Value adding to clinical care – randomised controlled trials (RCTs) in palliative care

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Flinders University receives funding for PaCCSC from the Australian Government Department of Health and Ageing under the National Palliative Care Program.
‘If you always do what you’ve always done, you will always get what you always had’

Albert Einstein (1879-1955)
Evidence-based palliative care; Research questions and their ideal design

- Prevalence of a symptom:
  - consecutive cohort study

- understanding how people feel about taking on the caring role:
  - qualitative study

- testing a new intervention:
  - randomised controlled trial

- finding if there is a relationship between increasing doses and increasing toxicity with a medication:
  - dose-ranging study
1. Why do we need to improve the care we offer?
2. What I have learnt from clinical trials
3. What patients and their caregivers say about clinical trials
1. Why do we need to improve the care we offer?

2. What I have learnt from clinical trials

3. What patients and their caregivers say about clinical trials
Why do we need to improve the care we offer?

- Palliative Care Outcomes Collaborative patient and caregiver survey
- Up to 50 consecutive patients per service per year (2008-2011)
- 49 services
- 35% community only, 33% combined community / inpatient
- 1800 respondents

Pidgeon T et al. BMJ Support Palliat Care 2015
Why do we need to improve the care we offer?

- Palliative Care Outcomes Collaborative patient and caregiver survey

- Palliative Outcomes Scale (version 2)
  - 8 items – symptoms, psychological support and information
  - 2 items – practical matters

Why do we need to improve the care we offer?

- **Pain** – 83%  
  (25% of respondents had overwhelming pain)

- **Other symptoms** – 80%  
  (17% had severe or overwhelming symptoms)

Pidgeon T et al. BMJ Support Palliat Care 2015
Why do we need to improve the care we offer?

- Caregiver anxiety – 78% (22% had severe or overwhelming anxiety)
- Family anxiety - 89% (45% of respondents had overwhelming anxiety)

Pidgeon T et al. BMJ Support Palliat Care 2015
Couple of great one liners from colleagues...

- When discussing the potential for broader availability of the medication if the study showed a positive outcome...
  - ‘I have no problems getting it from my pharmacy department’
Palliative care patients and their health care

- Rigorous, scientifically evidenced health care is an expectation of patients and their families and should be a reality across the entire life/health care journey.

- The reality is that medication prescribing in palliative care is often based on clinical opinion and anecdotal knowledge – until recently there has been limited real science to support clinical decision making in this area of health care.
PaCCSC exists to:

- Give patients with life-threatening illnesses who are approaching the end of life, and their family and caregivers, a better experience that is based on quality use of medications to reduce or alleviate symptoms as safely and predictably as possible.
PaCCSC exists to:

● The palliative care population is the frailest population in clinical practice, and any iatrogenic harm is likely to have irreversible consequences.
We serve a population that becomes increasingly frail as death approaches.

This is the population who is most at risk of iatrogenic harms.

We can, and do, cause morbidity and premature mortality.

If nothing else, a clinical trials program can help each of us to minimise any toxicities and harms, and maximise the benefits that people experience.
PaCCSC aims to do improve evidence by:

- Conducting research across a range of symptoms commonly experienced with a life-limiting illness. Symptom nodes for phase II, III and IV studies include:
  - Pain
  - Breathlessness
  - Nausea
  - Appetite / anorexia / cachexia
  - Confusion / cognition
  - Gastrointestinal problems (bowel obstruction, constipation)
- Ultimately enabling the registration of a range medicines used in palliative care
PaCCSC is doing improving evidence by:

- Building a research culture and capacity to not only conduct research but to understand and adopt research findings into everyday clinical practice
- Disseminating the findings from the research to colleagues in palliative care and other disciplines
- Conducting critical appraisal workshops
PaCCSC is:

- a member based research collaborative
- made up of more than 20 palliative care / respiratory / oncology services across Australia that recruit participants to phase II and III studies; and, internationally, more than 50 sites in more than 10 countries who collect data for phase IV pharmacovigilance studies.
So...

- Are such studies feasible?
PaCCSC undertakes public interest studies:

- The studies are being done for off-patent medications in palliative care will never be supported by the pharmaceutical industry.
- The Collaborative operates at ‘arms length’ from Government, but the need for the research is acknowledged by Government and they review the study design.
- Medications being studied are essential drugs in palliative care, and are particularly needed in the community setting where access is limited.
To date, PaCCSC has:

- Completed 6 phase III studies which have randomised more than 1700 participants
- Completed six phase IV studies (5 pharmacological studies, 1 non-pharmacological studies)
- Generated key studies in correlative science to better understand the underlying mechanisms of symptoms or their management (including healthy volunteer studies)
"If this medication should cause death, stop taking it immediately."
1. Why do we need to improve the care we offer?

2. What I have learnt from clinical trials

3. What patients and their caregivers say about clinical trials
Research in Palliative Care

- How do we further build the evidence in each of the following areas?
  - Basic sciences
  - Phase I, II, III and IV studies
  - Population-based studies
  - Qualitative studies
  - Systematic reviews / meta-analyses
What have I learnt?

In brief, I have learnt:

- We cannot be complacent about the quality of the symptom control that we achieve.
What have I learnt?

In brief, I have learnt:

– We can instantly make a symptom disappear NATIONALLY – simply open a clinical trial to study the symptom
What have I learnt?

In brief, I have learnt:

– Despite doing large numbers of descriptive studies, we know little about the natural history of most of the symptoms we treat – and simple prospective work here can really make a difference.
1/122 clinical trials ever published is in palliative care

Cumulative percentage growth in palliative care literature

(Palliative Care/Total Medline Citations)
What have I learnt?

Breadth of practice = breadth of evidence base

(n=3171 clinical trials up to 2005)

- Top 0.125 3 journals
- Top 0.250 8 journals
- Top 0.500 43 journals
- Top 0.750 164 journals
- All 712 journals

The situation of Mount Lofty was found from hence and from some other cross bearings, to be 34° 59' south and 138° 42' east. No land was visible so far to the north as where the trees appeared above the horizon, which showed the coast to be very low, and our soundings were fast decreasing.

From noon to six o'clock we ran thirty miles to the northward, skirting a sandy shore at the distance of five, and thence to eight miles; the depth was then 5 fathoms, and we dropped the anchor upon a bottom of sand, mixed with pieces of dead coral.

### Table 1

Study Type, Research Topic, and Funding of Palliative Care Studies (n = 189<sup>a</sup>)

<table>
<thead>
<tr>
<th>Topics of Research</th>
<th>All Studies, n (%)</th>
<th>Prospective Studies&lt;sup&gt;b&lt;/sup&gt;, n (%)</th>
<th>Other Studies, n (%)</th>
<th>Pharmaceutical Company Funding, n (%)</th>
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<tbody>
<tr>
<td>Palliative care patient</td>
<td>106 (56)</td>
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<td>80 (42)</td>
<td>8 (4)</td>
<td>44 (23)</td>
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<td>Caregiver/family</td>
<td>17 (9)</td>
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<td>Health professional</td>
<td>41 (21)</td>
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<td>Service provision</td>
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<td>16 (8)</td>
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<td>Tool development</td>
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<td>3 (2)</td>
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<tr>
<td>Healthy volunteer</td>
<td>2 (1)</td>
<td>1 (1)</td>
<td>1 (1)</td>
<td>1 (1)</td>
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<tr>
<td>Medication compatibility</td>
<td>1 (1)</td>
<td>0 (0)</td>
<td>1 (1)</td>
<td>0 (0)</td>
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<td>0 (0)</td>
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<tr>
<td>Community at large</td>
<td>3 (2)</td>
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<td>189 (100)</td>
<td>34 (18)</td>
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<sup>a</sup>Articles published in 2007, reporting new empirical data, retrieved from three journals: *Journal of Pain and Symptom Management*, 47% (51/113); *Palliative Medicine*, 58% (66/115); and *Journal of Palliative Medicine*, 40% (72/181).

<sup>b</sup>Only five of these studies were RCTs: four on patients and one about physician behavior. Three of the four patient RCTs were sponsored by the pharmaceutical industry. Three of the five were from the U.S., and one each was from Colombia and Australia.
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Why do we need to have a control arm in our studies?
Non-randomised versus randomised controlled clinical trial exploring the same question

Differences may range from a 90% underestimate of effect to a 150% overestimate mostly with wider confidence intervals.

...but I saw the medication work (and I trust my own judgment over any data in the literature)

- Placebo rates can be very high and often far higher than 1/3 of the population even in ‘refractory’ symptoms
- Nocebo rates can also be very high and shouldn’t be overlooked

What have I learnt?

In brief, I have learnt:

- We can use the phrase ‘it’s just the disease getting worse’ too glibly
Let’s characterise two of the RCTs done by PaCCSC

- Ketamine (while participant and clinician is still blinded)
- Response rate
  - Ketamine 29/93
  - Placebo 25/92
- Toxicity sufficient to cause withdrawal
  - Ketamine 17/93
  - Placebo 2/92
- No clinico-demographic predictors of responders
Let’s characterise two of the RCTs done by PaCCSC

- Octreotide (while participant and clinician is still blinded)
- Response rate
  - Octreotide 17/45
  - Placebo 14/42
- Toxicity sufficient to have additional medications
  - Octreotide twice as likely to have hyoscine butylbromide administered over the three days (more than three times as like 49-72/72 hours)
- No clinico-demographic predictors of responders
'When the facts change, I change my mind.'

John Maynard Keynes
(1883-1946)
In brief, I have learnt:

- Multi-site studies are the only way we can recruit to these studies in a timely way
What have I learnt?

In brief, I have learnt:

- There are often simple collateral benefits from accurately measuring what we do as part of a clinical trial.
What do we really know about bowel function at the end of life?

- Investigating bowel function
  1. Prolonged transit time
  2. Impaired function of the structures of defaecation
  3. Both

Clark K et al. J Palliat Med 2013;16(5):1-4
What do we really know about bowel function at the end of life?

- Investigating bowel function
  1. Prolonged transit time – radio-opaque markers / plain abdominal x-ray on the 6th day. (normal <5/24 markers at that time)
  2. Impaired function of the structures of defaecation – anal manometry (resting, squeeze, cough), balloon expulsion

Clark K et al. J Palliat Med 2013;16(5):1-4
What do we really know about bowel function at the end of life?

- Investigating bowel function
- Anal manometry
- Resting pressure – internal anal sphincter tone
- Squeeze - external anal sphincter tone and puborectalis sling (pelvic floor)
- Cough – intact recto-anal contractile reflex?

Clark K et al. J Palliat Med 2013;16(5):1-4
What do we really know about bowel function at the end of life?

- Investigating bowel function
- Pilot study: n = 10
  1. Prolonged transit time: med 11.5 (0-24) markers
  2. Impaired function of the structures of defaecation
- Balloon expulsion – all participants failed this

Clark K et al. J Palliat Med 2013;16(5):1-4
What do we really know about bowel function at the end of life?

- Investigating bowel function
- Pilot study: n = 10
  1. Prolonged transit time 2 people
  2. Impaired function of the structures of defaecation 2 people
  3. Both 5 people
  4. Neither 1 person

- Clark K et al. J Palliat Med 2013;16(5):1-4
In brief, I have learnt:

- Shooting the messenger is still a time-honoured sport in our clinical community
Couple of great one liners from colleagues...

The response I get most often from clinicians reflecting on studies’ findings is that

‘a medication is no longer available’ and *not*

‘look at the toxicity we have been causing with no symptomatic advantage’
So... Are such studies useful?
Changing Practice

- Critical appraisal skills
- Ketamine study presented May 2011; 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; 91% had prescribed ketamine
- 65% of respondents had changed practice: 17% ceased to use the drug; 46% used less; 2% increased use

1. Why do we need to improve the care we offer?
2. What I have learnt from clinical trials
3. What patients and their caregivers say about clinical trials
Couple of great one liners from colleagues...

- When faced with a patient with a signed consent form who repeatedly said she wanted to be in the study...
  - ‘Don’t worry about the study. I know the medication works and I want you to have it’
How patient-centred are we?

- Do we see evidence of ‘gate-keeping’?
- (This person wouldn’t want to participate in a clinical trial. I won’t even give them the option)
How patient-centred are we?

- Yet, the evidence is that palliative care patients want to participate in clinical trials and value the experience having done so.
- (Are patients tacitly telling us that the symptom control we offer is not as good as they hoped?)
How patient-centred are we?

- Views of palliative health care professionals on referring to clinical trials
- 198/597 surveys
- More likely to refer to non-pharmacological studies
- Needed to minimise participant inconvenience
- Previous research experience improved likelihood

White C et al. Support Care Cancer 2008;16(12):1347-1405
How patient-centred are we?

- General unwillingness to refer to randomised controlled trial in palliative care
- Gatekeeping ...(blocks) recruitment and has the potential to introduce a selection bias.

White C et al. Support Care Cancer 2008;16(12):1347-1405
So...

- Are such studies desirable?
How patient-centred are we?

- Patients’ (100) with advanced cancer and caregivers’ (101) views on randomised trials
- 92% would participate in studies with simple interventions; 26% with complex interventions
- More than 75% of people wanted to help others
- Many prepared to complete short questionnaires, accept extra medications and investigations and undertake additional hospital visits
- Increasing age predicted lower willingness to participate

How patient-centred are we?

- Patients’ with advanced cancer and caregivers’ views on randomised trials – a systematic review

- Key themes
  - Altruism
  - The wish to avoid complex studies
  - Desire to retain autonomy

- The views of palliative care patients towards research are similar to those of other patient populations

White C et al. Support Care Cancer 2010;18(8):905-911
Design

- Practical questions that address day-to-day problems
- Clinically meaningful outcomes FOR PATIENTS
- Shortest possible duration to maximise participation and minimise withdrawal rates
- Minimal inconvenience to patients
- As close to normal clinical care pathways as possible
- Widest possible inclusion criteria

# Symptom Node Hypothesis generating idea (Pharmacovigilance & other) Phase I/II; pilot; feasibility Phase III (initiation or open to recruitment) Dissemination & knowledge transfer (post close to recruitment)

## Cognitive disorders
- Midazolam for agitation
- Palliative sedation (audit)  
  - Palliative sedation
  - Melatonin for delirium  
  - Risperidone/haloperidol for delirium dissemination

## Nausea
- Haloperidol
- Cyclizine  
  - New nausea
  - Nausea 3  
  - Nausea 1 & 2 analysis

## Pain
- Amitriptyline  
  - Targin; CADET; Lignocaine  
  - PAX-1

## Gastro intestinal
- Macrogol (Movicol) for constipation  
  - Pyridostigmine for constipation; PERT; Ranitidine/dexamethasone for bowel obstruction  
  - Octreotide survey

## Breathlessness
- Lorazepam  
  - OPRA  
  - Sertraline; Early intervention PC in Lung Cancer  
  - MOP dissemination; Sertraline protocol publication & survey

## Anorexia/appetite
- Mirtazapine; Fn14 Cancer Induced Cachexia  
  - Cannabis  
  - Megestrol analysis

## Collateral Studies
- Missing data
- Hypodermoclysis  
  - Deprescribing  
  - Renal Supportive Care;  
  - Blood Transfusions dissemination
‘The core of science is not controlled experiment or mathematical modelling; it is intellectual honesty

... one is either engaged in an honest appraisal of the evidence and logical arguments, or one isn’t’

Sam Harris (1967 - )
Letter to a Christian Nation p64-65