PaCCSC

Palliative Care Clinical Studies Collaborative

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.

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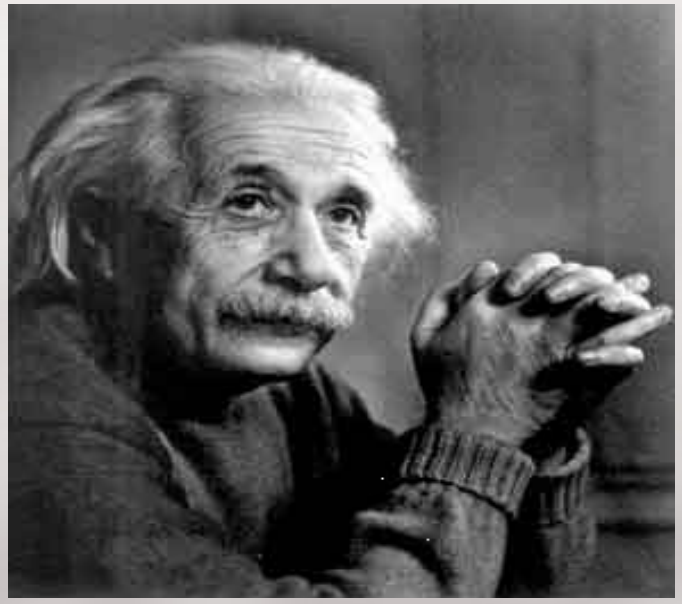
'If you always do what you've always done, you will always get what you always had'



Albert Einstein (1879-1955)

Palliative Care Clinical Studies Collaborative Sites

New South Wales

- Braeside Hospital (also including Camden and Liverpool Hospitals)
- Calvary Health Care
- Calvary Mater Newcastle / John Hunter Hospital
- Greenwich Hospital
- Nepean Hospital
- Royal Prince Alfred Hospital
- Sacred Heart Hospice
- Westmead Hospital

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Victoria

- Alfred Health
- Austin Health
- Ballarat Health Service
- Barwon Health (including Geelong Hospital and McKellar Centre)
- Cabrini Hospital
- Peter MacCallum Cancer Centre
- Royal Melbourne Hospital
- St Vincent's Health Care Melbourne (including Fitzroy and Kew campuses)

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South Australia

- Blackwood Private Hospital
- Flinders Private Hospital
- Lyell McEwin Hospital
- Modbury Hospital
- Repatriation General Hospital / Flinders Medical Centre / Southern Adelaide Palliative Services

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Queensland

- Mater Health Services
- St Vincent's Hospital Brisbane
- Sunshine Coast Hospital
- The Prince Charles Hospital

Western Australia

- Hollywood Private Hospital
- St John of God Subiaco and Murdoch campuses

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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’

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Palliative care patients and their health care

- Rigorous, scientifically evidenced health care is an expectation of all Australians and should be a reality across the entire life/health care journey. But the reality is that medication prescribing in palliative care is heavily 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.

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PaCCSC exists to:

- Give patients with life-threatening illness 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 safely.

PaCCSC aims to do this by:

- Conducting research that addresses a range of symptoms commonly experienced by individuals with advanced or incurable disease such as:
  - Nausea
  - Breathlessness
  - Pain
  - Appetite/anorexia
  - Confusion / cognition
  - Gastrointestinal problems
- Ultimately enabling the registration of a range medicines used in palliative care

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PaCCSC aims to do this 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 other disciplines

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PaCCSC is:

- a member based research collaborative
- made up of more than 20 palliative care/ respiratory/ oncology services across Australia that recruit participants to pilot studies; phase III clinical trials and phase IV pharmacovigilance studies.

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.

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Review process before the start of the original PaCCSC studies

- Clinical trial committee (including clinicians from other disciplines who were likely to manage that particular clinical presentation)
- PaCCSC Scientific Committee (with some members external to palliative care)
- Therapeutic Goods Administration / Pharmaceutical Benefits Branch

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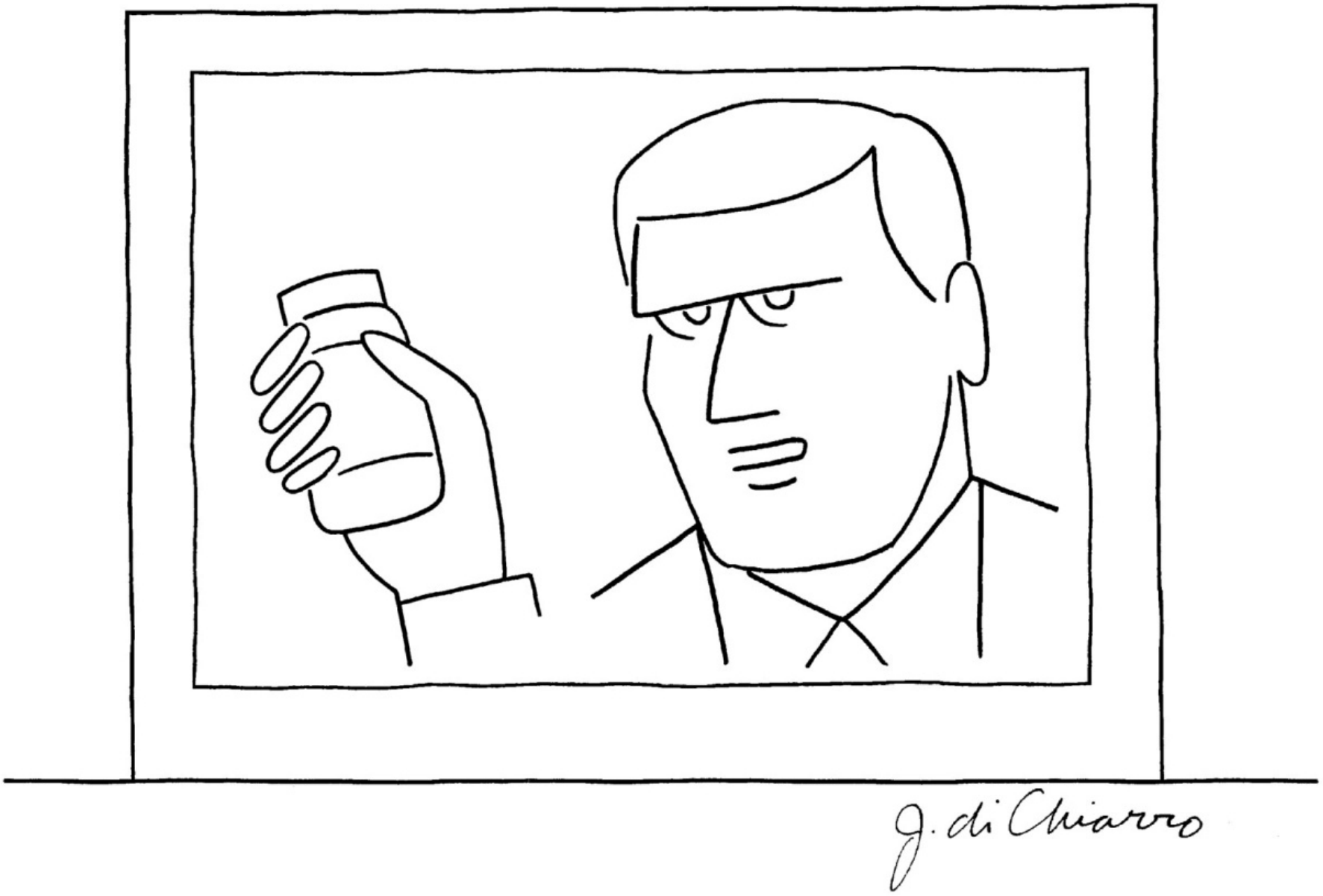
The hospice / palliative care population

- 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



"If this medication should cause death, stop taking it immediately."

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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

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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

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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**

Pidgeon T et al. BMJ Support Palliat Care 2015; Hearn J et al Qual in Health Care 1999.

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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

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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

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MEDICAL RESEARCH

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…OR what doing clinical trials has taught me

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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

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What have I learnt?

In brief, I have learnt:

- We cannot be complacent about the quality of the symptom control that we achieve

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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

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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

Vol. 43 No. 6 June 2012 Journal of Pain and Symptom Management 987

Original Article

Key Characteristics of Palliative Care Studies Reported in the Specialized Literature

Jane L. Wheeler, MSPH, Aine Greene, RN, FRCNA, Jennifer J. Tieman, BSc, MBA, Amy P. Abernethy, MD, and David C. Currow, BMed, MPH, FRACP

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Table 1

Study Type, Research Topic, and Funding of Palliative Care Studies ($n = 189$[a])

Topics of Research	All Studies, *n* (%)	Study Type: Prospective Studies,[b] *n* (%)	Study Type: Other Studies, *n* (%)	Funding: Pharmaceutical Company Funding, *n* (%)	Funding: Other Funding, *n* (%)	Funding: Unfunded, *n* (%)
Palliative care patient	106 (56)	26 (14)	80 (42)	8 (4)	44 (23)	55 (29)
Caregiver/family	17 (9)	2 (1)	15 (8)	0 (0)	11 (6)	6 (3)
Health professional	41 (21)	5 (3)	36 (19)	1 (1)	16 (8)	24 (13)
Service provision	16 (8)	0 (0)	16 (8)	2 (1)	11 (6)	3 (2)
Tool development	3 (2)	0 (0)	3 (2)	0 (0)	2 (1)	1 (1)
Healthy volunteer	2 (1)	1 (1)	1 (1)	1 (1)	0 (0)	1 (1)
Medication compatibility	1 (1)	0 (0)	1 (1)	0 (0)	0 (0)	0 (0)
Community at large	3 (2)	0 (0)	3 (2)	0 (0)	2 (1)	1 (1)
Total	189 (100)	34 (18)	155 (82)	12 (6)	86 (46)	91 (48)

[a]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).

[b]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?

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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 .

Kunz R, Oxman AD. The unpredictability paradox: review of empirical comparisons of randomised and non-randomised clinical trials. BMJ. 1998 Oct 31;317(7167):1185-90.

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…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

Turner JA et al. JAMA 1994;271(20):1609-1614.
Sanderson C. JPSM 2013;46(5):722-730.

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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

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‘When the facts change, I change my mind.’

John Maynard Keynes
(1883-1946)

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What have I learnt?

In brief, I have learnt:

- Multi-site studies are the only way we can recruit to these studies in a timely way

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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

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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**

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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

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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

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What have I learnt?

- In brief, I have learnt:
  - Shooting the messenger is still a time-honoured sport in our clinical community

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What have I learnt?

In brief, I have learnt:

- As a clinical community, we are good at pointing out the failings of our colleagues in other disciplines as we watch their end-of-life care provision, but we really struggle to evaluate our own practice.

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What have I learnt?

- Choosing Wisely^{R} – 5 low value things that could stop without compromising clinical care.
- Rather than look at palliative care and its practices, the list looks at:
  - Cardiology
  - Radiation oncology
  - Geriatricians

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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

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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)

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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?)

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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

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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

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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

White C et al. Eur J Cancer 2008;44(13):1820-1828

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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

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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

White C et al. Eur J Cancer 2008;44(13):1820-1828

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‘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

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Survey on oxygen prescribing

- A 10 year follow-up to a survey of palliative care and respiratory clinicians practices in prescribing palliative oxygen

- On the Flinders' stand