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Planning phase III multi-site clinical trials in palliative care: the role of consecutive cohort audits to identify potential participant populations.

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Key words:
Palliative care
Audit
Clinical trials methodology
Participant recruitment
Randomised controlled trials
Phase III studies

ABSTRACT

Goals of Work: 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. The proposed studies are to improve the evidence-base for registration and subsidy applications for frequently encountered symptoms where current pharmacological interventions are being used 'off-licence'.

Methods: Six services participated in a standardized, retrospective, consecutive cohort audit of five symptoms of their inpatient populations to inform the design of double blind randomised controlled phase III studies to which each site would recruit simultaneously. 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 regardless of when the person was referred to the service. The audits were based around inclusion and exclusion criteria for the proposed studies.

Main Results: 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: pain 17.7%; delirium 5.8%; anorexia 5.1%; bowel obstruction 2.8% and cholestatic itch 0%. For those people with a symptom of interest, it was noted at the beginning of the inpatient admission more than half the time. Of all inpatients, fewer then one third would be eligible to participate in at least one study.

Conclusions: These data provide a baseline estimate of potential people to approach about clinical trials in supportive care but do not account for clinician 'gate-keeping', lack of interest in participating nor withdrawal from the study once initiated. The data are retrospective and therefore limited by clinical documentation. The audit directly informed an increase in the number of participating sites.

INTRODUCTION

Large scale trials in supportive, palliative and hospice care are feasible, especially if protocols can be designed appropriately for use in several sites simultaneously [6]. One reason for the failure of many studies in palliative care is an over-estimation of likely recruitment even for frequently encountered symptoms. A more comprehensive understanding of patterns of symptom occurrence for each participating site (given local variations in referral patterns) and general factors that may affect potential phase III study participation in a supportive and palliative care population need to be included in feasibility assessment. The design needs to take careful account of such findings if studies are going to be successful, and key performance indicators for each site can be tailored to local symptom patterns to monitor trial progress.

Rigorous phase III studies need to be undertaken to widen existing medication registration criteria (clinical indication, target population, formulation, route of administration) and to demonstrate cost effectiveness for subsidy applications in supportive and palliative care. The Australian Government has provided funds for a national multi-site Palliative Care Clinical Studies research Collaborative (PaCCSC) to undertake a series of phase III studies to improve the evidence base for the use of key symptom control medications and evaluate their cost-effectiveness across the community. [18] The medications chosen in this process defined the symptoms that are audited in this report. There is an expectation that PaCCSC will also be a catalyst for capacity building to improve clinical research capability in supportive and palliative care nationally and improve the way cost-effectiveness is analysed in this population. All the studies have been designed to meet CONSORT guidelines [12] and achieve the highest possible Jadad scores [13], while also using standardised toxicity reporting (National Cancer Institute common terminology criteria) and measurement tools validated in the study population for primary end points [4].

The PaCCSC collaborative research team encompasses key skills in supportive and palliative care clinical trials research, clinical pharmacology, pharmaco-economics, biostatistics and drug regulatory affairs. The research team is overseen by a national Management Advisory Board, and supported by a Scientific Committee providing an internal peer review process for trial development. A Trial Management Committee with representatives from each trial and each participating site oversees the development and execution of individual studies.

Participating sites represent the diversity of models of supportive and palliative care service provision in metropolitan Australia. PaCCSC sites vary in terms of size, sources of referrals, resources, and the local clinical team's experience with, and attitudes towards clinical trials. This variety of service settings helps to optimise the generalizability of any subsequent findings [1] but may limit the ability of each site to recruit to each study at the same rate.

Audit methodology has been used by researchers in other disciplines conducting multi-site studies to determine a site's ability to recruit to specific studies [19]. The aim of this paper is to describe a multi-site, retrospective consecutive cohort feasibility audit of five symptoms of interest and its implications for the phase III randomised controlled trials that will be run subsequently.

PATIENTS AND METHODS

Development of the audit. The audit was developed to determine the frequency with which symptoms of interest occurred in the clinical services, and the likely proportion of people who would meet general and study-specific eligibility criteria for the proposed phase III studies. Symptom frequencies were sought for complex pain (that has not responded to appropriate combination therapy), anorexia, acute confusion / delirium, malignant bowel obstruction and cholestatic itch. The audit was developed from draft protocols for each phase III study under consideration by clinical trialists, a research statistician, health economist and a clinical pharmacist.

Study setting

Six specialist palliative care services drawn from all mainland states of Australia were involved, having competed for participation in PaCCSC. These sites had demonstrated experience in randomised controlled trials and were a combination of 'consultation only' teaching hospital services (n=1), regional services encompassing inpatient, outpatient and community services (n=3), and those with inpatient and consult services (n=2). All sites for the audit were metropolitan services with people with cancer as the predominant referral source. (Table 1)

Participants: A consecutive cohort of all people who died within a three month period (where the most recent death was at least six months before the audit to allow time for the collation of all relevant medical records) and had at least one inpatient admission between referral and death (as studies were to be for inpatients only) was generated by each of the six PaCCSC sites (Figure 1). The inpatient admission needed to have formally involved the supportive and palliative care service (either as direct care, shared care or consultative input). The audit did not include people only referred for community support who were not admitted to hospital between referral and death.

Data Collection: The retrospective chart review of clinical care data was conducted in the second half of 2007. A project officer with an appropriate health-related background was employed for 3 months to conduct the audit at each site. From the medical records of the service (inpatient, outpatient and community care) and the health services through which care was provided, patient demographics, primary diagnosis, reasons for referral to the specialist palliative service, reasons for admission to an in-patient unit (where the first admission after referral to the specialist palliative care service was used for data collection), functional status, prevalence of symptoms and medication use during the first hospital admission were recorded. Data both at the time of, and during the course of this admission were captured in the audit. Data were collected from routine clinical records with services using a variety of ways of capturing data, none of which was the same between the participating services.

A comprehensive data collection guide and glossary were developed to ensure consistent coding across all sites. Training and support was provided nationally to assist the project officers coding and entering the data. Key definitional issues included prevalent symptoms (those present on admission to the inpatient unit), incident symptoms (those symptoms that occurred or recurred during the person's inpatient stay) and the distinction between general criteria for inclusion /

exclusion (those common to all studies and related to global abilities to participate in clinical trials) and those specific to individual studies. (Table 4)

Data management. Data were recorded on paper-based case report forms and then entered electronically onto a password protected, web-based access database (www.caresearch.com.au). Each new record with completed data uploaded on the web system generated an automatic email to the coordinating site to enable real time checking of data against copied source records before the new file was merged into the master database. As expected, there were missing data, and these fields in the audit were left blank**.**

Ethics approval. The symptom audit was deemed a quality assurance exercise by the sites' respective Human Research Ethics Committees (HREC). All data were de-identified and aggregated for each site. Permission was granted by all HRECs to publish the outcomes of the audit.

RESULTS

Characteristics of potential participants

A total of 468 deaths occurred in the six services in a three months period where the deceased had at least one admission to an inpatient unit between referral and death. (Table 1) Of these people, 66% were male, and 54% were aged 65 or older at the time of the audit. Eighty percent of admissions were initiated because of symptom control. Eleven percent (n= 53) of individuals did not have English as their first language and required an interpreter, a key general inclusion criterion for participation where validated study tools were not available in the person's usual language.

The number of inpatient admissions for participating services each month ranged from 15 to 92 people. The main sources of referral for the services were for people already hospitalised. The most frequently encountered diagnosis was lung cancer, (Table 2) and pain, dyspnoea, nausea and vomiting, and caregiver needs were the most frequently cited reasons for referral to the services.

Two hundred and thirty two (50%) people had performance status recorded in 4 sites. The Eastern Cooperative Group (ECOG) measure was used in 144 cases and the Australian-modified Karnofsky Performance Scale (AKPS) in 88. Overall performance status was poor with 75% having an AKPS of 50 or less, or 72% an ECOG score of 2 or greater.

Evaluation of symptoms

Both the prevalence of symptoms on admission and the incidence of that symptom occurring for the first time or reoccurring during the admission were coded. Between 50% and 91% of all occurrences of a symptom of interest were present on admission to the inpatient unit. (Table 3)

Eligibility factors

All general and study specific reasons for trial eligibility and ineligibility are outlined in Table 4.

Frequency of a person qualifying for a study

Individual studies had potential participation rates varying between 0% (cholestatic itch) and 62% (malignant bowel obstruction) if the symptom was present either on or during an admission. (Table 3). 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: pain 17.7%; delirium 5.8%; anorexia 5.1%; bowel obstruction 2.8% and cholestatic itch 0%. (Table 3) Of the 468 people with a palliative diagnosis who had their clinical records examined, a total of 134 (29%) would have met eligibility criteria. Of these people, 117 (88%) would have qualified for one study, 16 (12%) for two studies and 1 (1%) for three or more of the proposed studies.

DISCUSSION

There is a continuing ethical imperative to improve the clinical evidence for quality supportive and palliative care in areas that are of relevance to patients and their caregivers [17]. This audit, in preparing for a series of adequately powered phase III studies with embedded patient-defined clinical outcomes and cost-effectiveness analyses, provides a unique basis for estimating the population of potential participants. Such research aims to improve the quality of care by measuring the net clinical effect of pharmacological interventions in clinical presentations in supportive and palliative care incorporating the benefits and toxicities. As each of the medications being studied through PaCCSC is out of patent, public funding is an appropriate way to do this research. To achieve such an ambitious program of work, trial design needs to be informed by as much information in the planning stage as possible.

What data are supported by the current study?

This audit provided a snapshot of the patient population in a number of inpatient clinical settings around Australia and found that 29% of people were potentially eligible to participate in the target clinical studies. The total symptom prevalence patterns (including those symptoms prevalent on inpatient admission and those that developed or recurred during the inpatient stay) were similar to that of other audits conducted in supportive and palliative care [20]. A systematic review of symptom prevalence in the last weeks of life found that 5 symptoms, (fatigue, pain, lack of energy, weakness and anorexia) occurred in more than 50% of all people [21]. The findings are also consistent with the data on the reasons that referral to specialized supportive and palliative care services occurs [14].

The clinical conditions being studied fit into two general categories – those that can occur consistently with advanced disease often presenting with an insidious onset where prevalence is crucial (pain, anorexia) and those that are less likely to occur but often precipitate unexpected changes in care where incidence is more important (delirium, bowel obstruction). Both general criteria (inability to complete study questionnaires, poor cognition, and poor performance status) and specific inclusion and exclusion criteria for each symptom were evaluated in the audit.

Given that 12% of potentially eligible people could theoretically participate in two or more studies, there is the need to understand from the data in this audit which studies are likely to have the most difficulty recruiting. It is important to prioritise participation in studies where enrollment rates are likely to be lower.

There are a number of factors in the literature that will affect the participation in supportive and palliative care clinical studies that cannot be estimated from the audit. These include reasons that people do not want to participate in *any* study [3,23] and clinicians who will not refer an apparently eligible person to study staff [10,22]. Other factors such as staff enthusiasm and the underlying (lack of) research culture for each participating clinical unit will be of relevance to final participation rates.

Monitoring of trials will need to consider key performance indicators including the rates at which, and reasons people decline to participate in the study, withdraw from a study between consent and randomization, or between randomization and completion [5,11,15]. These considerations will influence recruitment and retention strategies. Although in these studies it is not expected that there will be high rates of withdrawal as a consequence of the study itself, there will be people who withdraw as they become too frail to continue participation.

The studies have been designed as effectiveness studies including the widest possible group of participants (in contrast to a highly selected sub-population in an efficacy study). Despite this, up to 28% of people referred to the services with a symptom of interest are not even likely to meet general eligibility criteria. The majority of people are unable to participate because of the very poor functional status, which is also reflected in the relatively low discharge rate back to the community in some of the participating inpatient units.

Direct modifications to study design / conduct as a result of the audit
Given the complexity of running a multi-site study in any population, it is important that each site understands the performance criteria for its continued participation in the collaborative. This audit has helped to set realistic goals for each study in each site by establishing the baseline practice in which the studies will be conducted. As some of the variations between sites can be explained by the referral-dependent nature of supportive and palliative care, key performance indicators (KPIs) tailored to each site based on its referral patterns have resulted from the audit.

Study design was refined as a result of the audit by:
- defining two studies that would need more recruiting sites to meet timelines;
- identifying objectively sites that would be unable to recruit effectively to one or more studies;
- identifying that some studies are likely to accrue participants more slowly, requiring protocols to ensure every single potential participant is identified systematically; and
- changing the studies from running sequentially to simultaneously given the small numbers of potential participants who had more than one symptom of interest.

A crucial finding that is still to be fully implemented in each site is that in more than one in two people, the symptom of interest was present at the time of admission to the inpatient unit. (Table 3) As such, adequate screening at admission for eligibility becomes an imperative process to institute.

Other collateral benefits of the audit
It is difficult to bring together palliative clinicians, researchers and policy makers for such an ambitious program of research, especially when some of the researchers had been competitors for very limited palliative care research funds in the recent past. The audit allowed the committee

structure of the collaborative to establish its processes away from the pressure of the actual clinical studies. The audit provided an opportunity for each site to start to work collaboratively with the national coordinating centre and to finalise and test the Standard Operating Procedures and online data entry systems. It also allowed the national coordinating centre to start working with each site, its research ethics committee and their clinicians.

The audit allowed the inclusion and exclusion criteria of each study to be critically tested and refined in the light of the clinical settings in which the studies are being conducted. The audit also encouraged sites to identify and engage with other clinical units in their institutions whose patients could be eligible for the studies.

Limitations - Methods

As with any retrospective chart review, there are significant limitations as they only allow information that has been recorded to be collected [8]. The audit highlighted the lack of documentation of key data variables of interest. For example, only one half of the people had functional status recorded in their clinical records despite this being a patient-valued metric, and a surprisingly small proportion of patients had anorexia documented. These data elements are now included in a national benchmarking project which is collecting point of care data on more than 75% of all people referred to specialized supportive and palliative care services nationally at point of clinical contact [7].This should lead to better levels of comparable documentation fields in the future.

The symptom of greatest concern was delirium. Most units had no routine screening processes despite its prevalence in cancer care [16]. The tools that will be used in the studies (which could be reasonably used in clinical practice) will be the Memorial Delirium Assessment Scale [2] and the Nursing Delirium Screening scale [9]. No unit was routinely using a screening scale or diagnostic tool even when a new episode of delirium was clinically suspected.

The study chose to use deaths and retrospectively assess for study eligibility from the first inpatient admission after referral to the palliative care service (Table 3). This ensured the best possible longitudinal data for study eligibility at any time after admission. Because only one inpatient admission was used for each participant, this may systematically underestimate the overall incidence of symptoms of interest given that they may develop at any time along the disease trajectory. New inpatient admissions could equally have been the point at which data collection started, but for an audit, this would have been more resource intensive, without increasing the detail or quality of the data collected.

Limitations - Sample

The most obvious limitation in the sample is that it did not include patients for whom the supportive and palliative care service was being consulted in the community. At least one of the studies (malignant bowel obstruction) will now enroll participants in the community if their symptoms are uncontrolled. None of the services involved has any particular local relationships or referral patterns that differ markedly from the general patterns of referral other than one service that has very limited after hours capacity for surgery, potentially limiting the likelihood of recruiting to the study on bowel obstruction.

Implications for palliative care research more generally
The most important findings from this audit are that it has helped to foster a new collaborative, allowed expansion of site numbers for specific studies and refinement of trial design in order to optimise successful outcomes for the phase III studies. These issues will be judged ultimately by successful completion of the definitive studies.

Complete Funding Declaration
Direct costs of this study were provided through a grant from the Palliative Care Branch of the Australian Department of Health and Ageing (Canberra, Australia), under the National Palliative Care Strategy. Flinders University is technically the sponsor organisation for the individual studies proposed. The design, conduct, analysis and write-up of the study were performed independently from any funding or sponsoring agency.

Research Support
Palliative Care Branch of the Australian Department of Health and Ageing (Canberra, Australia),

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Figure 1: Illustrative figure of admissions to and death whilst being supported by a specialised palliative care service in relation to the audit of potential trial participants. Admission to inpatient unit is noted separately. All deaths within a three month period became the basis of the audit, irrespective of when a person was referred to the service.

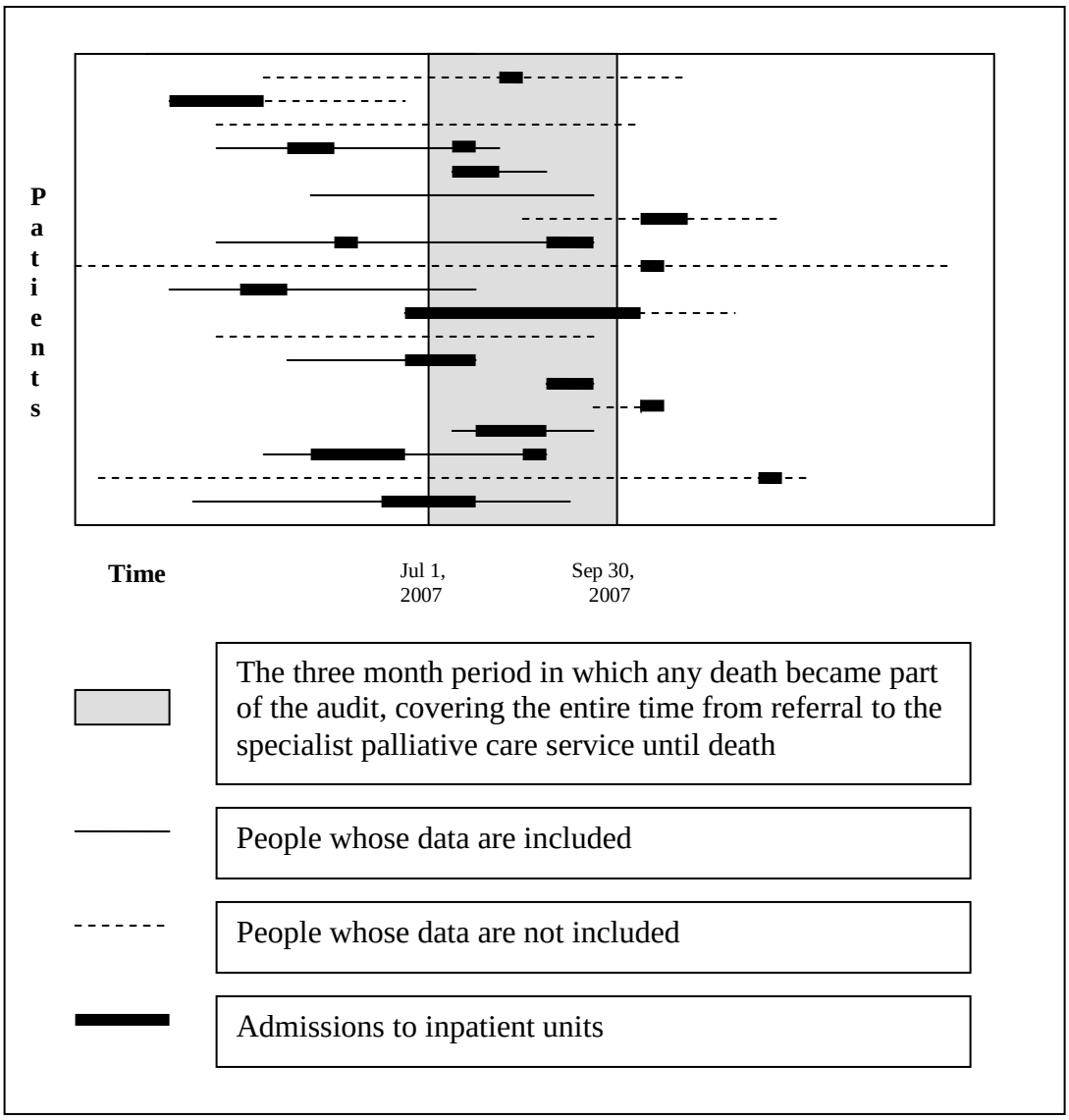

Table 1. Demographic and admission data on 468 consecutive admissions to six services across Australia for palliative care in a retrospective cohort study.

7 Sites	Mean duration referral to death (median; SD; range) Days	Mean length of inpatient admission (median; SD; range) Days	Mean age (Median; SD; range) Years	Percentage of population…			
				who are male	who are >65	with cancer (n)	who required an interpreter (n)
A* n=78	30 (10; 46; 0-237)	14 (11, 10, 0 -42)	69 (72; 14; 32-93)	69	53	74 (58)	13 (10)
B* n=30	87 (45, 101; 0-413)	10 (6,10, 1-51)	65 (67; 20; 20-93)	29	55	87 (26)	3 (1)
C n=83	170 (103, 203, 1-1037)	28 (15, 40, 0-308)	75 (80; 14; 34-96)	59	56	87 (72)	5 (4)
D n=90	131 (26, 503, 1-4674)	19 (16, 16, 1-93)	74 (70; 11; 34-100)	68	56	93 (84)	18 (16)
F n=53	19 (11,20, 1-90)	8 (8,6,1-24)	73 (77, 13, 38-96)	75	64	89 (47)	2 (1)
G n=71	51 (25, 86, 1-512)	15 (11, 12, 1-60)	65 (65, 15, 21-89)	46	54	99 (70)	6 (4)
H n=63	92 (60,93, 0-357)	14 (15,10, 1-31)	67 (68, 12, 37-91)	56	69	94 (59)	27 (17)
All n = 468	**92 (30; 257; 0-4674)**	**18 (13; 22; 0-308)**	**69 (72; 15; 20-96)**	**66**	**54**	**89 (416)**	**11 (53)**

* Sites A and B were two teaching hospital inpatient campuses of the same regional palliative care service

Table 2. The three most frequently encountered life-limiting illnesses for each audited site from a consecutive, multi-site, retrospective cohort study evaluating potential phase III symptom control clinical trial participation.

7 Sites n=468	**1**	**2**	**3**
A* n=78	Lung cancer 12 (16%)	Other GIT cancer 12 (16%)	Unknown primary 11 (15%)
B* n=30	Lung cancer 5 (17%)	Colo-rectal cancer 4 (14%)	Heart failure 4 (14%)
C n=83	Lung cancer 24 (29%)	Heart failure 24 (29%)	Respiratory failure 17 (21%)
D n=90	Lung cancer 18 (20%)	Other GIT cancer 12 (14%)	Colo-rectal cancer 10 (12%)
F n=53	Lung cancer 13 (25%)	Prostate cancer 9 (17%)	Pancreatic cancer 6 (12%)
G n=71	Lung cancer 24 (34%)	Head and Neck cancer 8 (12%)	Other GIT cancer 7 (10%)
H n=63	Lung cancer 14 (23%)	Other GIT cancer 11 (18%)	Breast cancer 6 (10%)

* Sites A and B were two teaching hospital inpatient campuses of the same regional palliative care service

Table 3: Likely eligibility of a consecutive, retrospective multi-site cohort of 468 people with life-limiting illnesses admitted to seven inpatient units for potential participation in clinical studies.

Column number; Cn						
C1	**C2**	**C3**	**C4**	**C5**	**C6**	**C7**
Symptom / sign	**Prevalence - present on admission; Symptom is present on admission as a percentage of all people who have the symptom at any time (C2/C4)*100**	**Incidence - developed or recurred during admission**	**Symptom present at any time (on or after admission) ***	**Broadly eligible for PaCCSC studies; (C5/C4)*100; Dominant reason for broad ineligibility**	**Specifically eligible for a PaCCSC study with this symptom present at some time; (C6/C4)*100; Dominant reason for specific ineligibility**	**Overall eligibility in the cohort (C6/468)*100**
Pain -	199 (84%)	126	237	200 (85%) Incapable of complying with study procedures	83 (35%) Planned chemotherapy/radiotherapy	17.7%
Delirium	39 (53%)	59	73	66** (90%) Difficulty swallowing	27** (37%) Anti-psychotic medication use	5.8%
Anorexia	127 (91%)	85	140	101 (72%) Performance status	24 (17%) Glucocorticoid use	5.1%
Bowel obstruction secondary to malignancy	18 (86%)	11	21	21^^ (100%)	13 (62%) Planned surgery	2.8%
Cholestatic itch	1 (50%)	2	2	2 (100%)	0 (0%) Ondansetron use	0
None	75	29	29			
Not stated	41	15	15			

***** Numbers with the condition "Any Time" may be less than the sum of "On Admission" and "During Admission" as a patient may have had the condition on admission, had it resolve and again developed the problem during the admission.
** Does not include specific assessment of the Memorial Delirium Assessment Score nor the Nursing Delirium Assessment scores as these were not routinely collected in any of the participating sites before the study
^^ Excludes vomiting

Table 4 – General and study specific inclusion and exclusion criteria for clinical studies

	Inclusion criteria	Exclusion criteria
General		
	Palliative diagnosis Prognosis sufficient to warrant entry into the study* Over 18 years of age Proficiency in English sufficient to complete the study measures Mini-Mental State Examination >23 Able to comply with study procedures Able to give written informed consent (or has an appropriate proxy)	Previous documented adverse reaction to any of the study medications Unable to comply with study procedures Currently (or recently) on the study medication Participation in a study with a new chemical entity in the previous month Women who are pregnant, lactating or have not had adequate advice about birth control if fertile
Study-specific		
Pain	- Chronic pain related to cancer or its treatment Brief Pain Inventory >3 in the previous 24 hours - Stable opioids for last 48 hours with the intention for stable opioids for the next 5 days - Likely to be inpatient for 5 days - Adequate trial of relevant co-analgesics	- Exposure to ketamine in the previous six months - Radiotherapy to painful sites recent or planned - Chemotherapy or hormone therapy started within the last month - History of psychoses, acute intermittent porphyria, uncontrolled hyperthyroidism, uncontrolled epilepsy, uncontrolled hypertension. Uncontrolled raised intraocular pressure, recent alcohol or illicit drug misuse or recent use of mono amine oxidase inhibitors
Delirium	- DSM IVR[1] diagnostic criteria for delirium MDAS[2] $\geq$ 7 - NuDesc[3] score of 1 on questions 2 and/or 3 and/or 4 - Likely to be inpatient for 4 days - Able to take oral solution - availability of an acceptable proxy to give consent	- Delirium due to withdrawal from medications or alcohol - History of neuroleptic malignant syndrome, extrapyramidal disorders including Parkinson's or prolonged QT syndrome - Antipsychotic use in the last week - Cerebrovascular accident or seizure in the last month
Anorexia	- Self-reported loss of appetite for at least 2 weeks on numerical rating scale of 4 or less (0 = no appetite) - Able to take and absorb oral medications - anti-depressants, antipsychotics and omega 3 fatty acids stable for at least one month	- History or proven thromboembolic disease or long-term vascular access device without adequate anticoagulation - Use of glucocorticoids or progestogens, androgens, cannabinoids, olanzapine, psychostimulants -Tube feeding or parenteral nutrition - Clinically significant ascites - poorly controlled NYHA[4] grade IV heart failure or uncontrolled hypertension - unmonitored diabetes mellitus - uncontrolled diarrhoea, nausea or vomiting - active systemic infection at the study start.
Bowel obstruction	- Vomiting as a result of a bowel obstruction that necessitates a change in clinical management - Advanced cancer where therapy is unlikely to change the clinical course	- Australian-modified Karnofsky performance score of <30 at beginning of trial - Calculated creatinine clearance <10ml/min - Clinically significant cirrhosis - Venting or feeding gastrostomy / jejunostomy - Bowel surgery planned within the next 72 hours
Cholestatic itch	- Self –reported itch 3 or more on a 0-10 rating scale not responding to current treatment	- Recent use of ondansetron - History of uncontrolled constipation - History of uncontrolled headaches

* Varied on the duration of the proposed studies

[1] Diagnostic and Statistical Manual of Mental Disorders, fourth edition revised
[2] Memorial Delirium Assessment Scale
[3] Nursing Delirium Screening Scale
[4] New York Heart Association