# Safety reporting in multi-site clinical trials in Palliative Care

PaCCSC

Palliative Care Clinical Studies Collaborative

Belinda Fazekas
Linda Devilee
Zac Vandersman
David Currow

Flinders UNIVERSITY

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

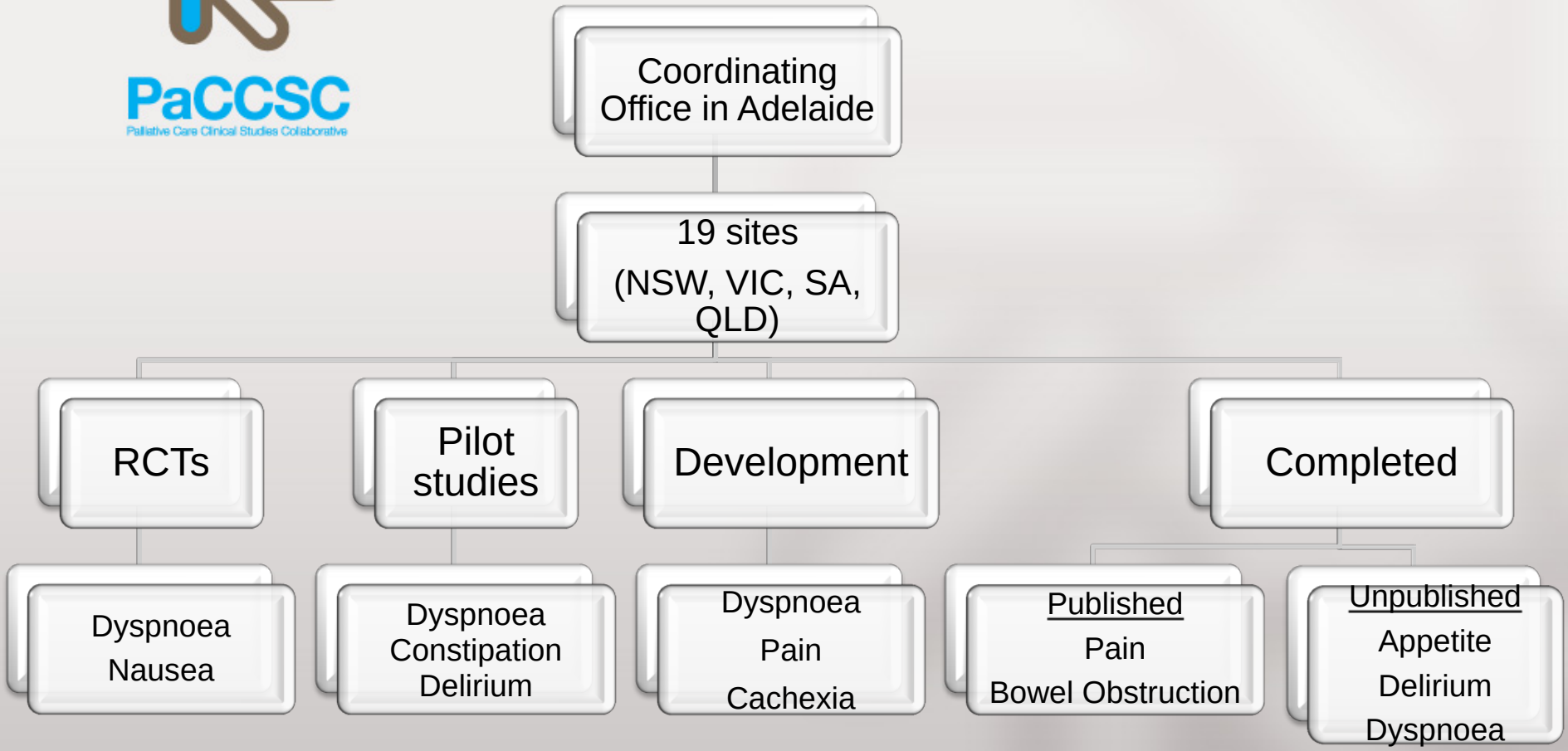
# Clinical Trials

- Test a new intervention
  - New to that population
  - New to the symptom or indication
- Does the intervention work
- Is it better
- Is it safe

# Safety in Clinical Trials

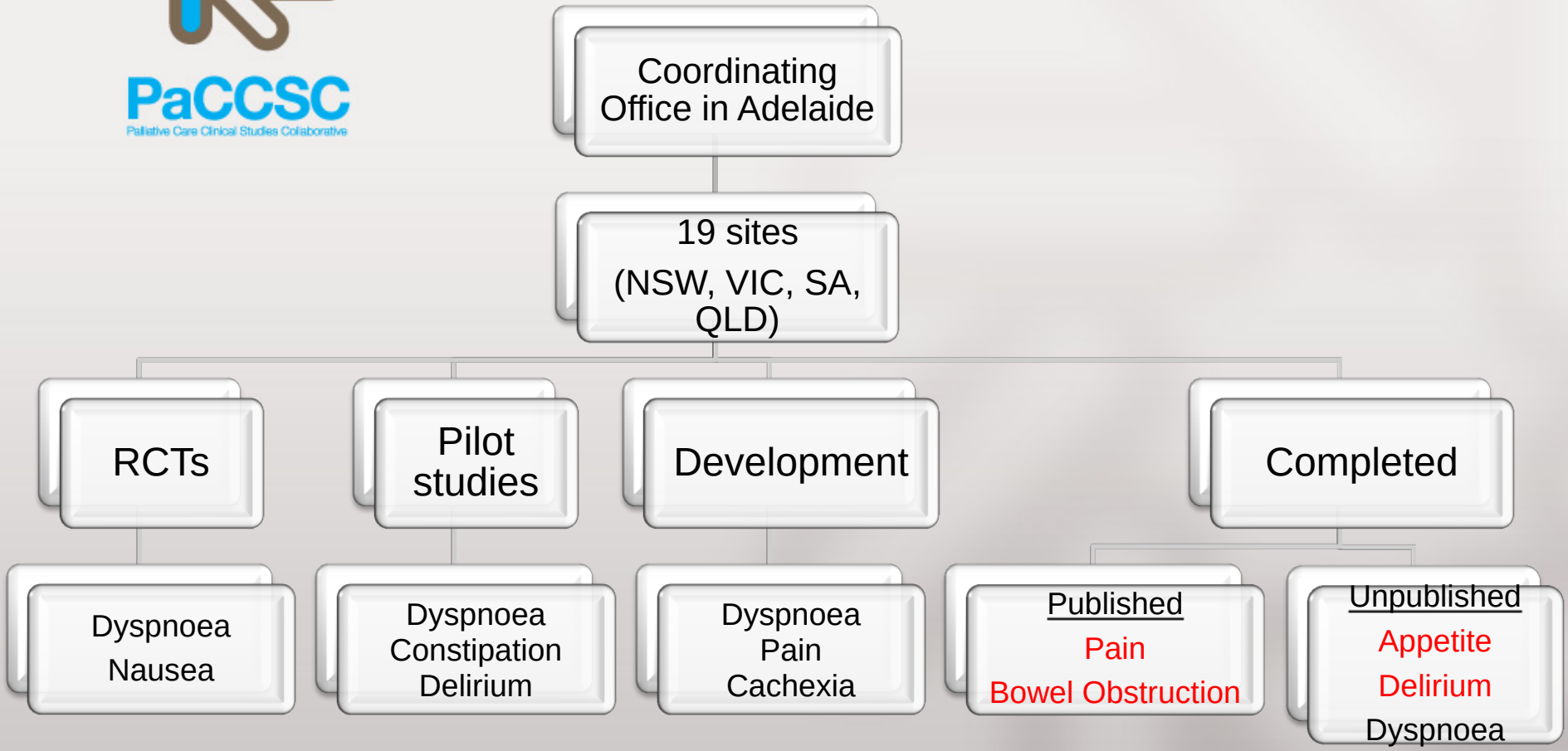
- Is the intervention safe
  - Effects of the drug/medication under study
- Is the study safe
  - Dosing
  - Measures
  - Timeframe
- How does PaCCSC measure and report safety

# Who are PaCCSC?



# Who are PaCCSC?

PaCCSC
Palliative Care Clinical Studies Collaborative



PaCCSC
Palliative Care Clinical Studies Collaborative

# The studies

- Ketamine for cancer pain
  - Inpatient
  - 5 days of sc infusion
  - Issue – stable pain for 48 hours
- Octreotide for secretions in bowel obstruction
  - Inpatient
  - 3 days of sc infusion
  - Issue – identifying patients prior to other treatment
- Risperidone for delirium
  - Inpatient
  - 3 days of oral solution
  - Issue – consent via proxy
- Megestrol for appetite
  - Outpatient
  - 1 to 4 weeks of oral capsules
  - Issue – swallowing large capsules

PaCCSC
Palliative Care Clinical Studies Collaborative

# The studies

- Results for the first 3 of those studies have been presented and discussed at this conference
  - Main results, primary outcome
  - Secondary outcomes (safety)
  - Economic outcomes
  - Complete/***did not complete***

Toxicity

Adverse events

Side effects

Safety

# Assessing safety in Clinical Trials

National Cancer Institute (NCI)

Common Terminology Criteria for Adverse Events

- Provides common terms for events by body system class
- Provides grading system based on severity of the event
- Definitions
  - Grade 1 – Mild, asymptomatic, based on observation only, intervention not indicated.
  - Grade 2 – Moderate, local or non-invasive intervention required
  - *Grade 3 – Severe of medically significant, hospitalisation indicated, limiting ADL*
  - *Grade 4 – Life threatening, urgent intervention required*
  - *Grade 5 – Death related to event*

# Assessing safety in Clinical Trials

Example

- Hypoxia
  - Grade 1 – No grade
  - Grade 2 – Decreased oxygen saturation with exercise (e.g., pulse oximeter <88%); intermittent supplemental oxygen
  - Grade 3 – Decreased oxygen saturation at rest (e.g., pulse oximeter <88% or PaO2 <=55 mm Hg)
  - Grade 4 – Life-threatening airway compromise; urgent intervention indicated (e.g., tracheotomy or intubation)
  - Grade 5 – Death
- Constipation
  - Grade 1 – Occasional or intermittent symptoms.
  - Grade 2 – Persistent symptoms with regular laxatives
  - Grade 3 – Obstipation with manual removal indicated
  - Grade 4 – Life threatening consequences
  - Grade 5 – Death

# Assessing safety in PaCCSC

Example from data forms (ketamine)

| | 1 | 2 | 3 | 4 | 5 |
|---|---|---|---|---|---|
| Cardiac arrythmia | ○ | ○ | ○ | ○ | ○ |
| Cognitive disturbance | ○ | ○ | ○ | ○ | ○ |
| Confusion | ○ | ○ | ○ | ○ | ○ |
| Constipation | ○ | ○ | ○ | ○ | ○ |
| Dizziness | ○ | ○ | ○ | ○ | ○ |
| Hypertension | ○ | ○ | ○ | ○ | ○ |
| Hypoxia | ○ | ○ | ○ | ○ | ○ |
| Injection site reaction | ○ | ○ | ○ | ○ | ○ |
| Nausea | ○ | ○ | ○ | ○ | ○ |
| Somnolence | ○ | ○ | ○ | ○ | ○ |
| Vomiting | ○ | ○ | ○ | ○ | ○ |

# Assessing safety in Clinical Trials

## Severity vs seriousness

- Severity
  - Based on NCI grade of 1-5
- Seriousness
  - Adverse events
    - all events occur from randomisation to end of participation
  - Serious adverse events
    - Life threatening
    - Results in death
    - Results in prolonged hospitalisation or admission
    - Therefore usually grade 3, 4 or 5
    - Consider this definition in palliative care population

# Reporting safety in Clinical Trials

PaCCSC
Palliative Care Clinical Studies Collaborative

## Adverse events

- Graded 1-5 in the study completed data collection forms
- Usually assessed by study nurse, medical investigator, or from medical notations in clinical record

## Serious Adverse Events

- Within study data collection forms
- Additional online report form
- Report to approving ethics committee
  - Within 48 hours if under ethics jurisdiction
  - In annual report
  - Exemptions can be applied due to patient population, study specific
- Report and review by Data Safety Monitoring Committee
  - Each event at time of report
  - Overall at 6 monthly meetings
- Review by Trials Management Committee

PaCCSC
Palliative Care Clinical Studies Collaborative

# Safety review - Aim

- To identify all adverse and serious adverse events reported since recruitment commenced in 2008
- To evaluate the event rate, severity, relatedness and withdrawals

PaCCSC
Palliative Care Clinical Studies Collaborative

# Safety review - Method

- Review 4 completed studies
  - Ketamine
  - Octreotide
  - Risperidone
  - Megestrol
- Examine the events recorded within the data collection forms (grade 3 and above)
- Examine the events reported via online reporting of serious adverse events
- Included – Present at randomisation through to end of 4 week follow-up period
- Excluded grades 1-2
  - Minor and numerous

PaCCSC
Palliative Care Clinical Studies Collaborative

# Safety review - Results

| | Referred | Randomised | % |
|---|---|---|---|
| Ketamine | 682 | 185 | 27.13 |
| Octreotide | 502 | 106 | 21.12 |
| Risperidone | 1819 | 246 | 13.52 |
| Megestrol | 1502 | 198 | 13.18 |
| **Total** | **4505** | **735** | **16.32** |

PaCCSC
Palliative Care Clinical Studies Collaborative

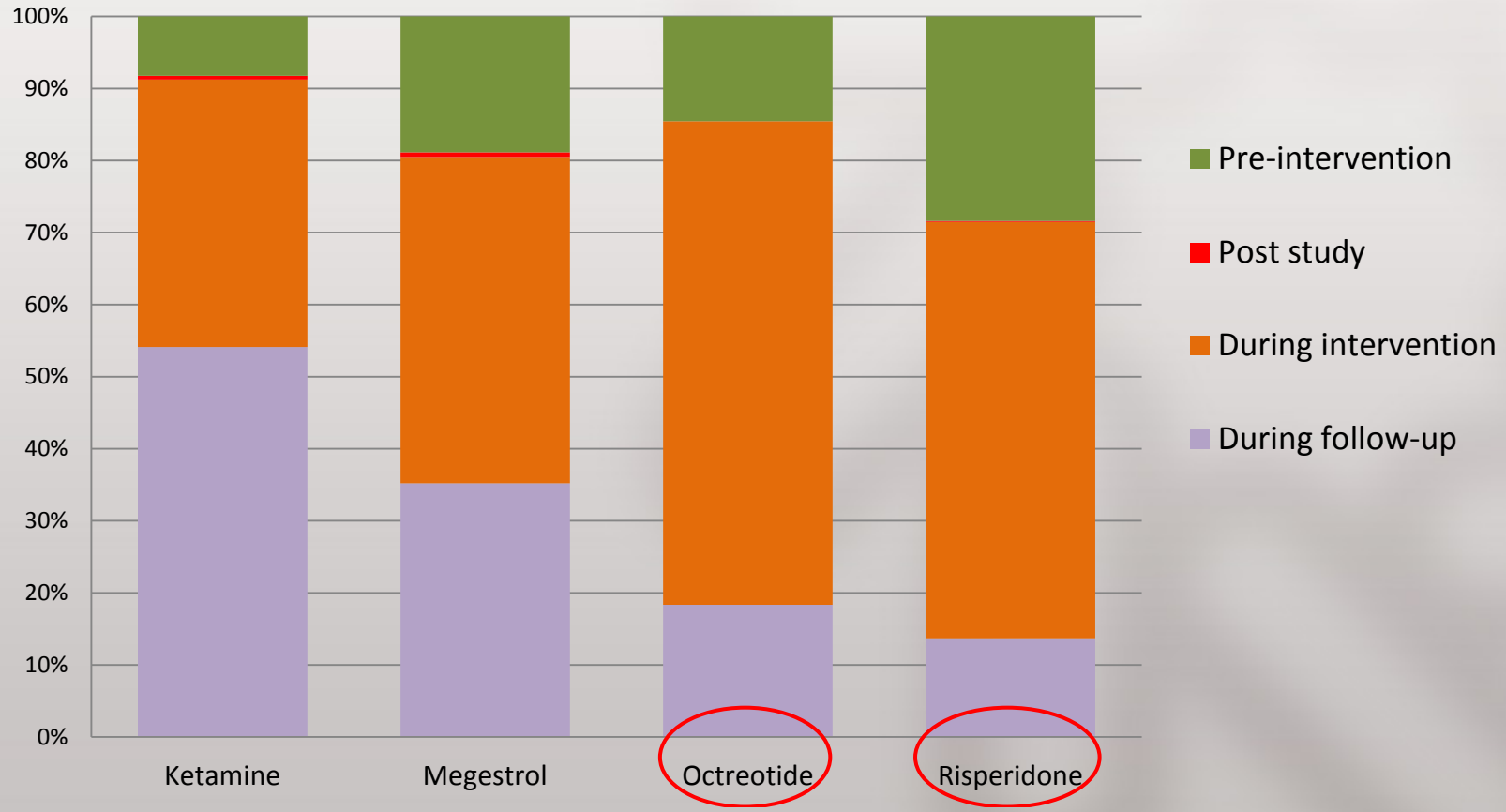
# Safety review - Results

- 735 people randomised to 1 of 4 studies between 28th March 2008 and 31st March 2015
- 375 people experienced an event of grade 3 or more (51%)
- Total of 1308 events
  - 3.4 events per person of the 375
  - 49% of study participants had no adverse events of grade 3 or more during their participation

PaCCSC
Palliative Care Clinical Studies Collaborative

# Safety review - Results

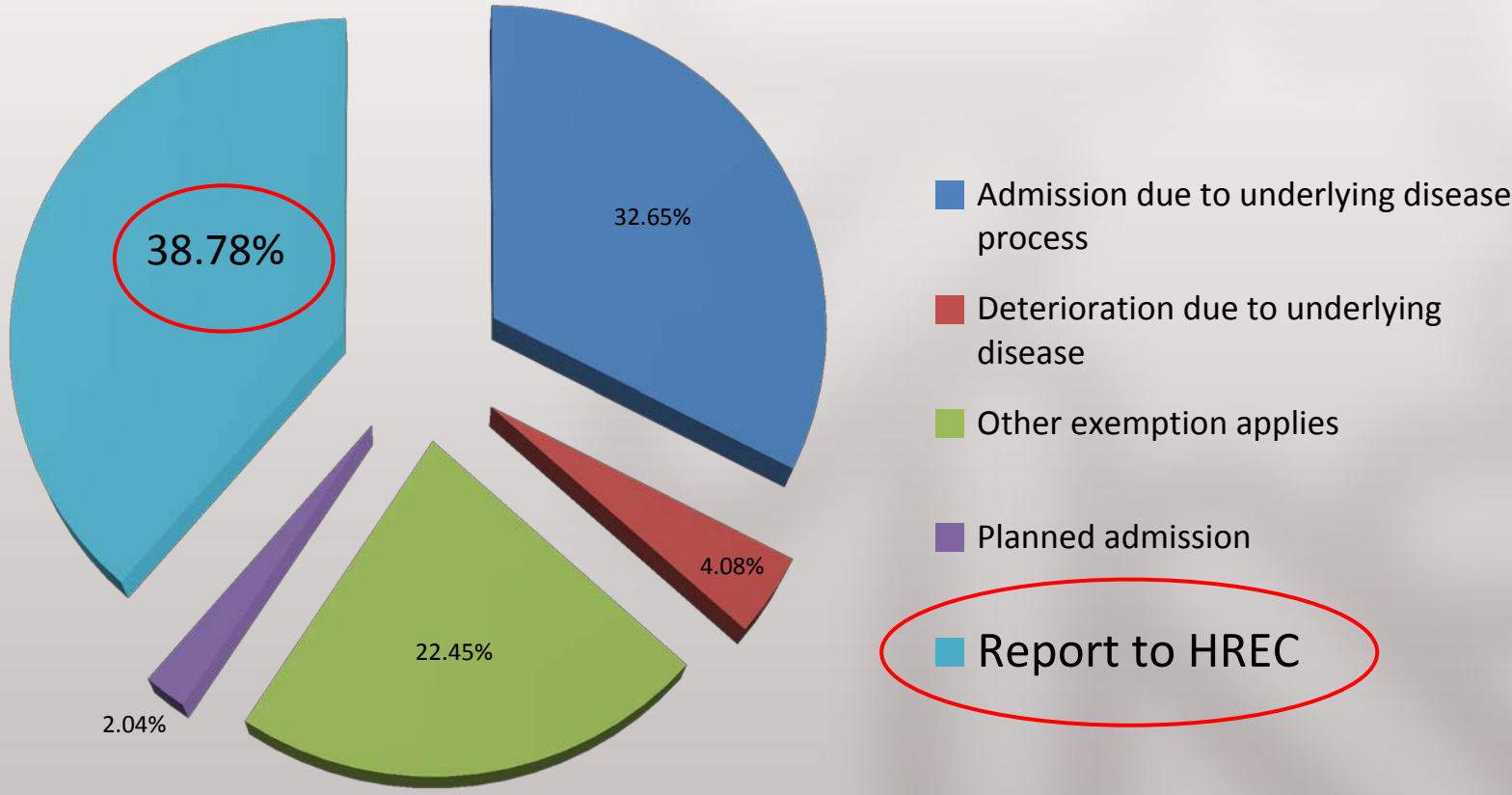
**When did these events occur?**



PaCCSC
Palliative Care Clinical Studies Collaborative

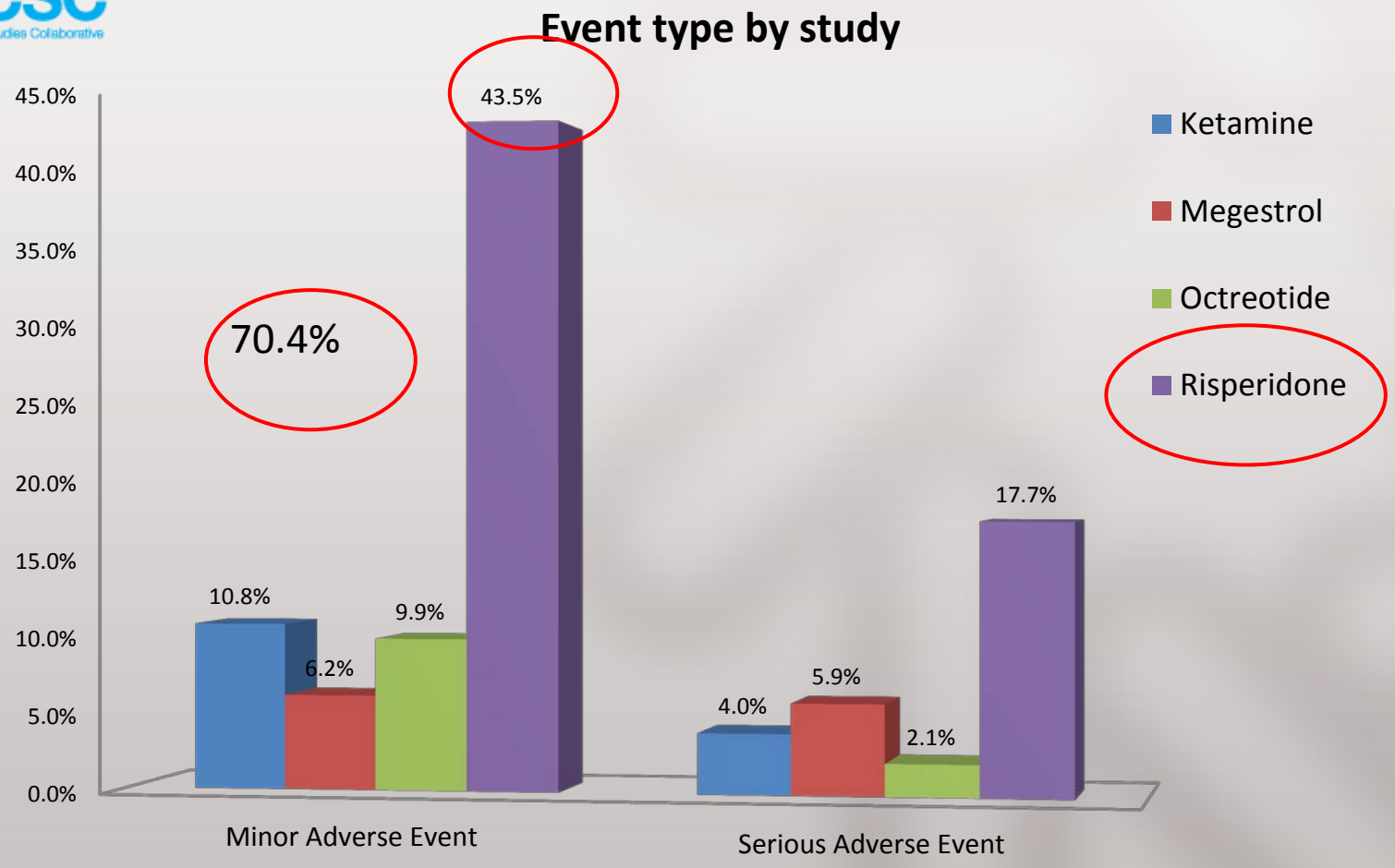
# Safety review - Results

**Reporting assessment - During intervention**



PaCCSC
Palliative Care Clinical Studies Collaborative

# Safety review - Results

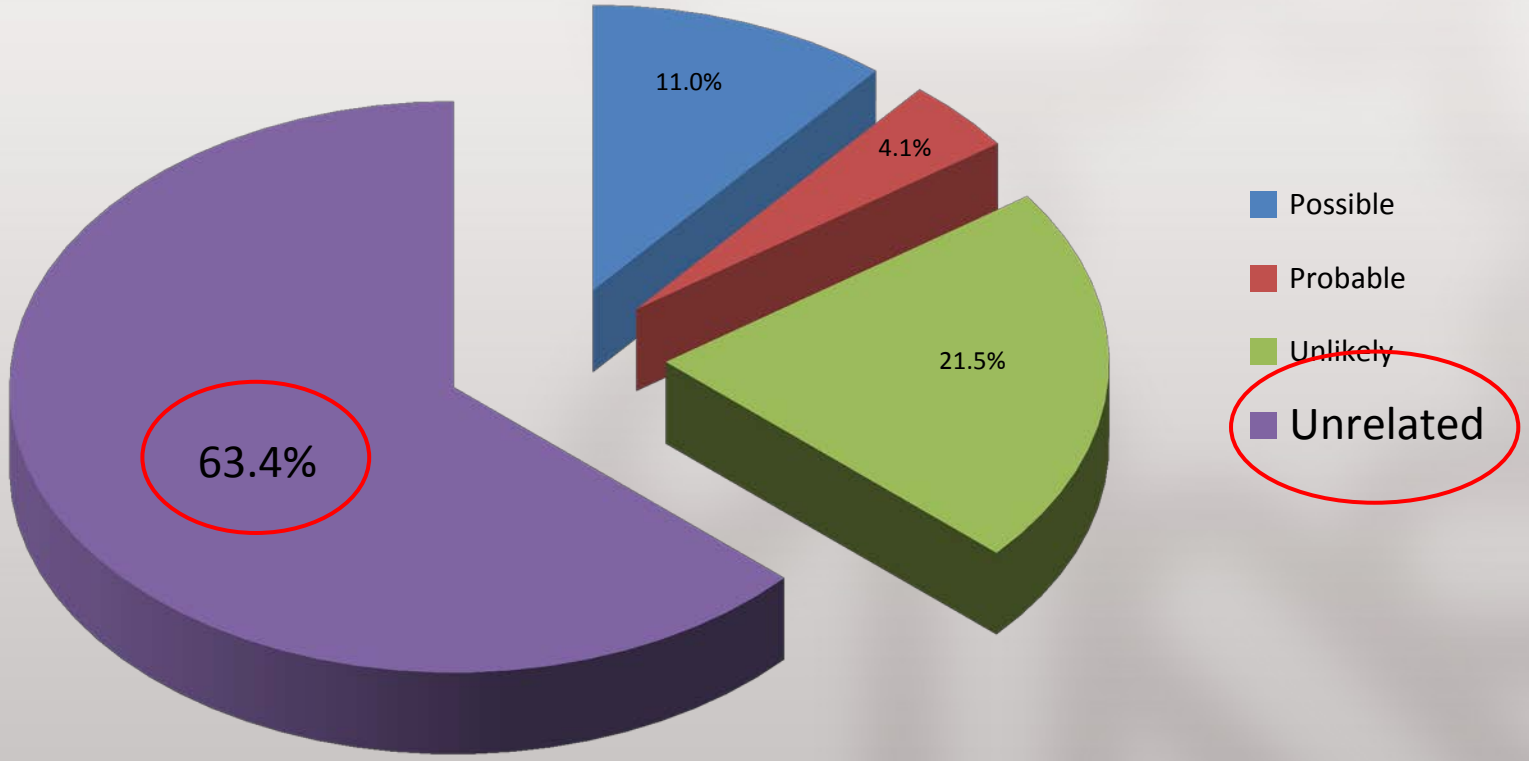


# Safety review – Related to intervention

- All serious adverse events (grade 4 or 5, admission, prolonged hospitalisation, death etc) are assessed for the likelihood of the event being related to the study intervention
  - Unrelated
  - Unlikely
  - Possible
  - Probable
- This assessment is made while the intervention is still blinded, so this remains a clinical assessment

# Safety review – Related to intervention

**Assessment of relatedness to the intervention**



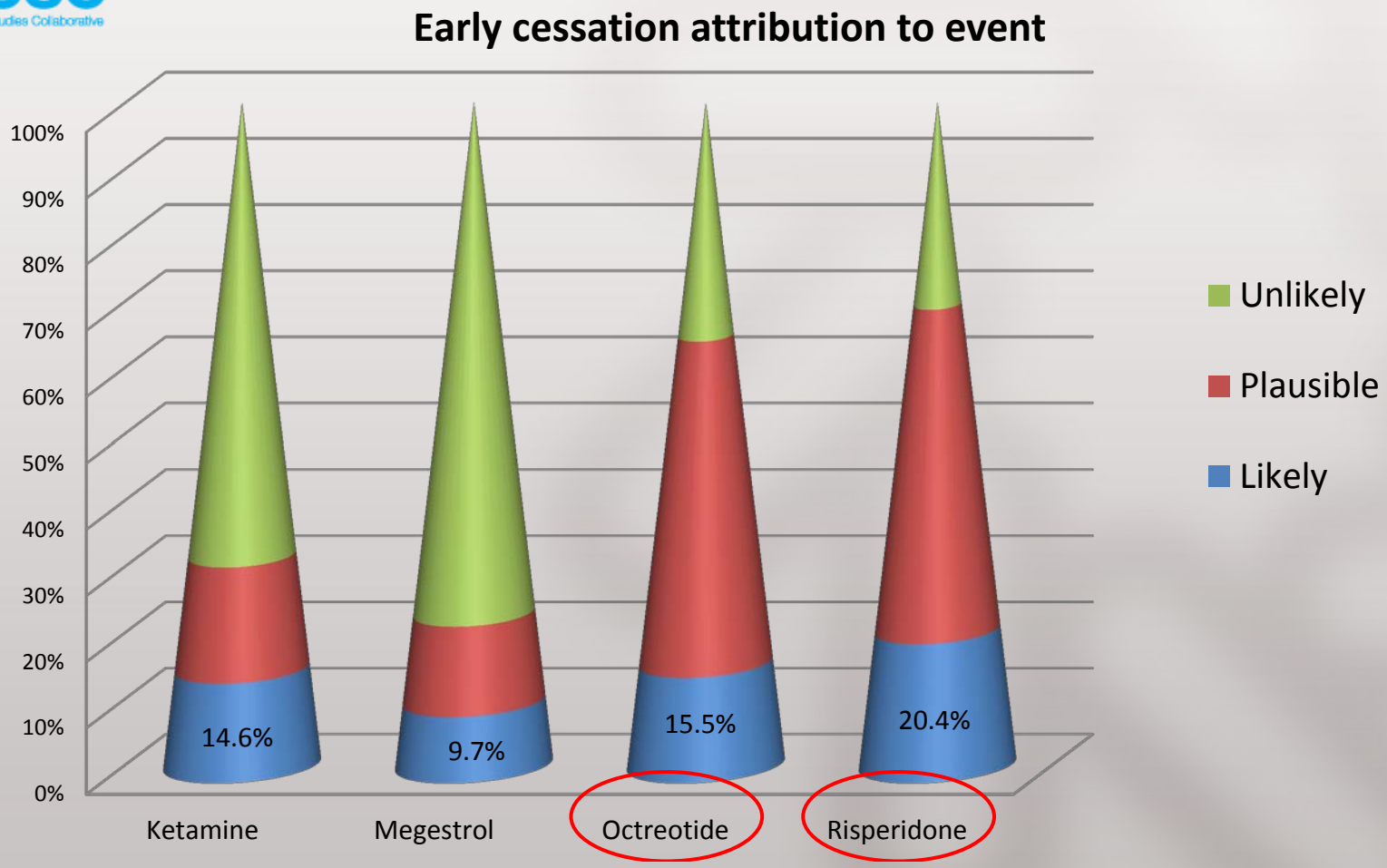
PaCCSC
Palliative Care Clinical Studies Collaborative

# Safety review – Early cessation

- Across all studies, patients are unable to complete the study for a variety of reasons.
- We looked at
  - dates of study commencement
  - date of the adverse event
  - assessed the likelihood of an early cessation of the study intervention being related to the event.

PaCCSC
Palliative Care Clinical Studies Collaborative

# Safety review – Early cessation



PaCCSC
Palliative Care Clinical Studies Collaborative

## One patient

I would like to talk about one patient.

- Randomised to the risperidone study on 7/4/2011 and completed the intervention 3 days later on the 10/4/2011
- The patient died on the 5/5/2011 after repeated debulking surgery
- A total of 21 events (grades 3 or more) were reported for this patient.

PaCCSC
Palliative Care Clinical Studies Collaborative

# One patient

| Symptom | Pre study | During study | Follow-up |
|---|---|---|---|
| Anaemia | | 1 | 2 |
| Anorexia | | | 2 |
| Back pain | | 1 | 1 |
| Cognitive disturbance | 1 | 2 | |
| Gait problems | 1 | 2 | 1 |
| Insomnia | 1 | 2 | |
| Hyponatraemia | | | 2 |
| Haemorrhage | | | 1 |
| Somnolence | | 1 | |
| Total | 3 | 9 | 9 |

PaCCSC
Palliative Care Clinical Studies Collaborative

# Conclusions

1. Clinical trials have a critical role in improving the evidence base for clinical practice
   - Medications in common use may not have current evidence for use in this population or for the indication
     - Example – ketamine for pain
   - Patient population should not preclude the conduct of clinical trials

# Conclusions

2. People who participate are often very sick, with multiple pre-existing problems
   - It is important to assess this burden prior to starting the study
     - Burden for patient and family
     - Appropriateness to participate
     - Likelihood of completing the study intervention

# Conclusions

3. Safety of the patient is the first priority and should be comprehensively assessed, reported and monitored
   - PaCCSC makes use of:
     - Routine assessment tools
     - Common terminology
     - Real time reporting and prompt assessment
     - Ethical overview of reported events
     - Review of all events by independent safety committee

PaCCSC
Palliative Care Clinical Studies Collaborative

# Conclusions

4. While an important issue, correct study design and assessment strategies, safety concerns should not exclude participation
   - Different for each study
   - Safety is also an issue when the medication is being used in clinical care without the evidence

PaCCSC
Palliative Care Clinical Studies Collaborative

## Acknowledgements


- Study investigator teams responsible for the design and conduct of these high quality clinical trials
- Study coordinators and investigators who recruited patients to the studies
- The clinical teams at the organisations who showed enough interest to refer patients in their care to the studies

# Sites Recruiting PaCCSC Studies

Mater Health Services, Queensland
The Prince Charles Hospital, Queensland
St Vincent's Hospital, Queensland
Nambour Hospital, Queensland
Southern Adelaide Palliative Services, South Australia
Lyell McEwin Hospital, South Australia
Braeside Hospital, New South Wales
Calvary Mater Newcastle, New South Wales
Sacred Heart Hospice, New South Wales
Calvary Health Care, Kogarah, New South Wales
Greenwich Hospital, New South Wales
Westmead Hospital, New South Wales
John Hunter Hospital, New South Wales
Liverpool Hospital, New South Wales
Concord Hospital, New South Wales
St Vincent's Hospital, Victoria
The Royal Melbourne Hospital, Victoria
The Austin Hospital, Victoria
Barwon Health, Geelong, Victoria

Ballarat Health Service, Victoria
Hollywood Hospital/Curtin University, Western Australia
St John of God Hospitals, Western Australia
The Alfred Hospital, Victoria

PaCCSC
Palliative Care Clinical Studies Collaborative

## Acknowledgements


- Patients and their carers who participated in the knowledge that the results were unlikely to be of benefit to them, but wanting to help others in the future.