multi-site, double-blind, placebo controlled, parallel arm, dose increment randomised trial of regular, low dose extended release morphine for chronic refractory breathlessness.

2. **MELATONIN** - Randomised, double-blind, placebo-controlled phase III trial of oral melatonin for the prevention of delirium in hospital in people with advanced cancer (MELATONIN)

3. **PEARL** – A randomised phase 3 trial of Palliative care Early in Advanced Lung Cancers (This study is a collaboration between the Australasian Lung Cancer Trials Group, the PaCCSC and the NHMRC Clinical Trials Centre, University of Sydney.)
Rapid – Phase IV Studies

Aim to prospectively collect information on:

1. The therapeutic benefit of medications commonly used in palliative care;
2. The toxicity of medications commonly used in palliative care; and
3. Any significant drug/drug interactions of medications commonly used in palliative care.
Phase IV pharmacovigilance audit/studies - *RAPID*

Designed to monitor medications as they’re being prescribed in the real world and collect information about the symptoms of interest

- Prospective, point of care, data collection
- Clinical information about benefit and toxicity at defined time-points = net clinical benefit
  - Toxicity at any time-point
- 100+ sites from 20+ countries currently participating with constantly growing membership
- 12 months from commencement to completion each medication
- Reporting of outcomes at the conclusion of each medication
- Continued efficient building of the evidence base for medicines use in palliative care
RAPID - pharmacovigilance

- 6 medication/indication dyads completed (M/N, H/D, P*G/P, H/N, D/A)
- Current series Amitriptyline for neuropathic pain,
- 2016 - expansion to study a medication series for each symptom node –
  - Lorazepam for breathlessness
  - Movicol for constipation
  - Cyclizine for nausea, midazolam for agitation and mirtazapine for appetite to follow
- Program also studying non-pharmacological interventions
  - RBC Tranfusions
  - Hyperdermoclysis
RAPID influence on clinical practice

This program:

• Standardises clinical assessment
• Evaluates both benefits and harms from prescribed medications
• Records events in a consistent and systematic way
• Provides feedback on practice in a standardised way
• Compares practices across the world
**RAPID** influence on clinical practice

Less tangible influences

- Participating sites adopt a questioning culture
- Harms as well as benefits become routine questions
- Provides an avenue to participate in clinical research without the normal significant resource implications
- Individual learning
- Part of an international research network
New studies – the importance of pilot/feasibility studies

- Crucial element of good study design
- Doesn’t guarantee success in the main study, but it does increase the likelihood of success
- PaCCSC have adopted a ‘pipeline approach’ so that there are a range of pilot/feasibility studies at different stages being undertaken at any one time.
- The data that results from a pilot is critical in underpinning future submissions for competitive grant funding for Phase III trials – without pilot data larger trial funding support from the NHMRC is rare.
Pilot/Feasibility Studies


2. Phase I/II, dose ranging study of the pharmacokinetics dose-response parameters, and feasibility of vapourised botanical cannabis flower bud in advanced cancer

3. **A multi-centre double blind randomised controlled trial of continuous subcutaneous lidocaine (lignocaine) for the management of neuropathic cancer pain**

4. A randomised, double-blind, multi-site, parallel arm, fixed dose, placebo-controlled trial of the effects of morphine on outcomes of pulmonary rehabilitation in COPD

5. A prospective, randomised, cross-over trial of the efficacy and side effect profile of gabapentin, gamma-linolenic acid, independently and in combination, in the management of uraemic pruritus in patients with End Stage Kidney Disease.
New Study Ideas/Proposals

The SOP provides information to researchers regarding:

1. How the assessment of new study ideas that are brought to PaCCSC is undertaken;
   • Stage 1 – presentation to key stakeholders (TMC), member evaluation (again with criteria)
   • Stage 2 – draft protocol submitted for scientific review (SC)
   • Stage 3 – finalised protocol, ethical approval, funding
New Study Ideas/Proposals

2. Following acceptance of the new study idea, the clinical research infrastructure and support structures available to researchers through the PaCCSC central coordinating office, including:
   - Sponsorship
   - Legals, CTN, CTRA's
   - Insurance
   - Quality assurance, quality control systems (SOP’s in place)
   - Monitoring, agreements regarding randomization, blinding, investigational product manufacture and handling, DSMC or medical monitor.
   - Safety reporting
Average Phase III Clinical Trial Life Cycle

Year 1
- New idea
- Protocol development
- Sponsor
- Peer/scientific review
- Funding

Year 2
- Trial Governance
- Agreements
- Site selection
- Investigational Product
- Data Management
- SOPs
- Regulatory
- Ethics/governance
- Budget
- Equipment/licences

Year 3
- Site start up

Years 4-8
- Recruitment
- Data management
- Protocol amendments
- Site payments
- Dissemination plan
- Undertake analysis

Year 9
- Reach sample size
- Data management
- Finalise SAP
- Draft publication

Year 10
- HREC final reporting
- Clinical study report
- Dissemination activities
- Study closure
Governance

Established governance structure including:

- Management Advisory Board (MAB)
- Scientific Committee (SC)
  - Publications Sub-Committee
  - Pilot Studies Sub-Committee
- Trials Management Committee (TMC)
  - Individual Trial Sub-Committees
- Independent Data & Safety Monitoring Committee
- Individual members – 3 levels of membership: full clinical researcher; associate member; expert member
Standard Operating Procedures (SOPS)
Elements of a successful collaboration

• Shared values, vision and common purpose
• Working as a team to advance science and clinical care
• Creating opportunities to promote the best interactive processes
• Trusting and respectful: honour confidentiality, IP and value the input of others
• Robust governance systems and processes
• Work collaborative to resolve the challenges
• Celebrate the successes and disseminate the results
Acknowledgements

Chief Investigator Prof David Currow

National Program Manager, Linda Brown

National Coordinator, Belinda Fazekas
Can PaCCSC assist your next study?

- Membership
- Quarterly Newsletter
- Annual Research Forum
THANK YOU